Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques

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ABSTRACT

BACKGROUND

Surgical, traumatic and obstetric bleeding are important causes of mortality and morbidity. The antifibrinolytic drug, tranexamic acid (TXA), inhibits clot breakdown and may have a role in the management of excessive bleeding.

AIM

Evaluate the evidence from randomised trials for the effects of TXA in patients with surgical bleeding, traumatic bleeding, and for preventing postpartum haemorrhage (PPH).

METHODS

Using systematic reviews and meta-analytic techniques, evaluate the evidence from randomised trials to: i) quantify the effects of TXA for surgical bleeding; ii) investigate the quality of trials of TXA for surgical bleeding; iii) to quantify the effects of TXA for traumatic bleeding; iv) estimate the number of avoidable trauma deaths by the routine use of TXA; v) quantify the effects of TXA for preventing PPH; and vi) propose a trial of TXA for preventing PPH.

RESULTS

A systematic review including 129 trials involving 10,488 patients suggests that TXA reduces bleeding in surgical patients by about one third, although its effect on death and thromboembolic events is uncertain. Evidence that TXA reduces surgical bleeding has been available for many years, although, poor methodological quality of trials may mean that it is unreliable.

There is reliable evidence that TXA reduces death due to bleeding in trauma patients. This evidence originates from a large, high quality randomised trial in 20,211 patients. If TXA was given to all patients soon (<3 hours) after injury over 100,000 deaths could be prevented every year.

A systematic review including 26 trials involving 4191 women suggests that there is no reliable evidence for the effects of TXA for preventing PPH. The trials are poor quality and contain serious flaws. The proposed WOMAN-2 trial of TXA for preventing PPH in 10,000 women with anaemia aims to resolve the uncertainties.

CONCLUSIONS

Most trials assessing the effect of TXA for surgical bleeding and for preventing PPH are small and poor quality. Although together they provide promising evidence that TXA reduces bleeding,

further evidence from large trials at low risk of bias is required to determine reliably the effects of TXA for these indications.

There is reliable evidence that TXA reduces the risk of death in trauma patients and no further trials are required. Instead, dissemination of the evidence and implementation of TXA into trauma protocols worldwide, should be a priority.

Although there is no evidence from randomised trials that it increases risk, the effect of TXA on thromboembolic events remains uncertain.

CONTENTS

TABLE OF ABBREVIATIONS

CI	Confidence Interval
CTU	Clinical Trials Unit
dl	Decilitre
g	Gram
Hb	Haemoglobin
IPD	Individual Patient Data
kg	Kilogram
l	Litre
LMICs	Low and middle income countries
LSHTM	London School of Hygiene & Tropical Medicine
mg	Milligram
ml	Millilitre
NHS	National Health Service
PCV	Packed Cell Volume
PPH	Postpartum haemorrhage
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Relative Risk
TBI	Traumatic Brain Injury
TSA	Trial Sequential Analysis
TXA	Tranexamic acid
UK	United Kingdom

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

1.0 INTRODUCTION TO THESIS

1.1 EPIDEMIOLOGY OF SURGICAL, TRAUMATIC AND OBSTETRIC BLEEDING

Haemorrhage[i] is a major cause of mortality and morbidity worldwide. Acute severe haemorrhage resulting from vascular injury during surgery, trauma, and childbirth account for much of the morbidity and are responsible for many premature deaths.

Surgical haemorrhage

Surgery is an essential component of health systems in high, middle and low-income countries. In 2012, there were an estimated 310 million surgical procedures worldwide, a number expected to increase in subsequent years in line with ageing populations and shifting patterns of disease towards chronic illnesses.[1]

Blood loss and exposure to blood transfusion are common complications of surgery and are associated with poorer patient outcomes. In addition to its adverse physiological impact, bleeding impairs the visibility of the surgical site compromising the success of the procedure. Bleeding can prolong the surgery and require further interventions such as blood transfusion and re-operation.

A retrospective cohort study conducted in the USA included over 1.6 million procedures across eight surgical specialities and observed that on average 30% suffered a bleeding-related complication, with blood product transfusions being the most common.[2] The authors also estimated the additional costs and resource use incurred. After adjusting for covariates, patients with bleeding complications stayed in hospital six days longer than those without. The cost of treating these patients was also higher, varying between 31-93% more depending on the surgery type.[2]

Death during surgery is relatively rare, although in the presence of acute severe bleeding it increases from less than 1% to 20%.[3] A cohort study of cardiac surgery patients found that 10% of patients suffered blood loss severe enough to receive five or more units of blood within 24 hours of surgery, which was associated with an eight-fold increase in the odds of death.[4]

The challenge of managing severe bleeding during surgery is likely to become more common as the number of complex procedures rises, alongside the advancing age of surgical patients and the growing use of anti-coagulants, which increase the risk of bleeding.

[i] I use the terms 'haemorrhage' and 'bleeding' interchangeably throughout this thesis.

Traumatic haemorrhage

There are an estimated five million deaths due to trauma every year, which account for 9% of global mortality.[5] Almost half of trauma deaths are young adults aged 15-44 years, and over 90% of deaths occur in low and middle income countries (LMICs).[5, 6] Many millions more experience non-fatal injuries and suffer long-term disability.

Haemorrhage is second only to traumatic brain injury as the leading cause of death in trauma victims. It is responsible for up to 40% of deaths, most of which occur in the first 24 hours after injury.[7-11] Furthermore, bleeding contributes to other leading causes of death, including central nervous system injury and multi-organ failure.[8] In trauma patients who survive, haemorrhage is associated with complications such as organ failure and sepsis, with greater blood loss associated with poorer outcomes.[8, 12]

A cross-sectional study involving bleeding trauma patients presenting to 22 hospitals in England and Wales estimated the prevalence, patterns of blood use, and outcomes of patients with major haemorrhage.[11] A quarter (26.5%) of patients with major haemorrhage (≥4 units red blood cells in first 24 hours) and one-third (38.5%) of those with massive haemorrhage (≥10 units red blood cells in first 24 hours) died in hospital. Most patients died within 24 hours and most of these deaths occurred within four hours of arriving at hospital.

There is a substantial economic burden of treating bleeding trauma patients. Estimates based on resource use data from 22 NHS hospitals, suggest that it costs an average of £20,000 to treat a trauma patient with severe bleeding, of which the cost of blood components accounts for 12% (£2,300).[13] When extrapolated to the national (England) level, this costs the NHS £148 million per year.[13]

Obstetric haemorrhage

Severe bleeding is a common complication of childbirth. Primary postpartum haemorrhage (PPH), commonly defined as blood loss ≥500 mL within 24 hours of birth, follows 6% to 10% of all births and accounts for 50,000 to 100,000 maternal deaths every year.[14-17] Although PPH is common throughout the world, 99% of deaths occur in LMICs.[18] Similar to traumatic bleeding, most deaths from PPH occur early. The majority of deaths occur within 24 hours of delivery, many within the first few hours.[14] The leading cause of PPH is uterine atony, followed by bleeding due to trauma to the genital tract, retention of placental tissue, and failure of the coagulation system.[16]

Many women who survive PPH experience severe morbidity that may require costly, urgent care, and a prolonged hospital stay. Many women need surgery to control the bleeding and some require a hysterectomy.[19] PPH can lead to, or worsen existing, anaemia, which can result

in debilitating fatigue that interferes with the woman's ability to care for herself and her baby.[20] There is also evidence that morbidity resulting from PPH adversely affects a mother's ability to breast-feed and bond with her baby.[21] PPH can be an extremely frightening experience that may have a long-term psychological impact.[22]

Although death due to PPH is rare in high income countries, it is an important cause of maternal morbidity and there is some evidence to suggest that the incidence is increasing.[23] The reasons for this increase are uncertain but may be due to increasing maternal age, obesity, higher rates of intervention and caesarean sections.[23, 24]

Blood transfusion

The administration of blood and blood products is a common intervention for the management of excessive surgical, traumatic and obstetric bleeding, which together place enormous pressure on donor blood supplies.

One third of transfused blood in the UK is used for surgical patients who each receive an average of two units.[25] Blood usage data from the UK suggest that 63% of patients with significant trauma receive a blood transfusion, over half of whom receive eight or more units.[26] A survey of hospital data from 28 countries suggests that one third (32.5%) of women with PPH receive blood products.[27]

However, blood for transfusion is a scarce and costly resource and most people in the world do not have access to donor blood. The blood donation rate in Africa is 5 per 1000 population compared to 47 per 1000 population in the USA, and it is estimated that 35 of the 40 sub-Saharan countries collect less than half of the donor blood required to meet the needs of their populations.[28] It is estimated that 26% of maternal haemorrhagic deaths in sub-Saharan Africa are due to lack of blood for transfusion.[29]

Where it is available, safe blood for transfusion is expensive. In the UK, for example, a single unit of blood costs of £125, presenting an annual cost to the NHS of £266 million.[30]

As well as issues with cost and availability, the practice of giving blood for transfusion is not without risk and it may not improve patient outcomes. A systematic review of randomised trials comparing 'liberal' and 'restrictive' transfusion protocols, found that patients in the restrictive group were less likely to receive a blood transfusion (RR=0.57, 95% CI 0.49 to 0.65), but found no difference in 30 day mortality (RR=0.97, 95% CI 0.81 to 1.16).[31]

Moreover, blood transfusion is associated with several infectious and non-infectious risks. The extent and type of the risk posed by blood transfusion varies considerably by country and the adequacy of the donation and blood screening systems. In countries with comprehensive blood

screening processes such as the UK, the transmission of known infections is very rare (0.2 events per 100,000 components) and most (~70%) harm results from transfusion of mismatched blood.[32]

However, not all countries are able to provide comprehensive screening of donor blood and transfusion-transmitted infections are the primary concern. In 2004, 88% of blood collected in sub-Saharan Africa was not tested for HIV in a quality-assured manner. [28] A mathematical model of the risk of transfusion-transmitted viral infections in sub-Saharan Africa estimated that the median overall risks of infection with HIV, HBV, and HCV from blood transfusion were 1, 4.3, and 2.5 infections per 1000 units, respectively.[33] Between 5-10% of global HIV infections were acquired through transfusion of contaminated blood.[34]

Because of the scarcity, cost and associated risks of blood transfusion, the identification of cost-effective alternatives is a public health priority and treatments that can safely reduce bleeding are needed.

1.2 HAEMOSTASIS

Maintenance of the circulating blood volume is a basic homeostatic mechanism essential for supporting life.[35] Bleeding caused by vascular injury, leads to a reduction in the amount of haemoglobin in the circulation and loss of blood volume (*hypovolaemia*) which if extensive or uncontrolled, leads to haemorrhagic shock and ultimately organ failure and death.[36]

In response to blood loss, the body initiates a series of compensatory mechanisms that allow low levels of blood loss to be tolerated without notable adverse health effects. However, the loss of relatively minor amounts of blood can be harmful in individuals who are less able to compensate for the loss, such as the elderly, those with anaemia or with existing cardio-respiratory or hepatic disease.[36]

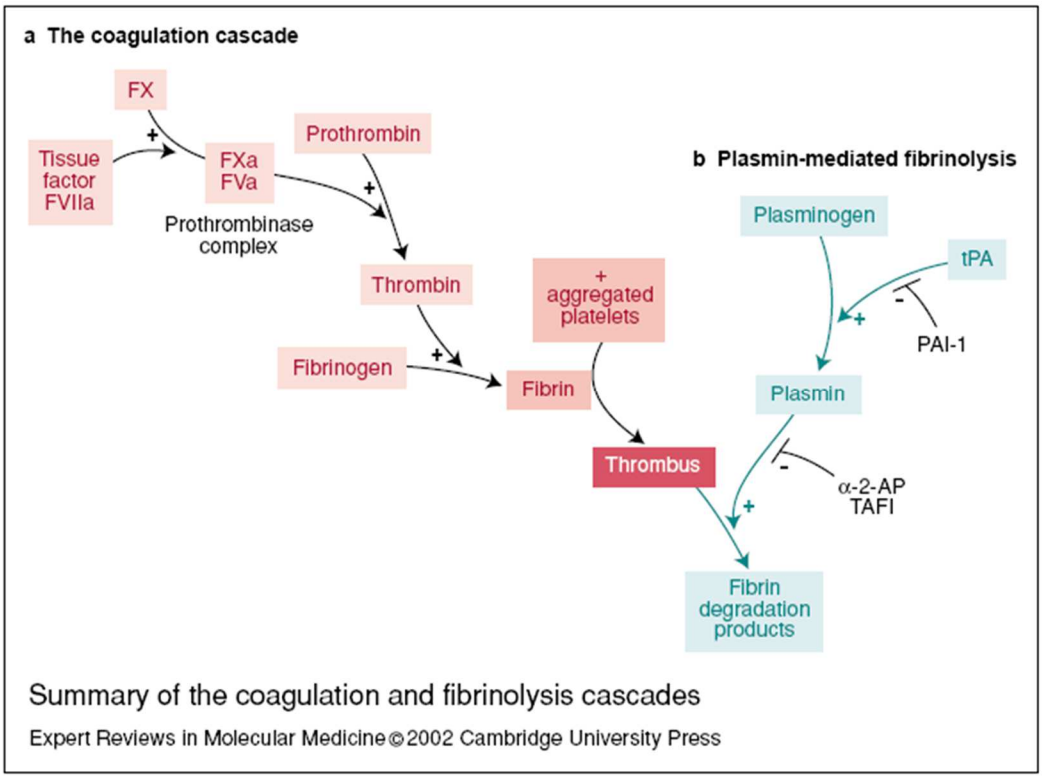
Trauma, surgery and childbirth are leading causes of acute haemorrhage, the complications of which result in substantial global mortality and morbidity and are the focus of this thesis. Vascular injury, regardless of cause, initiates a common haemostatic response. Recommendations for the haematological management of major haemorrhage are common across clinical situations.[37] As a result, those seeking to improve the management of bleeding in trauma and obstetric patients have looked to use evidence from surgical disciplines and vice versa.

1.3 COAGULATION AND FIBRINOLYSIS

Vascular injury, irrespective of the cause, triggers a series of physiological responses aimed at maintaining the integrity of the circulatory system.[38] Two regulatory responses are involved: the

coagulation cascade leading to clot formation, and the *fibrinolytic* response leading to clot breakdown.[39] The coagulation and fibrinolysis cascades are summarised in Figure 1.1.

Figure 1.1 Summary of the coagulation and fibrinolysis cascades[ii]



The immediate haemostatic response to vascular injury is localised vasoconstriction and movement of blood into the surrounding tissues that reduces the flow through the damage vessel. This is followed by the aggregation and deposition of platelets at the point of injury.[39] Activation of thrombin results in the production of fibrin which interacts with the platelet plug, and produces a clot resistant to dissolution that acts as a haemostatic seal at the point of damage.[41]

The coagulation response is accompanied by a *fibrinolytic* response that results in the breakdown of the fibrin mesh. Tissue plasminogen activator (t-PA) secreted from the endothelial cells, converts plasminogen trapped within the clot into plasmin.[41] Plasmin attaches to and digests the fibrin causing clot breakdown.

A delicate balance of these regulatory responses prevents inevitable death that would be caused by either uncontrolled bleeding or uncontrolled clotting.[38] However, in the context of major blood loss, this delicate balance can be compromised by the accompanying physiological stresses, including over-activation of t-PA that can lead to hyperfibrinolysis (a state of excessive

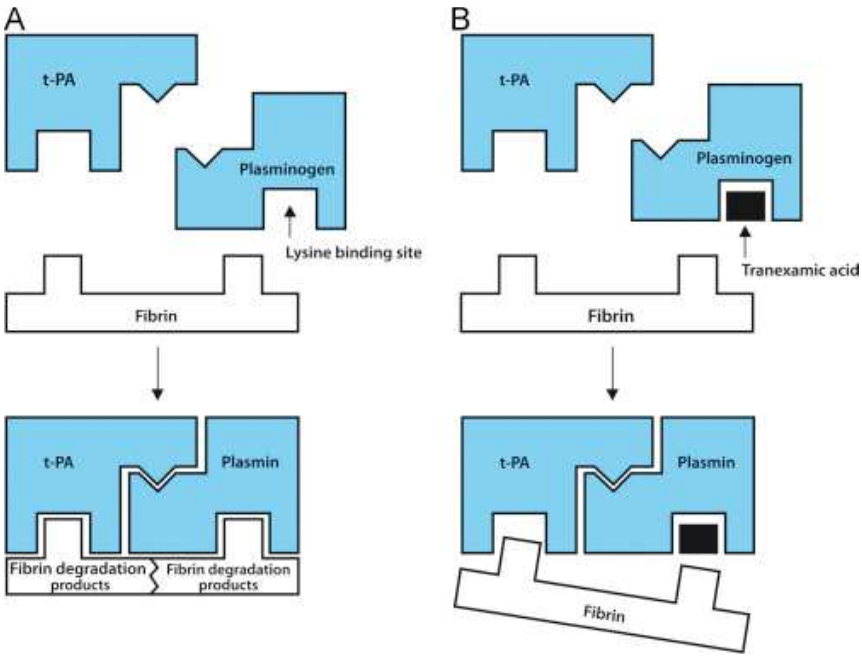
[ii] Reproduced from Bodary *et al*[40]

fibrinolysis and uncontrolled bleeding). Hyperfibrinolysis is associated with a range of bleeding conditions including trauma, surgical, and obstetric haemorrhage and causes excessive or recurrent bleeding,[41] the outcomes of which includes death, organ dysfunction, multiple organ failure and sepsis.[42] The latter of which can be exacerbated by immunologic stress associated with blood transfusion.[42]

1.4 TRANEXAMIC ACID AND ITS EFFECT ON BLEEDING

TXA is a synthetic lysine amino acid derivative that inhibits fibrinolysis by blocking the interaction between plasmin and fibrin (Figure 1.2).[41]

Figure 1.2 Antifibrinolytic action of tranexamic acid[iii]



TXA exerts its antifibrinolytic effect by forming a reversible bond with the lysine binding site on the plasminogen molecule. Plasmin is therefore prevented from interacting with fibrin and clot stability is achieved. It is marketed in tablet and injection form as a treatment for a variety of chronic and acute bleeding conditions.

In the UK, TXA injection is licensed for administration as a slow intravenous injection for short-term use for the prophylaxis and treatment of patients at high risk of perioperative bleeding associated with prostatectomy, conisation of the cervix, surgical procedures and dental extractions in people with haemophilia; haemorrhage complications in association with thrombolytic therapy; and haemorrhage associated with disseminated intravascular coagulation with predominant activation of the fibrinolytic system.[44] TXA is a relatively inexpensive drug -

[iii] Reproduced from Dunn & Goa[43]

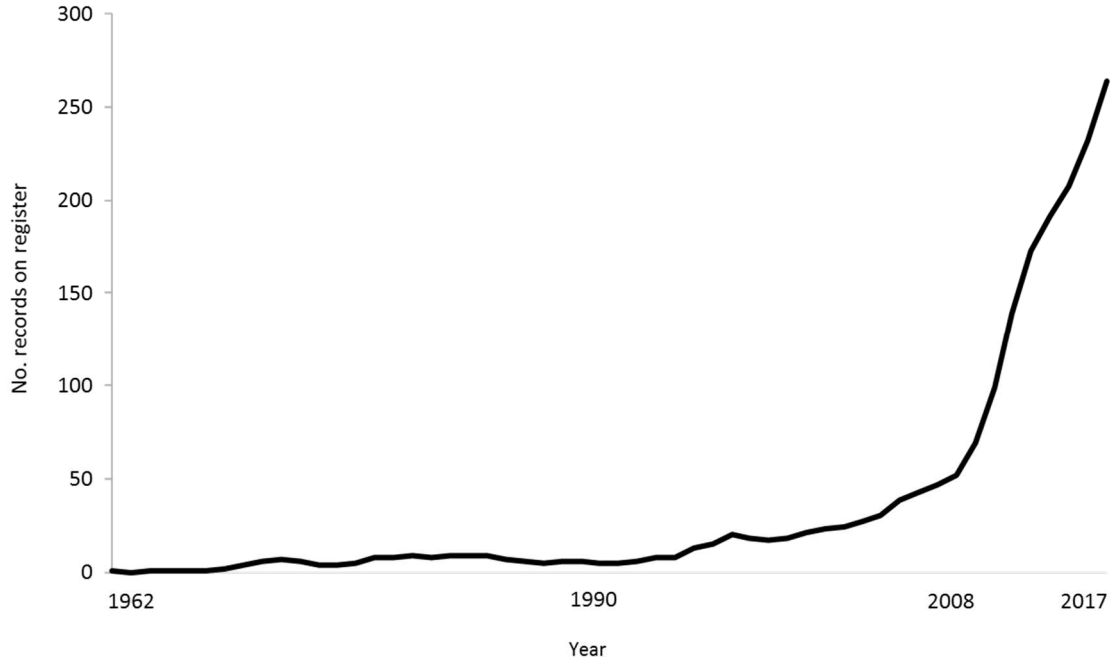
the total cost of administering a dose is about US$13 ($8 drug, $2 staff time and $3 supply cost).[45]

In view of the antifibrinolytic effect of TXA, there is interest in its use in a range of conditions involving excessive bleeding.

1.5 ROLE OF SYSTEMATIC REVIEWS AND META-ANALYSES FOR ASSESSING THE EFFECTS OF TRANEXAMIC ACID

Since husband and wife team Shosuke and Utako Okamoto first described TXA as an inhibitor of fibrinolysis in 1962,[46] there has been interest in its use for a range of bleeding conditions. Although research into TXA has been published in the medical literature for many decades, the last 10 years or so has seen rapid growth in the number of publications. The LSHTM CTU maintains a register of bibliographic records of publications about TXA. Figure 1.3 shows the number of records included in the register by publication year.

Figure 1.3 Number of TXA research publications published per year from 1962 to 2017.[iv]



The LSHTM CTU maintains a register of publication records identified through comprehensive searches of bibliographic databases. This register includes 2225 records of articles published up to the end of 2017, most of which were published in the last decade. Over the last 10 years, there has been a five-fold increase (from 46 in 2008 to 286 in 2017) in the number of publications. This abundance of research presents a considerable challenge for those who are looking to understand the evidence for the effects of TXA. To stay up-to-date with the articles

[iv] Numbers extracted from the register of bibliographic records maintained by the LSHTM CTU.

published in 2017 alone would require reading 5-6 articles every week. Systematic reviews therefore have an important role for translating the existing abundance of research into manageable, valid syntheses.

A systematic review is an epidemiological study design that uses explicit and systematic methods to collate all evidence that meet pre-defined inclusion criteria to answer a well-defined question.[47] Systematic reviews are key tools in the practice of evidence-based medicine that has guided medical practice and teaching since the 1990s. Systematic reviews often include meta-analysis, the statistical pooling of aggregate data from individual studies, to increase statistical precision and generate a summary effect estimate.

Systematic reviews of randomised controlled trials are often considered to be at the top of the hierarchy of evidence and increasingly support the development of health care guidelines at the national and international level.[48, 49] They also have an important research role. Systematic reviews are useful for identifying treatment uncertainties, which initiate the conduct of further primary research. However, like all epidemiological study designs, systematic reviews are vulnerable to bias, which requires careful consideration when planning, conducting, and interpreting the results.

Systematic review methodology has evolved rapidly as its role in healthcare decision-making has grown. As well as improvements in techniques for searching and assessing the methodological quality of trials, extensions to standard meta-analytic techniques have allowed for further investigation into the quality, reliability, and heterogeneity of the evidence.

This thesis presents a series of Research Papers in which I have explored the evidence for the effects of TXA. Using systematic reviews alongside standard and more novel meta-analytic techniques, I have undertaken a detailed investigation into the effects of TXA for surgical bleeding, traumatic bleeding, and for preventing postpartum bleeding.

1.6 AIMS AND OBJECTIVES

I have undertaken a programme of work using systematic review methodology to evaluate the evidence from randomised trials for the effects of TXA in patients with surgical bleeding, traumatic bleeding, and for preventing postpartum haemorrhage.

My specific aims and objectives are:

1) To evaluate the evidence from randomised trials for the effects of TXA in patients undergoing surgery, specifically to:

- quantify the effects of TXA on bleeding, blood transfusion, death and thromboembolic events in surgical patients;

- investigate the quality of randomised trials of TXA for surgical bleeding.

2) To evaluate the evidence from randomised trials for the effects of TXA in patients with traumatic bleeding, specifically to:

- quantify the effects of TXA on death, blood transfusion, and thromboembolic events in bleeding trauma patients;
- estimate the number of avoidable trauma deaths by the routine use of TXA.

3) To evaluate the evidence from randomised trials for the effects of TXA for preventing postpartum bleeding, specifically to:

- quantify the effects of TXA on postpartum bleeding, blood transfusion, death and thromboembolic events in women giving birth;
- outline a proposed trial of TXA for preventing postpartum bleeding in women with anaemia.

1.7 STRUCTURE OF THESIS

I have prepared a paper-style thesis. It comprises six Research Papers published in peer-reviewed journals, as well as one submitted manuscript currently under journal review.

The submitted and approved versions of the published papers are presented in the main text with abstracts and endnotes omitted for clarity. Copies of the full, published versions are included in the Appendices. The Research Papers are presented in Chapters 2-4.

The three Research Papers included in Chapter 2 address the effects of TXA in patients with surgical bleeding. Research Papers 1 and 2 present the results of a systematic review of 129 trials assessing the effect of TXA in surgical patients. In Research Paper 3, I present the results of my further investigations into the quality of the evidence from the randomised trials.

Research Papers 4 and 5 included in Chapter 3 address the effects of TXA in patients with traumatic bleeding. In Research Papers 4 and 5, I describe my research to quantify the effects of TXA in bleeding trauma patients and the potential public health impact in terms of deaths averted by the routine use of TXA.

Research Papers 6 and 7 included in Chapter 4 address the effects of TXA for preventing postpartum haemorrhage. Research Paper 6 presents the evidence for the effects of TXA for preventing postpartum bleeding and Research Paper 7 presents the protocol for a trial of TXA for preventing postpartum bleeding in anaemic women.

Chapter 5 is the concluding section in which I summarise how, together, the results of the individual papers further our understanding of the evidence from randomised trials for the

effects of TXA in patients with surgical bleeding, traumatic bleeding, and for preventing postpartum haemorrhage, including implications for clinical practice and future research.

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2.0 WHAT ARE THE EFFECTS OF TRANEXAMIC ACID IN PATIENTS UNDERGOING SURGERY?

2.1 INTRODUCTION TO RESEARCH PAPERS 1, 2 AND 3

As described in Chapter 1, surgical haemorrhage is an important cause of morbidity and is a common indication for blood transfusion. TXA has been used in some surgical patient groups for many years. However, uncertainties about its effects have prevented its routine use.

This chapter addresses Aim 1 of this thesis in which I use systematic review and meta-analytic techniques to evaluate the evidence from randomised trials for the effects of TXA in surgical patients. The chapter includes Research Papers 1-3.[v]

[v]Copies of the PDF versions of the published manuscripts are included in Appendix D, Appendix J and Appendix P

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, If not please move to Section C

SECTION B – Paper already published

Where was the work published?	**BMJ**		
When was the work published?	**2012**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**Yes (see Appendix C)**	Was the work subject to academic peer review?	**Yes**

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I designed the study with input from Ian Roberts. I conducted the electronic searches with advice from an Information Specialist. I screening the search output, assessed papers for eligibility and extracted data. I analysed the data, interpreted the results and prepared the tables and figures. I wrote the manuscript according to PRISMA guidelines with input from my co-authors. I also addressed the editorial and peer referee comments on final draft prior to publication.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

2.2 TRANEXAMIC ACID FOR SURGICAL BLEEDING: SYSTEMATIC REVIEW AND CUMULATIVE META-ANALYSIS

Katharine Ker, Phil Edwards, Pablo Perel, Haleema Shakur, Ian Roberts

BMJ. 2012 May 17;344:e3054. doi: 10.1136/bmj.e3054.

Introduction

In October 2011, the BMJ published a randomised controlled trial of the effect of tranexamic acid (TXA) on blood transfusion in patients undergoing radical retro-pubic prostatectomy.[1] The authors pointed out that this was the first trial to assess the effect of TXA on blood transfusion in this particular operation. Whilst this may be the case, it was not the first trial to examine the effect of TXA on blood transfusion in surgery more generally. A systematic review published in 2001 presented data from 18 clinical trials and showed that TXA reduces the probability of blood transfusion in elective surgery by 34% (RR=0.66, 95% CI 0.54 to 0.81; p=0.004).[2] In this paper, we assess the current evidence for the effect of TXA on blood transfusion, thromboembolic events and mortality in surgical patients and use cumulative meta-analyses to examine how the evidence has changed over time.

Methods

Methods of the analysis and inclusion criteria for this systematic review were specified in advance and documented, although the protocol was not registered. The PRISMA checklist is presented in Appendix E. We searched for all randomised controlled trials comparing TXA with no TXA or placebo in elective and emergency surgery. There was no age restriction. Potentially eligible trials were identified by searching the Cochrane Central Register of Controlled Trials (2011, issue 3), MEDLINE (1950 to September 2011) and EMBASE (1980 to September 2011), using a combination of subject headings and text words to identify randomised controlled trials of any antifibrinolytic drug (the MEDLINE search strategy is presented in Appendix F). Searches were not restricted by language or publication status. The WHO International Clinical Trials Registry Platform was searched to identify ongoing or unpublished trials. The reference lists of eligible trials and reviews were also examined. The search output was screened by two authors working independently to identify records of potentially eligible trials, the full texts of which were then retrieved and assessed for inclusion.

Outcome data

Outcome measures of interest were the number of patients receiving a blood transfusion, the number of patients suffering a myocardial infarction, stroke, deep vein thrombosis and

pulmonary embolism, and the number of deaths. We contacted trial authors to obtain any missing outcome data.

Data extraction and risk of bias assessment

We extracted data on the age and gender of trial participants, type of surgery, dose and timing of TXA, type of comparator and outcome data. We also collected information on whether a systematic review had been conducted to support the rationale of the trial and whether a systematic review was cited in the trial report. We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding and the completeness of outcome data. As the risk of bias for blinding may vary according to outcome, it was assessed separately for each outcome. Risk of bias was rated as being low, unclear or high according to established criteria.[3]

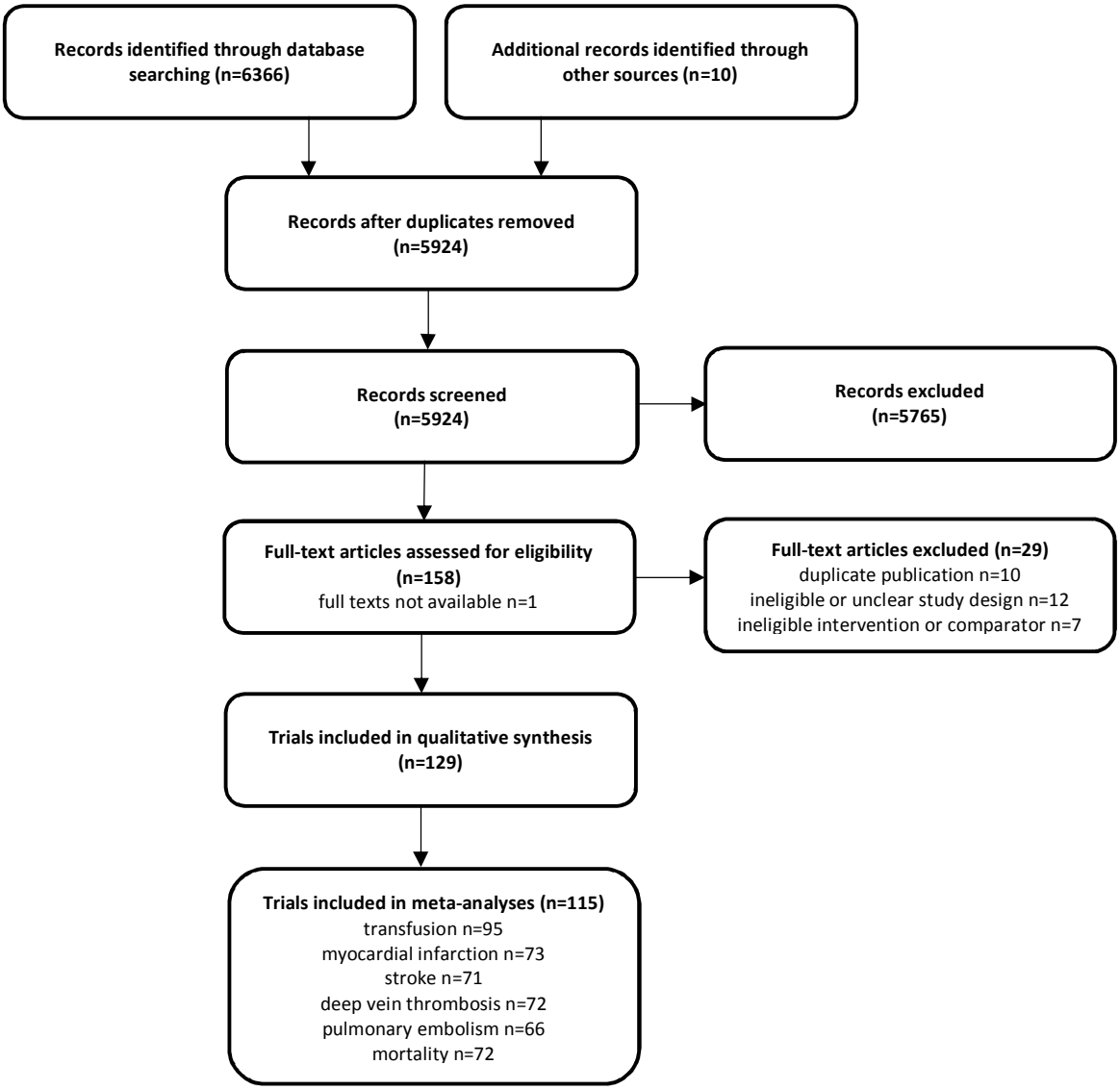
Statistical analysis

Risk ratios (RR) and 95% confidence intervals (CI) were calculated for each outcome and pooled using a fixed effect model. Subgroup analyses were carried out to examine whether the effect of TXA on blood transfusion varies by type of surgery. Sensitivity analyses were conducted to quantify the effect of TXA on all outcomes when restricted to trials with adequate allocation concealment and blinded outcome assessment. We conducted a cumulative meta-analysis of the effect of TXA on blood transfusion based on the date of publication and cumulative meta-analyses of the effect of TXA on blood transfusion, myocardial infarction and mortality when restricted to adequately concealed trials. Heterogeneity was examined by visual inspection of forest plots, the I-squared statistic and the chi-squared test. We inspected funnel plots for the presence of small study effects. Statistical analyses were conducted using STATA version 11 and RevMan version 5. [4, 5]

Results

Figure 2.1 shows the trial selection process. We identified 127 articles[1, 6-131] describing 129 randomised controlled trials that included 10,488 patients 5,484 were allocated to TXA and 5,004 were allocated to a control group. The median sample size was 60 patients (range 10 to 660). There were 126 (98%) trials in elective surgery and three trials (2%) in emergency surgery. Eleven (8%) trials involved paediatric patients.

Figure 2.1 PRISMA flow diagram of the selection of trials



We contacted the authors of 86 trials for missing data, 39 of whom provided additional information. Blood transfusion data were available for 95 (74%) trials, myocardial infarction data for 73 (56%) trials, stroke data for 71 (55%) trials, deep vein thrombosis data for 72 (56%) trials, and pulmonary embolism data for 66 (51%) trials and mortality data for 72 (56%) trials. Seven (5%) trials did not present any data on the outcome measures of interest to this review or reported data in a format that was unsuitable for inclusion in the analyses.

We identified 14 ongoing trials [110-123] with a median planned sample size of 130 patients. The 14 trials were in orthopaedic (n=5), cardiac (n=4), cranial (n=2), hepatic (n=1), ENT (n=1) and gynaecological (n=1) surgery. In 12 of the 14 trials blood transfusion was a main outcome measure.

Risk of bias

The risk of bias judgements for each methodological quality item for the included trials are presented in Appendix G. We judged 44 (34%) trials to be at low risk of bias for sequence generation and five (4%) trials to be at high risk. The risk of bias in the remaining 80 (62%) trials was unclear due to lack of information. Allocation was adequately concealed in 36 trials (28%), inadequately concealed in six (5%) trials, with the other 87 (67%) trials presenting insufficient information to allow judgement. For blinding, of the 95 trials with data on blood transfusion, 69 (73%) were judged low risk, four (4%) at high risk and 22 (23%) were unclear. The risk of bias for blinding was similar for thromboembolic outcomes (myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism), with approximately 70% judged to be at low risk, 5% at high risk and 25% at unclear risk. All 72 trials with mortality were judged to be at low risk of bias for blinding. Of 115 trials reporting eligible outcome data, 72 (63%) were at low risk of bias for incomplete outcome data, 17 (15%) at high risk, and 26 (23%) trials did not describe adequate information to permit judgement.

Quantitative data synthesis

The results of the meta-analysis are presented in Table 2.1.

Table 2.1 Meta-analysis of effect of TXA on blood transfusion, thromboembolic events and mortality

	Events (TXA/control)	**Pooled Risk Ratio (95% CI)**	**Test for effect (p value)**	**Heterogeneity (I^2; p value)**
Blood transfusion				
All trials	1067/1520	0.62 (0.58 to 0.65)	<0.001	69%; <0.001
Well concealed trials	459/ 609	0.68 (0.62 to 0.74)	<0.001	55%; <0.001
Adequate blinding	847/ 1182	0.63 (0.59 to 0.68)	<0.001	54%; <0.001
Myocardial infarction				
All trials	23/35	0.68 (0.42 to 1.09)	0.11	0%; p=0.90
Well concealed trials	16/25	0.70 (0.39 to 1.25)	0.22	0%; p=0.82
Adequate blinding	18/33	0.59 (0.36 to 0.98)	0.04	0%; p=0.81
Stroke				
All trials	23/16	1.14 (0.65 to 2.00)	0.65	0%; p=0.92
Well concealed trials	5/4	1.18 (0.36 to 3.83)	0.78	0%; p=0.92
Adequate blinding	23/16	1.14 (0.65 to 2.00)	0.65	0%; p=0.92

Deep vein thrombosis				
All trials	25/29	0.86 (0.53 to 1.39)	0.54	0%; p=0.96
Well concealed trials	13/14	0.92 (0.45 to 1.85)	0.81	0%; p=0.81
Adequate blinding	18/22	0.82 (0.46 to 1.44)	0.49	0%; p=0.98
Pulmonary embolism				
All trials	4/8	0.61 (0.25 to 1.47)	0.27	0%; p=0.96
Well concealed trials	1/3	0.52 (0.10 to 2.75)	0.44	0%; p=0.80
Adequate blinding	4/6	0.70 (0.26 to 1.87)	0.48	0%; p=0.91
Mortality				
All trials	20/34	0.61 (0.38 to 0.98)	0.04	0%; p=0.97
Well concealed trials	9/15	0.67 (0.33 to 1.34)	0.25	0%; p=0.85
Adequate blinding	20/34	0.61 (0.38 to 0.98)	0.04	0%; p=0.97

Risk of blood transfusion

Data on blood transfusion were available for 95 trials including a total of 7,838 patients. TXA reduced the probability of receiving a blood transfusion by 38% (pooled RR=0.62, 95% CI 0.58 to 0.65; p<0.001). When the analysis was restricted to the 32 adequately concealed trials involving 3,408 patients, TXA reduced the risk of receiving a blood transfusion by 32% (pooled RR=0.68, 95% CI 0.62 to 0.74; p<0.001). When the analysis was restricted to the 69 trials involving 5,968 patients with adequate blinding for this outcome, TXA reduced the risk of blood transfusion by 37% (pooled RR=0.63, 95% CI 0.59 to 0.68; p<0.001).

The trials with blood transfusion data involved cardiac (n=42), orthopaedic (n=36), cranial & orthognathic (n=7), gynaecological (n=5), hepatic (n=2), urological (n=2), and vascular (n=1) surgery. There was a statistically significant reduction in blood transfusion in cardiac, orthopaedic, cranial & orthognathic, hepatic, and urological surgery (Table 2.2). The pooled estimates for blood transfusion were consistent with a reduction in the TXA group amongst trials in vascular and gynaecological surgery although the results were imprecise. Heterogeneity in the effects of TXA by surgery type: I^2 = 59%, p=0.02.

Table 2.2 Meta-analysis of effect of TXA on risk of blood transfusion, stratified by type of surgery

Type of surgery	Events (TXA/control)	Pooled Risk Ratio (95% CI)	Test for effect (p value)	Heterogeneity (I^2; p value)
Cardiac	622/835	0.65 (0.60 to 0.70)	<0.001	60%; p<0.001
Orthopaedic	298/462	0.55 (0.49 to 0.61)	<0.001	83%; p<0.001
Hepatic	29/54	0.52 (0.39 to 0.68)	<0.001	93%; p<0.001
Urological	40/60	0.66 (0.48 to 0.91)	0.01	2%; p=0.31

Type of surgery	Events (TXA/control)	Pooled Risk Ratio (95% CI)	Test for effect (p value)	Heterogeneity (I^2; p value)
Vascular	11/19	0.58 (0.34 to 0.99)	0.05	-
Gynaecological	17/50	0.86 (0.48 to 1.54)	0.61	65%; p=0.06
Cranial & orthognathic	52/76	0.63 (0.45 to 0.86)	0.004	46%; p=0.12

Thromboembolic events

There was uncertainty regarding the effect of TXA on myocardial infarction (RR=0.68, 95 % CI 0.43 to 1.09; p=0.11), stroke (RR=1.14, 95 % CI 0.65 to 2.00; p=0.65), deep vein thrombosis (RR=0.86, 95 % CI 0.53 to 1.39; p=0.54) and pulmonary embolism (RR=0.61, 95% CI 0.25 to 1.47; p=0.27). The results were similar when the analyses were restricted to trials with adequate allocation concealment and trials with blinded outcome assessment.

Mortality

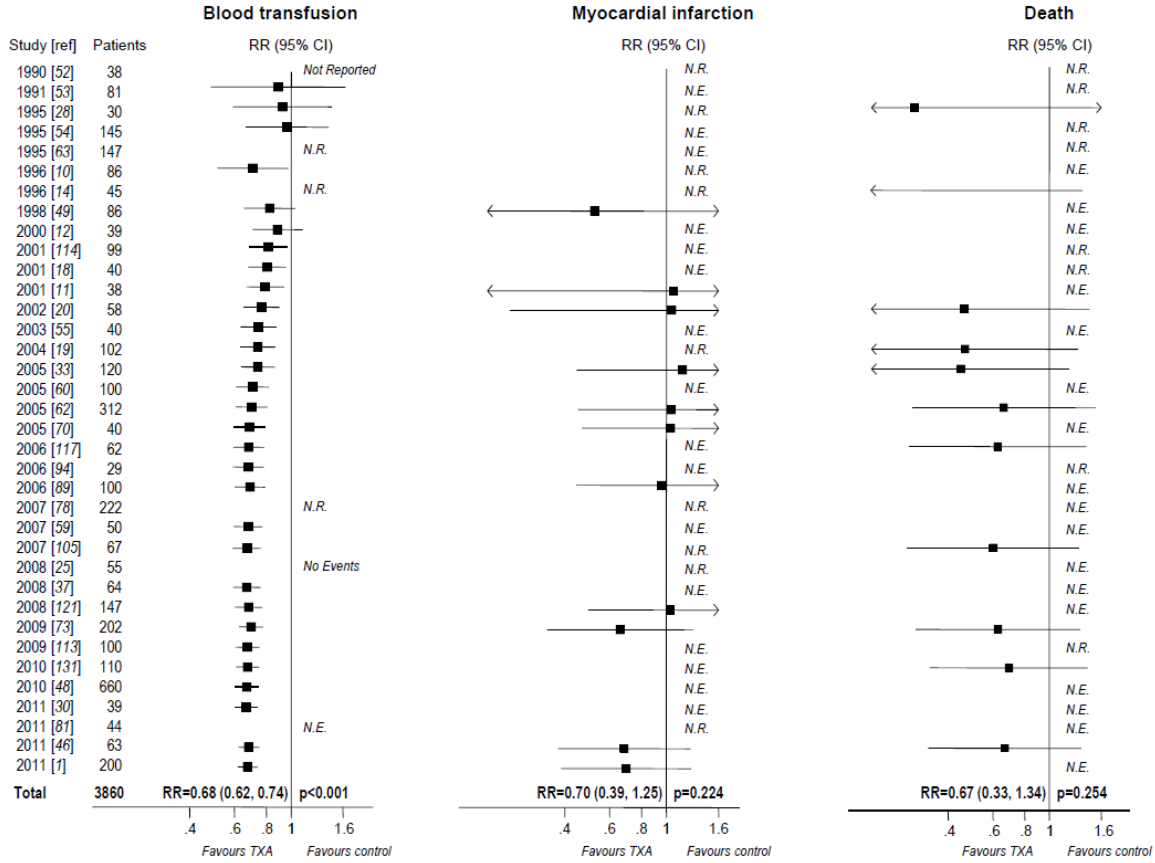
There were fewer deaths in the TXA treated group (RR=0.61, 95% CI 0.38 to 0.98; p=0.04) although there was uncertainty regarding this effect particularly when the analysis was restricted to the 28 adequately concealed trials (RR=0.67, 95% CI 0.33 to 1.34; p=0.25).

Cumulative meta-analyses

The results of the cumulative meta-analysis of the 95 trials with data on blood transfusion are presented in Appendix H. A statistically significant effect of TXA on transfusion was first observed after publication of the third trial in 1993 (RR=0.59, 95% CI 0.43 to 0.80; p=0.001). Although subsequent trials have increased the precision of the point estimate, there has been no substantive change in the direction or magnitude of the treatment effect.

Figure 2.2 shows the cumulative meta-analyses of the effect of TXA on blood transfusion, myocardial infarction and mortality amongst the trials with adequate allocation concealment. A statistically significant effect of TXA on blood transfusion was consistently observed after publication of the tenth trial in 2001.

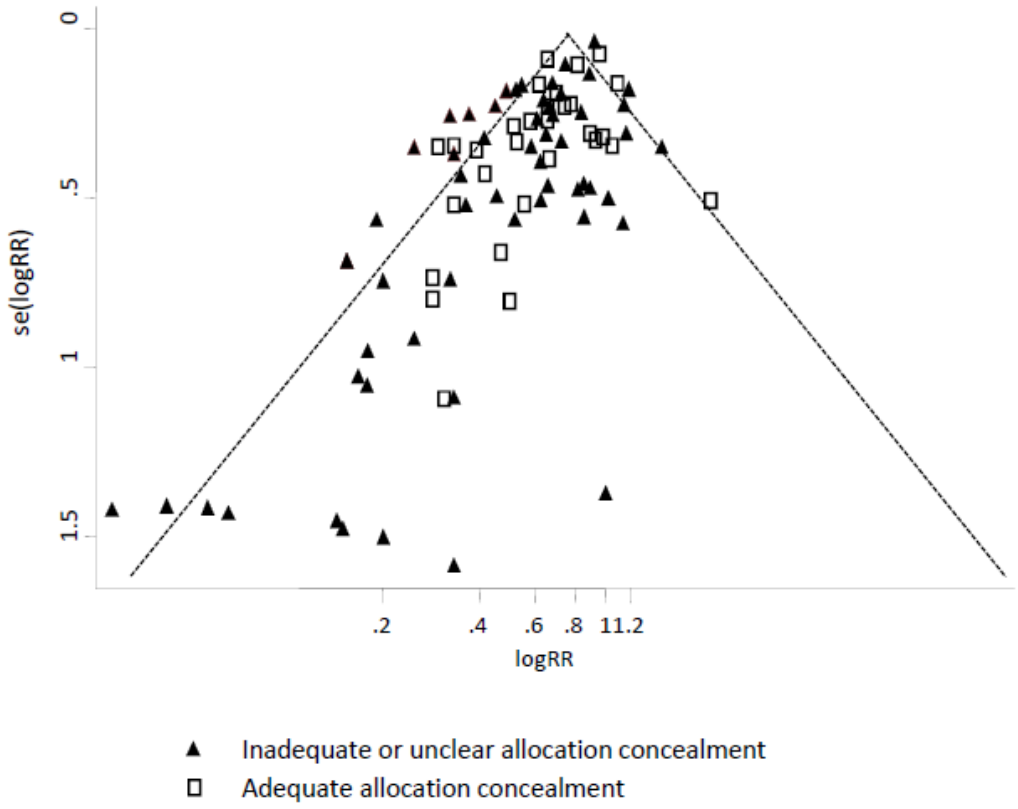
Figure 2.2 Meta-analysis and cumulative meta-analysis of effect of TXA in surgery on risk of blood transfusion, myocardial infarction and mortality in adequately concealed trials



Small study effects

Inspection of the funnel plot (Figure 2.3) for the outcome blood transfusion suggested the presence of small study effects favouring TXA. There was no clear asymmetry in the funnel plots for the other outcomes.

Figure 2.3 Funnel plot with pseudo 95% confidence limits for meta-analysis of effect of TXA on risk of blood transfusion



Citation of previous systematic reviews

We identified 30 systematic reviews of the effects of TXA in surgery published between 1994 and 2011.[2, 89, 132-161] Assuming a 12 month publication time lag, 98 of the 116 (84%) included trial reports published as full journal articles were published when at least one systematic review was available. Examination of the references lists of these reports indicated that 45 (46%) did not cite any of the available systematic reviews. The authors of two of the 116 trial reports had conducted a systematic review and presented the findings within the final trial publication.

Discussion

Principal findings

Reliable evidence that tranexamic acid (TXA) reduces blood transfusion in surgical patients has been available for over a decade. The treatment effect varies somewhat according to the type of surgery but the effect is consistently large and remains so when the analysis is restricted to trials with adequate allocation concealment. The effect of TXA on thromboembolic events and mortality has not been adequately assessed by clinical trials in surgery and remains uncertain. In view of the evidence, those planning further placebo controlled trials should explain why they

think that TXA might not reduce blood transfusion in the particular group of surgical patients under consideration, and focus their efforts on resolving the uncertainties about the effect of TXA on thromboembolic events and mortality.

Strengths and weaknesses

The inferences that can be made from the included trials depend on their quality and many had methodological limitations. However, the large and statistically significant effect on blood transfusion remained when the analysis was restricted to trials with adequate allocation concealment and with adequate blinding.

We systematically searched a range of databases for published and unpublished trials. However, we cannot exclude the possibility that some were missed. Indeed, the observed asymmetry in the funnel plot could be explained by publication bias. If there are many unpublished trials showing little or no effect of TXA on blood transfusion, then this meta-analysis may have overestimated the treatment effect. Although some degree of overestimation is likely, it seems improbable that publication bias could account for all of the observed effect.

Although there was no obvious asymmetry in the funnel plots for the mortality and thromboembolic outcomes, publication and other reporting biases remain a potential threat to the validity of the effect estimates. Mortality data were reported in only one third of the included trials and less than half reported data on myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism. Inadequate reporting of adverse events is not unusual in reports of clinical trials and hinders the reliable estimation of treatment effects.[162, 163] After contacting the trial authors we obtained some missing data and were able to include mortality data for three-quarters of the included trials and data on myocardial infarction, stroke, deep vein thrombosis and pulmonary embolism for about half of the trials. However, the effect of outcome reporting bias in this review remains open to question. Even if there was no significant bias, the precision of the estimates is low and the data are compatible with either a moderate increase or a moderate decrease in the risk of thromboembolic events.

Implications

The evidence in this review suggests that the uncertainty regarding the effect of TXA on blood transfusion in surgical patients was resolved over a decade ago however, uncertainties about its effect on thromboembolic events and mortality persist. Despite this, trials of TXA continue to assess the effect on blood transfusion. One reason may be a reluctance to generalise the evidence across surgery types, although there is no evidence that the relative effect of TXA on blood transfusion varies by type of surgery. A second reason may be that trialists are unaware of the existing evidence when initiating a new trial. Our observation that only half of the trials

cited one or more of the available systematic reviews and just two conducted their own systematic review, does suggest that many trialists are indeed failing to adequately consider the existing evidence.

Blood is a scarce and costly resource and blood transfusion is not without risk. The cost of a unit of red cells to the NHS has increased from £78 in the year 2000 to £125 in 2011 and blood transfusion has a number of rare but serious adverse effects. Worldwide, most people do not have access to safe blood. Globally, the most important transfusion-related risks are HIV, hepatitis B virus and hepatitis C virus, due to their high prevalence. That TXA safely reduces the need for blood transfusion in surgery has important health and economic implications in high, middle and low income countries. The evidence that TXA reduces transfusion is strong but the safety of the routine administration of TXA to surgical patients remains uncertain. A modest increase in the risk of thromboembolic effects could outweigh the benefits of reduced blood use. Although some increased risk might be expected on theoretical grounds, recent evidence from the CRASH-2 trial of TXA in bleeding trauma patients showed a statistically significant reduction in mortality with no increase in thromboembolic effects. Indeed, there was a statistically significant reduction in the risk of myocardial infarction in trauma patients who received TXA.[164]

Further small trials of TXA in surgical patients considered in isolation will not resolve the uncertainties about the effects on thromboembolic events and mortality. Because thromboembolic events are relatively rare, such trials lack statistical power to detect clinically important increases in risk, and a meta-analysis of small trials remains vulnerable to publication bias. The ongoing ATACAS trial[165] with a planned sample size of 4,300 high-risk coronary artery surgery patients, should contribute importantly to resolving the uncertainty about the effect of TXA on mortality and thromboembolic events in this specific group. We urge investigators involved in all ongoing trials of TXA in surgery to collect data on thromboembolic events and mortality, for inclusion in a prospective meta-analysis until the uncertainties are resolved. However, there remains a need for a large pragmatic clinical trial of the effect of the routine administration of TXA in a heterogeneous group of surgical patients. The possibility that TXA might reduce mortality without any increase in the risk of thromboembolic events would justify the effort and expenditure involved.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	**British Journal of Surgery**		
When was the work published?	**2013**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**No (see Appendix I)**	Was the work subject to academic peer review?	**Yes**

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I designed this study with my co-authors David Prieto-Merino and Ian Roberts. I designed and conducted the systematic review; I extracted data and performing the data analyses with support from David Prieto-Merino. I interpreted the results and prepared the tables and figures. I drafted the manuscript incorporating comments from my co-authors and external peer referees.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

2.3 SYSTEMATIC REVIEW, META-ANALYSIS AND META-REGRESSION OF THE EFFECT OF TRANEXAMIC ACID ON SURGICAL BLOOD LOSS

Katharine Ker, David Prieto-Merino, Ian Roberts

British Journal of Surgery 2013 Sep;100(10):1271-9.

Introduction

Tranexamic acid (TXA) reduces the probability of receiving a blood transfusion in surgery. A systematic review of randomised controlled trials showed that TXA reduces the probability of blood transfusion by 38% (pooled risk ratio=0.62, 95% CI 0.58 to 0.65; p<0.001).[1] However, the extent to which TXA reduces surgical bleeding and its relationship with the dose of TXA and type of surgery remains uncertain. Because the decision to transfuse depends on factors other than blood loss, the effect on blood transfusion may not be an accurate indicator of the effect of TXA on surgical bleeding.

Clinical trials of TXA in surgery usually report the mean blood loss in each group. Previous systematic reviews have combined these data to obtain the average difference in mean blood loss between the TXA and control groups. However, the usefulness of such a measure is questionable. It would be surprising if TXA reduced blood loss by the same volume in surgical procedures that involve different amounts of bleeding. On the other hand, it may be reasonable to expect a similar percentage reduction in blood loss with TXA.

The objective of this study is to examine whether the effect of TXA on blood loss varies with the extent of surgical bleeding. The magnitude of the percentage reduction in blood loss with TXA is estimated and how the effect varies by type of surgery, timing of TXA administration, trial quality, and dose is assessed.

Methods

A systematic review of randomised controlled trials of TXA in surgical patients was conducted. The methods used to identify trials for the review are described in detail elsewhere[1]. In brief, a comprehensive search was undertaken for all randomised controlled trials comparing intravenous TXA with placebo or no intervention in elective or emergency surgery. Two authors screened the search output and the full texts of all eligible trials were obtained. Information was extracted on patient characteristics, type of surgery, dose and timing of TXA administration and average blood loss (mean and standard deviation). The risk of bias associated with sequence generation, allocation concealment, blinding, and the completeness of outcome data was assessed for each trial.

Data analysis

To explore the relationship between the reduction blood loss with TXA and the extent of bleeding, for each trial the mean blood loss in the TXA group was plotted against the mean blood loss in the control group. This relationship was examined using a linear regression estimated using a Bayesian model as proposed by Thompson *et al*[2] to account for random sampling error in the estimates of the regression variables (i.e. in the sample means from each trial). Statistical details of the model are given in Appendix K.

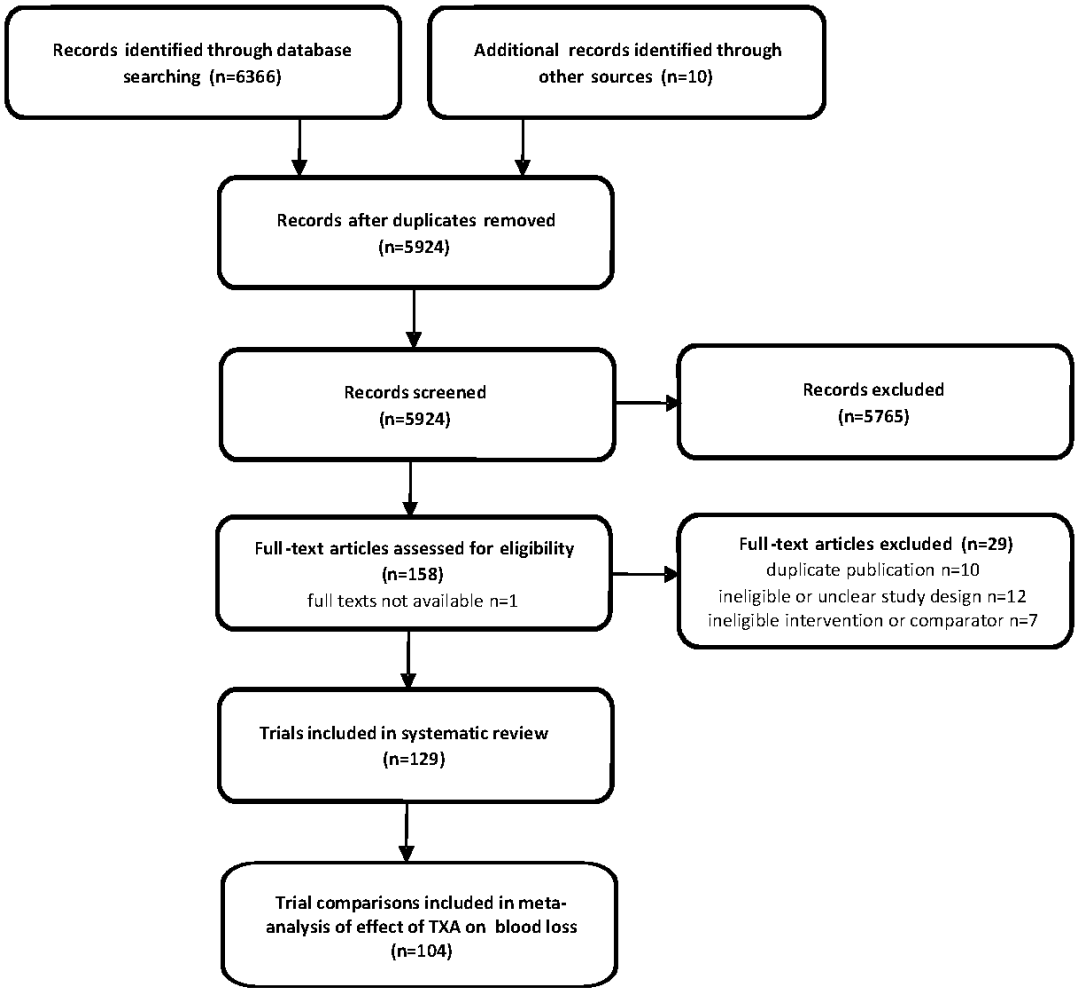
To quantify the effect of TXA on the percentage reduction in blood loss, a meta-analysis using both fixed and random effects models was conducted. For the purpose of the meta-analysis, blood loss data were log transformed and the analysis conducted using the transformed values. The formulae used for the transformations are given in Appendix K. A meta-analysis (using arithmetic means) of the differences in means using the transformed blood loss data corresponds to a meta-analysis (using geometric means) of the ratio of means in the original scale. The pooled estimates were back-transformed to give the blood loss ratios and 95% confidence intervals on the original scale. Statistical heterogeneity was examined by visual inspection of forest plots, the I^2 statistic and the χ^2 test.

Subgroup analyses were undertaken to assess the effect of TXA by the type of surgery, timing of TXA administration (pre-incision, post-incision), allocation concealment (adequate, unclear, inadequate) and type of comparator (placebo or no intervention). Heterogeneity between subgroups was assessed using the χ^2 test (fixed effect analysis only). Finally, a random effects meta-regression was carried out to investigate the association between the effect of TXA on blood loss and the total dose of TXA (mg/kg) as a continuous variable. If a fixed dose was used in the trials (e.g. 1000mg) it was converted to mg/kg by dividing by 70kg. A funnel plot was inspected for the presence of small study effects. We used STATA (version 12)[3] statistical software for all analyses.

Results

Figure 2.4 PRISMA flow diagram for the selection of trials shows the trial selection process.

Figure 2.4 PRISMA flow diagram for the selection of trials



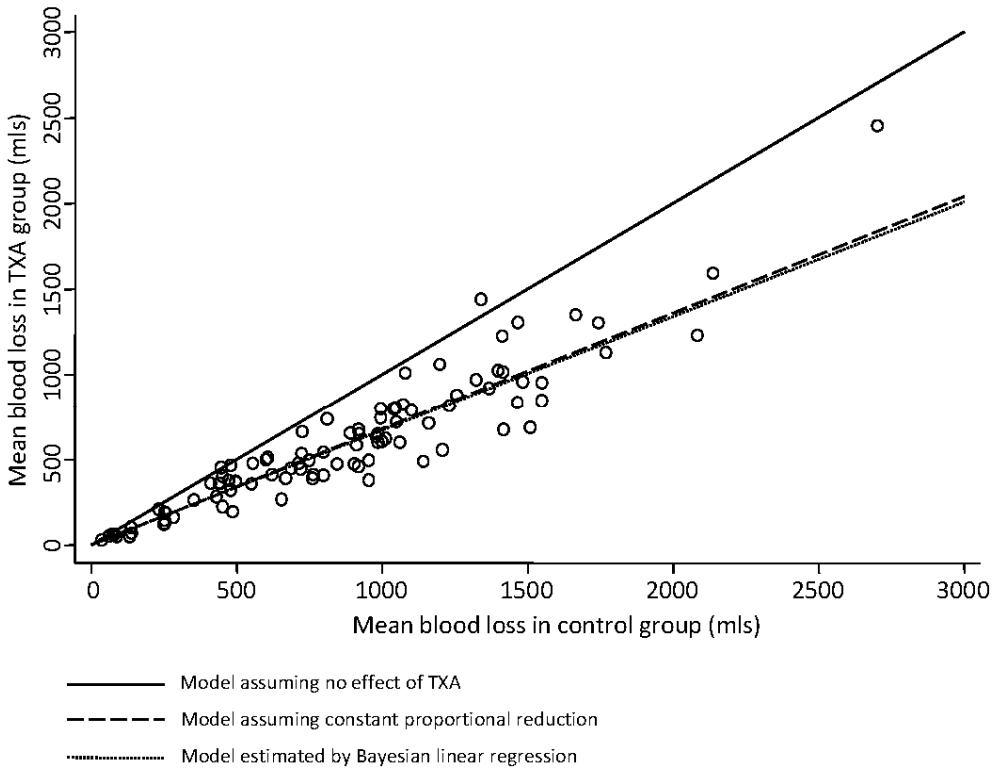
One hundred and twenty-nine randomised controlled trials were identified. The characteristics of the included trials are summarised in (Appendix L). Nine reports described multi-arm trials involving a total of 23 eligible pair-wise comparisons; each of these was included in the analysis as separate trials. One hundred and four randomised comparisons described in 90 articles,[4-93] reported data on blood loss in a format suitable for this analysis. These trials involved a total of 8030 patients, 4224 received TXA and 3806 received a placebo or no intervention.

The trials involved cardiac (n=54), orthopaedic (n=33), obstetric & gynaecological (n=7), head & neck (n=7), breast cancer (n=1), hepatic (n=1) and urological (n=1) surgery. Eighty trials gave TXA prior to surgical incision and 24 trials gave TXA after incision. Thirty-three trials were assessed as being adequately concealed (low risk of bias), five trials as inadequately concealed (high risk of bias). The remaining 66 trials presented insufficient information on allocation concealment to allow judgement and were rated as unclear. Seventy-five trials were placebo-controlled, whereas a no intervention group was used as the control in the remaining 29 trials.

Effect of TXA on blood loss

Figure 2.5 shows the relationship between mean blood loss in the TXA group and mean blood loss in the control group.

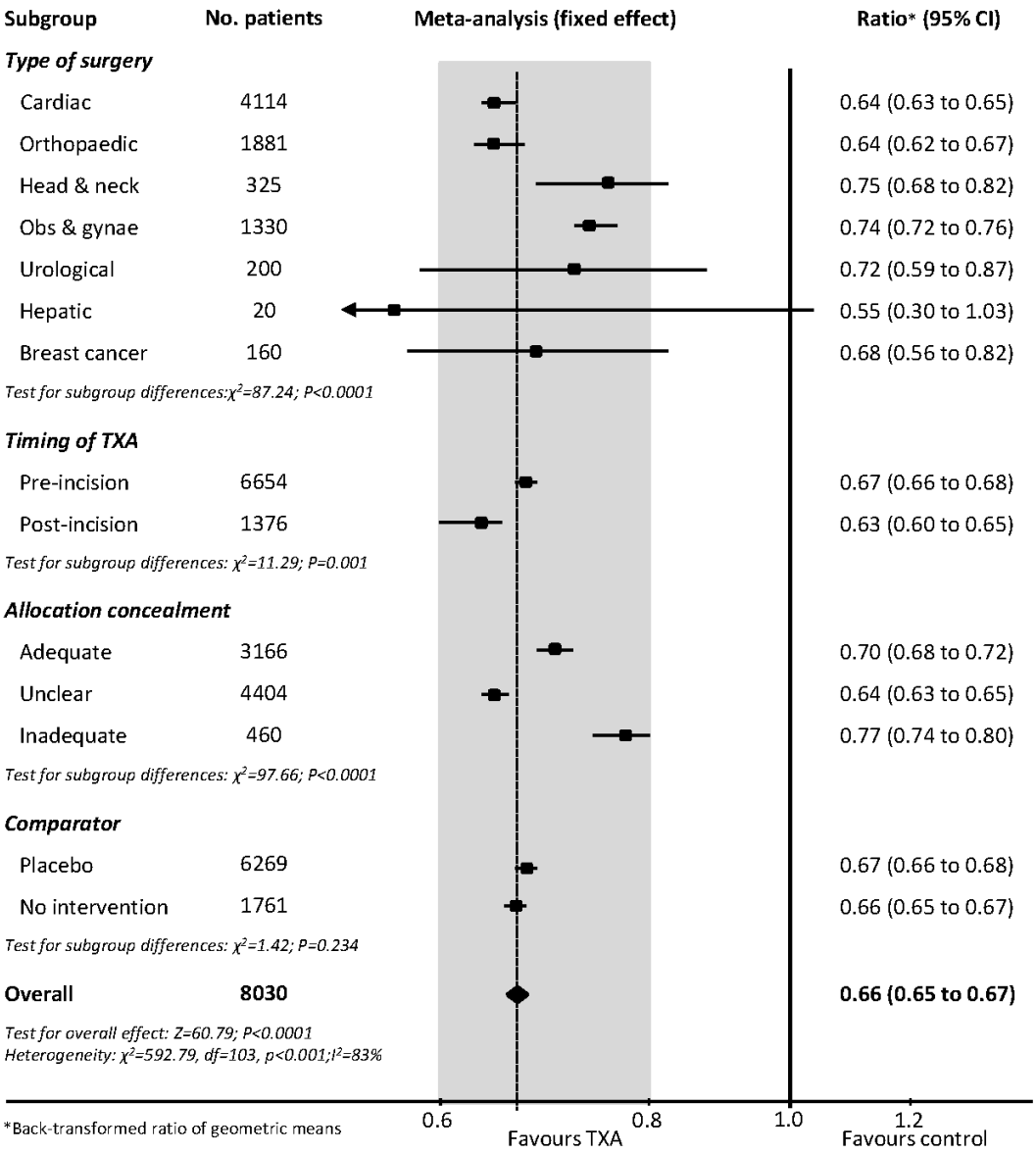
Figure 2.5 Mean blood loss in the TXA group versus mean blood loss in the control group with regression lines



The mean blood loss in the TXA group increased as the mean blood loss in the control group increased, but to a lesser extent. The intercept of the regression line (dotted line) estimated by the Bayesian model was 4 ml (95% credibility interval -8 ml to 18 ml), a negligible value in the context of the observed blood loss estimates. The Bayesian model corresponded closely with the regression line predicted assuming a constant percentage reduction in blood loss (dashed line) and an intercept of zero.

Figure 2.6 shows the summary results of a fixed effect meta-analysis of the percentage reduction in blood loss with TXA.

Figure 2.6 Results of fixed effect meta-analysis of the effect of TXA on blood loss stratified by type of surgery, timing of TXA administration, adequacy of allocation concealment and type of comparator.



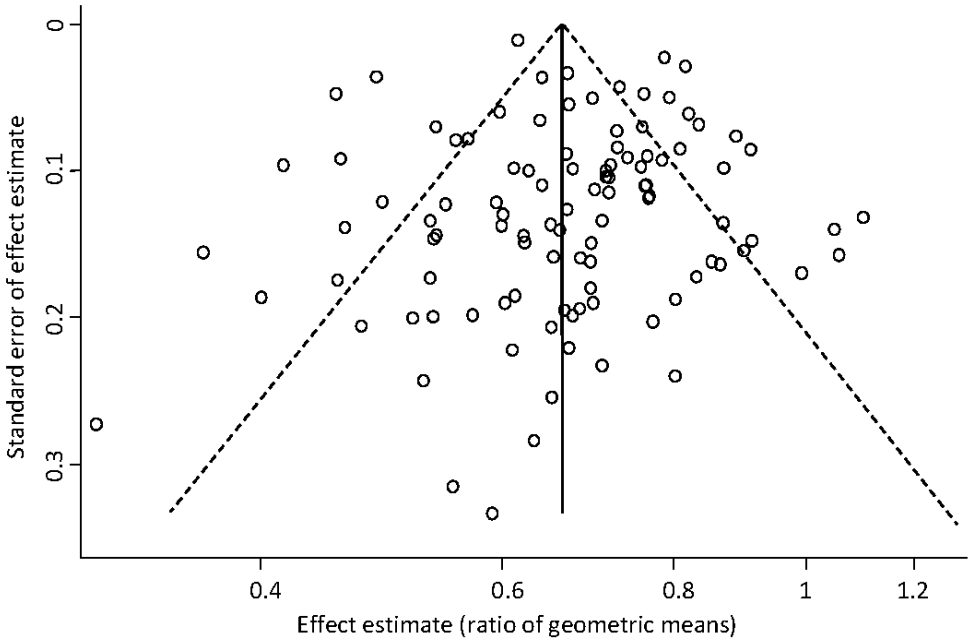
A forest plot showing the estimates from each trial is shown in Appendix M. The back-transformed pooled ratio of blood loss with TXA was 0.66 (95% CI 0.65 to 0.67; p<0.001) indicating that TXA reduced blood loss by 34%. There was substantial statistical heterogeneity between trials (I^2=83%). There was heterogeneity in the magnitude of effect by type of surgery although the extent of the variation was small. All of the subgroup estimates were consistent with a reduction in blood loss, and all but one was statistically significant at the 5% level. TXA had a greater effect on blood loss when given after incision, although the difference between the pre and post-incision estimates was small. There was heterogeneity in the magnitude of effect by adequacy of allocation concealment. When the analysis was restricted to the 33

adequately concealed trials, TXA reduced blood loss by 30% (0.70, 95% CI 0.68 to 0.72; p<0.001). There was no evidence for heterogeneity in the estimated effects of TXA when compared to a placebo or a no intervention control group. The results from random effects meta-analyses were similar to the fixed effect analyses and are shown in (Appendix N).

A fixed dose was converted to the equivalent mg/kg dose in 21 trials. The total dose of TXA used in the trials ranged from 5.5mg/kg to 300mg/kg. The median dose was 22mg/kg with the majority of trials (70%) using a total dose of 30mg/kg or less. Results from the meta-regression suggested that the effect of TXA on blood loss did not vary over the dose range assessed (coefficient=0.889, 95% CI 0.787 to 1.004; p=0.059).

There was no clear asymmetry in the funnel plot (Figure 2.7).

Figure 2.7 Funnel plot with pseudo 95% confidence limits for meta-analysis of effect of TXA on blood loss



Discussion

Tranexamic acid reduces surgical blood loss by about a third. Although the magnitude of the reduction differs by type of surgery and timing of TXA administration, the differences are small and are unlikely to be clinically important. A total dose of 1g is likely to be sufficient for most adults and there is no evidence to support the use of high doses.

The validity of these results depends on the quality of the included trials and many were of low quality. Less than a third of trials were judged to be at low risk of bias on the basis of allocation

concealment. Nevertheless, even when the analysis was restricted to adequately concealed trials, the effect of TXA on blood loss remained large and highly statistically significant.

Statistical heterogeneity between trials was substantial and was not explained by type of surgery, trial quality, the timing of TXA administration or dose. Differences in the methods used to estimate blood loss, the duration over which blood loss was measured, and other aspects of trial quality may explain some of the heterogeneity.

The subgroup analyses showed that the effect of TXA on blood loss varied by type of surgery, trial quality and timing of TXA. However, the extent of the variation was small and the clinical importance of such small variations is questionable.

There was no obvious asymmetry in the funnel plot, but reporting bias remains a concern particularly as about one fifth of trials were not included in the analysis due to unsuitable data or inadequate reporting. If many of these or other unpublished trials, showed little or no effect of TXA on blood loss, the analysis would have overestimated the treatment effect. Although, in consideration of the magnitude and precision of the effect, it is unlikely that any such bias would account for all of the observed effect.

The reduction in bleeding with TXA is almost identical to the reduction in the risk of receiving a blood transfusion with TXA suggesting that in surgery, transfusion may be closely titrated to blood loss. This might not be the case in trauma patients. The CRASH-2 trial found that early administration of TXA reduced the risk of death due to bleeding by about one third but there was no clear reduction in the risk of receiving a blood transfusion.[94, 95]

Although there is reliable evidence that TXA reduces bleeding and blood transfusion in surgery, its effect on other important outcomes including death and thromboembolic events remains uncertain.[1] There is no evidence that it increases the risk of thromboembolic events but it is a theoretical concern that may deter some surgeons from using TXA. These uncertainties need to be resolved before TXA can be recommended for routine use in surgery.

The apparent lack of a dose-response relationship across the range of doses examined (5.5 to 300 mg/kg) has important implications for the use of TXA in surgery. TXA crosses the blood brain barrier and there is some evidence from observational studies of patients undergoing cardiac surgery that high-dose TXA (≥100 mg/kg) may cause seizures.[96, 97] Our results imply that the clinical benefit of TXA on bleeding can be achieved at doses much lower than those associated with such adverse effects. Indeed, a total dose of about 14 mg/kg (or about 1g in adults) appears to be sufficient for most patients.

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2.4 EXPLORING REDUNDANT RESEARCH INTO THE EFFECT OF TRANEXAMIC ACID ON SURGICAL BLEEDING: FURTHER ANALYSIS OF A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

Introduction to paper 3

The results of the systematic review described in Research Papers 1 and 2 suggest that TXA reduces surgical bleeding. The results of the cumulative meta-analysis in Research Paper 1 suggest that this has been known for many years. Despite this, trials continued to be initiated. To explore this further, I undertook further analyses to explore possible explanations for the continued trial activity. The results of these analyses are presented in Research Paper 3.

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	**BMJ Open**		
When was the work published?	**2015**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**Yes (see Appendix O)**	Was the work subject to academic peer review?	**Yes**

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I designed the study with Ian Roberts. I extracted the data, conducted the analyses and prepared the figures. I interpreted the results and wrote the manuscript with input from Ian Roberts. I addressed the editorial and peer review comments prior to publication.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

Exploring redundant research into the effect of tranexamic acid on surgical bleeding: further analysis of a systematic review of randomised controlled trials

Katharine Ker, Ian Roberts

BMJ Open. 2015 Aug 24;5(8):e009460.

Introduction

Results from cumulative meta-analyses are often cited as proof that many researchers fail to systematically review the evidence from existing trials before initiating new trials. For example, a cumulative meta-analysis of aprotinin in cardiac surgery[1] showed that trials were initiated long after the pooled estimates showed a statistically significant effect. Commenting on the paper, Chalmers observed that it *"compellingly demonstrates why all new research – whether basic or applied – should be designed in the light of scientifically defensible syntheses of existing research evidence, and reported setting the new research in the light of the totality of the available evidence".*[2] Similar conclusions have been made on the basis of other cumulative meta-analyses.[3-5]

When the apparently redundant aprotinin trials were conducted, systematic reviews were relatively uncommon and failure to review the previous trials was a plausible explanation for the redundancy. However, given the increase in published reviews and their easy availability, lack of awareness of what has gone before is nowadays a less credible explanation for redundancy. We found that seemingly redundant trials of the effect of tranexamic acid (TXA) on blood transfusion were conducted even though many of them cited a systematic review concluding that the uncertainty had been resolved.[6] Habre *et al*[7] found that 73% of trials of an anaesthetic intervention, cited a systematic review showing that the uncertainty about its effects had been resolved. They also observed that the number of new trials increased after publication of the review and suggested that the strong pressure to publish and the failure of ethics committees to ensure the clinical relevance of new trials could be the main reasons.

We considered two alternative explanations for the apparent redundancy. First, that trialists may be sceptical about the results of even seemingly conclusive reviews. Such scepticism may arise from concerns about systematic or random errors distorting the results. Poor quality trials can introduce bias and multiple statistical testing as new trials accumulate may increase the risk of false positive results. Second, even in the absence of substantial bias or random error, there may be a reluctance to generalise trial results to different patient groups. If this were the case, strong evidence of a treatment effect might be expected to lead to more trial activity rather than less, as researchers examine the impact of patient or intervention characteristics on the results.

We used data from a cumulative meta-analyses of trials examining the effect of TXA on blood transfusion in surgery, to explore whether deficiencies in the quality of the evidence justify the continuation of trial activity. We explored the impact of trial quality on effect estimates and used trial sequential analysis to quantify required information sizes and construct monitoring boundaries to assess the risk of random error affecting the cumulative estimate. We examined whether patient characteristics changed over time and the reasons given by the trial investigators for conducting their trial.

Methods

Systematic review

We extracted data from trials included in our previous systematic review of tranexamic acid (TXA) for surgical bleeding. The methods used to the identify trials are described in detail elsewhere.[6] Briefly, we searched for all randomised controlled trials comparing TXA with placebo or a no treatment control. We searched the Cochrane Central Register of Controlled Trials, Medline, Embase and the WHO International Clinical Trials Registry Platform, using a combination of subject headings and text words to identify randomised controlled trials of any antifibrinolytic drug (see Appendix Q for Medline search strategy). We updated our searches to May 2014 to incorporate trials published since the original version of the review. Data were extracted on patient characteristics, type of surgery and the number of patients who received a blood transfusion. We used the Cochrane Collaboration's tool for assessing risk of bias in the included trials.[8] We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding and the completeness of outcome data. Trials were rated as being at high, low or unclear risk of bias for each domain. We considered trials with adequate allocation concealment and blinded outcome assessment to be at low risk of bias.

Analysis

Systematic review and meta-analyses

We calculated risk ratios and 95% confidence intervals to assess the effect of TXA on blood transfusion. We pooled the data in a fixed effect cumulative meta-analysis based on date of publication. We conducted separate meta-analysis for all trials, trials at low risk of bias, and trials at low risk of bias that had pre-specified blood transfusion as an outcome on a registration record.

Trial sequential analyses

We used trial sequential analyses (TSA) to examine the reliability of the cumulative meta-analysis. TSA involves calculating the number of participants (i.e. information size) required

before the result of a meta-analysis can be considered reliable and constructs statistical monitoring boundaries to account for type I and type II errors due to multiple testing.[9] We conducted three analyses: (1) all trials, (2) trials at low risk of bias, and (3) prospectively registered, low risk of bias trials with blood transfusion as a pre-specified outcome. We calculated the required meta-analysis information size assuming a type I error of 5% and 90% power, a baseline event rate of 40% and a relative risk reduction of 15%. We chose a relative risk reduction of 15% as we judged this to represent a minimally clinical important effect. The estimate was adjusted for maximum anticipated heterogeneity of I^2=75%.

We used Microsoft Excel, STATA version 13[10], RevMan 5.3[11] and the TSA Software version 0.9 beta[12] for the analyses.

To explore the hypothesis that reliable demonstration of a treatment effect leads to an increase in trial activity, we plotted the precision of the pooled effect estimate (described by the standard error of the cumulative pooled risk ratio) against the number of new trials initiated (defined as start date of recruitment) per year. We did this both for all trials and for the subset of cardiac surgery trials.

We also plotted the publication date of each trial stratified by surgery type.

We examined trial reports to explore the reasons given for trial initiation and categorised the reasons into main themes.

Finally, we explored how the size and quality of trials changed over time. We compared the mean sample size and the proportion of trials at low risk of bias that were published before and after the Cochrane systematic review by Henry *et al*.[13] This systematic review was chosen as it was the first and most comprehensive review conducted on the effect of TXA in surgical bleeding. The review was published in October 1999. We allowed for a five year time lag for the results of the review to have an impact on published research and compared trials published before and after 1 November 2004.

Results

Systematic review and meta-analyses

We found 126 trials with 12,429 patients of the effect of tranexamic on blood transfusion in surgery with data suitable for analysis. One hundred and twenty trials (95%) were conducted in a single-centre. The median sample size was 79 patients (range 10 to 660). The trials involved cardiac (n=51), orthopaedic (n=49), obstetric and gynaecological (n=10), cranial (n=9), urological (n=3), hepatic (n=2), vascular (n=1), and abdominal (n=1) procedures. Thirty-eight (30%) trials had adequate allocation concealment and blinded outcome assessment and were considered at

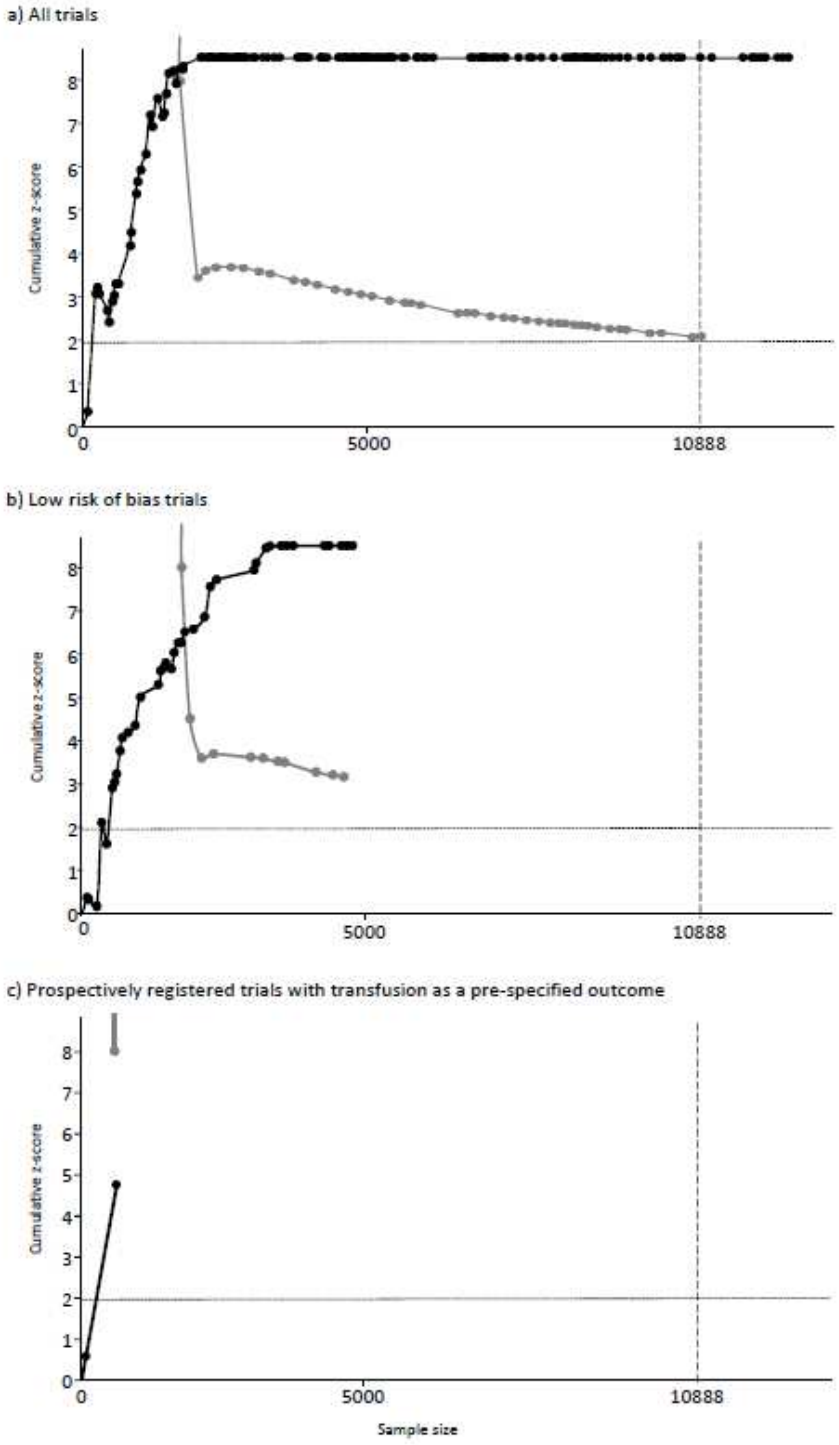
low risk of bias. We identified a clinical trial registration record for 24 (19%) trials. Six (5%) trials had been prospectively registered, four (3%) of which had pre-specified blood transfusion as an outcome and two of these (2%) were at low risk of bias. Allowing for a 12 month publication time lag, 110 of the 118 (93%) trial reports published as journal articles were published when at least one systematic review was available. Examination of the references lists showed that 68 (62%) cited one of the available systematic reviews.

Based on all 126 included trials, TXA administration appeared to reduce the risk of receiving a blood transfusion by 38% (pooled RR=0.62; 0.59 to 0.65; p<0.0001). The cumulative estimate was statistically significant (p<0.05) after the second trial (published in August 1993) and remained so thereafter. Based on data from the 38 trials at low risk of bias, TXA appeared to reduce the risk of receiving a blood transfusion by 32% (pooled RR=0.68; 0.63 to 0.73; p<0.001). The cumulative estimate was first statistically significant after the fourth high quality trial but remained statistically significant after the sixth trial. For all trials and for trials at low risk of bias, we observed funnel plot asymmetry consistent with a deficit of small trials showing no treatment effect. When the analysis was limited to the two low risk of bias, prospectively registered trials that pre-specified blood transfusion as an outcome measure, TXA appeared to reduce the risk of transfusion by 21% (pooled RR=0.79, 0.71 to 0.87; p<0.001).

Trial sequential analyses

Figure 2.8 shows the results of the trial sequential analyses. The required information size was estimated at 10,888 patients. For each analysis an information size (IS) was calculated on the basis assuming α=5%, β=10%, control group event rate of 40%, relative risk reduction of 15% and anticipated maximum heterogeneity of I^2=75%. The solid black line illustrates the cumulative z curve, the solid grey line shows the trial sequential monitoring boundary.

Figure 2.8 Results of trial sequential analyses for a) all trials; b) trials at low risk of bias; and c) low risk of bias trials with transfusion pre-specified on prospective registration record.



Based on data from all 126 trials, there appears to be strong evidence that TXA reduces the risk of blood transfusion in surgery. The z-curve crosses the monitoring boundary before the heterogeneity-adjusted information size is achieved when the 28th trial published in March

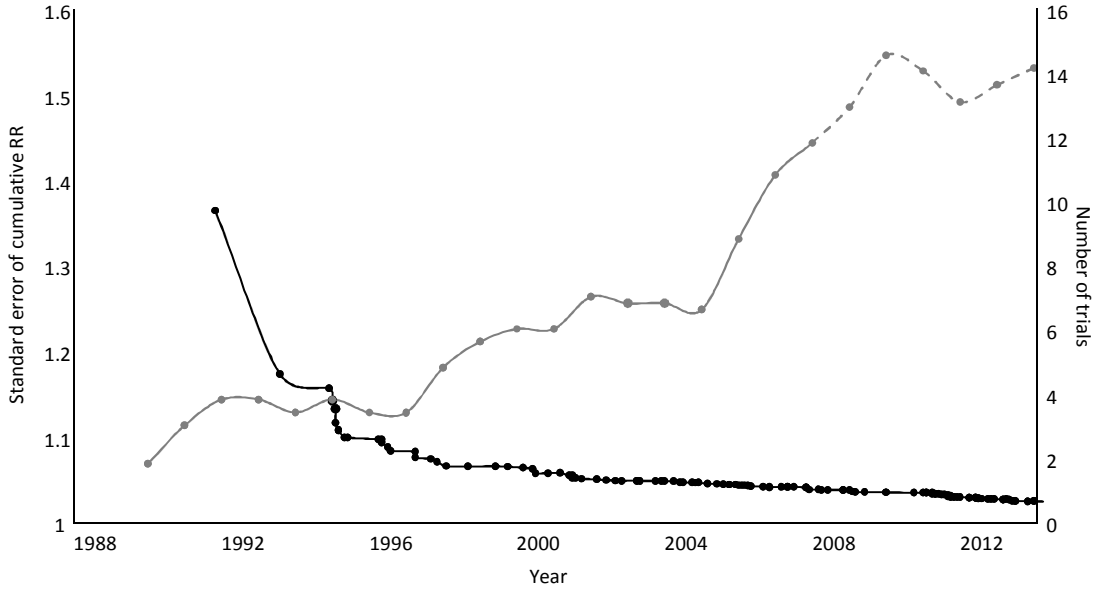
2001. Prior to this point there were 26 potentially spurious p-values. Since the monitoring boundary was crossed, a further 98 trials have been published.

Based on the 38 low risk of bias trials, there appears to be strong evidence that TXA reduces blood transfusion. The z-curve crosses the monitoring boundary after the 22nd high quality trial published in November 2008. Prior to this point there were 18 potentially spurious p-values. Since the monitoring boundary was crossed, a further 15 high quality trials have been published.

When the analysis is restricted to the two low risk of bias trials which had pre-specified blood transfusion as an outcome, the z-curve does not cross the monitoring boundary and the heterogeneity-adjusted information size is not achieved. There is one potentially spurious p-value.

Figure 2.9 shows the precision of the cumulative pooled estimate (standard error of the log cumulative RR) and the number of trials initiated per year from 1991 to 2014.

Figure 2.9 Precision of the cumulative pooled estimates described by the standard error of the RRs (left hand axis) and the number of trials (five year moving averages, right hand axis) initiated per year.



As the precision of the pooled estimate increases (i.e. decrease in the standard error), the number of new trials initiated each year also increases. A similar pattern is observed for trials in cardiac surgery (Figure 2.10).

Figure 2.10 Precision of the cumulative pooled estimates for the effect of TXA in cardiac surgery described by the standard error of the RRs (left hand axis) and the number of trials (five year moving averages, right hand axis) initiated per year.

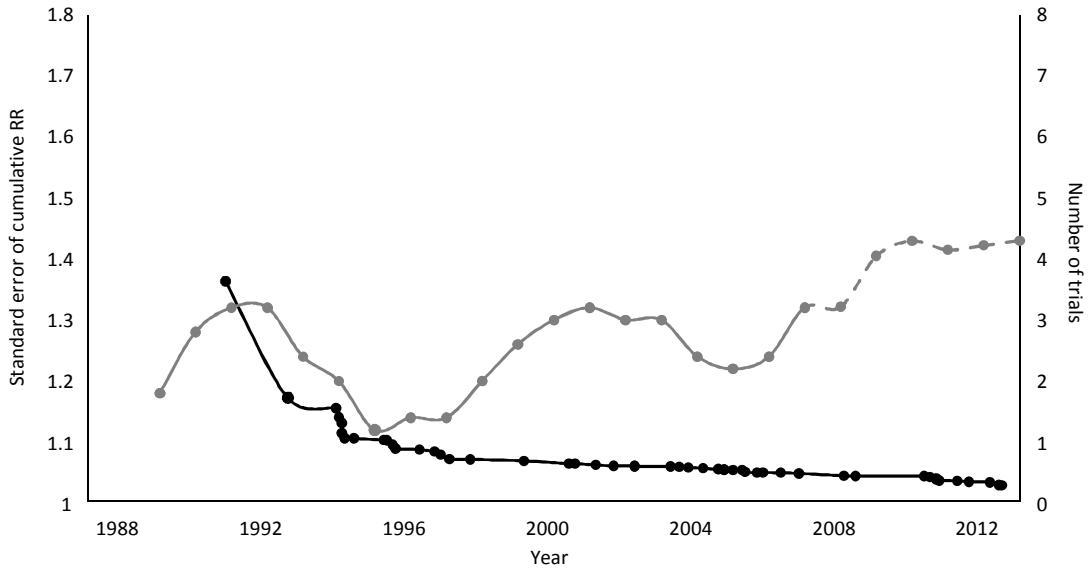
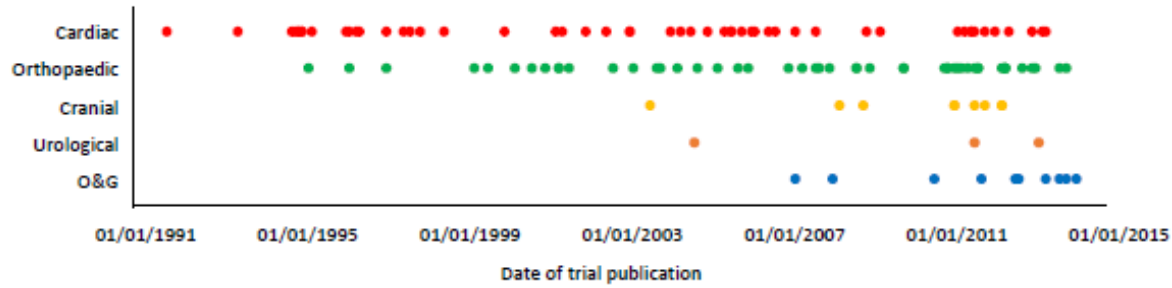


Figure 2.11 shows a timeline of the publication of the trials, stratified by surgery type. It appears that trials were first conducted in cardiac surgery and shortly afterwards in orthopaedic surgery. Trial activity then expands to other types of surgery namely cranial, urological and gynaecological surgery.

Figure 2.11 Timeline of publication of trials of TXA stratified by type of surgery.



Qualitative review of trial justifications

Eight trials were reported in abstract or summary form only, leaving 118 trials reported in sufficient detail to extract information on the rationale. A summary of the extracted information is shown in Table 2.3. Concerns about the generalisability of the available evidence was used to justify 71 (60%) trials. These trials sought to replicate a previously observed beneficial effect of TXA on surgical bleeding but in a different group of patients, such as those undergoing a different type of surgical procedure. Thirty-one (26%) trials were initiated to answer a different research

question to the effect of TXA on bleeding. Most of these trials were conducted to examine the effect of different doses or timings of TXA despite the inclusion of a placebo or no-TXA control group. Five (4%) trials appeared to have been conducted because of a failure to synthesise prior evidence. The trial rationale was unclear in four (4%) trials.

Table 2.3 Summary of reasons for initiating trials of TXA for surgical bleeding based on information extracted from the final reports

	Failure to synthesise evidence	**Confirmatory**	**Generalisability**	**Assessing a different research question**	**Unclear**
Trials citing ≥1 available systematic review (n=68)	-	2	51	11	4
Trials not citing an available systematic review (n=42)	2	3	21	16	-
Trials published before a systematic review was available (n=9)	3	-	-	6	-
All trial reports (n=118)	5 (4%)	5 (4%)	72 (61%)	33 (28%)	4 (3%)

Comparison of trials conducted before and after publication of the Henry et al systematic review

Of the 126 trials, 47 (37%) were published before 1 November 2004 compared to 79 (63%) published afterwards up to May 2014. The average sample size had increased between the two periods (mean ± standard deviation, 64±50 versus 119±103; p<0.0001). A larger proportion of trials published after November 2004 were judged to be at low risk of bias for both allocation concealment and blinding (12 [26%] versus 28 [35%]; P=0.23).

Discussion

Principal findings

We examined two hypotheses for the redundancy in a cumulative meta-analysis. First, that despite the apparently conclusive results, legitimate concerns about bias and random error justified new trials. We found some support for this. Most trials were small, single centre, low quality and hardly any were prospectively registered. Nevertheless, when only high quality trials were considered, with steps taken to reduce the risk of false positive results, there remained strong evidence that TXA reduces transfusion.

Our second hypothesis was that new trials are conducted because of concerns about the generalisability of the results. We found strong support for this. Increasing evidence that TXA decreases the need for blood transfusion resulted in more trial activity and not less. The change in patient characteristics over time and the rationales given by trialists also indicate that generalisability concerns motivated the new trials. That over half of trials cited at least one of the existing systematic reviews, suggests that ignorance of the existing evidence does not fully explain ongoing trial activity.

The average sample size of trials has increased and there is some suggestion that the quality of trials has improved over time.

Strengths and weaknesses

We examined trial reports to find the reasons authors gave for conducting new trials. This process was inevitably subjective and different assessors might have made different judgements. Furthermore, trial reports might not accurately reflect the rationale at trial inception. We did not contact authors, although whether this would have provided more reliable information is uncertain. There are other, non-scientific motivations, such as monetary and academic, for initiating a new trial which would not be publically reported. Nevertheless, the reasons given in trials reports are the openly given justifications that are accepted by the scientific community and are therefore a reasonable focus for review.

Our study was based on clinical trials of TXA in surgery and the extent to which the results apply to other topics is questionable. However, we have also found that publication of a systematic review showing strong evidence that TXA reduces mortality in bleeding trauma patients also resulted in increased trial activity rather than less. A 2004 systematic review of TXA in acute traumatic injury[14] found no eligible trials even though TXA was commonly used in other bleeding conditions. The review prompted the CRASH-2 trial which included 20,211 bleeding trauma patients and showed that TXA reduces death due to bleeding and all-cause mortality.[15] The subsequently updated review included two trials and reported that the uncertainty had been resolved.[16] Nevertheless, some authors, pointing out that many of the patients in the CRASH-2 trial were recruited from hospitals in Africa, Asia and Latin America, questioned whether the results can be applied in "modern" trauma care systems[17] and have initiated new clinical trials rather than implementing the results.[18, 19] Although subgroup analyses show that the CRASH-2 trial results do not vary by geographical region,[20] two placebo controlled trials are underway. [14, 15] Habre *et al*[7] also found that publication of a conclusive review coincided with increased trial activity and that most new trials cited the conclusive review.

There are other potential explanations for the continuation of trial activity that we have not explored. Habre *et al* suggested that redundant trials of an anaesthetic intervention may have been motivated by the self-interest of researchers wishing to gain more research publications. In relation to our study, trials of the effect of TXA on blood transfusion are relatively easy to conduct and since a treatment effect is highly likely, it would be an attractive topic for research.

Implications

Our results raise questions about the process of scientific generalisation. If there is strong evidence that TXA reduces bleeding in cardiac and orthopaedic surgery, is it necessary to examine its effect in obstetric surgery? Rothman *et al*[21] argues that the reluctance to generalise results to populations that were not represented in the original research confuses statistical and scientific inference. Statistical inference, the process of using sample information to reach conclusions about the population from which it was drawn, is helped by having a representative sample. However, generalising trial results involves scientific inference, a process of reaching general conclusions about how a treatment works. The main prerequisite for scientific inference is a biological insight into the mechanism of action of the treatment and an awareness of the circumstances that may be relevant to this mechanism. Rather than using statistical reasoning, it is more appropriate to use biological reasoning and ask whether there is any good reason why TXA would work differently in orthopaedic or urological surgery?

A further concern is the number of inappropriately designed trials. This typically concerns trials which aimed to build on the existing knowledge by comparing different doses or timings of TXA, yet opted to include a no-treatment comparison group. The inclusion of a no-treatment comparison group in such trials is wasteful and unethical - failings that implicate both trialists and the ethical review committees approving the trials. In this article we focus on the potential explanations for trialists' decision to initiate further trials of TXA, yet there is also a question regarding why patients continue to agree to participate in apparently 'redundant' trials in which there is a chance they will forego receiving an effective treatment. We did not attempt to obtain the patient information sheets used in the trials, and there remains an unanswered question regarding the extent to which trial participants are made aware of the existing evidence as part of the consent giving process.

Our results suggest that low quality trials are a more important cause of 'research waste' than the failure to systematically review the existing evidence. When only high quality trials are considered, the number of statistically 'redundant' trials was reduced from 98 to 15. Most trial reports clearly indicated an awareness that TXA had been shown to reduce bleeding but sought to examine its effect in different types of surgery. For this reason, more systematic reviews and greater attention to existing reviews will only increase research waste unless determined efforts

are made to increase quality in the form of adequately powered trials that are properly randomised with adequate allocation concealment and blinding.

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3.0 WHAT ARE THE EFFECTS OF TRANEXAMIC ACID IN PATIENTS WITH TRAUMATIC BLEEDING?

3.1 INTRODUCTION TO RESEARCH PAPER 4

As described in Chapter 1, bleeding is an important cause of death and morbidity in trauma patients. As an inhibitor of fibrinolysis, tranexamic acid (TXA) has the potential to reduce bleeding.

Based on evidence from trials in surgery, it was surmised that TXA might also be effective in bleeding trauma patients, although no randomised trials had been conducted in this patient group.[1] The CRASH-2 trial involving 20,211 bleeding trauma patients was conducted to resolve this uncertainty.[2]

The CRASH-2 trial results were published in June 2010. As the results of all trials should be interpreted in the context of a systematic review,[3] I updated the Cochrane systematic review of 'Antifibrinolytic drugs for acute traumatic injury' to incorporate the results of the CRASH-2 trial and any other trials of antifibrinolytic drugs that had been conducted since the first publication of the review in 2004.[1]

The updated review was published as a 'substantive update' in November 2010. I completed a further update in November 2012 to incorporate findings of subgroup analyses of the CRASH-2 trial data and it is this version that I have included in this thesis.

The inclusion criteria of the review include all antifibrinolytic drugs (aprotinin, tranexamic acid and epsilon-aminocaproic acid). Since I am focussing on the effects of TXA in this thesis, I have only included results relevant to the evidence from trials of TXA in the proceeding section; however, the full published version of the review is presented in Appendix T.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	**Cochrane Database of Systematic Reviews**		
When was the work published?	**2012**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**Yes (see Appendix S)**	Was the work subject to academic peer review?	**Yes**

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I led on the update of the review. The inclusion criteria and methods were already prespecified in the original version of the review. I joined the author team and updated the review following these predefined methods. I screened the search output for trials, extracted data for the two newly identified trials, performed the meta-analyses and revised the text to reflect the new evidence.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

3.2 ANTIFIBRINOLYTIC DRUGS FOR ACUTE TRAUMATIC INJURY

Ian Roberts, Haleema Shakur, Katharine Ker, Tim Coats, on behalf of the CRASH-2 Trial collaborators

Cochrane Database Systematic Reviews 2012;12:CD004896

Background

Description of the condition

For people aged five to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma,[1] many after reaching hospital. Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths in some settings.[2] Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding.[3]

Clotting helps to maintain the integrity of the circulatory system after vascular injury, whether traumatic or surgical in origin.[4] Major surgery and trauma trigger similar haemostatic responses and the consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma in any patient, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some cases. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, without apparently increasing the risk of post-operative complications.

Description of the intervention

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. A Cochrane systematic review of randomised controlled trials of antifibrinolytics (mainly aprotinin or tranexamic acid [TXA]) in elective surgical patients showed that antifibrinolytics reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding.[5] These differences were all statistically significant at the $p<0.01$ level. Specifically, aprotinin reduced the rate of blood transfusion by 34% (relative risk [RR]=0.66; 95% confidence interval [CI] 0.60 to 0.72) and TXA by 39% (RR=0.61; 95% CI 0.53 to 0.70). Aprotinin use saved 1.02 units of red blood cells (RBCs) (95% CI 0.79 to 1.26) in those requiring transfusion, and TXA use saved 0.87 units (95% CI 0.53 to 1.20). There was a non-significant reduction in mortality with both aprotinin (RR=0.81; 95% CI 0.63 to 1.06) and TXA (RR=0.60; 95% CI 0.33 to 1.10).

How the intervention might work

Because the coagulation abnormalities that occur after injury are similar to those after surgery, it is possible that antifibrinolytic agents might also reduce blood loss and mortality following trauma. A simple and widely practicable intervention that reduced blood loss following trauma might prevent tens of thousands of premature deaths. A reduction in the need for transfusion would also have important public health implications. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Trauma is particularly common in parts of the world where the safety of blood transfusion cannot be assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around two percent although some estimates are much higher.[6, 7]

Objectives

To quantify the effect of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT), as per the following definition.

RCT: A study involving at least one intervention and one control treatment, concurrent enrolment and follow-up of the intervention and control groups, and in which the interventions to be tested are selected by a random process, such as the use of a random numbers table (coin flips are also acceptable). If the study author(s) state explicitly (usually by using some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as an 'RCT'.

Types of participants

People of any age following acute traumatic injury.

Types of interventions

The interventions considered are the antifibrinolytic agents: aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).[vi]

Types of outcome measures

Primary outcome

[vi] Sections relating to the effects of aprotinin and EACA have been omitted from this thesis for clarity.

Mortality at the end of the follow up.

Secondary outcomes

- Number of patients experiencing an adverse event, specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism).
- Number of patients undergoing surgical intervention.
- Number of patients receiving blood transfusion.
- Volume of blood transfused (units).

Search methods for identification of studies

Searches were not restricted by date, language or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group's Specialised Register (searched July 2010)
- Cochrane Central Register of Controlled Trials Issue 3, 2010 (The Cochrane Library)
- MEDLINE (1966 to July week 2, 2010)
- PubMed (searched March 17, 2004)
- EMBASE (1980 to week 28, July 2010)
- Science Citation Index (searched March 17, 2004)
- National Research Register (issue 1, 2004)
- Zetoc (searched March 17, 2004)
- SIGLE (searched March 17, 2004)
- Global Health (searched March 17, 2004)
- LILACS (searched March 17, 2004)
- Current Controlled Trials (searched March 17, 2004)

The search strategies used in the latest update are listed in full in Appendix U.

Searching other resources

All references in the identified trials and background papers were checked and study authors contacted to identify relevant published and unpublished data. Pharmaceutical companies were contacted in 2004 to obtain information on ongoing trials.

Data collection and analysis

Selection of studies

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches and contacts with experts, two authors independently selected trials meeting the inclusion criteria. There were no disagreements on study inclusion.

Data extraction and management

Two authors independently extracted information on the following: number of randomised participants, types of participants and types of interventions. The outcome data sought were: numbers of deaths in each group, numbers with vascular occlusive events, numbers requiring surgical intervention, and the amount of blood transfused. Information on loss to follow up, blinding, and whether an intention-to-treat analysis was performed was also extracted. The authors were not blinded to the authors or journal when doing this. Results were compared and differences would have been resolved by discussion had there been any. Where there was insufficient information in the published report, we attempted to contact the authors for clarification.

Assessment of risk of bias in included studies

Two authors assessed the risk of bias for allocation concealment. Each trial was assessed as being at high, low or unclear risk of bias according to the criteria presented in Higgins et al 2008.[8]

Assessment of heterogeneity

The presence of heterogeneity of the observed treatment effects were assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2>50%.[9] The following were specified a-priori as factors that could explain any observed heterogeneity: adequacy of allocation concealment; injury severity based on the injury severity score (an ISS of greater than or equal to 16 defines the severely injured strata); and according to whether the study population included predominantly blunt or penetrating trauma.

Assessment of reporting biases

We planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis.

Data synthesis

Risk ratios (RR) and 95% confidence intervals (95% CI) were calculated. The risk ratio was chosen because it is more readily applied to the clinical situation. For transfusion volumes, the mean difference (MD) in the units of blood transfused were calculated with 95% CI.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore whether effect sizes vary according to the type of antifibrinolytic agent and the dosing regimen. However, there were too few trials for such analyses.

Results

Tranexamic acid

Two trials compared TXA with placebo in trauma patients. The CRASH-2 trial recruited 20,211 trauma patients with, or at risk of, significant haemorrhage.[10, 11] A trial in Thailand by Yutthakasemsunt *et al* recruited 240 trauma patients with moderate to severe traumatic brain injury.[12] As of November 2012, the Thai trial Yutthakasemsunt *et al* was only available as an abstract with publication of the full trial report pending. The trial has been included based on the data reported in the abstract. The full trial data will be incorporated into this systematic review once the full trial report is available.

See 'Characteristics of included studies' in Appendix V for further details.

Risk of bias in included studies

The CRASH-2 trial was judged to be at low risk of bias. It was a large randomised controlled trial involving 20,211 adult trauma patients who were randomly allocated to receive TXA or placebo. TXA and placebo were packaged in identical ampoules. Hospitals with reliable telephone access used a telephone randomisation service, hospitals without used a local pack system; allocation concealment was adequate. Participants and trial staff were blinded to treatment allocation. Over 99% of patients were followed up.

There was insufficient information presented in the abstract to assess the risk of bias of the trial by Yutthakasemsunt *et al*.

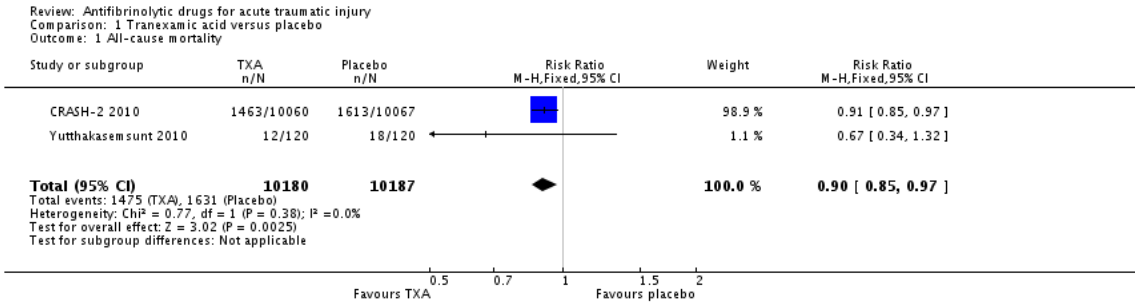
Effects of interventions - Tranexamic acid versus placebo

Mortality

Both the CRASH-2 trial and the trial by Yutthakasemsunt *et al* reported mortality data.

All-cause mortality was significantly reduced with tranexamic acid (pooled risk ratio (RR) 0.90, 95% CI 0.85 to 0.97; p=0.003: Figure 3.1*)*. There was no evidence of statistical heterogeneity (Chi^2=0.77, df=1 (p=0.38); I^2=0%).

Figure 3.1 Comparison 1 Tranexamic acid versus placebo, Outcome 1 All-cause mortality.



The CRASH-2 trial also presented mortality data by cause. The risk of death due to bleeding and myocardial infarction were significantly reduced with TXA. There were no statistically significant differences in the risk of death from other causes:

- Bleeding: RR 0.85, 95% CI 0.76 to 0.96; p=0.0077
- Myocardial infarction: RR 0.32, 95% CI 0.14 to 0.75; p=0.0053
- Vascular occlusion: RR 0.69, 95% CI 0.44 to 1.07; p=0.096
- Stroke: RR 1.60, 95% CI 0.52 to 4.89; p=0.40
- Pulmonary embolism: RR 0.86, 95% CI 0.46 to 1.61; p=0.63
- Multi-organ failure: RR 0.90, 95% CI 0.75 to 1.08; p=0.25
- Head injury: RR 0.97, 95% CI 0.87 to 1.08; p=0.60
- 'Other' causes: RR 0.94, 95% CI 0.74 to 1.20; p=0.63

Although not prespecified subgroup analyses of this review, the effects of TXA on death due to bleeding by time to treatment, severity of haemorrhage, Glasgow coma score, and type of injury were assessed in the CRASH-2 trial.[11] The results are presented below.

Analysis of the risk of death due to bleeding indicated that the effect of TXA varied by time to treatment. Treatment within one hour of injury was associated with a 32% relative reduction in risk of death due to bleeding (RR 0.68, 95% CI 0.57 to 0.82; p<0.0001) and treatment between 1 and 3 hours after injury was associated with a 21% reduction (RR 0.79, 95% CI 0.64 to 0.97; p=0.03). Treatment with TXA after three hours of injury was associated with a 44% relative increase in risk of death due to bleeding (RR 1.44, 95% CI 1.12 to 1.84; p=0.004). Test for subgroup differences: Chi^2=23.51, P<0.00001.

There was no evidence that the effect of TXA on death due to bleeding varied by the severity of haemorrhage, Glasgow coma score, or type of injury:

- Severity of haemorrhage (as assessed by systolic blood pressure): >89 mm Hg (RR 0.88, 95% CI 0.71 to 1.10); 76-89 (RR 1.01, 95% CI 0.79 to 1.30); ≤75 (RR 0.81, 95% CI 0.69 to 0.95). Test for subgroup differences: Chi^2=2.24, p=0.33.

- Glasgow coma score: severe (RR 0.92, 95% CI 0.76 to 1.13); moderate (RR 0.77, 95% CI 0.59 to 0.99); mild (RR 0.86, 95% CI 0.72 to 1.02). Test for subgroup differences: Chi^2=1.28, p=0.53.
- Type of injury: blunt (RR 0.89, 95% CI 0.77 to 1.04); penetrating (RR 0.79, 95% CI 0.66 to 0.96). Test for subgroup differences: Chi^2=0.92, p=0.34.

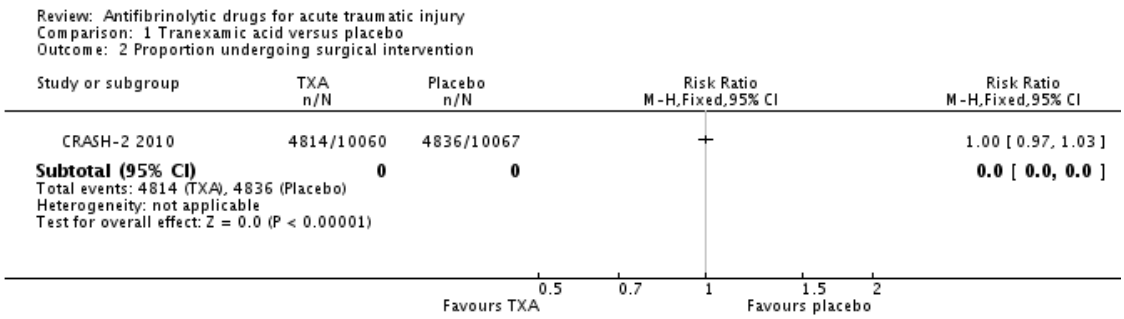
Vascular occlusive events

The CRASH-2 trial reported data on vascular occlusive events. There was no difference in the risk of experiencing one or more vascular occlusive events (fatal or non-fatal; myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) between the TXA and placebo groups (RR 0.84, 95% CI 0.68 to 1.02; p=0.084). TXA reduced the risk of myocardial infarction (RR 0.64, 95% CI 0.42 to 0.97; p=0.035). There was no difference in the risk of stroke (RR 0.86, 95% CI 0.61 to 1.23; p=0.42), pulmonary embolism (RR 1.01, 95% CI 0.73 to 1.41; p=0.93) or deep vein thrombosis (RR 0.98, 95% CI 0.63 to 1.51; p=0.91).

Surgical intervention

Data from the CRASH-2 trial suggest that there is no statistically significant difference in the risk of receiving one or more surgical interventions (neurosurgery, chest, abdominal or pelvic surgery) (RR 1.00, 95% CI 0.97 to 1.03; p=0.79) (Figure 3.2).

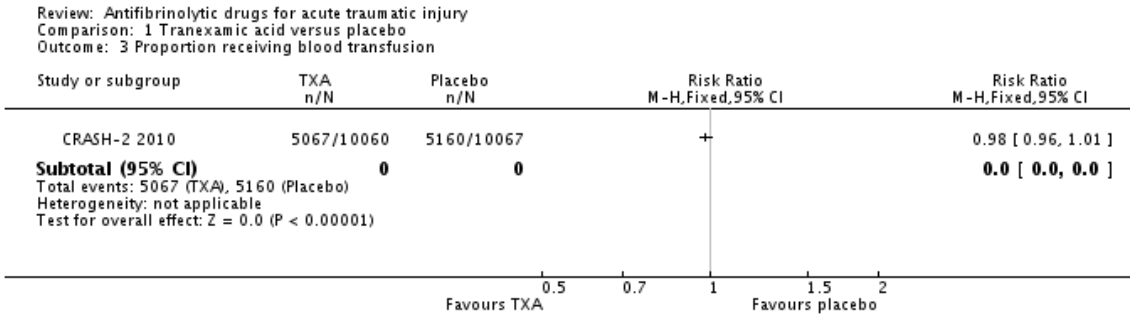
Figure 3.2 Comparison 1 Tranexamic acid versus placebo, Outcome 2 Proportion undergoing surgical intervention.



Receipt of blood transfusion

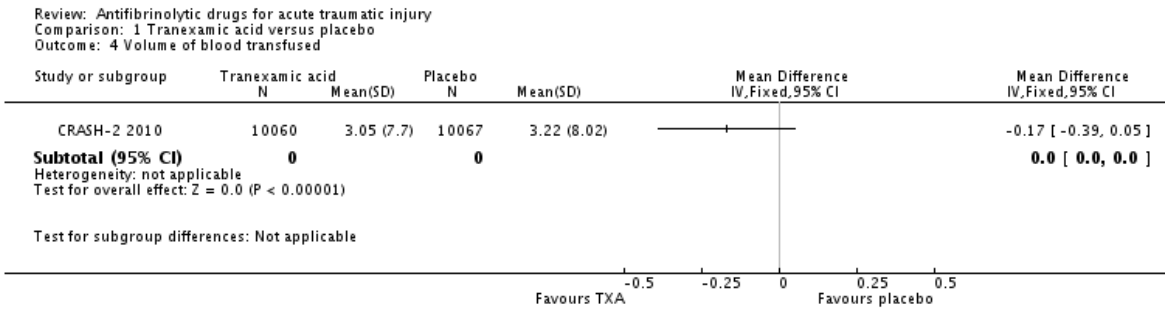
Of the patients allocated to TXA in the CRASH-2 trial, 5067 (50.4%) received a blood product transfusion versus 5160 (51.3%) of the patients allocated to placebo (RR 0.98, 95% CI 0.96 to 1.01; p=0.21) (Figure 3.3).

Figure 3.3 Comparison 1 Tranexamic acid versus placebo, Outcome 3 Proportion receiving blood transfusion.



There was no difference in the average number of blood units transfused (MD -0.17; 95% CI -0.39 to 0.05; p=0.13) (Figure 3.4).

Figure 3.4 Comparison 1 Tranexamic acid versus placebo, Outcome 4 Volume of blood transfused.



Discussion

Summary of main results

Tranexamic acid reduces all-cause mortality in bleeding trauma patients, with no apparent increase in the risk of vascular occlusive events. This conclusion is based on the results of the CRASH-2 trial which recruited 20,211 bleeding trauma patients from 274 hospitals in 40 countries.

Overall completeness and applicability of evidence

The large numbers of patients in a wide range of different health care settings around the world studied in the CRASH-2 trial help the result to be widely generalised. The treatment is effective in patients with blunt and penetrating trauma. Because TXA is inexpensive and easy to administer, it could readily be added to the normal medical and surgical management of bleeding trauma patients in hospitals around the world.

Each year, worldwide, about four million people die as a result of traumatic injuries and violence. Approximately 1.6 million of these deaths occur in hospital and about one third of these deaths (480,000) are from haemorrhage. The CRASH-2 trial has shown that TXA reduces mortality from haemorrhage by about one sixth. If this widely practicable intervention was used worldwide in the treatment of bleeding trauma patients, it could prevent over 70,000 deaths each year (see Table 3.1).

Table 3.1 Deaths that could be avoided by the administration of TXA to bleeding trauma patients (ten countries with the highest numbers of avoided deaths shown)

Country	Trauma deaths	Haemorrhage deaths	Deaths averted with TXA
India	714,730	85,768	12,865
China	667,277	80,073	12011
Indonesia	279,499	33,534	5030
Russia	246,836	29,620	4443
Brazil	122,953	14,754	2206
USA	122,529	14,703	2206
Iraq	99,968	11,996	1799
Nigeria	87,811	10,537	1581
Bangladesh	76,938	9233	1385
DRC	73,579	8829	1324
World	4,100,645	492,077	73,812

Many trauma patients suffer a brain injury. Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and regardless of location, haemorrhage size is strongly correlated with outcome. If TXA reduced intracranial bleeding after isolated TBI then this could improve patient outcomes. Although, many of the bleeding trauma patients included in the CRASH-2 trial also suffered a brain injury, it is possible that the effects of TXA may differ in patients with isolated TBI. The trial by Yutthakasemsunt *et al* provides some promising evidence for the beneficial effect of TXA on mortality in patients with isolated TBI; however, further evidence is required from larger trials which also assess the effect on disability.

The quality of the evidence supporting the use of tranexamic acid for trauma is high. The findings of this review are based primarily on the results of the CRASH-2 trial. This was a large, high quality randomised trial with low risk of bias. Sequence generation was appropriately

randomised, allocation was concealed and participants, trial personnel and outcome assessors were all blinded. Furthermore, there were minimal missing data with over 99% of patients followed up.

Potential biases in the review process

This systematic review addresses a focused research question and uses pre-defined inclusion criteria and methodology to select and appraise eligible trials.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

Agreements and disagreements with other studies or reviews

A systematic review of randomised trials assessing the effects of TXA in patients undergoing elective surgery has been conducted.[5] This review found that compared to control, TXA reduced the need for blood transfusion without any apparent increase in the risk of adverse events. Unlike the Henry *et al* review, we found no evidence of any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. One possible explanation is that in the CRASH-2 trial, following the loading dose, TXA was infused over a period of eight hours, whereas decisions about transfusion are made very soon after hospital admission. The absence of any large effect on blood transfusion may also reflect the difficulty of accurately estimating blood loss in trauma patients when assessing the need for transfusion. Finally, the absence of any substantial reduction in transfusion requirements in patients treated with TXA acid may reflect the fact that there were fewer deaths in patients allocated to TXA acid than to placebo and patients who survive as a result of TXA administration would have had a greater opportunity to receive a blood transfusion (competing risks).

Authors' conclusions

Implications for practice

Tranexamic acid (TXA) safely reduces mortality in bleeding trauma patients. As there is evidence that the effect on death due to bleeding depends on the time interval between the injury and treatment, TXA should be given as early as possible and within three hours of the injury as treatment later than this is unlikely to be effective.

Implications for research

The knowledge that TXA safely reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations where bleeding can be life threatening or disabling and further research is warranted to explore this potential. Randomised

trials involving patients with isolated traumatic brain injury that assess both mortality and disability outcomes are required before TXA can be recommended for use in these patients. The ongoing CRASH-3 trial with a planned sample size of 10,000 patients with traumatic brain injury, will contribute to resolving the uncertainty about the effects of TXA in this group.

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3.3 INTRODUCTION TO RESEARCH PAPER 5

The results of the Cochrane systematic review updated with the CRASH-2 trial results described in Research Paper 4, showed that TXA reduces the risk of death in bleeding trauma patients. It also showed that early treatment (<3 hours) with TXA is superior to late treatment (>3 hours).

These results along with the fact that TXA is cheap and a widely practicable treatment, suggests that it has the potential to save the lives of many trauma victims including in LMICs where most trauma deaths occur.

Estimates of the number of deaths averted worldwide, along with country-specific estimates can be valuable for targeting dissemination efforts. In the Discussion section of Research Paper 4, we estimated the number of bleeding deaths that could be avoided through the routine use of TXA when given within 8 hours of injury. However, in light of the knowledge the late treatment with TXA is unlikely to be effective (and may even be harmful), treatment with TXA if more than three hours after injury is not recommended. Therefore, I undertook further analyses to estimate the number of deaths that could be averted by the routine, early use of TXA. These analyses are presented in Research Paper 5 and include a systematic review of the literature which informed the parameter estimates.[vii]

[vii] A copy of the PDF version of the published manuscript is included in Appendix Z.

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	**BMC Emergency Medicine**		
When was the work published?	**2012**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**Yes (see Appendix Y)**	Was the work subject to academic peer review?	**Yes**

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I designed the study with my co-authors. Pablo Perel performed the subgroup analysis of the CRASH-2 trial data. My specific contributions to this study were: **• designing methods and leading on all tasks involved in the systematic review of recent trauma death epidemiology literature (i.e. running electronic searches, screening search output, assessing for inclusion, data extraction, data analysis) (with Junko Kiryu);** **• extracting data from WHO global mortality database and CRASH-2 trial;** **• designing analysis to estimate number in-hospital trauma deaths due to bleeding and number of deaths averted (with advice from Ian Roberts and Phil Edwards);** **• undertaking analysis to estimate number in-hospital trauma deaths due to bleeding and number of deaths averted;** **• interpreting results and preparing tables and figures;** **• preparing manuscript for publication with input from my co-authors;** **• addressing editorial and peer referee comments on final draft prior to publication.**

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

3.4 AVOIDABLE MORTALITY FROM GIVING TRANEXAMIC ACID TO BLEEDING TRAUMA PATIENTS: AN ESTIMATION BASED ON WHO MORTALITY DATA, A SYSTEMATIC LITERATURE REVIEW AND DATA FROM THE CRASH-2 TRIAL

Katharine Ker, Junko Kiriya, Pablo Perel, Phil Edwards, Haleema Shakur, Ian Roberts

BMC Emergency Medicine. 2012 Mar 1;12:3.

Background

Trauma is a leading cause of death and disability. Each year, worldwide, an estimated 5.8 million people die as a result of trauma,[1] many after reaching hospital. Among trauma patients who survive to reach hospital, bleeding is a common cause of death, accounting for around 40% of in-hospital trauma deaths.[2]

The CRASH-2 trial was an international randomised controlled trial of the early administration of tranexamic acid (TXA) to bleeding trauma patients. The trial recruited 20,211 patients from 274 hospitals in 40 countries. The results show that TXA reduces mortality in trauma patients with or at risk of bleeding, with no apparent increase in side effects.[3] If given within three hours of injury, TXA reduces the risk of death due to bleeding by about a third.[4] TXA administration has been shown to be highly cost-effective in high, middle or low income countries.[5] On the basis of the results of the CRASH-2 trial, TXA has been included on the WHO Essential Medicines List.[6]

Since publication of the trial results, TXA has been included into trauma care guidelines in many high income countries. In March 2010, the British Army incorporated TXA into combat care treatment protocols[7] and in July 2011 the UK NHS ambulance service agreed that TXA would be given to all adults and teenagers who suffer major injury in the UK. In 2011, the US Army reviewed the evidence from the CRASH-2 trial and included TXA into its trauma treatment protocols. However, bearing in mind that 90% of trauma deaths are in low and middle income countries,[8] the potential of TXA to reduce premature mortality is likely to be much greater in these settings. An estimation of the number of deaths that could be averted through the use of TXA for in traumatic haemorrhage would allow better targeting of dissemination and implementation activities. In this study we used data from the CRASH-2 trial, WHO mortality database and a systematic review of the recent literature, to estimate the potential number of deaths that could be averted through the early administration of TXA to bleeding trauma patients.

Methods

Estimation of effect of TXA on death due to bleeding by geographical region

We used individual patient data from the CRASH-2 trial to assess the extent to which the effect of TXA on death due to bleeding varied according to geographical region. Hospitals participating in the CRASH-2 trial were grouped into four geographical regions: (1) Africa, (2) Asia, (3) Europe, Australia, North America, and (4) Central & South America. Heterogeneity in treatment effect by geographical region was assessed by a χ^2 test. We pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$), the overall risk ratio (RR) would be considered to be the most reliable guide to the approximate RRs in all regions.

Estimation of number of in-hospital trauma deaths due to bleeding per year

The number of in-hospital trauma deaths that are due to bleeding and thus potentially avoidable through the early administration of TXA was estimated in three steps. First, we obtained estimates of the number of trauma deaths (N) by country. Second, we estimated the proportion of trauma deaths that occur in hospital (P). Third, we estimated the proportion of in-hospital trauma deaths that were due to bleeding (B). The number of in-hospital trauma deaths due to bleeding per year (HBD) was then estimated according to the following equation:

$$HBD = N \times P \times B$$

Since the proportion of deaths due to bleeding (B) may vary according to type of injury (i.e. blunt or penetrating)[9], we obtained data on the proportion of blunt trauma deaths (PB) that was due to bleeding (BDB) and the proportion of penetrating trauma deaths (PP) that was due to bleeding (PDB). These estimates were combined to derive the overall proportion (B) using the equation:

$$B = (PB \times BDB) + (PP \times PDB)$$

The number of premature deaths potentially averted by TXA was then estimated by applying the relative risk reduction from the CRASH-2 trial to the number of in-hospital deaths due to bleeding as follows:

$$\text{Premature deaths averted} = HBD \times (1 - RR)$$

Data sources

Data from the WHO, the CRASH-2 trial and a systematic review of literature published since 2004 were used to parameterise the equations. The number of trauma deaths for each country, were obtained from the WHO for the year 2008, the most recent year for which data were available. Blunt trauma deaths were estimated by adding the number of deaths from road traffic crashes, falls and other unintentional injuries. Penetrating trauma deaths were estimated by adding the number of deaths from violence and war. Deaths from drowning, poisoning, self-inflicted injuries or burns were not included as these injuries are not usually associated with life-threatening

bleeding. Estimates of the proportion of trauma deaths that are in-hospital and the proportion caused by bleeding were based on data from the CRASH-2 trial and from studies identified through a systematic review.

S*ystematic review methods*

We searched for studies containing original data describing the epidemiology of trauma deaths. We searched MEDLINE, EMBASE and Cab Abstracts on 2 March 2011 using a combination of subject headings and key words based on the following terms; injuries, trauma, mortality, death, fatality, burden, epidemiology. We searched the internet and checked the reference lists of eligible articles. The searches were not restricted by language or publication status. To improve the applicability of the extracted data to the current patterns in trauma death epidemiology, we limited our search to studies published since 2004.

Record screening, full text review and data extraction were performed independently by two authors (KK and JK), with any disagreements resolved through discussion. Data were extracted on study design, setting, sample size, the proportions of deaths occurring in hospital and due to bleeding, using a pre-designed form. Studies that did not provide data on any of the parameters of interest were excluded.

To obtain a summary estimate for each parameter, the study proportions were transformed according to the Freeman Tukey variant of the arcsine square root transformed proportions to correct for over-dispersion.[10] Pooled proportions were calculated as the back-transformation of the weighted mean of the transformed proportions using the random effects model.[11]

Data analysis

For each country, the number of in-hospital trauma deaths due to bleeding was calculated by applying the corresponding estimated proportions to the mortality data, as described above. For the primary analysis, the relative risk reduction from the CRASH-2 trial was applied to estimate the number of premature deaths that could be averted (1) if all patients received TXA within one hour of injury, and (2) if all patients received TXA within three hours of injury. The numbers of deaths averted in each country were combined to give an overall global estimate. To identify the countries with the greatest potential for benefit from TXA, countries were ranked in order of the estimated number of premature deaths averted.

To investigate the impact on the results of uncertainty in the parameter estimates used in the modelling, a number of sensitivity analyses were conducted. First, the analysis was repeated using the lower and upper bounds of the 95% confidence intervals for the parameter estimates to explore the effect of parameter uncertainty. Second, we repeated the analysis using the relative risk estimate for all-cause mortality rather than death due to bleeding. This analysis was

conducted to take account of the possibility that some patients who do not die from bleeding because of TXA administration would nevertheless die of other causes such multi-organ failure or brain injury. Third, we repeated the analyses using the relative risk estimate for all-cause mortality with TXA when given at any time within eight hours of injury. Although, previously published subgroup analyses show that early treatment is more effective it is possible that treatment within three hours is not possible in some settings.

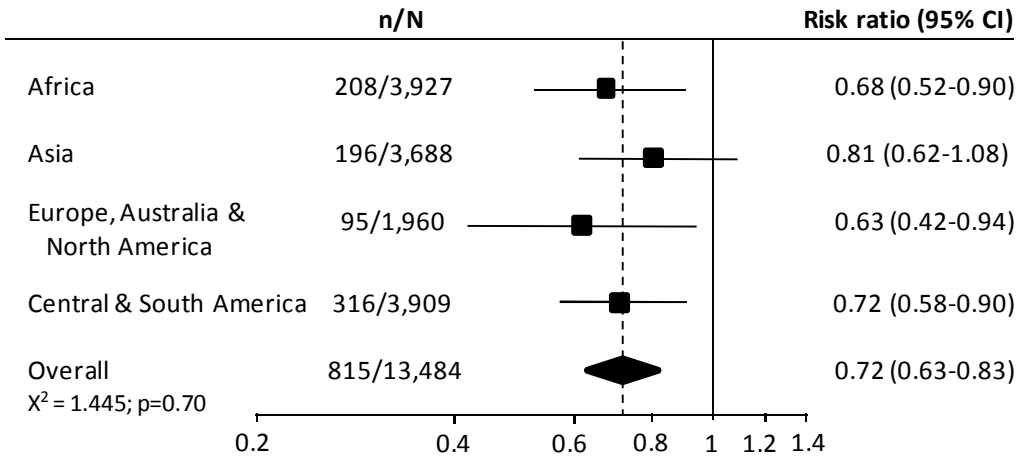
For each estimate, to reflect statistical uncertainty around the relative risks of TXA, an uncertainty range was estimated by calculating the numbers of deaths averted based on the 95% confidence intervals for the relative risks. The analyses were conducted using Microsoft Excel and STATA 11[12] software.

Results

Estimation of the effect of TXA on death due to bleeding by geographical region

Figure 3.5 shows the effect of TXA given within three hours of injury on death due to bleeding by geographical region.

Figure 3.5 Risk ratio (95% CI) for death due to bleeding with TXA given within three hours of injury, overall and by geographical region.

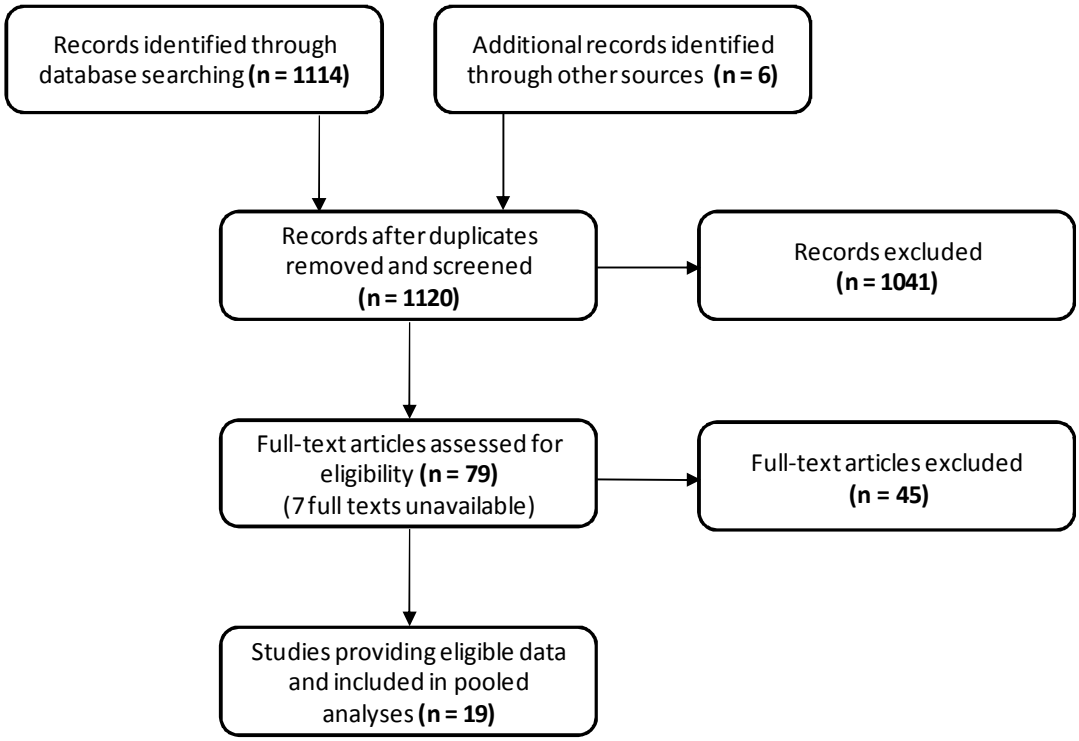


There was no evidence for heterogeneity in the effect of TXA by region (χ^2=1.445; p=0.70). The overall RRs for the effect of TXA on death due to bleeding when given within one hour (RR=0.68; 95% CI 0.57 to 0.82) and within three hours (RR=0.72; 95% CI 0.63 to 0.83) of injury were therefore taken as the most reliable guide as to the approximate RRs in all regions, and were used to estimate the number of deaths that could be averted with TXA.

Estimation of the annual number of in-hospital trauma deaths due to bleeding

We identified 18 studies, described in 17 reports,[13-29] which presented data on the parameters of interest and were included in the systematic review. Studies were conducted in 13 countries; USA, Canada, UK, Australia, Brazil, Denmark, Norway, Mozambique, South Africa, Italy, France, Spain and India. In addition, we obtained data collected as part of the CRASH-2 trial, which recruited patients from hospitals in 40 countries throughout the world. The study selection process is summarised in Figure 3.6. Data extracted from the studies are summarised in Appendix AA.

Figure 3.6 Flow diagram of the study selection process for systematic review

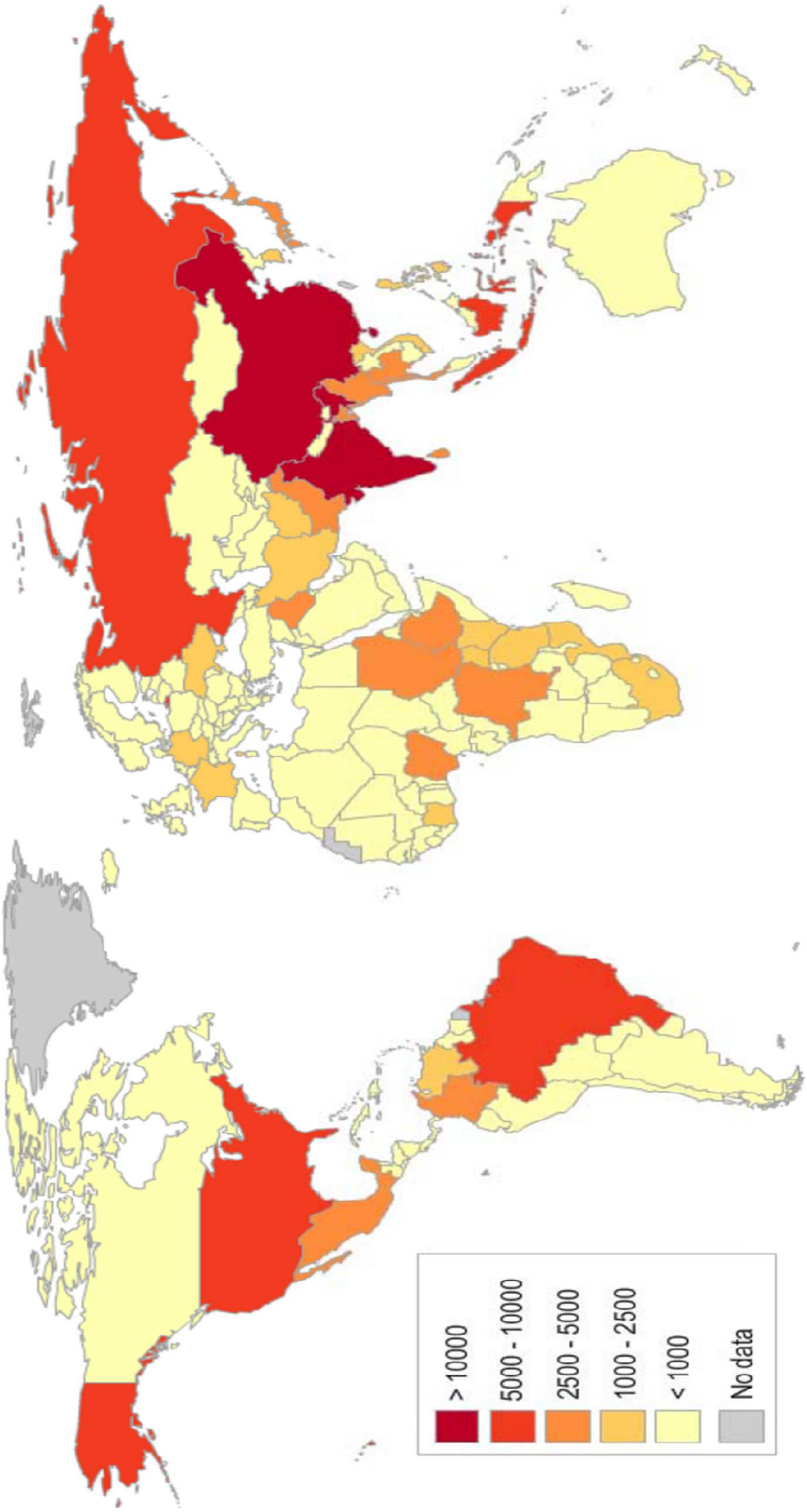


Fourteen studies[14-16, 18, 20-28] involving 24,831 trauma deaths provided data on the proportion of deaths occurring in-hospital; the pooled proportion was 44% (95% CI 33 to 56%). Five studies[3, 13, 17, 19, 29] involving 9684 deaths presented data on the proportion of blunt trauma deaths due to haemorrhage; the pooled proportion was 18% (95% CI 13 to 23%). Four studies[3, 13, 17, 29] involving 2256 deaths presented data on the proportion of penetrating trauma deaths due to haemorrhage; the pooled proportion was 55% (95% CI 49 to 62%).

After applying these parameter estimates to the WHO data, we estimate that worldwide every year approximately 400,000 trauma patients die in-hospital from bleeding. If all of these patients receive TXA within one hour of injury the about 128,000 (uncertainty range [UR] ≈ 72,000 to 172,000) deaths could be averted. If all of these patients receive TXA within three hours of injury about 112,000 (UR ≈ 68,000 to 148,000) deaths could be averted. The global distribution of

number of premature deaths averted by TXA when administered within three hours of injury is shown in Figure 3.7.

Figure 3.7 Global distribution of number of deaths averted with TXA administration within three hours of injury



Results for the countries where more than 1000 deaths could be averted are shown in Table 3.2.

Table 3.2 Estimated number of premature trauma deaths averted by TXA per year

	In-hospital trauma deaths from bleeding	Deaths averted TXA≤1 hour	Deaths averted TXA≤3 hours
Worldwide	400,467	128,149	112,131
Countries with >1000 deaths averted			
India	58,801	18,816	16,464
China	54,241	17,357	15,187
Brazil	19,187	6,140	5,372
Russian Federation	16,731	5,354	4,685
Myanmar	13,193	4,222	3,694
Iraq	12,786	4,091	3,580
USA	12,489	3,996	3,497
Indonesia	11,033	3,531	3,089
DR Congo	9,373	2,999	2,624
Sri Lanka	8,979	2,873	2,514
Pakistan	8,770	2,806	2,456
Ethiopia	8,768	2,806	2,455
Nigeria	8,258	2,643	2,312
Colombia	7,348	2,352	2,058
Sudan	7,292	2,334	2,042
Bangladesh	7,210	2,307	2,019
Mexico	7,059	2,259	1,976
Philippines	6,119	1,958	1,713
Thailand	5,572	1,783	1,560
Afghanistan	4,774	1,528	1,337
Uganda	4,620	1,478	1,294
South Africa	4,245	1,359	1,189
Venezuela	4,172	1,335	1,168
Kenya	4,029	1,289	1,128
Tanzania	3,969	1,270	1,111
Iran	3,921	1,255	1,098

The largest numbers of deaths from haemorrhage and consequently the largest numbers of deaths averted are in Asia. The largest numbers of premature deaths averted are in India (*TXA≤1 hr* ≈ 19,000; *TXA≤3 hrs* ≈ 16,500) and China (*TXA≤1 hr* ≈ 17,000; *TXA≤3 hrs* ≈ 15,000). When ranked by the number of premature deaths potentially averted, nine of the top ten countries are low or middle income, the exception being the USA where approximately 4,000 and 3,500 deaths would be averted by TXA given within one hour and three hours of injury, respectively.

Sensitivity analyses

When the analyses were repeated using the values of the lower and upper 95% CIs of the pooled parameter estimates, the global number of deaths averted ranged from approximately 76,000 to 198,000 if TXA is given within one hour of injury and from 67,000 to 173,000 if given with three hours of injury. When the analysis was carried out using the relative risk estimate for all-cause mortality if TXA is given within one hour (RR=0.87; 0.78 to 0.97) and within three hours

(RR=0.87; 0.80 to 0.94) of injury, the number of premature deaths averted was 52,000 (TXA≤1 hr ≈ 12,000 to 88,000; TXA≤3 hrs ≈ 24,000 to 80,000). When the analysis was repeated using relative risk estimate for death due to bleeding when TXA is given at any time within eight hours of injury (RR=0.85; 0.76 to 0.96), the number of premature deaths averted was 60,000 (UR ≈ 16,000 to 96,000). Finally, using the relative risk estimate for all-cause mortality when TXA is given within eight hours of injury (RR=0.91; 0.85 to 0.97), an estimated 36,000 (UR ≈ 12,000 to 60,000) premature deaths could be averted.

Discussion

Based on WHO mortality data and a systematic review of the literature we estimate that there are about 400,000 in-hospital deaths from bleeding each year worldwide. If all hospitalised bleeding trauma patients could be treated with TXA within an hour of injury then up to 128,000 of these premature deaths could be averted. If they could be treated within three hours of injury then up to 112,000 premature deaths could averted. Although there is considerable uncertainty in the estimates even the most conservative suggest that tens of thousands of deaths could be averted every year.

We found no compelling evidence that the effect of TXA on death due to bleeding varies by geographical region. Our conclusion is based on a statistical test of interaction which is considered to be the most appropriate way to evaluate subgroup effects.[30] As recommended by methodologists, we pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$), that the overall risk ratio (RR) would be considered to be the most reliable guide to the approximate RRs in all regions. We found no statistical basis to reject the null hypothesis.

The data sources used to parameterise the model are subject to a number of limitations which may have affected our results. First, although the WHO database provides the best available country-level mortality data, poor coverage and coding of mortality registration systems may affect the accuracy of the number of trauma deaths for some countries. Second, our classification of trauma deaths into blunt or penetrating trauma based on the cause of death categories in the WHO data was somewhat arbitrary and would have resulted in some misclassification. However, in the absence of accurate country-specific data, we judged that this approach would provide the most reliable estimates. Third, due to the absence of country-specific data for the proportions of deaths occurring in hospital and the proportion of deaths caused by haemorrhage, we chose to apply average global estimates. We were therefore unable to incorporate between-country variations in these parameter estimates into our analysis. Nevertheless, our estimates were derived from a systematic review of the recent literature and data from the CRASH-2 trial, and thus represent the most accurate estimates available. We also

performed sensitivity analyses to assess the impact of uncertainty around the parameter estimates.

Since many deaths from self-inflicted injuries are not usually associated with life-threatening haemorrhage (e.g. self-poisoning, hanging) we excluded this category to avoid over-estimating the number of deaths due to bleeding. However, this is likely to have led to the exclusion of some self-inflicted deaths that were associated with haemorrhage, in which case we may have underestimated the potential of TXA administration.

Our analysis was based on a number of assumptions. We have assumed that there was no use of TXA as a treatment for traumatic bleeding prior to publication of the CRASH-2 trial results. It is possible that a small proportion of the trauma deaths in our sample did receive TXA prior to their death, which may over-estimate the number of deaths averted. However, given that any such prior use of TXA would have been minimal it is unlikely to have greatly affected our overall estimates.

The objective of our analysis was to estimate the potential number of deaths that could be averted assuming TXA use under optimal conditions, that is, when administered appropriately and within three hours of injury, to all eligible bleeding trauma patients. It is unrealistic that such conditions are consistently and fully achieved in clinical practice. For example, the opportunity to treat some eligible patients will be missed and errors in the dose used or its administration may reduce the beneficial effect of TXA.

We assumed that the results of the CRASH-2 trial could be extrapolated to all hospitalised bleeding trauma patients. The CRASH-2 trial used clinical criteria to recruit a large number of patients from 274 hospitals in 40 countries, which helps the results to be generalised widely. Whilst we acknowledge that the underlying risk of death will vary in different settings, this does not necessarily imply that that the relative effect will vary. Indeed, relative effects are often remarkably homogeneous despite differences in underlying risk. This is supported by empirical evidence from a range of trials in which the relative effects are constant across variations in baseline risk.[31] Furthermore, there is no reason to suppose that the mechanism of action of TXA would vary in different populations. However, we acknowledge that the appropriateness of such extrapolation is a matter of judgement.

A further assumption is that all trauma patients reached hospital in time to receive early treatment with TXA; that is either within one hour or within three hours of injury. Such a time frame is unlikely to be realistic in many settings where long distances and other logistical difficulties may delay arrival at hospital. For this reason we performed sensitivity analyses based on the relative effect of TXA from a more conservative estimate of time-to-treatment of within

eight hours of injury, the results of which still suggest that up to 60,000 deaths could be averted. Besides, there is reason to predict that time between injury and treatment would be shorter in clinical practice than in the CRASH-2 trial as delays caused by consent procedures would be avoided.[32]

In applying the RR of death due to bleeding in our primary analysis we assumed that all deaths in this group would be avoided. However, it is possible that whilst TXA may prevent death due to bleeding, some patients would die from other causes instead. If this is the case, then our primary analysis would over-estimate the number of death averted. To address this we performed a sensitivity analysis in which the effect of TXA on all-cause mortality was used. Even using this smaller relative reduction, up to 50,000 deaths could be averted.

We restricted our analysis to the potential benefit of in-hospital use of TXA. However, our parameter estimate of the proportion of in-hospital trauma deaths indicates that most trauma deaths occur before arrival at hospital. TXA is a practicable treatment suitable for use in a range of health-care settings, including pre-hospital. If TXA was used in the pre-hospital setting then many more premature deaths might be averted.

Conclusions

Our analysis shows the potential of TXA to reduce trauma deaths worldwide. Realisation of this potential is likely to require further efforts in dissemination and implementation, particularly in low and middle income settings.

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4.0 WHAT ARE THE EFFECTS OF TRANEXAMIC ACID FOR PREVENTING POSTPARTUM HAEMORRHAGE?

4.1 INTRODUCTION TO RESEARCH PAPER 6

This Chapter includes Research Papers 6[viii] and 7, which address Aim 3 of my thesis - the effects of TXA for preventing postpartum haemorrhage. Despite one of discoverers earmarking TXA as a potential intervention for PPH back in the 1960s, she was unable at the time to persuade obstetricians to initiate trials[1] and it is only more recently that its effects for this indication have been explored.

Despite reassuring evidence from trials in surgery and trauma, differences in the coagulation profile observed in women immediately before, during, and after childbirth,[2] raises questions concerning the effectiveness and safety in this patient group.

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[viii] Copy of the PDF version of the published manuscript is included in Appendix CC

RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?	**British Journal of Obstetrics & Gynaecology**		
When was the work published?	**2016**		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	**n/a**		
Have you retained the copyright for the work?*	**No (see Appendix BB)**	Was the work subject to academic peer review?	**Yes**

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	
Please list the paper's authors in the intended authorship order:	
Stage of publication	

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I designed the study with input from Ian Roberts (IR) and Haleema Shakur (HS). I screened the search output and extracted data with assistance from Haleema Shakur. I carried out the analyses. I wrote the manuscript with contributions from both co-authors.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature Date: 06/08/2018

4.2 DOES TRANEXAMIC ACID PREVENT POSTPARTUM HAEMORRHAGE? A SYSTEMATIC REVIEW OF RANDOMISED CONTROLLED TRIALS

Katharine Ker, Haleema Shakur, Ian Roberts

British Journal of Obstetrics & Gynaecology. 2016 Oct;123(11):1745-52.

Introduction

Postpartum haemorrhage (PPH), one of the most common obstetric emergencies, occurs in about 10% of deliveries.[1] It is the leading cause of maternal mortality worldwide, responsible for about 50,000 deaths each year.[2] Because hysterectomy is sometimes carried out to control the bleeding, PPH deprives thousands of women of their ability to bear children. Anaemia is another important consequence that limits a mother's wellbeing and her ability to work and care for children.[3]

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin blood clots. The WOMAN trial is currently evaluating the effect of TXA on death and hysterectomy in women with established PPH.[4] However, for many women, treatment of PPH is too late. Over one third of pregnant women in the world are anaemic and many are severely anaemic.[5] In these women, even moderate bleeding can be life threatening and by worsening their anaemia, can cause disabling fatigue that limits their ability to care for themselves and their baby.[6] TXA given at the time of delivery could prevent severe postpartum bleeding. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth.[7]

We conducted a systematic review of randomised controlled trials to assess the effects of TXA on the risk of postpartum haemorrhage and other clinically relevant outcomes.

Methods

We specified the methods in advanced and registered the review on PROSPERO (CRD42015020670).

Selection criteria and search strategy

We searched for randomised controlled trials comparing TXA with no TXA or a placebo in women delivering vaginally or by caesarean section. The primary outcome was the number of women with a clinical diagnosis of postpartum haemorrhage. Trials of TXA for the treatment of established postpartum haemorrhage were not eligible. Secondary outcomes were death, blood loss, blood transfusion, thromboembolic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), surgical intervention, maternal wellbeing and quality of life, and adverse events in baby.

Eligible trials were identified from a register of randomised controlled trials of antifibrinolytic drugs maintained by the London School of Hygiene & Medicine's Clinical Trials Unit (LSHTM CTU). The register contains records of trials identified through searches of MEDLINE, CENTRAL, EMBASE, PubMed, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Each database was searched using a combination of subject headings and keywords (Appendix DD). In addition, we checked reference lists of relevant articles and searched the internet using the Google search engine for further potentially eligible trials. The searches were run to 13th May 2015 and were not restricted by date, language or publication status.

Procedures

One author screened the titles and abstracts of the search output to identify potentially eligible trials. The full texts of these reports were then retrieved and assessed for eligibility. Data on the number of participants, type of delivery, dose and timing of TXA, type of comparator and outcome data were extracted by two authors using a form developed specifically for the review. We used the Cochrane Collaboration's tool for assessing the risk of bias. The risk of bias assessments were based on the information presented in the trial report.[8] We assessed the sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting as being at low, high, or unclear risk of bias for each trial.

Statistical analysis

For dichotomous outcomes, we calculated risk ratios and 95% confidence intervals. For continuous outcomes, we calculated the mean difference and 95% confidence interval. However, for blood loss, we estimated the proportional change in blood loss with TXA. Full details of the method used are described elsewhere.[9] In brief, we expressed the change in blood loss with TXA as a proportion of the blood loss in the control group. As estimates of average blood loss are not normally distributed, we transformed blood loss data into a logarithmic scale and conducted the analysis using the transformed values. A meta-analysis of the differences in means using the transformed data on blood loss corresponds to a meta-analysis of the ratio of the geometric means on the original scale. The estimates were back-transformed to give the blood loss ratios and 95% confidence intervals on the original scale. If sufficiently homogeneous in terms of patients, intervention and outcome measurement, we planned to pool the trial data using the fixed effect model.

We planned to conduct subgroup analyses to examine whether the effect of TXA on the risk of PPH varied according to whether or not the women were anaemic at baseline (anaemic Hb<11g/dL, vs non-anaemic Hb≥11g/dL). We also planned a sensitivity analysis restricted to trials at low risk of bias for allocation concealment. Analyses were carried out using Stata

version 13 and RevMan version 5.3.5. We reported the review in accordance with the PRISMA Statement (Appendix EE).

Results

Trial characteristics

We identified 31 reports[10-40] describing 26 trials involving a total of 4,191 women (Appendix FF). The trial reports were published between 2001 and 2015. Five trials were Master's degree projects that were later published in medical journals. Two trials were reported as conference abstracts only.

The characteristics of the included trials are shown in Appendix GG. The median sample size was 120 (min-max=74-740). They were conducted in China (n=3), Egypt (n=2), India (n=9), Iran (n=5), Malaysia (n=1), Pakistan (n=2), Turkey (n=3) and the Ukraine (n=1). All but one were single-centre trials. Twenty-two trials assessed the effect of TXA in women giving birth by caesarean section and four in women giving birth vaginally. One trial was restricted to anaemic women (Hb 7-10g/dL).

TXA was given within 30 minutes prior to incision in all of the caesarean delivery trials except for one in which TXA was administered at delivery of anterior shoulder. Of the four trials involving vaginal delivery, TXA was given at delivery of anterior shoulder in three and at delivery of the placenta in one. The TXA dose ranged from 0.5g to 1g. TXA was compared to placebo in 13 trials and to a no-TXA group in 13 trials.

The number of patients allocated to each group was not reported in one trial and so the data could not be used. The frequency of PPH was reported in 13 (50%) trials, blood loss in 24 (92%), thromboembolic events in 16 (62%), death in six (23%), surgical intervention in five (19%), and blood transfusion in 10 (38%). None of the trials collected data on maternal wellbeing or quality of life.

Risk of bias

A summary of the risk of judgements is shown in Appendix HH. The method used to generate the allocation sequence was adequate in eight trials and inadequate in four. The remaining 14 trials did not describe the method used and so the risk was unclear. Allocation concealment was adequate in four, inadequate in seven, and unclear in 15 trials. Blinding was adequate in eleven trials, inadequate in 13 and unclear in two trials. There were no missing outcome data in four trials (low risk of bias). However, there were post-randomisation exclusions in three trials (high risk of bias). For the remaining 19 trials insufficient information was reported to judge the risk of bias from missing outcome data. In the one trial that was prospectively

registered, comparison of pre-specified and reported outcomes suggested selective outcome reporting. We could not determine the risk of bias for the remaining trials which were either retrospectively registered (n=5) or not registered (n=20).

Data reliability

Several reports raised concerns about the data and prompted further investigations. Eight reports contained sections of identical or very similar text despite purporting to be different trials (Appendix II), in addition, many of the results sections contained discrepancies and other errors. We therefore sought further information from the authors of all trial reports to reassure ourselves about the reliability of the data. We identified contact information for as many authors as possible. Each author was contacted and asked to provide the dates when the first and last patients were randomised; a copy of the ethics committee approval; and the anonymised individual patient data. Where possible we also contacted the ethics committee for confirmation of their approval.

We received responses for 13 (50%) trials (Appendix JJ). One author declined to provide the information requested. Authors of nine trials confirmed recruitment dates, one did not have a record of the dates and one did not include this information in the response. We received a copy of the ethics approval for 10 trials, one of which was granted after the start of recruitment. Two trials did not receive ethics approval. In one case, an author explained that the trial was undertaken for a student thesis and formal approval from the ethics committee was not required (this was confirmed in a separate response from the ethics committee). In the other, although the trial report stated that ethics approval had been obtained, the author stated this was not in fact the case. This was confirmed by the ethics committee who said that they had no record of the trial. No explanation was offered as to why approval was not obtained.

Seven of the 13 trials for which we received a response sent individual patient data. The authors of two trials did not respond to this part of our request and one author of two trials explained that he was unable to send us the data due to the theft of the laptop on which the data for both trials were stored.

We then explored the success of the randomisation process by conducting meta-analyses of selected baseline variables. As recommended by Clark *et al*,[41] we meta-analysed age as well as baseline haemoglobin (Hb) which we identified as another relevant prognostic covariate. The premise of this analysis is that if the trials are properly randomised, there will be no heterogeneity, i.e. I^2=0% and any difference in baseline variables will be minimal and the result of random error.[41] The results of the meta-analyses of age and baseline Hb are shown in

Appendix KK and Appendix LL. There was no heterogeneity (I^2=0%) observed for age. However, there was a statistically significant difference between groups suggesting that women allocated to the TXA group were younger than those in the control (p=0.01), although this difference was not observed when the analysis was restricted to adequately concealed trials (P=0.59). There was substantial heterogeneity between trials for baseline Hb (I^2=67%) and a statistically significant difference between groups indicating that women allocated to the TXA group had a lower Hb at baseline than those in the control (p=0.02). Substantial heterogeneity remained when the analysis was restricted to adequately concealed trials (I^2=62%), although the difference in Hb between groups was no longer statistically significant (p=0.79).

Data analysis

Although the patients, interventions and outcomes were sufficiently homogeneous to pool the data, because of our concerns about trial quality and data reliability we did not conduct a meta-analysis. However, effect estimates and 95% CIs were calculated and presented as Forest plots (Figure 4.1,Figure 4.2,Figure 4.3). We stratified the trials according to whether or not the final report contained similar text. Thirteen trials presented data on the number of women who developed postpartum haemorrhage (PPH). There was variation in the threshold used to diagnose PPH. Four trials applied the usual definition of blood loss ≥1000 ml after caesarean delivery or ≥500 ml after vaginal delivery. The remaining trials used other, lower thresholds including ≥500 ml after caesarean delivery or ≥400 ml after vaginal delivery. Because none of the trials were prospectively registered, we cannot discount the possibility that the selection of these thresholds was *post hoc* and data driven. In all trials fewer women in the TXA group developed PPH than in the control group.

Figure 4.1 Results of trial assessing the effect of TXA on postpartum haemorrhage

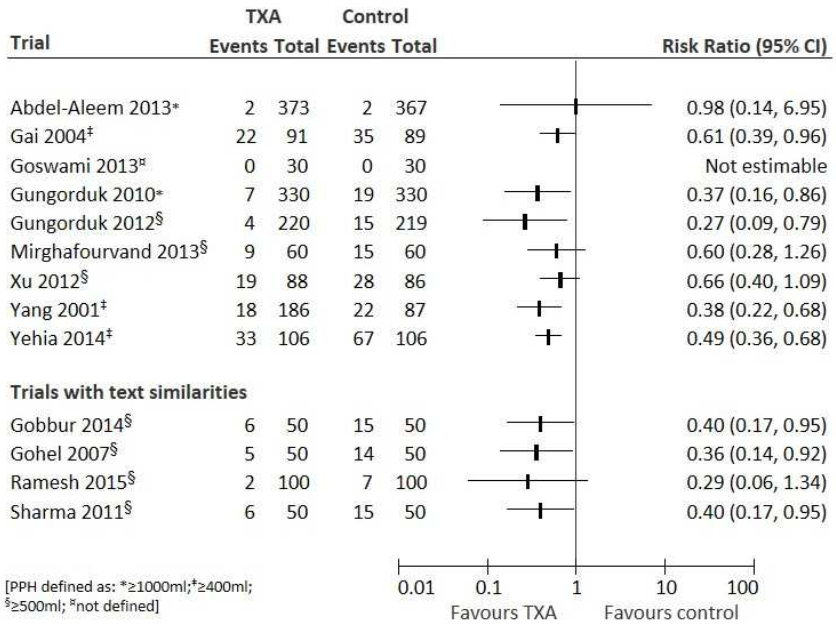


Figure 4.2 Results of trials assessing the effect of TXA on blood loss

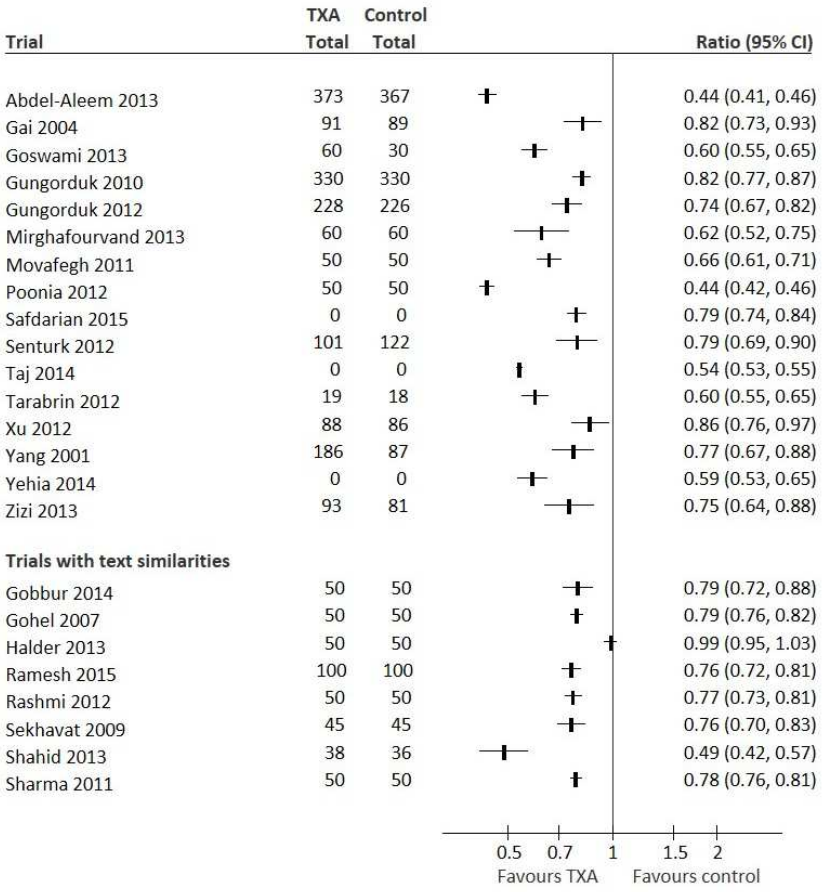
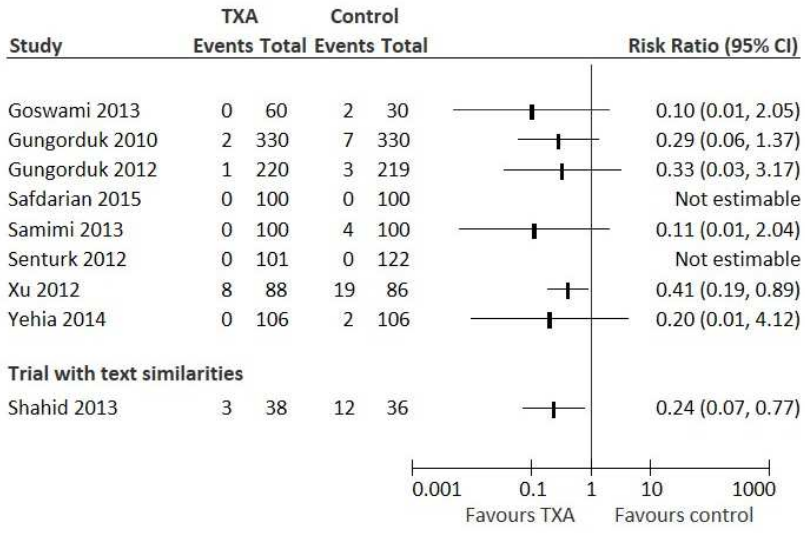


Figure 4.3 Results of trials assessing the effect of TXA on blood transfusion



Twenty-four trials presented data on average blood loss in both groups. All of the effect estimates are consistent with less blood loss in the TXA group; the difference is statistically

significant in all but one trial. There is notable variation in the magnitude of the effect estimates.

Nine trials reported blood transfusion data. There were no events in two trials. In all of the remaining seven trials, fewer women in the TXA group received a blood transfusion than those in the control group. There were no deaths, surgical interventions, or cases of myocardial infarction, stroke or pulmonary embolism in any of the trials reporting these outcomes. In one trial, four women suffered a deep vein thrombosis, there was no difference in risk between the groups (TXA 2/88 vs control 2/86; RR=0.98, 95% CI 0.14 to 6.78).

Discussion

Main findings

Worldwide, over 10 million women experience a postpartum haemorrhage each year. About 50,000 women die, many more lose their ability to bear children and hundreds of thousands suffer debilitating fatigue from anaemia. TXA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients.[42, 43] It is therefore unsurprising that there is interest in its role in the prevention of postpartum haemorrhage. However, our review shows that most trials of TXA are small, low quality, single-centre studies. We found that many trial reports shared similar or identical text, and contained important errors or inconsistencies. Two trials were conducted without ethics committee approval and only one was prospectively registered.

Strengths and limitations

Due to concerns about data quality and reliability we did not conduct a meta-analysis. When examined separately, the results of the individual trials were largely consistent with evidence from surgical bleeding, with most reporting less bleeding with TXA. However, the criteria used to diagnose PPH varied between trials and the absence of blinded outcome assessment in many trials may have introduced bias. Also, because the trials are too small to assess the effect of TXA on maternal health outcomes and none measured maternal wellbeing, the clinical importance of any reduction in bleeding is uncertain.

Most systematic reviews assume that trial reports provide an accurate description of the methods and results. However, after finding that eight trials contained identical text and that some of the trial results were also similar, we were obliged to question this assumption. We therefore asked the authors of all trials to provide dates of recruitment, a copy of the ethics committee approval and the anonymised individual patient data in an attempt to assess their reliability. We received a response for only half of the included trials and less than half of these provided all the information requested. Moreover, the meta-analysis of baseline variables

suggests that the randomisation process was inadequate in many trials. Although our review aimed to include only randomised controlled trials, many of the included trials were not properly randomised and were imbalanced for key prognostic variables.

Interpretation (in the light of other evidence)

Other systematic reviews have assessed the effect of TXA on obstetric bleeding.[44-46] However, ours is the first to describe the scale and nature of deficiencies in the evidence that go beyond the standard risk of bias assessment. Unless these deficiencies are brought to the attention of the maternal health community, treatment decisions could be based on unsound evidence, putting women at risk. Indeed, some of the trials have already informed the WHO's recommendations on the use of TXA for the treatment of postpartum haemorrhage.

As well as highlighting the poor quality of trial research in this area, the process of conducting this review has brought to our attention the lack of guidance on how systematic reviewers should deal with trial quality concerns that go beyond those assessed by the standard risk of bias approach.

Furthermore, because we were unwilling to ignore these concerns, we devised our own approach to investigating them. We do not claim that our approach is the best and welcome ideas on more effective ways to deal with similar situations in the future.

Conclusions

Although reducing maternal mortality has been a development goal for 15 years, this review suggests that in some areas the quantity and quality of the research needed to support this humanitarian aspiration is inadequate and is not commensurate with the level of political ambition. We do not doubt that most of the included trials were conducted in good faith with the patients' interests in mind. However, a problem of such global health importance requires a strategic response from professional research teams rather than the efforts of concerned clinicians at a single hospital. Large, high quality, multi-centre trials with end points that matter to women are urgently needed.

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4.3 INTRODUCTION TO RESEARCH PAPER 7

The results of the systematic review presented in Research Paper 6 show that the existing trial evidence for the effects of TXA for preventing PPH is inadequate.

Since I completed the review, two important randomised placebo-controlled trials have been completed - the TRAAP trial and the WOMAN trial. The TRAAP trial assessed the effect of TXA for preventing postpartum bleeding in 4079 women giving birth vaginally in hospitals in France. At the time of writing this thesis, the TRAAP trial results have not been published in full, although selected results were presented at the Society for Maternal-Fetal Medicine 38th Annual Meeting in February 2018.[1] These show that fewer women in the TXA group experienced postpartum blood loss of ≥500 mL compared to those in the placebo group, although the difference was not statistically significant (RR=0.83, 95% CI 0.68 to 1.01; p=0.07). The WOMAN trial assessed the effects of TXA in 20,060 women with PPH in 193 hospitals in 21 countries.[2] The results showed that TXA reduces the risk of bleeding to death after PPH (RR=0.81, 95% CI 0.65 to 1.00; p=0.045). However, data from the WOMAN trial also suggests that for many women treatment of PPH is too late. Most women who bled to death from PPH, did so very quickly, many within the first two hours after giving birth. A way of preventing excessive bleeding from occurring in the first place would therefore appear to be crucial in the effort to reduce mortality and morbidity from PPH.

Although the results of my systematic review (Research Paper 6) was that there is no reliable evidence for the effects of TXA for preventing PPH, the subsequently published evidence from the TRAAP and WOMAN trials, provide reason to hope that TXA may be effective, especially in women at high risk of PPH.

In response to this, the LSHTM CTU is embarking the WOMAN-2 trial, a randomised, placebo-controlled trial to assess the effects of TXA for preventing postpartum bleeding in 10,000 women with anaemia. I am a member of the Protocol Committee, a multidisciplinary team that has designed the WOMAN-2 trial building on the experience of CRASH-2 and WOMAN trials, which were also co-ordinated by the LSHTM CTU. I have taken a lead in the drafting of the protocol and am first author of the version submitted for publication in *Trials*. I am also a named co-applicant on the funding applications.

The trial is funded by Wellcome and the Bill & Melinda Gates Foundation and is due to randomise the first women by January 2019. Research Paper 7 is an abridged version of the trial protocol, which I have submitted for publication in *Trials*.

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RESEARCH PAPER COVER SHEET

PLEASE NOTE THAT A COVER SHEET MUST BE COMPLETED FOR EACH RESEARCH PAPER INCLUDED IN A THESIS.

SECTION A – Student Details

Student	**Katharine Ker**
Principal Supervisor	**Ian Roberts**
Thesis Title	**Effects of tranexamic acid on surgical, traumatic and obstetric bleeding: a critical analysis of the evidence from randomised trials using systematic reviews and meta-analytic techniques**

If the Research Paper has previously been published please complete Section B, if not please move to Section C

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion			
Have you retained the copyright for the work?*		Was the work subject to academic peer review?	

**If yes, please attached evidence of retention. If no, or if the work is being included in its published format, please attached evidence of permission from the copyright holder (publisher or author) to include this work.*

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	**Trials**
Please list the paper's authors in the intended authorship order:	**Ker K, Roberts I, Chaudhri R, Fawole B, Beaumont D, Balogun E, Prowse D, Pepple T, Javaid K, Kayani A, Arulkumaran S, Bates I, Shakur-Still H, on behalf of the WOMAN-2 trial collaborators**
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attached a further sheet is necessary)
I helped to design the trial with the other members of the Protocol Committee. I led on the drafting of the trial protocol with responsibility for ensuring it complied with all sections of LSHTM standard operating procedures. Other members of the Protocol Committee provided comments on the protocol or edited the text as appropriate. I led on the preparation of the manuscript for submission to *Trials*.

Student Signature: [redacted] Date: 06/08/2018

Supervisor Signature: [redacted] Date: 06/08/2018

4.4 TRANEXAMIC ACID FOR THE PREVENTION OF POSTPARTUM BLEEDING IN WOMEN WITH ANAEMIA: AN INTERNATIONAL, RANDOMISED, DOUBLE-BLIND, PLACEBO CONTROLLED TRIAL

Ker K, Roberts I , Chaudhri R, Fawole B, Beaumont D, Balogun E, Prowse D, Pepple T, Javaid K, Kayani A, Arulkumaran S, Bates I, Shakur-Still H, on behalf of the WOMAN-2 trial collaborators

Trials (submitted)

Background

Postpartum haemorrhage (PPH) is a leading cause of maternal mortality and morbidity. PPH follows 6% to 10% of all births and accounts for around 100,000 maternal deaths every year.[1-3] Ninety-nine percent of deaths are in low and middle income countries (LMICs).[4] Many women who survive experience severe morbidity. Some women need surgery to control the bleeding (e.g. exploratory laparotomy, uterine artery ligation, brace sutures) and many require a hysterectomy, thus removing the possibility of having more children. Severe morbidity due to PPH interferes with breastfeeding and bonding.[5] PPH is a frightening experience and some women develop post-traumatic stress disorder.[6]

Many women with PPH are given a blood transfusion. However, blood is a scarce and costly resource in LMICs and access to safe blood is limited. The blood donation rate in Africa is 5 per 1000 population compared to 47 per 1000 population in the USA and it is estimated that 35 of the 40 sub-Saharan countries collect less than half of the donor blood required to meet their population needs.[7] Even when blood is available, because of problems with screening, recipients are at risk of blood borne infections and adverse transfusion reactions are common.

Anaemia is a cause and consequence of PPH. A cohort study in Assam, India found that women with moderate or severe anaemia had a greatly increased risk of PPH.[8] Women with moderate anaemia had a 50% increased risk of PPH, whereas those with severe anaemia had a ten-fold increased risk. The reason for the increased risk is unclear but some researchers think that anaemic women are more susceptible to uterine atony due to impaired oxygen transport to the uterus. Anaemic women experience worse outcomes after PPH. An international survey of 275,000 women found that severe maternal outcomes after PPH were nearly three times more common in anaemic than in non-anaemic women.[9] Even moderate bleeding can be life threatening in anaemic women. Excessive bleeding after childbirth worsens maternal anaemia, raising the possibility of a vicious circle of bleeding and adverse outcomes. Fatigue due to anaemia limits a mother's wellbeing and her ability to care for her children.[10] Despite efforts to prevent anaemia, many women labour with low haemoglobin levels. Worldwide, over one third of pregnant women are anaemic and many are severely anaemic.[11] The prevalence is highest in

countries in central and West Africa as well as in South Asia where about half of pregnant woman are anaemic and it poses a severe public health problem.[11, 12] There is an urgent need to find an effective way to reduce postpartum bleeding in anaemic women.

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine, which inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. TXA reduces surgical bleeding and death due to bleeding in trauma patients. The WOMAN trial assessed the effects of TXA in 20,060 women with PPH.[13] TXA significantly reduced death due to bleeding with no adverse effects. When given within three hours of birth, TXA reduced death due to bleeding by nearly one third (RR=0.69, 95% CI 0.52 to 0.91; p=0.008). However, for many women, treatment is too late to prevent death from PPH. Most PPH deaths occur in the first hours after giving birth and women with anaemia are at increased risk. Whilst there have been some trials of TXA for the prevention of PPH, most have serious flaws and very few collected data on maternal wellbeing. There is very little reliable evidence about the effectiveness and safety of TXA for preventing postpartum bleeding, especially in high risk anaemic women.

The WOMAN-2 trial will determine the effects of TXA in women with moderate or severe anaemia who give birth vaginally. For pregnant women, the WHO defines moderate anaemia as haemoglobin levels of 70-99 g/L and severe anaemia as haemoglobin levels lower than 70 g/L.[14] Women with anaemia are at increased risk of PPH and experience worse outcomes should PPH occur. By including women with moderate or severe anaemia, participating women have the potential to benefit from the trial treatment. Results from clinical trials of TXA in elective surgery show that TXA reduces blood loss by about one third irrespective of baseline blood loss.[15] In other words, TXA treatment seems to move the entire distribution of bleeding towards reduced blood loss. If this is also the case in postpartum anaemic women, then trial participants have the potential to benefit whether or not they experience PPH, since even moderate or mild blood loss can have adverse health consequences in anaemic women.

Around 10,000 women with moderate or severe anaemia giving birth in hospitals primarily in Africa and Asia will be randomly allocated to receive TXA or matching placebo after the umbilical cord is cut or clamped. Although there is no evidence of any adverse effects on the baby, by randomising women after cutting or clamping the umbilical cord, any risk associated with placental transfer of the trial treatment to the baby is removed. The umbilical cord will be cut or clamped in the usual way and the timing will not be affected by the trial. TXA passes into breast milk in very low concentrations and so an antifibrinolytic effect in the baby is highly unlikely.

The ability to form a blood clot depends on fibrinogen levels. In both trauma and PPH, a low serum fibrinogen is a strong predictor of life threatening bleeding. Fibrinogen declines rapidly

during bleeding due to its consumption in fibrin clot formation. However, fibrinolysis due to the activation of plasmin by tissue plasminogen activator worsens fibrinogen depletion by breaking down clots. Tissue plasminogen activator mediated fibrinogenolysis also depletes fibrinogen levels. Early TXA administration has the potential to prevent excessive blood loss by interrupting the vicious circle of fibrinolysis and fibrinogen depletion. Women with anaemia are at increased risk of bleeding soon after delivery. If they can be treated with TXA before their fibrinogen levels fall, severe postpartum bleeding and its consequences may be prevented.

Rationale for trial

For some women the treatment of PPH is too late to prevent death and severe morbidity. Despite efforts to increase the availability of antenatal care, many women are anaemic at the time of giving birth and blood for transfusion is often unavailable. There is an urgent need to reduce postpartum bleeding and its adverse impacts on mothers, especially in anaemic women in LMICs. Knowing that TXA reduces deaths due to bleeding after PPH provides reason to believe that it might also prevent PPH. However, the evidence to date is insufficient to support the prophylactic use of TXA in routine clinical practice. Most of the available trials of TXA for preventing PPH are small and unreliable, and few collect information on maternal health and wellbeing.[16, 17] One exception is the TRAAP trial[18] which enrolled 4079 women who were giving birth vaginally in French hospitals. Women were randomised to receive 1 g TXA or matching placebo within two minutes after delivery. Although women who received TXA were less likely to experience a blood loss of ≥500 mL (the primary end point) the difference was not statistically significant (RR=0.83, 95% CI 0.68 to 1.01; p=0.07). Fewer woman in the TXA group received additional uterotonics (RR=0.75, 95% 0.61 to 0.92; p=0.006) however, there were no statistically significant differences in transfusion, change in haemoglobin or surgical intervention. The WOMAN-2 trial will provide reliable evidence on the effects of TXA when used to prevent PPH in anaemic women in LMICs. Although there was no increase in thrombotic events with TXA in the WOMAN or TRAPP trials, the administration of TXA to all women who give birth vaginally may be inappropriate. There is an increased risk of venous thrombosis in the postpartum period[19] and maternal anaemia is an established risk factor.[20] Treating all mothers would involve treating all women when only a proportion would benefit. However, in anaemic women the benefits could outweigh any harms so that a trial is justified. Inclusion in the trial will be limited to women giving birth vaginally. For women who give birth by caesarean section, especially for placenta abnormalities, the interval between cord clamping and PPH onset is short, often a matter of minutes, so the potential of TXA to prevent coagulopathy and PPH is limited.

Safety of tranexamic acid

TXA is a widely used treatment with a good safety profile. Although on pathophysiological grounds we might expect an increased risk of thrombosis with antifibrinolytic drugs, randomised trials including over 50,000 participants show no increased risk. High doses of TXA (doses from 7.5 g up to 20 g) have been associated with seizures in cardiac surgery but there was no increase in seizures in the CRASH-2 or WOMAN trials, which used a 1-2 g dose. TXA passes into breast milk in very low concentrations, approximately one hundredth of the concentration in maternal blood. An antifibrinolytic effect in the breast-fed infant is highly unlikely at this low concentration.[21, 22] No adverse events in breastfed babies were found in the WOMAN trial. Because TXA will be given after cutting or clamping the umbilical cord, there will be no risk of placental transfer to the baby. Nevertheless, we will collect data on nausea, vomiting, diarrhoea, maternal thrombotic events, seizures and thromboembolic events in breastfed babies, in all participants as outcomes. These outcome events will not be reported using the adverse event reporting procedure.

Objective

To determine the effects of TXA on postpartum bleeding and other health outcomes in women with moderate or severe anaemia.

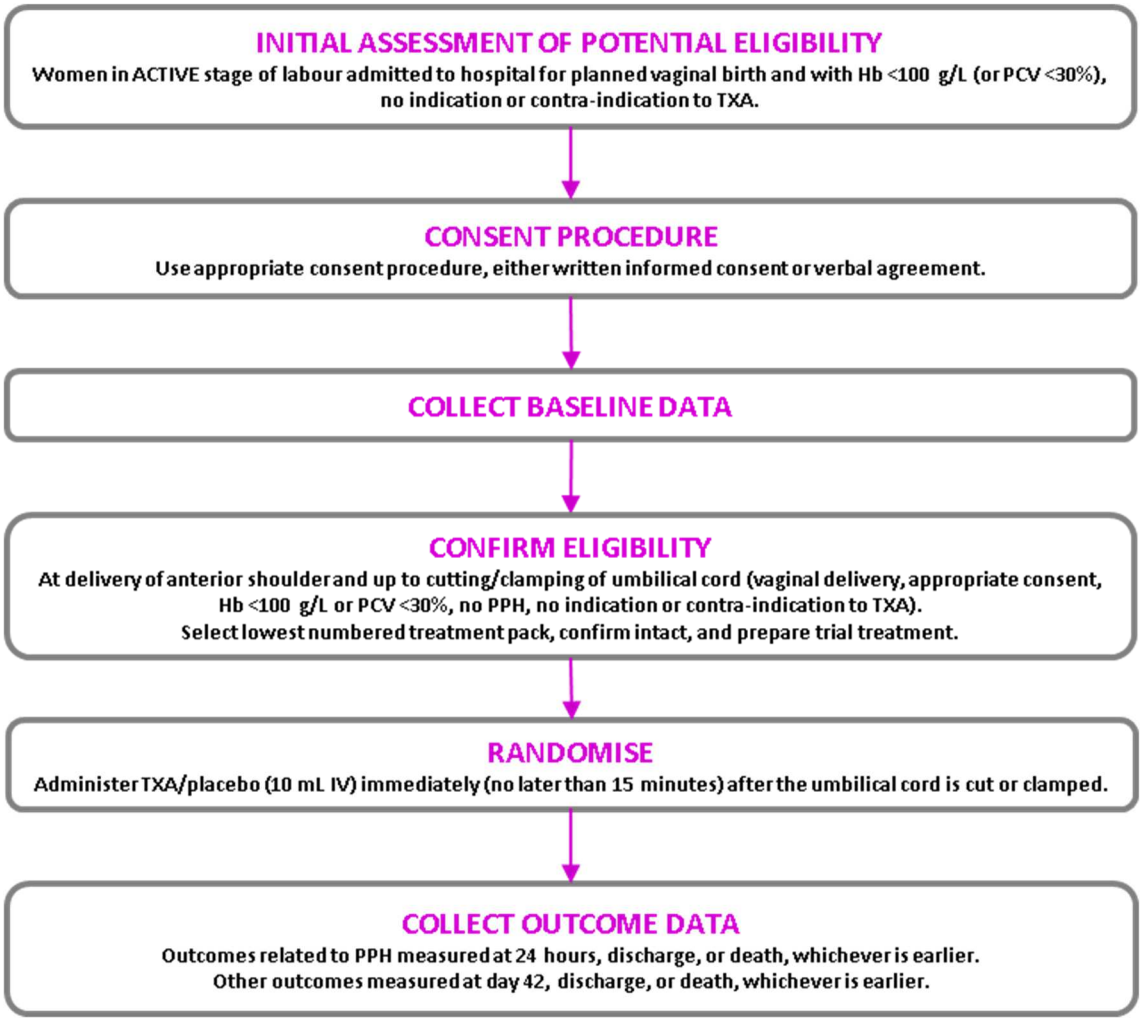
Methods/Design

This protocol has been prepared in accordance with the SPIRIT 2013 statement.[23]

Overview

The WOMAN-2 trial is a randomised, parallel group, double-blind, placebo controlled trial of the effects of TXA in women with moderate or severe anaemia who are giving birth vaginally. Ten thousand women with moderate or severe anaemia who are giving birth in hospitals will be randomised to receive 1 g of TXA or matching placebo (sodium chloride 0.9%) by intravenous injection immediately and no later than 15 minutes after the umbilical cord is cut or clamped (**Figure 4.4**).

Figure 4.4 Trial overview



Setting

Women from hospitals where anaemia in pregnancy is common, primarily Africa and Asia will be enrolled. All participating hospitals will have the facilities to provide comprehensive essential obstetric care as defined by the World Health Organization.

Number of participants needed

For the purpose of the sample size calculation, a baseline risk of PPH of 10% was assumed. A trial with 10,000 women would have over 90% power (two sided alpha=5%) to detect a clinically important 25% reduction from 10% to 7.5% in PPH. The sample size estimate is based on two key assumptions (1) the baseline event rate and (2) the size of the treatment effect. The primary endpoint is PPH. The prevalence of PPH is estimated at 6% world-wide but 10% in Africa and Asia. If the event rate is 10% then the trial has 99% power. However, if the event rates is lower, the study will have less power. For example if the 6% estimate applies, the trial would have just over 90% power. Planning for the possibility that the event rate may be lower than anticipated is a sensible precaution. It is also possible that the treatment effect is not as large as predicted.

Although a 25% reduction would be clinically important, a more modest reduction would also be worthwhile. The additional power also reduces the chance that a more modest treatment effect will be missed. Experience from the WOMAN trial shows that loss to follow-up will be minimal (less than 1%) and will not influence trial power. The LSHTM CTU has successfully recruited large sample sizes for previous international trials and is experienced at managing recruitment at sites to ensure that target recruitment is achieved. The main anticipated risk to recruitment to the WOMAN-2 trial is political instability in the participating countries. The main resource for mitigating this risk is the large international network of obstetric clinical trialists that was established during the WOMAN trial. If political instability prevents the recruitment of patients in any of the planned settings, recruitment in other sites will be initiated, thereby reducing the risk.

Identification of participating investigators and trial sites

Participating investigators and trial sites will be identified from the international network of obstetricians that was established during the WOMAN trial and includes hospitals where anaemia in pregnancy is common. Before the trial can start at any site, all relevant regulatory and ethics approvals must be in place and the site principal investigator must agree to conduct the trial according to the Protocol, Good Clinical Practice guidelines and all the relevant regulations. Names of participating sites will be listed on the trial website (http://woman2.lshtm.ac.uk/).

Eligibility of Participants

Inclusion criteria

Women with moderate or severe anaemia (haemoglobin level <100 g/L or packed cell volume <30%), who have given birth vaginally and for who the responsible clinician is substantially uncertain whether to use TXA.

Exclusion criteria

- Women who are not legally adult (<18 years) and permission not provided by a guardian.
- Women with a known allergy to TXA or its excipients.
- Women who develop PPH before umbilical cord is clamped/cut.

Screening and enrolment procedures

Routine clinical screening: Many pregnant women are likely to arrive to give birth at a participating hospital without antenatal care, or with low compliance with treatments for anaemia. It is important for her clinical care that her haemoglobin (Hb) or Packed Cell Volume (PCV) value is known before giving birth. If no test has been done on admission to give birth,

women planning to give birth vaginally will be offered a standard point of care haemoglobin assessment (HemaCue®) on arrival at hospital. Pregnant women will be informed about the purpose of the test before it is performed and they will have the right to accept or decline in line with any clinical care being offered. The test will be provided free of charge. Information on patients screened will be recorded on a Screening Log.

Women with a moderate or severe anaemia (haemoglobin level <100 g/L or PCV <30%) will be offered the opportunity to participate in the WOMAN-2 trial.

Baseline screening and eligibility confirmation: Following completion of the appropriate informed consent procedure, data on demographics, anthropometry, clinical signs, pregnancy and medical history, risk factors for postpartum haemorrhage, about the birth, about the baby/ies and baseline treatment plan for the anaemia, will be collected in the Case Report Form Booklet. Some data will be collected before a woman gives birth which will assess potential eligibility. Final eligibility will be confirmed at delivery of the baby's anterior shoulder up to when the cord is clamped or cut. This is because some women who plan to deliver vaginally and have provided consent may need a caesarean section or may develop PPH before the cord is cut or clamped which will make them ineligible for the trial.

Randomisation

An IT coding expert supported by a statistician who are not involved in the conduct of the trial will prepare the randomisation codes. They will give a copy to the Sponsor's representative, who is also not associated with the conduct of the trial, for manual back-up. The IT coding expert will also send the codes to the trial drug manufacturer so that treatment packs can be prepared in accordance with the randomisation list. Trial staff (coordinating centres and sites) and patients will not have access to the randomisation codes until final database lock or unless un-blinding of an individual patient is requested.

Women who are eligible for inclusion will be randomised to receive active (tranexamic acid) or placebo (sodium chloride 0.9%) by intravenous injection.

Once eligibility has been confirmed at delivery of the baby's anterior shoulder and up to when the cord is clamped/cut, the next lowest consecutively numbered pack will be taken from a box of 20 treatment packs. The participant is considered randomised to the trial once administration of the trial treatment has started. Each site will keep a log of women they randomise to the trial. Site investigators will need to explain any out-of-sequence use of the trial treatment.

Trial treatment

Name and description of investigational medicinal product

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that exerts an antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. TXA is sold under a variety of trade names for the treatment of bleeding due to general or local fibrinolysis in adults and children from one year of age.[24] TXA would be given in addition to all the usual interventions for preventing PPH thus WOMAN-2 will compare its effects with matching placebo (sodium chloride 0.9%) to ensure blinding.

Drug administration and dosage schedule

A single dose of 1 gram of TXA or placebo (sodium chloride 0.9%) by intravenous injection will be given immediately after the umbilical cord is cut or clamped, and no more than 15 minutes later. There should be no delay in administering the trial medication after the umbilical cord is cut or clamped. Each treatment pack contains two ampoules each containing 500 mg (5 mL) of TXA or placebo (5 mL), and one sterile 10 mL syringe and 21G needle. Appropriately qualified staff will prepare the treatment to be administered by drawing up the contents of both ampoules into the 10 mL syringe using the 21G needle provided. Before administration, the expiry date will be checked and the randomisation number confirmed. The contents of both ampoules (total volume 10 mL) will be administered as a slow intravenous injection at rate of about 1 mL/minute using standard local intravenous administration procedure.

In the event of multiple births, the trial drug will be given after cutting or clamping the umbilical cord of the last baby.

Outcome measures

Once randomised, we will collect follow-up data even if the trial treatment is not completed. Data will be collected within the first 24 hours after administration of the trial treatment and final outcome data will be collected when a woman is discharged from the randomising hospital, at death or 42 days post randomisation, whichever occurs first. In the event a woman is discharged or dies within 24 hours, all outcomes will be assessed at the same time. Adverse events will be collected from administration of the trial medication up to day 42.

Primary outcome:

The primary outcome is a clinical diagnosis of primary PPH. This may be an estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability within 24 hours of administration of trial medication. Haemodynamic instability is based on clinical judgement and assessed using clinical signs (low systolic blood pressure, tachycardia, reduced urine output). The cause of PPH will be described.

Secondary outcomes:

Maternal blood loss and its consequences:

- Postpartum blood loss (clinical estimation)
- Haemoglobin
- Haemodynamic instability
- Shock index
- Receipt of blood transfusion
- Use of interventions to control postpartum bleeding (medical and surgical)

Maternal health and wellbeing:

- Symptoms of anaemia (e.g. fatigue, headache, dizziness, palpitations, breathlessness)
- Exercise tolerance (short 6-minute walk test)
- Quality of Life (overall wellbeing, ability to care for herself and her baby, breastfeeding)

Other health outcomes:

- Vascular occlusive events (pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, myocardial infarction (MI)).
- Organ dysfunction
- Sepsis
- Expected side effects (nausea, vomiting, diarrhoea, seizure)
- Adverse events
- Death (cause and time to death will be described)
- Length of hospital stay
- Admission to and time spent in higher level facility
- Status of baby/ies and any thromboembolic events

Definition of end of trial

The end of trial will be day 42 of the last participant randomised.

Statistics and data analysis

A detailed Statistical Analysis Plan will be drafted and agreed with the DMC for their ongoing review and will be finalised before the trial database is locked for final analysis.

Main analysis

Analyses will be on an 'intention-to-treat' basis. Data will be analysed by randomised group, irrespective of whether they received the intervention. Demographic and other baseline characteristics will be tabulated. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range, and the number of observations. Categorical variables

will be presented as numbers, and as percentages of those participants who had the assessment. All statistics will be presented by treatment group. Effect measures will be relative risk and absolute risk reduction. Precision will be quantified using 95% confidence intervals. Planned subgroup analyses include analyses based on the severity of anaemia (moderate versus severe) and type of labour (induced or augmented versus spontaneous). In a large trial such as WOMAN-2, baseline characteristics of participants that may influence the outcome are expected to be evenly distributed between the treatment and placebo groups, so that any difference in outcome can be attributed to the intervention. However, it is still possible that a chance imbalance in important prognostic factors could influence the results. To investigate this possibility, an analysis of the effect of treatment that is adjusted for baseline risk will be conducted. A prognostic model will be built based on pre-specified baseline variables and use it to estimate the predicted risk of the outcome at baseline. Checks will be made to ensure that there are sufficient patients in the severe anaemia subgroup by limiting recruitment to these patients if necessary. For subgroups, relative risks and confidence intervals with two-sided p-values will be reported. Test of homogeneity of effect across the subgroups will be done and a p-value reported. Unless there is evidence against the null hypothesis of homogeneity of effects the overall RR will be taken as the most reliable guide to the approximate RR in all subgroups.

Sponsor

The London School of Hygiene & Tropical Medicine (LSHTM) will act as the Sponsor for this trial.

Funding

Wellcome and the Bill & Melinda Gates Foundation are funding this study.

Discussion

The WOMAN-2 trial will provide reliable evidence for the effects of TXA for preventing postpartum bleeding in women with anaemia. If the WOMAN-2 trial shows that TXA reduces PPH in anaemic women, we would have identified a way of improving the wellbeing of thousands of women world-wide.

Trial status

The protocol was approved by the London School of Hygiene & Tropical Medicine's Ethics Committee (ref: 15194). National ethics and regulatory approvals are in progress in three countries. Patient recruitment is planned to start by January 2019. End of recruitment is planned for January 2021 with end of follow-up in March 2021. Further information is available at http://woman2.lshtm.ac.uk/

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5.0 DISCUSSION, SUMMARY, CONCLUSIONS AND RECOMMENDATIONS

This thesis comprises a series of studies critically analysing the evidence from randomised trials for the effects of the antifibrinolytic drug, tranexamic acid (TXA) in patients with surgical bleeding, traumatic bleeding, and for preventing postpartum haemorrhage.

In this final Chapter, I summarise the principal findings of these studies and consider their implications for practice and future research. I will also reflect on the strengths and weaknesses of the methods used in the thesis before drawing my overall conclusions.

5.1 EFFECTS OF TRANEXAMIC ACID FOR SURGICAL BLEEDING

5.1.1 Principal findings

Chapter 1 included Research Papers 1-3 in which I evaluated the evidence from randomised trials for the effects of TXA in patients with surgical bleeding (Aim 1). On the basis of my results, I drew four main conclusions: 1) that TXA reduces the risk of receiving a blood transfusion by about one third; 2) that strong evidence that TXA reduces blood transfusion in surgery has been available for many years; 3) that the effects of TXA on the risk of death and thromboembolic events are uncertain; and 4) that trials continue to be conducted assessing the effect of TXA on bleeding despite awareness of the evidence. I consider these in more detail below.

Evidence from randomised trials of the effect of TXA on blood transfusion and blood loss in surgery

The pooled estimates from the meta-analyses were consistent with relative reductions in risk of blood transfusion and blood loss of 38% and 34% respectively. However, many trials were methodologically weak and fewer than half had adequate allocation concealment. When the analyses were restricted to adequately concealed trials, the estimated relative risk reductions were somewhat smaller; 32% and 30% respectively. They were also less precise albeit both remained statistically significant. There were also concerns about selective reporting and only two of the adequately concealed trials were prospectively registered and had pre-specified receipt of blood transfusion as an outcome. The pooled estimate of the effect on blood transfusion from these two trials was still consistent with a statistically significant relative risk reduction of 21% although, as suggested by the results of the trial sequential analysis (Research Paper 3), this may be a spurious result. Despite these shortcomings, due to the number of trials and the magnitude of the effect that remained when restricted to adequately concealed trials, I concluded that there was reliable evidence that TXA reduces bleeding in surgery. Furthermore, based on the results of the cumulative meta-analysis presented in Research Paper 1, I also concluded that the evidence that TXA reduces the risk of blood transfusion had been available for many years.

However, since I completed Research Papers 1-3, there have been two important developments which oblige me to reconsider these conclusions. First, are the serious deficiencies in the quality and integrity of the studies included in my systematic review of trials investigating TXA for preventing postpartum haemorrhage (Research Paper 6), which raise the possibility that similar deficiencies also affect the surgical trials. Whilst I did not have the same suspicions about the surgical trials when extracting data, it would be remiss of me not to consider that the same concerns could affect these trials at least to some extent. There seems no reason why such issues would be confined to the PPH prevention trials, so there is now a further question mark over the reliability of the trials in surgery.

The second development is the publication of the results of the ATACAS trial, a large, high quality trial of the effects of TXA in over 4000 cardiac surgery patients, in January 2017.[1] The ATACAS trial assessed the effects of TXA in patients undergoing coronary-artery surgery who were at risk of perioperative complications.[1] The trial was at low risk of bias (adequately concealed, double-blind, prospectively registered) and provided outcome data for 4631 patients (2311 in the TXA group and 2320 in the placebo group). Fewer patients in the TXA group received a blood transfusion than in the placebo group (37.9% vs. 54.7%; RR=0.69, 95% CI 0.65 to 0.74). To understand how these results contribute to the wider evidence from surgery trials, I have repeated the meta-analyses conducted for the systematic review to include data from the ATACAS trial. Table 5.1 (below) shows the results of the meta-analysis of the risk of receiving a blood transfusion, before and after the inclusion of data from the ATACAS trial.

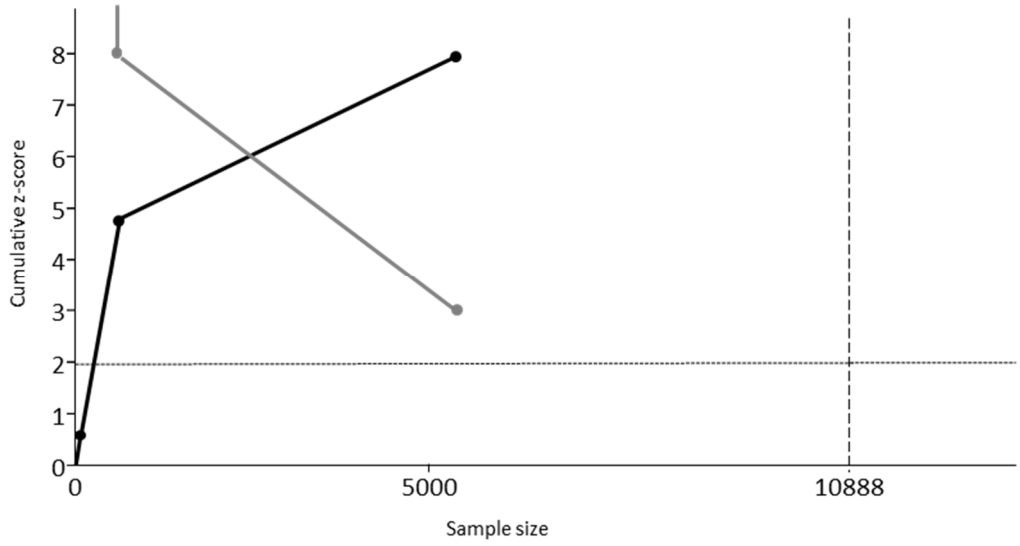
Table 5.1 Meta-analysis of effect of TXA on receipt blood transfusion reported in Chapter 2 with and without the addition of data from the ATACAS trial.

	Pooled RR without ATACAS	**Pooled RR with ATACAS**
Blood transfusion		
All trials	0.62 (0.58 to 0.65); p<0.001	0.65 (0.62 to 0.68); p<0.001
Adequately concealed trials	0.68 (0.62 to 0.74); p<0.001	0.69 (0.65 to 0.73); p<0.001
Prospectively registered, blood transfusion pre-specified	0.79 (0.71 to 0.87); p<0.001	0.71 (0.67 to 0.75); p<0.001

The magnitude of the effect after the inclusion of the ATACAS trial data is smaller although more precise. When data from the ATACAS trial are included in the pooled analysis based on adequately concealed trials, which were also prospectively registered and prespecified receipt of blood transfusion as an outcome, the pooled estimate is consistent with a 29% relative risk reduction. Although the required information size (n=10,888) is still not achieved, the results of

the updated trial sequential analysis show that the z-curve crosses the monitoring boundary after the addition of the ATACAS trial (Figure 5.1), thus I can be more confident that this is a reliable effect estimate.

Figure 5.1 Results of trial sequential analyses for trials at low risk of bias trials with transfusion pre-specified on prospective registration record, reported in Research Paper 3, updated to include data from the ATACAS trial.



In summary, due to further concerns about the quality of trials arising out of the systematic review of TXA trials for preventing PPH, my original conclusions regarding the reliability of the evidence for the effect on surgical bleeding were arguably too strong. Moreover, my statement that reliable evidence had existed for many years was incorrect. Rather it is only since the publication of the ATACAS trial in 2017 that reliable evidence has been available. Furthermore, the magnitude of the effect on blood transfusion (RR=0.62) estimated by the pooled analysis of all trials was inflated and a smaller effect (RR=0.71) seems likely to be closer to the true effect.

Evidence from randomised trials of the effect of TXA on risk of death and thromboembolic events in surgery

My third conclusion was that the effect of TXA on death and thromboembolic events in surgical patients is uncertain. Although there is no evidence that TXA increases the risk of death or thrombosis (indeed the effect estimates are consistent with a reduced risk), the estimates are imprecise. Whilst most trials reported data on bleeding or blood transfusion, data on mortality and thromboembolic events were only available for about half (even after contact with the original investigators) raising concerns about the potential for selective reporting bias. This, coupled with the concerns about the quality of trials arising from the PPH prevention systematic

review, further exacerbate these uncertainties. However, once again the ATACAS trial has since made a useful contribution to the evidence (Table 5.2).

Table 5.2 Meta-analysis of effect of TXA on risk of death and myocardial infarction conducted in Research Paper 1 before and after the addition of data from the ATACAS trial.

	Pooled RR without ATACAS	**Pooled RR with ATACAS**
Death		
All trials	0.61 (0.38 to 0.98); p=0.04	0.69 (0.49 to 0.97); p=0.04
Adequately concealed trials	0.67 (0.33 to 1.34); p=0.25	0.75 (0.50 to 1.13); p=0.16
Myocardial infarction		
All trials	0.68 (0.43 to 1.09); p=0.11	0.87 (0.76 to 1.01); p=0.07
Adequately concealed trials	0.70 (0.39 to 1.25); p=0.22	0.88 (0.76 to 1.03); p=0.11

The ATACAS trial data support a reduction in the risk of death although the magnitude of the effect is reduced when the data are added to the pooled analysis. The effect is no longer statistically significant at the 5% level, when restricted to adequately concealed trials and therefore remains open to question. Due to the relative rarity of events, the pooled effect estimate for myocardial infarction is uncertain even after the addition of the ATACAS trial data, although the lack of evidence for an increased risk from ATACAS provides some reassurance that TXA is safe. However, a high quality randomised trial, powered to detect the effect of TXA on death and thromboembolic events is still needed to resolve these uncertainties.

The continuation of trials assessing the effects of TXA on bleeding outcomes in surgery

My forth conclusion was that trials assessing the effect on bleeding in surgery continue to be conducted despite investigators being aware of existing evidence for effectiveness. This is contrary to a widely held view that the failure to systematically review the evidence prior to starting a trial is the main cause of research waste. Instead, much of the continuation of trial activity appears to be as a result of inappropriate trial design and the reluctance to generalise the existing evidence across surgery types.

Inappropriate study design typically described trials in which the investigators cited existing evidence for the effectiveness of TXA and sought to assess different dose regimens of TXA, yet also included a placebo group. A key justification for the use of a placebo in a clinical trial is that no proven intervention exists.[2] If the investigators truly believe that there is evidence that TXA is effective for reducing bleeding, the decision to include a placebo group is ethically inappropriate.

Another main motivation for embarking on new a trial was to ascertain if TXA was also effective in patients undergoing types of surgery yet to be investigated by the existing trials. The result has been the expansion in the number of trials into increasingly specific subtypes of surgery. Investigators appear to be unwilling to generalise results from one form of surgery (e.g. cardiac) to another (e.g. orthopaedic) or even to generalise within surgical areas (e.g. from hip to knee arthroplasty). It is of course appropriate that careful consideration is given before generalising trial results from one setting to another. However, it could be that investigators are confusing scientific and statistical inference.[3] This argument by Kenneth J Rothman, suggests that rather than seeking to replicate results in every subgroup of surgery, it is necessary to consider what is known about the mechanism of action of TXA and asking whether there is good reason to think that it would work differently between surgical types. Such scientific reasoning appeared to be absent when investigators outlined their rationale for initiating a new trial of TXA. One such example is the trial by MacGillivray *et al* which assessed the effect of TXA on bleeding in 60 patients undergoing bilateral total knee arthroplasty.[4] When describing the trial rationale in the final report, the authors cited the evidence from two meta-analyses of trials in patients undergoing total knee replacement, that TXA *"appears safe and effective in reducing allogeneic blood transfusion and blood loss"*. However, because the effect had not been assessed in patients undergoing concurrent, bilateral total knee replacement (a procedure typically associated with greater blood loss) MacGillivray *et al* embarked on a new trial in which 40 patients received TXA and 20 participants were randomised to receive placebo. The authors offer no biological reasoning why TXA might have a different effect in bilateral knee replacement. They note the greater blood loss associated with bilateral knee replacement, which is likely to mean that the absolute effect of TXA differs, but in most cases the relative effects of a treatment are consistent across different baseline risks.[5] The unwillingness of MacGillivray *et al* to generalise the evidence from the previous trials in knee arthroplasty meant that one third of their trial participants, who were undergoing a procedure known to be associated with greater blood loss than others, were denied treatment that the trial investigators themselves described as being effective for reducing bleeding.

5.1.2 Strengths and weaknesses

The Discussion sections of each Research Paper that make up this thesis, include consideration of the strengths and weaknesses of each paper. I will not repeat these here, but I will reflect on some further points.

The systematic review described in Research Papers 1 and 2 is not the first to assess the evidence of TXA in surgery patients, although I am only aware of one other review with broad inclusion criteria to include trials irrespective of surgery type. This is the Cochrane systematic review by

Henry *et al*, first published in 1999[6] and most recently updated with new trials in 2011[7] which assesses the effects of antifibrinolytic drugs in adult patients undergoing elective surgery. Unlike the review by Henry *et al*, I included trials involving paediatric and emergency surgery and focussed only on trials of TXA. I also identified and included a larger number of trials (129 versus 60). My review is also the first to estimate the proportional effect of TXA on blood loss and to conduct a meta-regression to explore the effect of total dose, using data from trials conducted across a range of surgery types. Furthermore, I am not aware of any other review that has undertaken detailed investigation into the evidence of effect of TXA on blood transfusion by conducting trial sequential analyses or cumulative meta-analyses.

The systematic review of randomised trials assessing the effects of TXA in surgery is a comprehensive review conducted in adherence to recommended methodology. Thus, at the time of its completion, it provided the most rigorous examination of the randomised trials and was deemed to be of sufficiently high quality to inform clinical practice. Indeed, the results have been used in the preparation of clinical guidelines, such as those prepared by NICE, and the Task Force on Patient Blood Management for Adult Cardiac Surgery of the European Association for Cardio-Thoracic Surgery and the European Association of Cardiothoracic Anaesthesiology, both of which recommend the use of TXA in surgery.[8, 9]

However, as is typical of systematic reviews based on aggregate data, my systematic review is largely based on information as presented by the investigators in the original trial reports. Although I contacted authors to obtain additional outcome data, I did not seek individual patient data or additional information to ensure that the information presented was accurate. Nor did I undertake additional analyses to assess the integrity of the data such as a meta-analysis of baseline information to assess the adequacy of randomisation. I cannot therefore be confident that the trials included in the meta-analysis were conducted as reported or indeed, if they were conducted at all. Although I cannot predict how this may have affected the results of the review, the publication of the ATACAS trial does provide reassurance that TXA does reduce bleeding in surgery.

5.1.3 Implications for future research

The publication of the ATACAS trial confirms the findings of my systematic review that TXA reduces bleeding in surgery although the magnitude of the effect may be somewhat smaller than estimated in my meta-analysis. It is, however, a relatively large treatment effect that is clinically relevant.

Without sound, biological reasoning why the effect would vary between different types of surgical patients, it is difficult to see how further trials of TXA designed to assess the effect on bleeding or blood transfusion in surgery can be justified.

Although clinically important questions may remain regarding optimal dose and timing of TXA that necessitate further trials, such questions do not require the inclusion of an inactive comparison group and it is difficult to see how such trials can be ethically justified. However, uncertainties regarding the effects of TXA on other outcomes in surgical patients remain. Indeed, it seems likely that concerns regarding a possible increase in thrombotic risk will somewhat limit the uptake of TXA into clinical practice, since an increase in thrombosis could outweigh the benefits of reduced blood use. In the Discussion section of Research Paper 1, I suggested that to resolve the uncertainties over the effect on death and thromboembolic events there is a *"need for a large pragmatic clinical trial of the effect of the routine administration of TXA in a heterogeneous group of surgical patients"*. Since this was published, a team of researchers based at the Population Health Research Institute in Canada have initiated a new trial of TXA (the POISE-3 trial) in 10,000 non-cardiac surgical patients to ascertain its effect on thromboembolic events.[10] The trial is expected to be completed by December 2022.

5.2 EFFECTS OF TRANEXAMIC ACID FOR TRAUMATIC BLEEDING

5.2.1 Principal findings

Chapter 2 included Research Papers 4 and 5 in which I evaluated the evidence from randomised trials for the effects of TXA in patients with traumatic bleeding (Aim 2). On the basis of my results, I drew four main conclusions: 1) that TXA reduces the risk of death to bleeding; 2) that the relative effect is largest when TXA is administrated within three hours of injury; 3) that there is no apparent increase in risk of thromboembolic events; and 4) that over 100,000 bleeding trauma deaths could be averted every year if all patients were given TXA within three hours of injury.

Effect of TXA in patients with traumatic bleeding

There is a marked difference in the nature of the evidence from randomised trials for the effects of TXA in traumatic bleeding compared with that for surgery. Instead of over one hundred small, generally poor quality trials conducted over decades as found for surgery, there are just two trials in trauma and the bulk of the evidence originates from one of these, the CRASH-2 trial. The CRASH-2 trial was a high quality trial involving a heterogeneous group of 20,211 adult trauma patients recruited from 274 hospitals in 40 countries. It provides reliable evidence that is not subject to the quality concerns affecting the surgery trials. The results suggest that TXA reduces the risk of death due to bleeding by 15% (RR=0.85; 95% CI 0.76 to 0.96). There is also evidence

for an important time to treatment interaction. Although not pre-specified in the systematic review, a pre-specified subgroup analysis of the trial data showed that early treatment (within three hours) was most effective. There was no apparent increase in the risk of thromboembolic events which is reassuring, although due to the relative rarity of events (<2%) the effect estimates are imprecise and neither an increase nor decrease in risk can be discounted. Nevertheless, the evidence for the effect on death due to bleeding is strong and as a result TXA has been implemented into trauma protocols worldwide and is now listed on the WHO List of Essential Medicines.[11]

Potential number of deaths averted

Applying the relative effect of TXA on death due to bleeding in trauma patients, to the data on the number of trauma death worldwide provides an indication of the enormous health impact that the routine use of TXA could have. Using data from the WHO and the literature, I estimated that worldwide about 400,000 trauma patients die in hospital from bleeding every year. Although subject to wide uncertainty intervals, the estimates in Research Paper 5 are consistent with up to 100,000 deaths potentially averted every year, by the routine, early use of TXA. Most of these potentially averted deaths are found in LMICs. These estimates have been useful for supporting the efforts to disseminate the results of the CRASH-2 trial, such as the Trauma Promise initiative.[12]

5.2.2 Strengths and limitations

As described in the Discussion section of Research Paper 5, the estimates of the number of deaths that could potentially be averted with TXA were based on a simple mathematical model, subject to several assumptions and were limited by a lack of data on the epidemiology of trauma deaths. Another limitation was that the information used to estimate the model parameters primarily originated from high income countries. There is therefore a question regarding the extent to which these apply to the situation in low income countries. Indeed, it is quite likely that the proportion of trauma deaths in hospital would be lower in low income countries where a lack of pre-hospital care may mean that fewer people survive to reach hospital.

5.2.3 Implications for research

The CRASH-2 trial provides reliable evidence for the effects of TXA in trauma patients, there is therefore no need for further trials. Efforts instead should be focussed on the dissemination of the evidence and implementation of early TXA use into trauma protocols worldwide.

There are uncertainties regarding its effects in isolated traumatic brain injury and these are currently being investigated by the ongoing CRASH-3 trial.[13] Another important research

opportunity is exploring ways to facilitate the pre-hospital use of TXA. As suggested by the estimates used to calculate the number of deaths that could be averted in Research Paper 5, most trauma deaths (approximately 60%) occur before arrival at hospital. Research into alternative routes of administering TXA that are amenable to use outside of hospital, such as intramuscular administration, would therefore be a worthwhile area for future research.

5.3 EFFECTS OF TRANEXAMIC ACID FOR PREVENTING POSTPARTUM HAEMORRHAGE

5.3.1 Principal findings

Chapter 3 focussed on assessing the evidence from randomised trials for the effects of TXA for preventing postpartum haemorrhage (Aim 3). Research Paper 6 described a systematic review including 26 trials involving 4191 women. There were serious deficiencies in the quality and integrity of the trials that meant that no reliable inferences on the effects of TXA for this indication could be made. Research Paper 7 presented the protocol for a new trial (WOMAN-2), which by randomising 10,000 women with moderate or severe anaemia after they have given birth vaginally, will address the existing uncertainties and provide reliable evidence for the effects of TXA in this patient group.

There is no reliable evidence for the effects of TXA for preventing PPH

Despite identifying 26 randomised trials involving a total of 4191 women, I concluded that there was no reliable evidence for the effects of TXA due to serious concerns about the quality and integrity of the trials. A crucial aspect of a systematic review is thorough assessment of methodological quality of the included trials, with Cochrane's risk of bias tool being a preferred approach. However, there were concerns and deficiencies affecting the included trials that were not captured by this assessment. The near identical sections of text shared by a number of the reports, alongside errors and inconsistencies, forced me to question the reported data and indeed, to question whether the trials were carried out as reported at all. Obtaining additional information from authors did not reassure me, rather it raised further concerns. The meta-analysis of baseline variables supported my concerns that these trials were unreliable by suggesting that the randomisation process may have been subverted.

The WOMAN-2 trial

The trials assessing the effect of TXA on preventing postpartum haemorrhage included in the systematic review described in Research Paper 6, provide no reliable evidence. However, the subsequently published TRAAP[14] and WOMAN[15] trials, coupled with the wider evidence from surgery and trauma, give reason to hope that it could be effective for reducing postpartum bleeding. The WOMAN-2 trial outlined in Research Paper 7, should provide a definitive answer

to the question of the effect of TXA on postpartum bleeding and wellbeing in women with anaemia.

5.3.2 Strengths and limitations

My systematic review is the first to highlight the wider deficiencies affecting trials assessing the effect of TXA for preventing PPH. The investigations I undertook to explore these concerns were not pre-specified but were initiated in response to issues observed during data extraction. Nor were the investigations based on a recommended approach. However, in the absence of guidelines, I believe that my approach was preferable to ignoring the concerns.

The planned WOMAN-2 trial is a large, multicentre, randomised trial that is designed to minimise bias (prospectively registered, adequately concealed, double-blind). It has been designed by a multidisciplinary team that has a proven track record in the delivery of large clinical trials of TXA, having previously co-ordinated the CRASH-2[16] and WOMAN[15] trials. The planned sample size of 10,000 women provides over 90% power to detect a 25% reduction from 10% to 7.5% in PPH. The large sample size also allows for reliable assessment of the effects of other patient-centred outcomes such as those pertaining to maternal wellbeing.

5.3.3 Implications for research

A key implication for research is being addressed by the WOMAN-2 trial, which will provide reliable evidence for the effects of TXA on postpartum bleeding and wellbeing in women with anaemia. Patient recruitment is expected to start by January 2019 and the trial will be completed by January 2022.

The results of the systematic review of trials has implications for the conduct of systematic reviews more generally. Many of the weaknesses of the trials such as near-identical texts of published reports, lack of ethics committee approval, apparent subversion of the randomisation process, alongside errors and inconsistencies in the results data, go beyond the standard checks and assessment of methodological quality typically used by systematic reviewers. This raises a fundamental question of the extent to which we can take the information presented in trial reports on trust. Most systematic reviews are based on aggregate data extracted from trial reports, with contact (if any) with the original trial investigators largely limited to seeking clarification of methods or obtaining unreported data. Rarely do systematic reviewers request basic information about the conduct of the trial such as proof of ethics approval or randomisation dates. However, the results of the systematic review described in Research Paper 6, highlight the potential problem with such an approach and the need for thorough investigations into the basic integrity of the data. There are previous examples of trials being included in systematic reviews and informing conclusions about intervention effectiveness, only

to be found at a later date to be fraudalent.[17, 18] As mentioned previously, there is no guidance for systematic reviewers on how to identify research misconduct or how to manage it when suspected. Given the influence that results of systematic reviews can have on clinical practice and policy, I believe that research to inform guidance that systematic reviewers can use to identify and manage research misconduct is urgently required.

5.4 IMPLICATIONS FOR MY RESEARCH INTO THE EFFECTS OF TRANEXAMIC ACID

I intend to continue participating in research to reliably assess the effects of TXA. In my role within the LSHTM CTU, I will be part of the team working over the next four years to ensure the successful completion of the WOMAN-2 trial.

Another project I plan to take forward is the establishment of the Antifibrinolytics Trialists Collaboration. As described in earlier sections, there are some unanswered questions regarding the effects of TXA, such as the effect on thromboembolic events. There are also other questions such as effects of TXA by time to treatment and by baseline risk. These cannot be answered reliably by the existing trials, either individually or by combining their aggregate data. However, such questions could be answered by individual patient data (IPD) meta-analyses. Systematic reviews and meta-analyses of IPD are the 'gold standard' for systematic reviews.[19] IPD systematic reviews can reduce the problem of selective reporting, which would reduce bias and increase statistical power. The increased statistical power also facilitates more reliable subgroup analyses. They also allow a detailed check of the primary data, which in light of the concerns raised by my systematic review of PPH prevention trials (Research Paper 6), may be crucial. In the context of the safety and effectiveness of TXA, an IPD systematic review can overcome several of the limitations of reviews based solely on aggregate patient data. This is an opportunity for future research that I am taking forward. On the 10-11th June 2018, I hosted the first meeting of the Antifibrinolytics Trialists Collaboration, supported by the LSHTM CTU. Investigators of completed and ongoing trials of TXA from all over the world, attended and agreed participate in an IPD meta-analysis to resolve the remaining uncertainties. Together these trials could provide data on over 100,000 bleeding patients and the results could provide the most reliable evidence for the effects of TXA.

5.5 CONCLUSIONS

Most of the randomised trials assessing the effects of TXA for surgical bleeding and for preventing PPH are small and poor quality. Although together they provide promising evidence that TXA reduces bleeding, large, well-conducted trials at low risk of bias are required to determine reliably the effects of TXA. Two additional trials of TXA in surgery, the recently completed ATACAS trial in coronary-artery surgery and the ongoing POISE-3 trial in non-cardiac

surgery, in addition to the ongoing WOMAN-2 trial of TXA for preventing PPH, should contribute importantly to resolving the uncertainties about the effects of TXA in these indications.

The evidence for the effects of TXA for traumatic bleeding originates from the CRASH-2 trial, a large, high quality trial in 20,000 bleeding trauma patients. It provides reliable evidence that TXA given soon after injury reduces the risk of death due to bleeding by about one third. The implication of this is that TXA has the potential to prevent thousands of trauma deaths worldwide.

There is remaining uncertainty regarding the effect of TXA on risk of thromboembolic events. There are also questions regarding the effects of TXA by time to treatment and baseline risk. An IPD meta-analysis could answer some of the questions about the effects of TXA that cannot be answered by systematic reviews and meta-analyses based on aggregate data.

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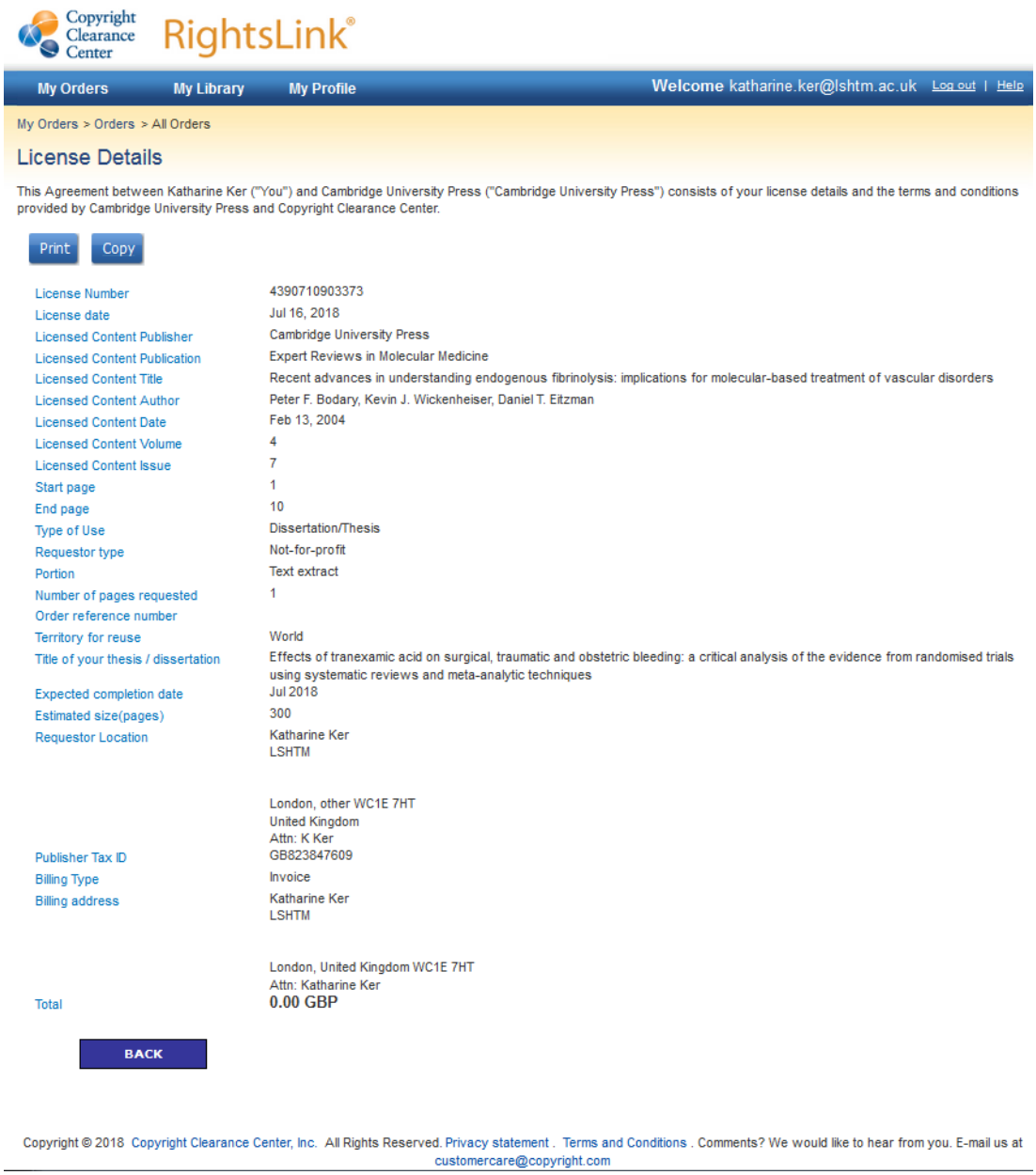

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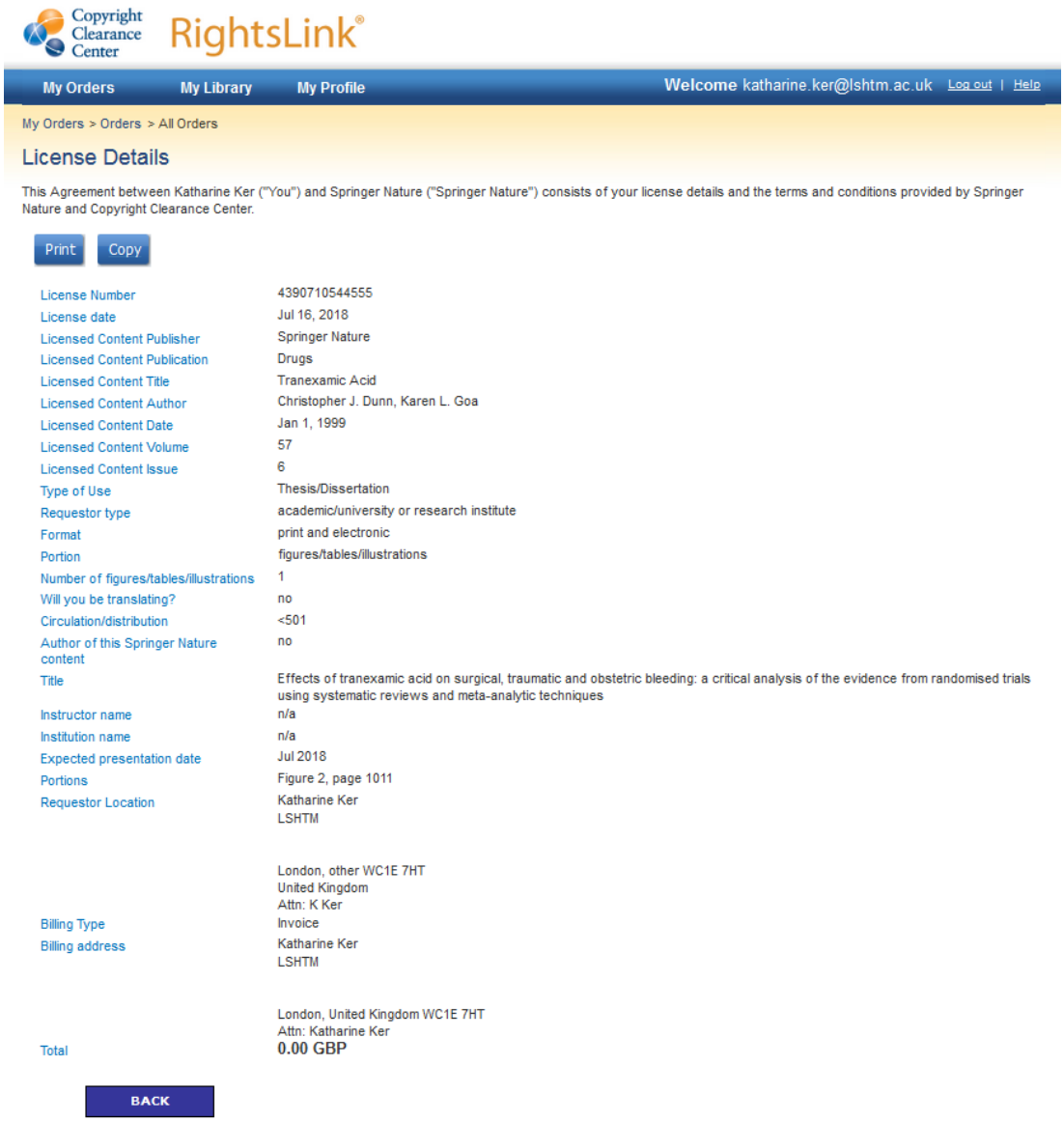

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Author: Katharine Ker, Phil Edwards, Pablo Perel, Haleema Shakur, Ian Roberts

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RESEARCH

Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis

OPEN ACCESS

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Abstract

Objective To assess the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in surgical patients.

Design Systematic review and meta-analysis.

Data sources Cochrane central register of controlled trials, Medline, and Embase, from inception to September 2011, the World Health Organization International Clinical Trials Registry Platform, and the reference lists of relevant articles.

Study selection Randomised controlled trials comparing tranexamic acid with no tranexamic acid or placebo in surgical patients. Outcome measures of interest were the number of patients receiving a blood transfusion; the number of patients with a thromboembolic event (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism); and the number of deaths. Trials were included irrespective of language or publication status.

Results 129 trials, totalling 10 488 patients, carried out between 1972 and 2011 were included. Tranexamic acid reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). This effect remained when the analysis was restricted to trials using adequate allocation concealment (0.68, 0.62 to 0.74; P<0.001). The effect of tranexamic acid on myocardial infarction (0.68, 0.43 to 1.09; P=0.11), stroke (1.14, 0.65 to 2.00; P=0.65), deep vein thrombosis (0.86, 0.53 to 1.39; P=0.54), and pulmonary embolism (0.61, 0.25 to 1.47; P=0.27) was uncertain. Fewer deaths occurred in the tranexamic acid group (0.61, 0.38 to 0.98; P=0.04), although when the analysis was restricted to trials using adequate concealment there was considerable uncertainty (0.67, 0.33 to 1.34; P=0.25). Cumulative meta-analysis showed that reliable evidence that tranexamic acid reduces the need for transfusion has been available for over 10 years.

Conclusions Strong evidence that tranexamic acid reduces blood transfusion in surgery has been available for many years. Further trials on the effect of tranexamic acid on blood transfusion are unlikely to add useful new information. However, the effect of tranexamic acid on thromboembolic events and mortality remains uncertain. Surgical patients should be made aware of this evidence so that they can make an informed choice.

Introduction

In October 2011 the *BMJ* published a randomised controlled trial on the effect of tranexamic acid on blood transfusion in patients undergoing radical retropubic prostatectomy.[1] The authors pointed out that this was the first trial to assess the effect of tranexamic acid on blood transfusion in this particular operation. While this may be the case, it was not the first trial to examine the effect of tranexamic acid on blood transfusion in surgery more generally. A systematic review published in 2001 presented data from 18 clinical trials and showed that tranexamic acid reduces the probability of blood transfusion in elective surgery by 34%.[2]

We assessed the current evidence for the effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality in surgical patients. To examine how the evidence has changed over time we used cumulative meta-analyses.

Methods

Although we specified and documented the methods of the analysis and inclusion criteria for this systematic review in advance, the protocol was not registered. We searched for all randomised controlled trials that compared tranexamic acid with no tranexamic acid or placebo in elective and emergency surgery. No age restriction was applied. Potentially eligible trials were identified by searching the Cochrane central register of controlled trials (2011, issue 3), Medline (1950 to September 2011), and Embase (1980 to September 2011), using a combination of subject headings and text words to identify

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Medline (Ovid) search strategy, 1950 to September 2011
Summary of the risk of bias judgments for each methodological quality domain
Forest plots of effects of tranexamic acid in surgery on risk of blood transfusion, thromboembolic events, and mortality

randomised controlled trials of any antifibrinolytic drug (see supplementary file for Medline search strategy). Searches were not restricted by language or publication status. To identify ongoing or unpublished trials we searched the WHO International Clinical Trials Registry Platform. We also examined the reference lists of eligible trials and reviews. Two authors independently screened the search output to identify records of potentially eligible trials, the full texts of which were retrieved and assessed for inclusion.

Outcome data

Outcome measures of interest were the number of patients receiving a blood transfusion; the number of patients with a thromboembolic event (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism); and the number of deaths. We contacted trial authors to obtain any missing outcome data.

Data extraction and risk of bias assessment

We extracted data on the age and sex of trial participants, type of surgery, dose and timing of tranexamic acid, type of comparator, and outcome data. We also collected information on whether a systematic review had been conducted to support the trial rationale and whether a systematic review was cited in the trial report. We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding, and the completeness of outcome data. As the risk of bias for blinding may vary according to outcome, we assessed this separately for each outcome. We rated the risk of bias as being low, unclear, or high according to established criteria.[3]

Statistical analysis

For each outcome we calculated risk ratios and 95% confidence intervals. We pooled these using a fixed effect model. Subgroup analyses were carried out to examine whether the effect of tranexamic acid on blood transfusion varied by type of surgery. Sensitivity analyses were done to quantify the effect of tranexamic acid on all outcomes when restricted to trials with adequate allocation concealment and blinded outcome assessment. We carried out a cumulative meta-analysis of the effect of tranexamic acid on blood transfusion based on the date of publication, and, when restricted to trials with adequate concealment, cumulative meta-analyses of the effect of tranexamic acid on blood transfusion, myocardial infarction, and mortality. Heterogeneity was examined by visual inspection of forest plots, the I^2 statistic, and the χ^2 test. We inspected funnel plots for the presence of small study effects. Statistical analyses were carried out using Stata version 11 and RevMan version 5.[4,5]

Results

Overall, 127 articles[1,6-131] describing 129 randomised controlled trials and totalling 10 488 patients were included; 5484 of these patients were allocated to tranexamic acid and 5004 to a control group (fig 1⇓). The median sample size was 60 (range 10-660) patients. In total, 126 (98%) trials were in elective surgery and three (2%) in emergency surgery. Eleven (8%) trials involved children.

The authors of 86 trials were contacted for missing data, 39 of whom provided additional information. Data were available on blood transfusion from 95 (74%) trials, on myocardial infarction from 73 (56%), on stroke from 71 (55%), on deep vein thrombosis from 72 (56%), on pulmonary embolism from 66 (51%), and on mortality from 72 (56%). Seven (5%) trials did not present any data on the outcome measures of interest to this review or reported data in a format that was unsuitable for inclusion in the analyses.

A further 14 ongoing trials were identified,[132-145] with a median planned sample size of 130 patients. The 14 trials were in orthopaedic (n=5), cardiac (n=4), cranial (n=2), hepatic (n=1), ear, nose, and throat (n=1), and gynaecological (n=1) surgery. In 12 of the 14 trials blood transfusion was a main outcome measure.

Risk of bias

Overall, 44 (34%) trials were judged to be at low risk of bias for sequence generation and five (4%) to be at high risk (see the supplementary file for the risk of bias judgments for each methodological quality item for the included trials). The risk of bias in the remaining 80 (62%) trials was unclear owing to lack of information. Allocation was adequately concealed in 36 trials (28%) and inadequately concealed in six (5%), with the other 87 (67%) presenting insufficient information to allow judgment. Of the 95 trials with data on blood transfusion, 69 (73%) were judged at low risk of blinding, four (4%) at high risk, and 22 (23%) were unclear. The risk of bias for blinding was similar for thromboembolic outcomes (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), with about 70% judged to be at low risk, 5% at high risk, and 25% at unclear risk. All 72 trials with mortality outcomes were judged to be at low risk of bias for blinding. Of 115 trials reporting eligible outcome data, 72 (63%) were at low risk of bias for incomplete outcome data, 17 (15%) at high risk, and 26 (23%) did not describe adequate information to permit judgment.

Quantitative data synthesis

Table 1⇓ presents the results of the meta-analysis.

Risk of blood transfusion

Data on blood transfusion were available for 95 trials, including a total of 7838 patients. Tranexamic acid reduced the probability of receiving a blood transfusion by 38% (pooled risk ratio 0.62, 95% confidence interval 0.58 to 0.65; P<0.001). When the analysis was restricted to the 32 adequately concealed trials involving 3408 patients, tranexamic acid reduced the risk of receiving a blood transfusion by 32% (0.68, 0.62 to 0.74; P<0.001). When the analysis was restricted to the 69 trials involving 5968 patients with adequate blinding for this outcome, tranexamic acid reduced the risk of blood transfusion by 37% (0.63, 0.59 to 0.68; P<0.001).

The trials with blood transfusion data involved cardiac (n=42), orthopaedic (n=36), cranial and orthognathic (n=7), gynaecological (n=5), hepatic (n=2), urological (n=2), and vascular (n=1) surgery. Blood transfusion was statistically significantly reduced in cardiac, orthopaedic, cranial and orthognathic, hepatic, and urological surgery (table 2⇓). The pooled estimates for blood transfusion were consistent with a reduction in the tranexamic acid group among trials in vascular and gynaecological surgery, although the results were imprecise. There was moderate heterogeneity in magnitude of the effects of tranexamic acid by type of surgery, although the direction of the effects was largely consistent.

Thromboembolic events

There was uncertainty about the effect of tranexamic acid on myocardial infarction (risk ratio 0.68, 95% confidence interval

0.43 to 1.09; P=0.11), stroke (1.14, 0.65 to 2.00; P=0.65), deep vein thrombosis (0.86, 0.53 to 1.39; P=0.54), and pulmonary embolism (0.61, 0.25 to 1.47; P=0.27). The results were similar when the analyses were restricted to trials with adequate allocation concealment and those with blinded outcome assessment.

Mortality

Fewer deaths occurred in the tranexamic acid group (risk ratio 0.61, 95% confidence interval 0.38 to 0.98; P=0.04), although there was uncertainty about this effect, particularly when the analysis was restricted to the 28 trials with adequate concealment (0.67, 0.33 to 1.34; P=0.25).

Cumulative meta-analyses

The supplementary file shows the results of the cumulative meta-analysis of the 95 trials with data on blood transfusion. A statistically significant effect of tranexamic acid on blood transfusion was first observed after publication of the third trial in 1993 (0.59, 0.43 to 0.80; P=0.001). Although subsequent trials have increased the precision of the point estimate, no substantive change has occurred in the direction or magnitude of the treatment effect.

Figures 2-4⇓⇓⇓ shows the cumulative meta-analyses of the effect of tranexamic acid on blood transfusion, myocardial infarction, and mortality among the trials with adequate allocation concealment. A statistically significant effect of tranexamic acid on blood transfusion was consistently observed after publication of the 10th trial in 2001.

Small study effects

Inspection of the funnel plot (fig 5⇓) for the outcome blood transfusion suggested the presence of small study effects favouring tranexamic acid. The other outcomes showed no clear asymmetry in the funnel plots.

Citation of previous systematic reviews

Between 1994 and 2011, 30 systematic reviews have been published on the effects of tranexamic acid in surgery.[2 89 146-175] Assuming a 12 month publication time lag, 98 of the 116 (84%) included trial reports published as full journal articles were published when at least one systematic review was available. Examination of the reference lists of these reports indicated that 45 (46%) did not cite any of the available systematic reviews. The authors of two of the 116 trial reports had carried out a systematic review and presented the findings within the final trial publication.

Discussion

Reliable evidence that tranexamic acid reduces blood transfusion in surgical patients has been available for many years. The treatment effect varies somewhat according to the type of surgery, but the effect is consistently large and remains so when the analysis is restricted to trials with adequate allocation concealment. The effect of tranexamic acid on thromboembolic events and mortality has not been adequately assessed by clinical trials in surgery and remains uncertain. In view of the evidence, those planning further placebo controlled trials should explain why they think that tranexamic acid might not reduce the risk of blood transfusion in the particular group of surgical patients under consideration and focus their efforts on resolving the uncertainties about the effect of tranexamic acid on thromboembolic events and mortality.

Strengths and weaknesses of the review

The inferences that can be made from the included trials depend on their quality, and many had methodological limitations. However, the large and statistically significant effect on blood transfusion remained when the analysis was restricted to trials with adequate allocation concealment and with adequate blinding.

We systematically searched a range of databases for published and unpublished trials. However, we cannot exclude the possibility that some were missed. Indeed, the observed asymmetry in the funnel plot could be explained by publication bias. If many unpublished trials show little or no effect of tranexamic acid on blood transfusion, then this meta-analysis may have overestimated the treatment effect. Although some degree of overestimation is likely, it seems improbable that publication bias could account for all of the observed effect.

Although mortality and thromboembolic outcomes showed no obvious asymmetry in the funnel plots, publication and other reporting biases remain a potential threat to the validity of the effect estimates. Mortality data were reported in only a third of the included trials, and less than half reported data on myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism. Inadequate reporting of adverse events is not unusual in reports of clinical trials and hinders the reliable estimation of treatment effects.[176 177] After contacting the trial authors we obtained some missing data and were able to include mortality data for three quarters of the included trials and data on myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism for about half of the trials. However, the effect of outcome reporting bias in this review remains open to question. Even if there was no significant bias, the precision of the estimates is low and the data are compatible with either a moderate increase or a moderate decrease in the risk of thromboembolic events.

Implications of the findings

The evidence in this review suggests that the uncertainty about the effect of tranexamic acid on blood transfusion in surgical patients was resolved over a decade ago; however, uncertainties about its effect on thromboembolic events and mortality persist. Despite this, trials of tranexamic acid continue to assess the effect on blood transfusion. One reason may be a reluctance to generalise the evidence across surgery types, although there is no evidence that the relative effect of tranexamic acid on blood transfusion varies by type of surgery. A second reason may be that trialists are unaware of the existing evidence when initiating a new trial. Our observation that only half of the trials cited one or more of the available systematic reviews and just two carried out their own systematic review, does suggest that many trialists are indeed failing to adequately consider the existing evidence.

Blood is a scarce and costly resource and blood transfusion is not without risk. The cost of a unit of red cells to the National Health Service has increased from £78 (€96; $126) in 2000 to £125 in 2011, and blood transfusion has several rare but serious adverse effects. Worldwide, most people do not have access to safe blood. Globally the most important transfusion related risks are HIV, hepatitis B virus, and hepatitis C virus, due to their high prevalence. That tranexamic acid safely reduces the need for blood transfusion in surgery has important health and economic implications in high, middle, and low income countries. The evidence that tranexamic acid reduces the need for blood transfusion is strong but the safety of routine use of tranexamic acid in surgical patients remains uncertain. A modest increase in the risk of thromboembolic effects could outweigh

the benefits of reduced blood use. Although some increased risk might be expected on theoretical grounds, recent evidence from the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial of tranexamic acid in bleeding trauma patients showed a statistically significant reduction in mortality with no increase in thromboembolic effects. Indeed, there was a statistically significant reduction in the risk of myocardial infarction in trauma patients who received tranexamic acid.[178]

Further small trials of tranexamic acid in surgical patients considered in isolation will not resolve the uncertainties about the effects on thromboembolic events and mortality. Because thromboembolic events are relatively rare, such trials lack statistical power to detect clinically important increases in risk, and a meta-analysis of small trials remains vulnerable to publication bias. The ongoing Aspirin and Tranexamic Acid for Coronary Artery Surgery trial[179] with a planned sample size of 4300 high risk patients undergoing coronary artery surgery, should contribute importantly to resolving the uncertainty about the effect of tranexamic acid on mortality and thromboembolic events in this specific group. We urge investigators involved in all ongoing trials of tranexamic acid in surgery to collect data on thromboembolic events and mortality for inclusion in a prospective meta-analysis until the uncertainties are resolved. However, a need remains for a large pragmatic clinical trial of the effect of routine use of tranexamic acid in a heterogeneous group of surgical patients. The possibility that tranexamic acid might reduce mortality without any increase in the risk of thromboembolic events would justify the effort and expenditure involved.

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Contributors: KK and IR conceived the study. KK is guarantor. IR is a National Institute for Health Research senior investigator. KK, IR, PE, PP, and HS screened the search output. KK extracted data and carried out the analyses. KK and IR wrote the manuscript with contributions from PP, PE, and HS. The final version was approved by all authors.

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Ethical approval: Not required.

Data sharing: No additional data available.

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What is already known on this topic

Small trials on the effect of tranexamic acid (TXA) on blood transfusion in surgical patients continue to be carried out and published in the medical literature

What this study adds

Evidence that TXA reduces blood transfusion in surgical patients has been available for over a decade, yet the effect on thromboembolic events and mortality remains uncertain

Further trials on the effect of TXA on blood transfusion are unlikely to add useful new information

A large pragmatic clinical trial of TXA in a heterogeneous group of surgical patients is needed to resolve the uncertainties about the effects on thromboembolic events and mortality

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135 Hemostatic and anti-inflammatory effects of ulinastatin and tranexamic acid in cardiopulmonary bypass cardiac surgery (NCT01060189) http://clinicaltrials.gov/ct2/show/NCT01060189.
136 Impact of tranexamic acid on red blood cell transfusion in spinal surgery (NCT01258010) http://clinicaltrials.gov/ct2/show/NCT01258010.
137 Tranexamic acid (TXA) versus epsilon aminocaproic acid (EACA) versus placebo for spine surgery (NCT00958581) http://clinicaltrials.gov/ct2/show/NCT00958581.
138 Intravenous tranexamic acid and intraoperative visualization during functional endoscopic sinus surgery (NCT01111669) http://clinicaltrials.gov/ct2/show/NCT01111669.
139 Multicenter, randomized placebo-controlled clinical trial to evaluate the effect of perioperative use of tranexamic acid on transfusion requirements and surgical bleeding in major spine surgery (NCT01138590) http://clinicaltrials.gov/ct2/show/NCT01138590.
140 Non-idiopathic scoliosis treated with tranexamic acid (NCT01089140) http://clinicaltrials.gov/ct2/show/NCT01089140.
141 Search for optimum dose and timing of tranexamic acid administration in cardiac surgery with cardiopulmonary bypass (JPRN-UMIN000003327) http://apps.who.int/trialsearch/trial.aspx?trialid=JPRN-UMIN000003327.
142 Tranexamic acid for craniofacial surgery (NCT00722436) http://clinicaltrials.gov/ct2/show/NCT00722436.
143 Tranexamic acid in surgery of advanced ovarian cancer (NCT00740116) http://clinicaltrials.gov/ct2/show/NCT00740116.
144 Tranexamic acid on blood loss and transfusion in cardiac surgery (NCT01060176) http://clinicaltrials.gov/ct2/show/NCT01060176.
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Tables

Table 1| **Meta-analysis of effect of tranexamic acid on blood transfusion, thromboembolic events, and mortality**

Outcomes	Events (tranexamic acid/control)	Pooled risk ratio (95% CI)	P value*	Heterogeneity I^2 (%)	Heterogeneity P value
Blood transfusion:					
All trials	1067/1520	0.62 (0.58 to 0.65)	<0.001	69	<0.001
Well concealed trials	459/ 609	0.68 (0.62 to 0.74)	<0.001	55	<0.001
Adequate blinding	847/1182	0.63 (0.59 to 0.68)	<0.001	54	<0.001
Myocardial infarction:					
All trials	23/35	0.68 (0.42 to 1.09)	0.11	0	0.90
Well concealed trials	16/25	0.70 (0.39 to 1.25)	0.22	0	0.82
Adequate blinding	18/33	0.59 (0.36 to 0.98)	0.04	0	0.81
Stroke:					
All trials	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Well concealed trials	5/4	1.18 (0.36 to 3.83)	0.78	0	0.92
Adequate blinding	23/16	1.14 (0.65 to 2.00)	0.65	0	0.92
Deep vein thrombosis:					
All trials	25/29	0.86 (0.53 to 1.39)	0.54	0	0.96
Well concealed trials	13/14	0.92 (0.45 to 1.85)	0.81	0	0.81
Adequate blinding	19/22	0.82 (0.46 to 1.44)	0.49	0	0.98
Pulmonary embolism:					
All trials	4/8	0.61 (0.25 to 1.47)	0.27	0	0.96
Well concealed trials	1/3	0.52 (0.10 to 2.75)	0.44	0	0.80
Adequate blinding	4/6	0.70 (0.26 to 1.87)	0.48	0	0.91
Mortality:					
All trials	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97
Well concealed trials	9/15	0.67 (0.33 to 1.34)	0.25	0	0.85
Adequate blinding	20/34	0.61 (0.38 to 0.98)	0.04	0	0.97

*Test for effect.

Table 2| **Meta-analysis of effect of tranexamic acid on risk of blood transfusion, stratified by type of surgery**

Type of surgery	No of events (tranexamic acid/control)	Pooled risk ratio (95% CI)	P value*	Heterogeneity	
Cardiac	622/835	0.65 (0.60 to 0.70)	<0.001	60	<0.001
Orthopaedic	298/462	0.55 (0.49 to 0.61)	<0.001	83	<0.001
Hepatic	29/54	0.52 (0.39 to 0.68)	<0.001	93	<0.001
Urological	40/60	0.66 (0.48 to 0.91)	0.01	2	0.31
Vascular	11/19	0.58 (0.34 to 0.99)	0.05	—	—
Gynaecological	17/50	0.86 (0.48 to 1.54)	0.61	65	0.06
Cranial and orthognathic	52/76	0.63 (0.45 to 0.86)	0.004	46	0.12

*Test for effect.

Figures

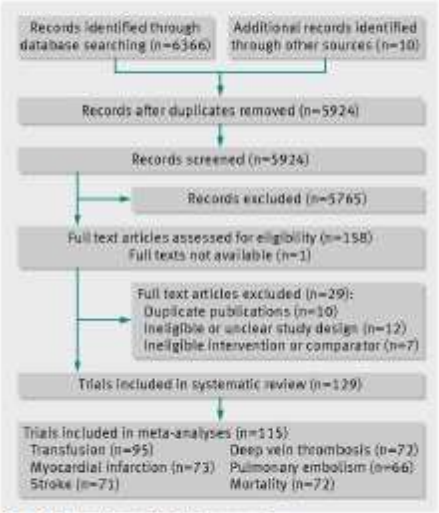


Fig 1 Selection of trials for review

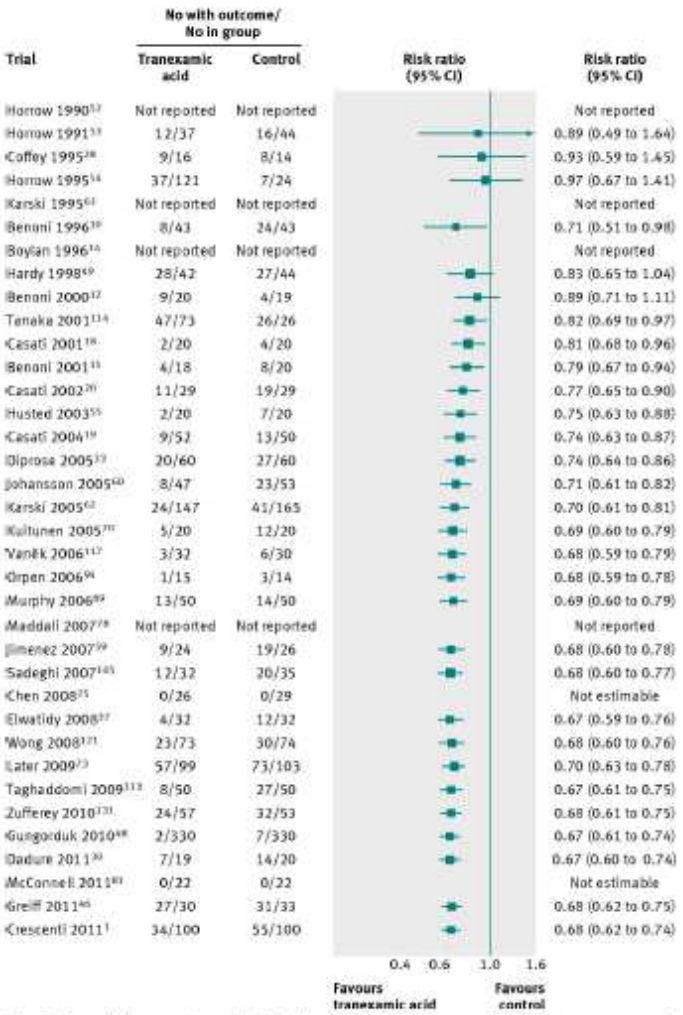


Fig 2 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of blood transfusion in adequately concealed trials

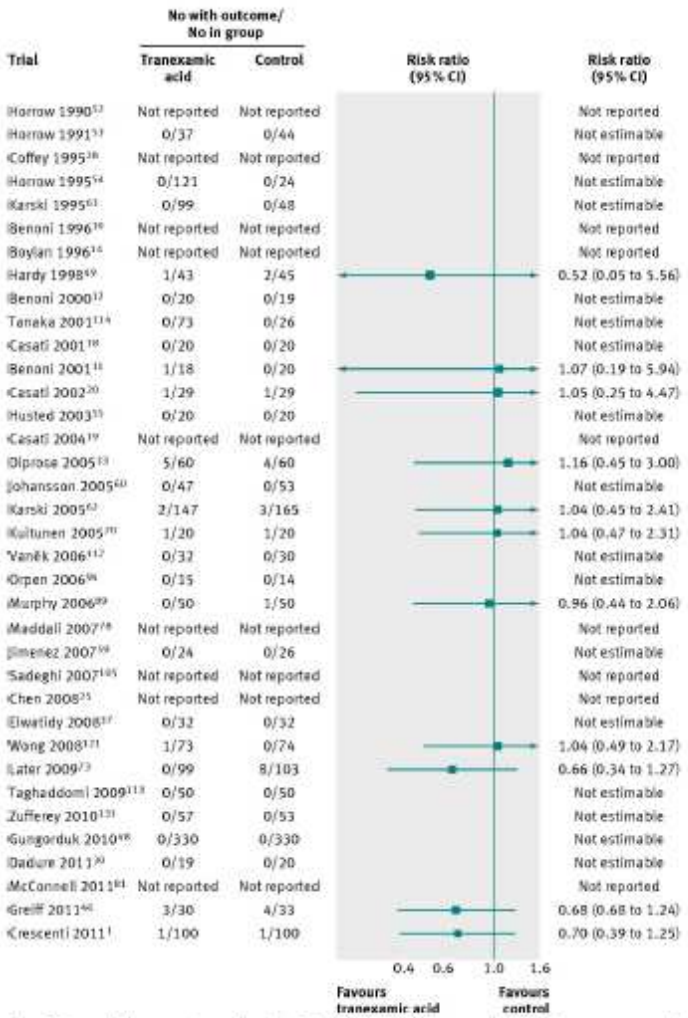


Fig 3 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of myocardial infarction in adequately concealed trials

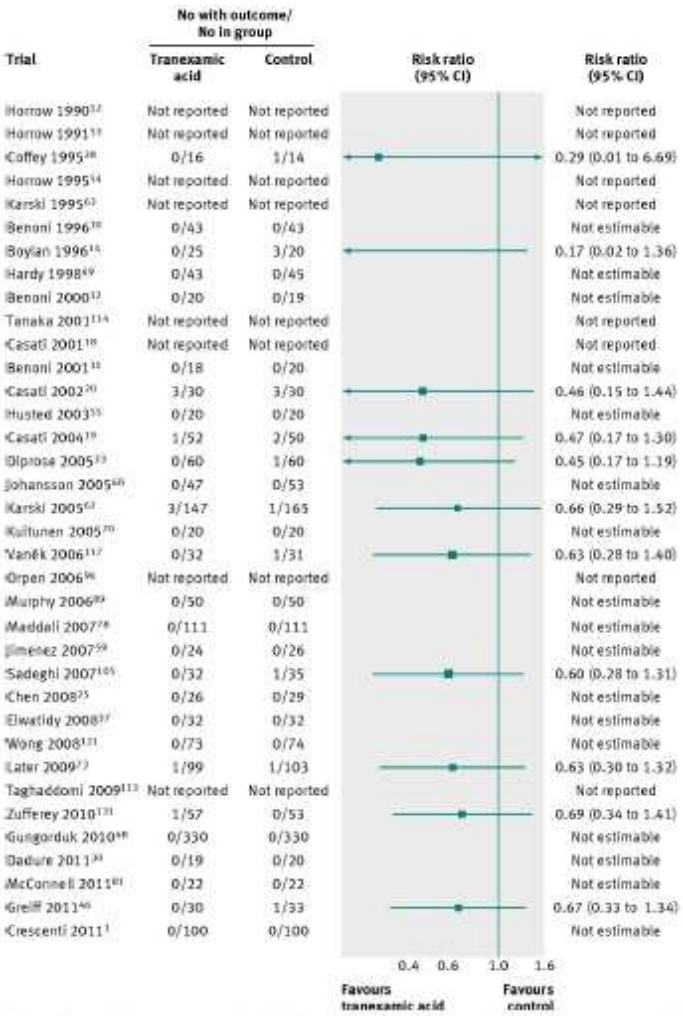


Fig 4 Cumulative meta-analysis of the effect of tranexamic acid in surgery on risk of death in adequately concealed trials

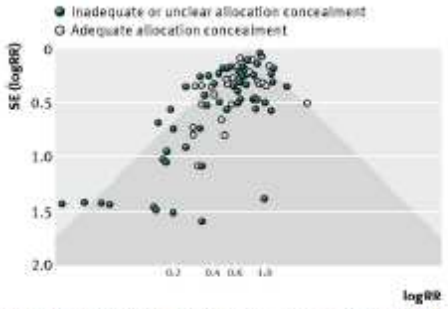


Fig 5 Funnel plot with pseudo 95% confidence limits for meta-analysis on effect of tranexamic acid on risk of blood transfusion

Appendix E. Research Paper 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page[ix]
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	web appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4

[ix]Corresponds to page numbers within the manuscript submitted to the journal

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Appendix F. Research Paper 1: MEDLINE (Ovid) search strategy, 1950 to September 2011

1. exp Antifibrinolytic Agents/
2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or antiplasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3. exp Aprotinin/
4. (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5. exp Tranexamic Acid/
6. (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethylcyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7. exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8. (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomi?ed.ab,ti.
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.
17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. (animals not (humans and animals)).sh.
19. 17 not 18
20. 9 and 19

Appendix G. Research Paper 1: Summary of the risk of bias judgements for each methodological quality domain

	Sequence generation	Allocation concealment	Blinding (transfusion)	Blinding (myocardial infarction)	Blinding (stroke)	Blinding (deep vein thrombosis)	Blinding (pulmonary embolism)	Blinding (mortality)	Incomplete outcome data
Alvarez 2008	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Andreasen 2004	LOW	UNCLEAR	LOW	LOW	LOW	*	*	LOW	UNCLEAR
Armellin 2001	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Auvinen 1987	UNCLEAR	UNCLEAR	*	LOW	LOW	LOW	LOW	*	LOW
Benoni 1996	UNCLEAR	LOW	LOW	*	*	LOW	LOW	LOW	UNCLEAR
Benoni 2000	UNCLEAR	LOW	LOW	LOW	LOW	LOW	*	LOW	UNCLEAR
Benoni 2001	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Blauhut 1994	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	*	UNCLEAR
Boylan 1996	UNCLEAR	LOW	*	*	*	*	*	LOW	LOW
Brown 1997	LOW	UNCLEAR	LOW	LOW	LOW	*	*	LOW	UNCLEAR
Bulutcu 2005	UNCLEAR	UNCLEAR	*	*	*	LOW	*	LOW	LOW
Caglar 2008	LOW	UNCLEAR	LOW	*	*	LOW	LOW	*	LOW
Casati 2001	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	*	LOW
Casati 2002	UNCLEAR	LOW	LOW	LOW	LOW	*	LOW	LOW	UNCLEAR
Casati 2004	LOW	LOW	LOW	*	LOW	*	LOW	LOW	LOW
Castelli 1977	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Chauhan 2003	UNCLEAR	HIGH	*	*	LOW	*	*	*	LOW
Chauhan 2004a	UNCLEAR	HIGH	*	*	UNCLEAR	*	*	*	LOW
Chauhan 2004b	UNCLEAR	UNCLEAR	*	*	UNCLEAR	*	*	*	LOW
Chen 2008	LOW	LOW	LOW	*	*	LOW	*	LOW	HIGH
Choi 2009	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Claeys 2007	UNCLEAR	UNCLEAR	LOW	*	*	LOW	*	*	LOW
Coffey 1995	UNCLEAR	LOW	LOW	*	*	*	*	LOW	LOW
Corbeau 1995	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	*	UNCLEAR
Crescenti 2011	LOW	LOW	LOW	LOW	*	LOW	LOW	LOW	LOW
Dadure 2011	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Dalmau 2000	UNCLEAR	UNCLEAR	LOW	*	*	*	*	LOW	UNCLEAR
Demeyere 2006	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Diprose 2005	LOW	LOW	LOW	LOW	*	*	*	LOW	HIGH
Dryden 1997	UNCLEAR	UNCLEAR	*	*	*	*	*	LOW	LOW
Durán de la Fuente 2003	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Ekback 2000	UNCLEAR	UNCLEAR	LOW	LOW	*	LOW	*	*	LOW
Elwatidy 2008	HIGH	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Engel 2001	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Gai 2004	LOW	UNCLEAR	*	*	*	*	*	*	*
Garneti 2004	LOW	UNCLEAR	LOW	*	*	LOW	LOW	*	LOW
Gill 2009	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Gobbur 2011	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Gohel 2007	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	LOW
Goobie 2011	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Good 2003	LOW	UNCLEAR	LOW	*	*	LOW	*	*	HIGH
Greiff 2011	UNCLEAR	LOW	LOW	LOW	LOW	*	LOW	LOW	LOW
Grundsell 1984a	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Grundsell 1984b	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Gungorduk 2010	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Hardy 1998	UNCLEAR	LOW	LOW	LOW	LOW	*	LOW	LOW	UNCLEAR
Hiippala 1995	LOW	UNCLEAR	UNCLEAR	UNCLEAR	*	UNCLEAR	UNCLEAR	*	HIGH
Hiippala 1997	UNCLEAR	UNCLEAR	LOW	*	*	LOW	LOW	LOW	UNCLEAR
Horrow 1990	LOW	LOW	*	*	LOW	LOW	LOW	*	UNCLEAR
Horrow 1991	LOW	LOW	LOW	LOW	LOW	LOW	*	*	LOW
Horrow 1995	LOW	LOW	LOW	LOW	LOW	LOW	LOW	*	UNCLEAR

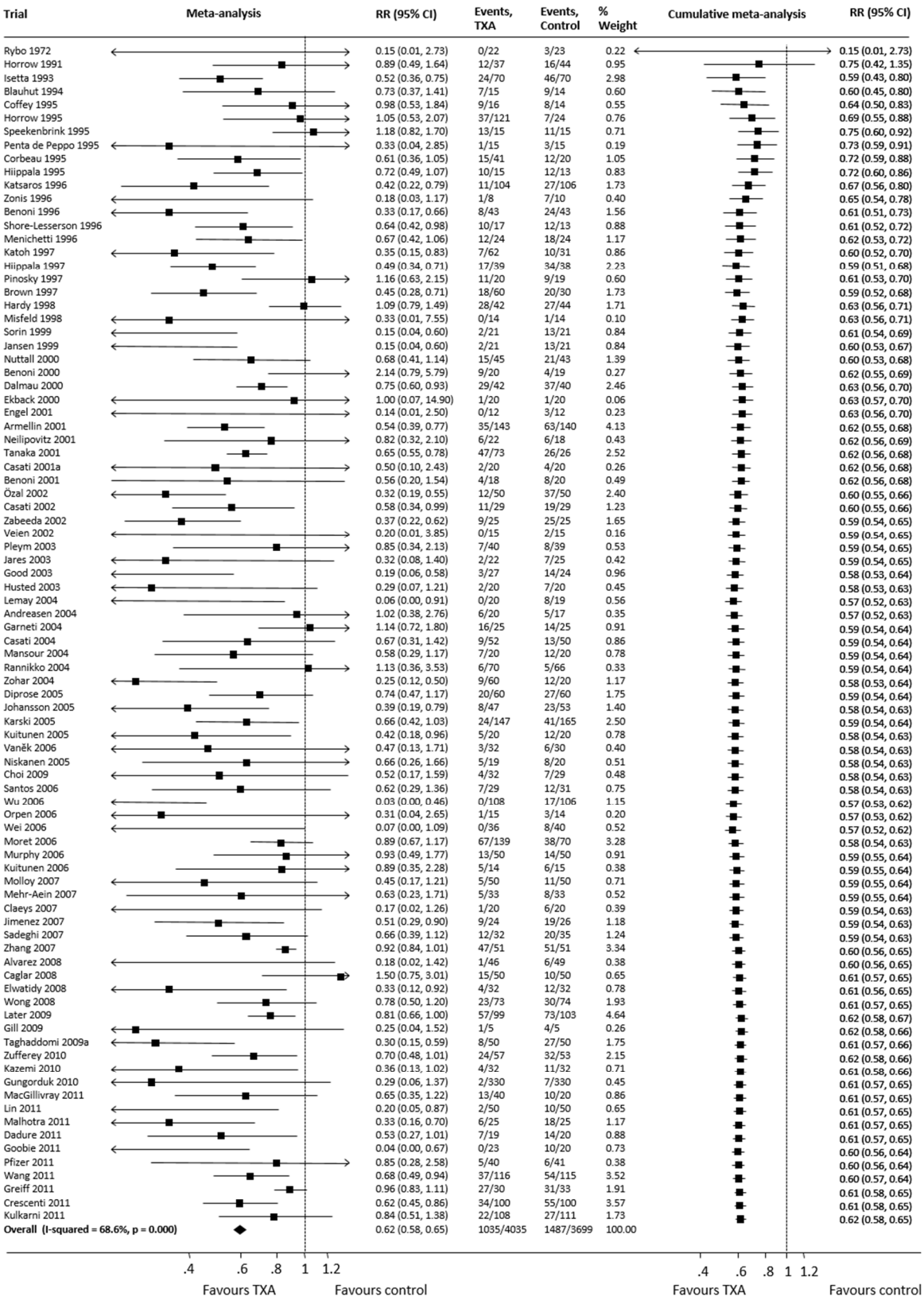
Husted 2003	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Isetta 1993	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	*	LOW
Jansen 1999	LOW	UNCLEAR	LOW	*	*	LOW	*	*	LOW
Jares 2003	UNCLEAR	UNCLEAR	HIGH	HIGH	HIGH	*	HIGH	LOW	LOW
Jimenez 2007	UNCLEAR	LOW	LOW	LOW	LOW	*	LOW	LOW	LOW
Johansson 2005	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Kakar 2009	UNCLEAR	UNCLEAR	*	LOW	LOW	LOW	LOW	LOW	LOW
Karski 1995	UNCLEAR	LOW	*	LOW	LOW	*	*	*	HIGH
Karski 2005	LOW	LOW	LOW	LOW	LOW	*	*	LOW	LOW
Kaspar 1997	UNCLEAR	UNCLEAR	*	*	*	*	*	LOW	LOW
Katoh 1997	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Katsaros 1996	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Kazemi 2010	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Klinck 1993	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Kojima 2001	UNCLEAR	UNCLEAR	*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Kuitunen 2005	UNCLEAR	LOW	LOW	LOW	*	*	*	LOW	LOW
Kuitunen 2006	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	*	HIGH
Kulkarni 2011	UNCLEAR	UNCLEAR	LOW	*	*	*	*	*	LOW
Later 2009	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Leelahanon 2002	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Lemay 2004	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Lin 2011	HIGH	HIGH	UNCLEAR	*	*	UNCLEAR	UNCLEAR	LOW	HIGH
MacGillivray 2010	UNCLEAR	UNCLEAR	LOW	*	*	*	LOW	*	LOW
Maddali 2007	LOW	LOW	*	*	LOW	*	*	LOW	LOW
Malhotra 2011	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Mansour 2004	LOW	UNCLEAR	LOW	LOW	*	*	*	*	UNCLEAR
McConnell 2011	UNCLEAR	LOW	UNCLEAR	*	*	*	*	LOW	LOW
Mehr-Aein 2007	UNCLEAR	UNCLEAR	LOW	LOW	*	*	*	LOW	LOW
Menichetti 1996	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	UNCLEAR	LOW	LOW
Miller 1980	HIGH	HIGH	*	*	*	UNCLEAR	UNCLEAR	*	LOW
Misfeld 1998	UNCLEAR	UNCLEAR	HIGH	HIGH	HIGH	HIGH	HIGH	LOW	LOW
Molloy 2007	UNCLEAR	UNCLEAR	LOW	*	*	LOW	LOW	LOW	LOW
Moret 2006	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Movafegh 2011	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Murphy 2006	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Neilipovitz 2001	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Niskanen 2005	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Nuttall 2000	LOW	UNCLEAR	LOW	*	*	*	*	LOW	UNCLEAR
Oertli 1994	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Orpen 2006	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	*	UNCLEAR
Özal 2002	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	*	LOW
Penta de Peppo 1995	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	*	LOW
Pfizer 2011	UNCLEAR	UNCLEAR	UNCLEAR	*	*	UNCLEAR	*	LOW	LOW
Pinosky 1997	UNCLEAR	UNCLEAR	LOW	*	*	*	*	*	LOW
Pleym 2003	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Pugh 1995	UNCLEAR	UNCLEAR	HIGH	*	*	*	*	*	UNCLEAR
Rannikko 2004	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	HIGH
Reid 1997	UNCLEAR	UNCLEAR	*	LOW	LOW	LOW	LOW	*	HIGH
Risch 2000	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Rybo 1972	UNCLEAR	UNCLEAR	LOW	*	*	*	*	*	HIGH
Sadeghi 2007	LOW	LOW	LOW	*	*	*	*	LOW	UNCLEAR
Santos 2006	UNCLEAR	UNCLEAR	LOW	LOW	LOW	*	*	LOW	LOW
Sekhavat 2009	UNCLEAR	UNCLEAR	*	*	*	UNCLEAR	*	*	LOW
Senghore 1999	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Sethna 2005	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Shore-Lesserson 1996	LOW	UNCLEAR	LOW	LOW	LOW	*	*	LOW	HIGH
Sorin 1999	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	LOW
Speekenbrink 1995	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	*	*	*	LOW

Taghaddomi 2009a	LOW	LOW	LOW	LOW	LOW	*	*	*	UNCLEAR
Taghaddomi 2009b	LOW	UNCLEAR	*	*	*	UNCLEAR	*	*	LOW
Taghaddomi 2009c	LOW	UNCLEAR	*	*	*	UNCLEAR	*	*	LOW
Tanaka 2001	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	*	LOW
Tsutsumimoto 2011	HIGH	HIGH	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	LOW	LOW
Uozaki 2000	UNCLEAR	UNCLEAR	*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	LOW
Vaněk 2006	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Veien 2002	LOW	UNCLEAR	LOW	*	*	UNCLEAR	UNCLEAR	*	LOW
Wang 2011	LOW	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Wei 2006	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	*	LOW	LOW
Wong 2008	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	UNCLEAR
Wu 2006	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	LOW
Yamasaki 2004	LOW	UNCLEAR	*	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	LOW
Yassen 1993	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Yepes 2002	UNCLEAR	UNCLEAR	*	*	*	*	*	*	*
Zabeeda 2002	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	*	LOW	UNCLEAR
Zhang 2007	UNCLEAR	UNCLEAR	UNCLEAR	*	*	UNCLEAR	*	*	UNCLEAR
Zohar 2004	LOW	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	UNCLEAR	*	LOW
Zonis 1996	UNCLEAR	UNCLEAR	LOW	LOW	LOW	LOW	LOW	LOW	HIGH
Zufferey 2010	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW	LOW

[trials rated as being at 'low', 'high' 'unclear' risk of bias or '*' if trial did not report data for the outcome]

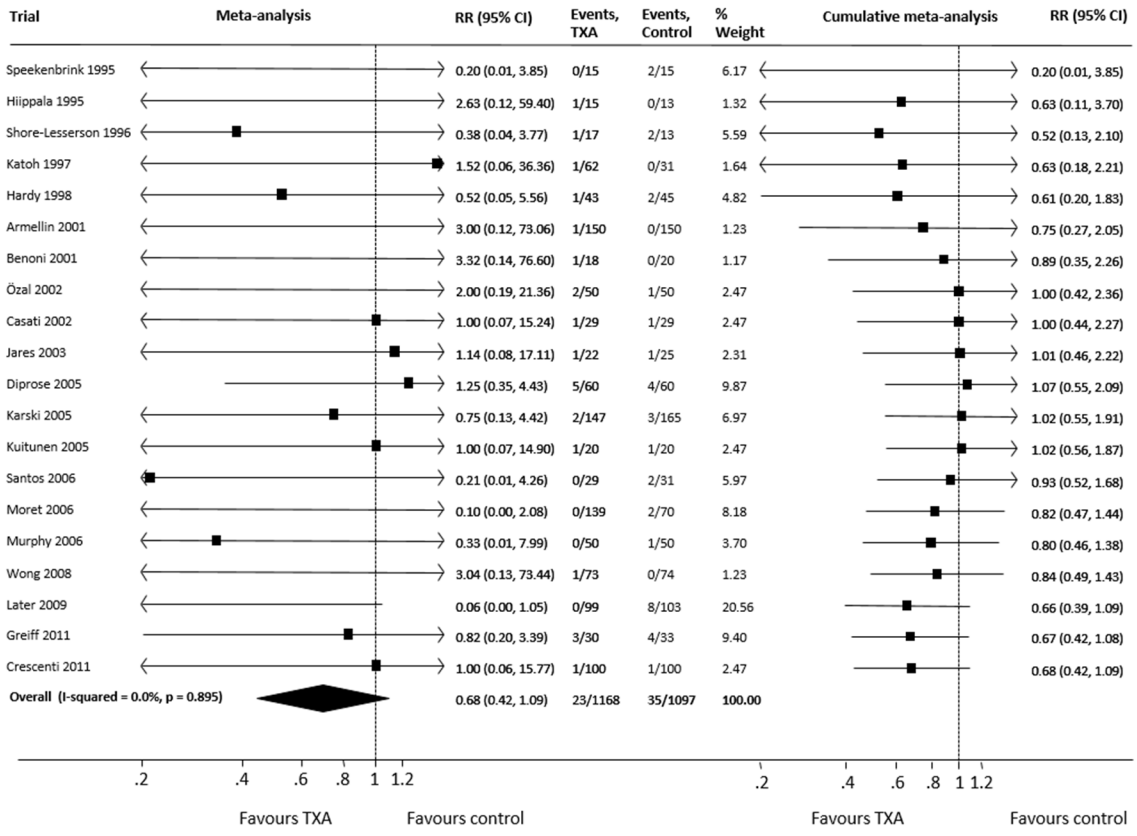
Appendix H. Research Paper 1: Forest plots of the effects of TXA in surgery on risk of blood transfusion, thromboembolic events and mortality

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of blood transfusion



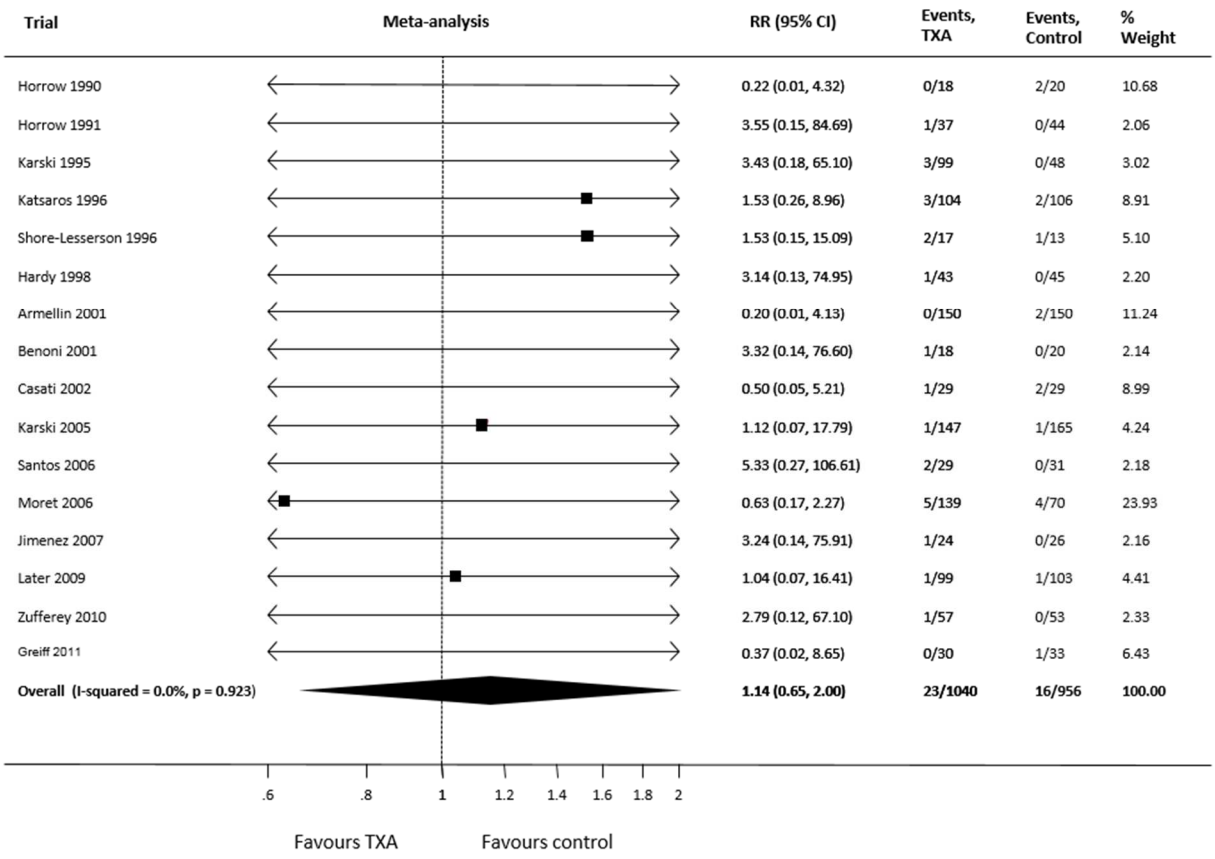
[Trials with zero events in both arms are omitted from the Forest plot for clarity]

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of myocardial infarction



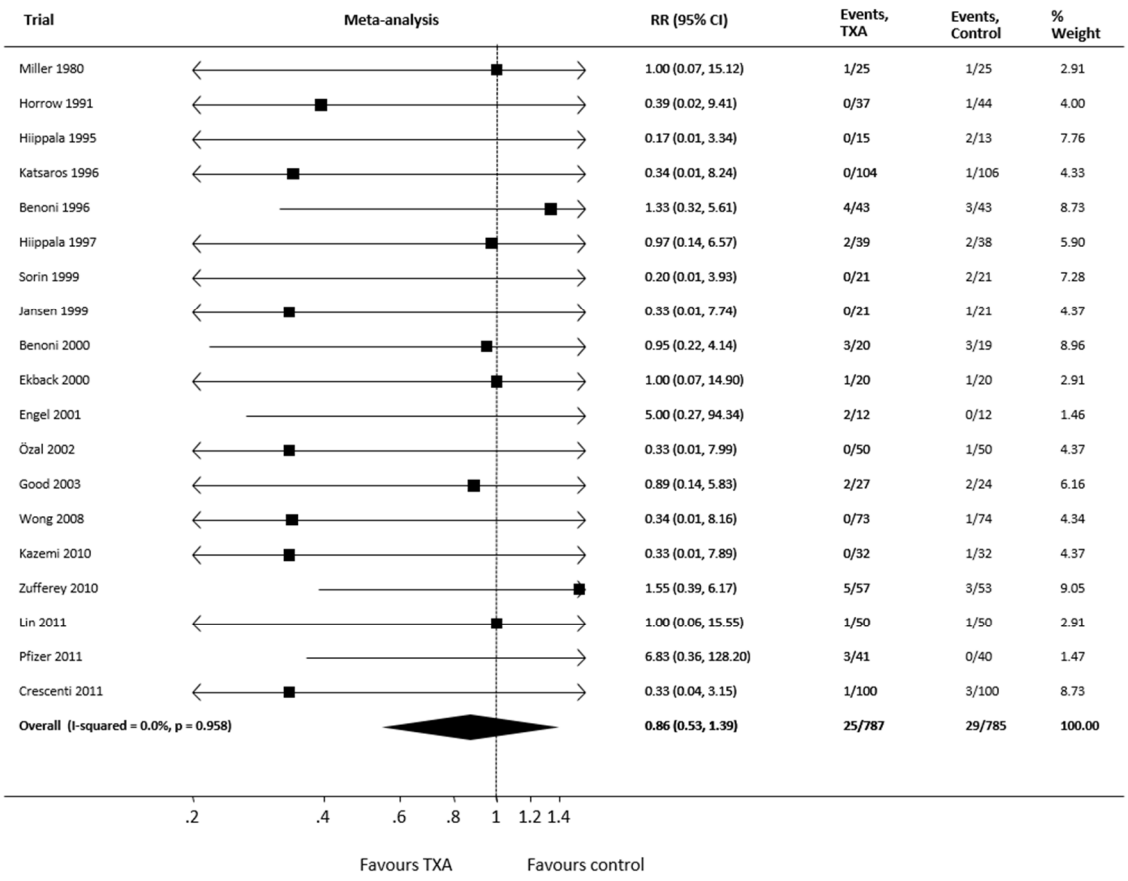
[Trials with zero events in both arms are omitted from the Forest plot for clarity]

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of stroke



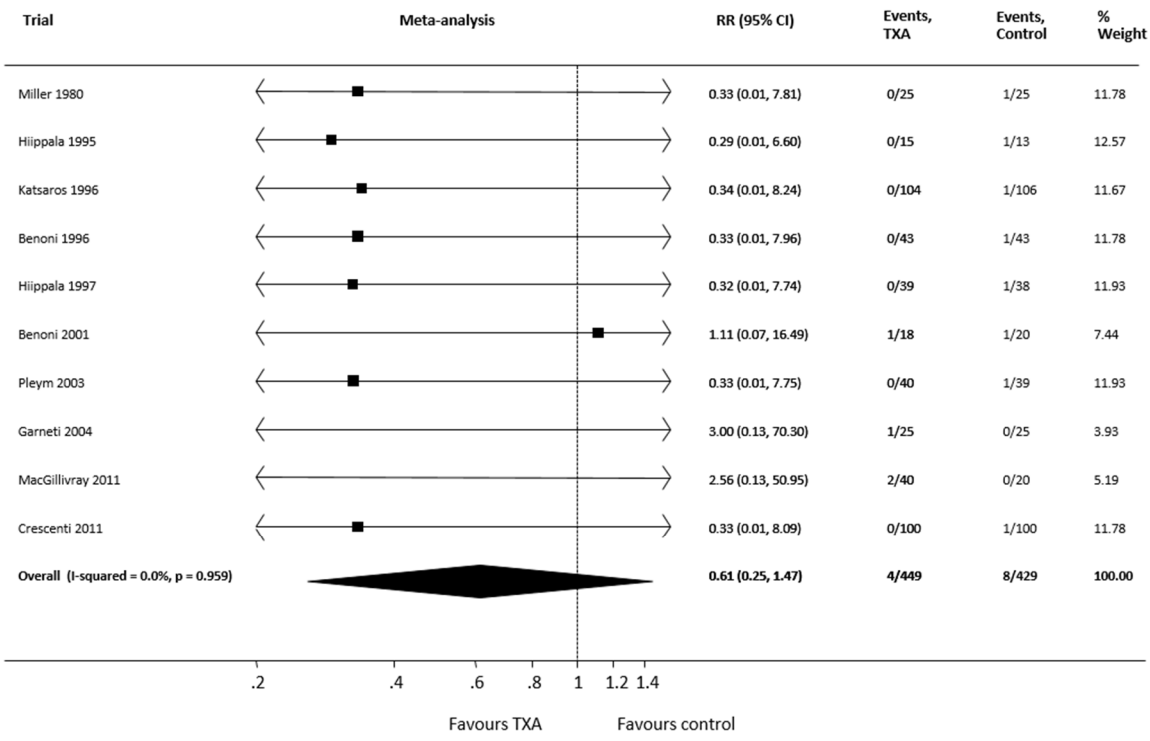
[Trials with zero events in both arms are omitted from the Forest plot for clarity]

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of deep vein thrombosis



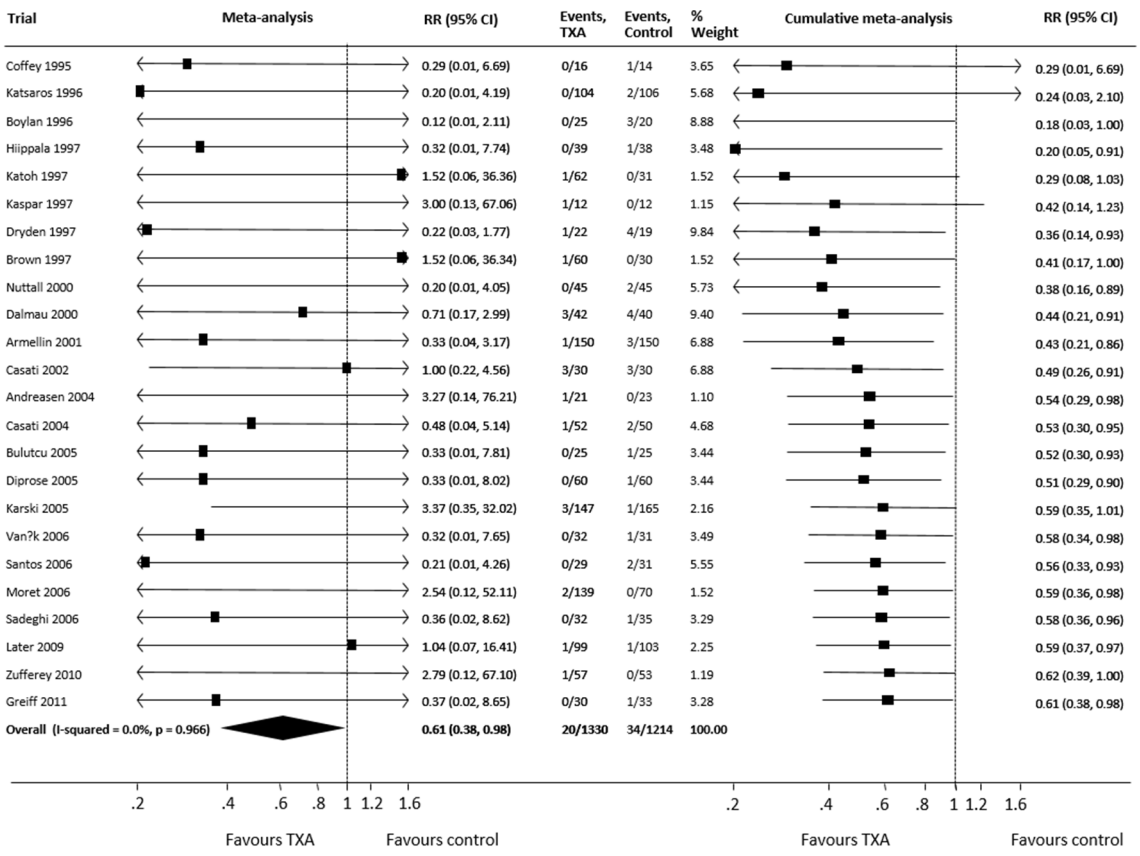
[Trials with zero events in both arms are omitted from the Forest plot for clarity]

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of pulmonary embolism



[Trials with zero events in both arms are omitted from the Forest plot for clarity]

Meta-analysis and cumulative meta-analysis of the effect of TXA in surgery on the risk of death



[Trials with zero events in both arms are omitted from the Forest plot for clarity]

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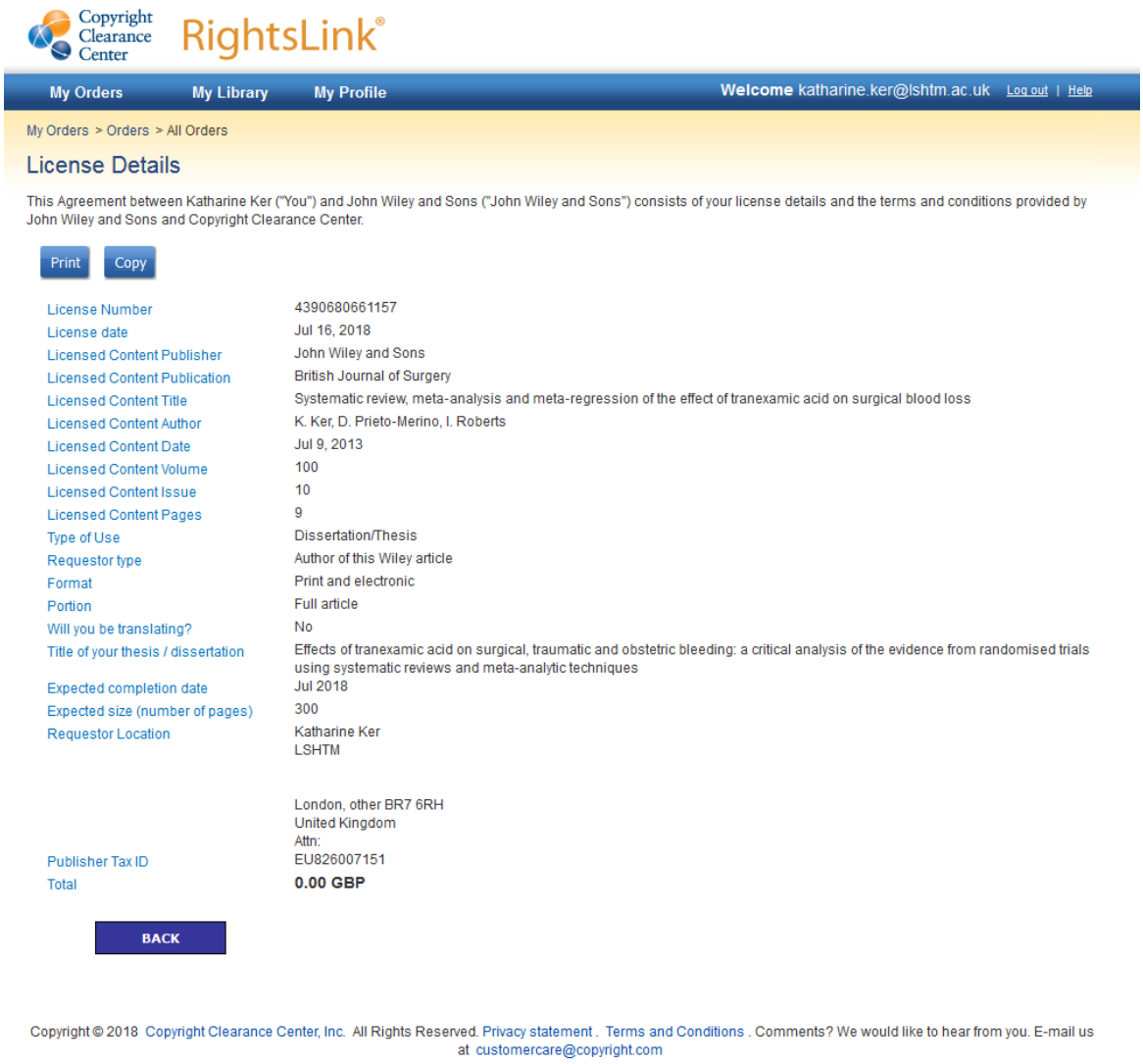

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Appendix J. Research Paper 2: Published article

Systematic review

Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss

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Correspondence to: Ms K. Ker (e-mail: katharine.ker@lshtm.ac.uk)

Background: Tranexamic acid (TXA) reduces blood transfusion in surgery but the extent of the reduction in blood loss and how it relates to the dose of TXA is unclear.

Methods: A systematic review of randomized trials was performed. Data were extracted on blood loss from trials comparing intravenous TXA with no TXA or placebo in surgical patients. A Bayesian linear regression was used to describe the relationship between the reduction in blood loss with TXA and the extent of bleeding as measured by the mean blood loss in the control group. A meta-analysis of the log-transformed data was conducted to quantify the effect of TXA on blood loss, stratified by type of surgery, timing of TXA administration and trial quality. Meta-regression was used to explore the effect of TXA dosage.

Results: Data from 104 trials were examined. Although the absolute reduction in blood loss with TXA increased as surgical bleeding increased, the percentage reduction was similar. TXA reduced blood loss by 34 per cent (pooled ratio 0·66, 95 per cent confidence interval 0·65 to 0·67; $P < 0·001$). The percentage reduction in blood loss with TXA differed by type of surgery, timing of TXA administration and trial quality, but the differences were small. The effect of TXA on blood loss did not vary over the range of doses assessed (5·5–300 mg/kg).

Conclusion: TXA reduces blood loss in surgical patients by about one-third. A total dose of 1 g appears to be sufficient for most adults. There is no evidence to support the use of high doses.

Paper accepted 9 May 2013
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Introduction

Tranexamic acid (TXA) reduces the probability of receiving a blood transfusion in surgery. A systematic review of randomized clinical trials showed that TXA reduces the probability of blood transfusion by 38 per cent (pooled risk ratio 0·62, 95 per cent confidence interval (c.i.) 0·58 to 0·65; $P < 0·001$)[1]. However, the extent to which TXA reduces surgical bleeding and its relationship with the dose of TXA and type of surgery remains uncertain. Because the decision to transfuse depends on factors other than blood loss, the effect on blood transfusion may not be an accurate indicator of the effect of TXA on surgical bleeding.

Clinical trials of TXA in surgery usually report the mean blood loss in each group. Previous systematic reviews have combined these data to obtain the average difference in mean blood loss between TXA and control groups. However, the usefulness of such a measure is questionable. It would be surprising if TXA reduced blood loss by the same volume in surgical procedures that involved different amounts of bleeding. On the other hand, it may be reasonable to expect a similar percentage reduction in blood loss with TXA.

The objective of this study was to examine whether the effect of TXA on blood loss varies with the extent of surgical bleeding. The magnitude of the percentage reduction in blood loss with TXA was estimated, and how the effect varies by type of surgery, timing of TXA administration, trial quality and dosage was assessed.

Methods

A systematic review of randomized clinical trials of TXA in surgical patients was conducted. The methods used to identify trials for the review have been described in detail elsewhere[1]. In brief, a comprehensive search was undertaken for all randomized clinical trials comparing intravenous TXA with placebo or no intervention in elective or emergency surgery. Two authors screened

the search output and the full texts of all eligible trials were obtained. Information was extracted on patient characteristics, type of surgery, dose and timing of TXA administration and average blood loss (mean and standard deviation). The risk of bias associated with sequence generation, allocation concealment, blinding and the completeness of outcome data was assessed for each trial.

Statistical analysis

To explore the relationship between the reduction in blood loss with TXA and the extent of bleeding, for each trial the mean blood loss in the TXA group was plotted against the mean blood loss in the control group. This relationship was examined using linear regression estimated using a Bayesian model as proposed by Thompson *et al.*[2] to account for random sampling error in the estimates of the regression variables (in the sample means from each trial). Statistical details of the model are given in *Appendix S1* (supporting information).

To quantify the effect of TXA on the percentage reduction in blood loss, a meta-analysis using both fixed-effect and random-effects models was conducted. For the purpose of the meta-analysis, blood loss data were log-transformed and the analysis was conducted using the transformed values. The formulae used for the transformations are given in *Appendix S1* (supporting information). A meta-analysis (using arithmetic means) of the differences in means using the transformed blood loss data corresponds to a meta-analysis (using geometric means) of the ratio of means in the original scale. The pooled estimates were back-transformed to give the blood loss ratios and 95 per cent c.i. on the original scale. Statistical heterogeneity was examined by visual inspection of forest plots, the I^2 statistic and the χ^2 test.

Subgroup analyses were undertaken to assess the effect of TXA by the type of surgery, timing of TXA administration (preincision, postincision), allocation concealment (adequate, unclear, inadequate) and type of comparator (placebo or no intervention). Heterogeneity between subgroups was assessed using the χ^2 test (fixed-effect analysis only). Finally, a random-effects meta-regression was carried out to investigate the association between the effect of TXA on blood loss and the total dose of TXA (mg/kg) as a continuous variable. If a fixed dose was used in the trials (for example 1000 mg), it was converted to milligrams per kilogram by dividing by 70 kg. A funnel plot was inspected for the presence of small study effects. STATA® version 12 (StataCorp, College Station, Texas, USA) statistical software[3] was used for all analyses.

Results

The trial selection process is shown in *Fig. 1*. One hundred and twenty-nine randomized clinical trials were identified. The characteristics of the included trials are summarized in *Table S1* (supporting information). Nine reports described multiarm trials involving a total of 23 eligible pair wise comparisons; each of these was included in the analysis as a separate trial. One hundred and four randomized comparisons, described in 90 articles[4–93], reported data on blood loss in a format suitable for this analysis. These trials involved a total of 8030 patients; 4224 received TXA and 3806 received a placebo or no intervention.

The trials involved cardiac (54 trials), orthopaedic (33), obstetric and gynaecological (7), head and neck (7), breast cancer (1), hepatic (1) and urological (1) surgery. Eighty trials gave TXA before surgical incision and 24 trials gave TXA after incision. Thirty-three trials were assessed as being adequately concealed (low risk of bias), and five trials as inadequately concealed (high risk of bias). The remaining 66 trials presented insufficient information on allocation concealment to allow judgement and were rated as unclear. Seventy-five trials were placebo-controlled, whereas a no-intervention group was used as the control in the remaining 29 trials.

Effect of tranexamic acid on blood loss

The relationship between mean blood loss in the TXA group and in the control group is shown in *Fig. 2*. Mean blood loss in the TXA group increased as that in the control group increased, but to a lesser extent. The intercept of the regression line (dotted line) estimated by the Bayesian model was 4 (95 per cent c.i. −8 to 18) ml, a negligible value in the context of the observed blood loss estimates. The Bayesian model corresponded closely with the regression line predicted, assuming a constant percentage reduction in blood loss (dashed line) and an intercept of zero.

The summary results of a fixed-effect meta-analysis of the percentage reduction in blood loss with TXA are shown in *Fig. 3*. A forest plot showing the estimates from each trial is shown in *Fig. S1* (supporting information). The back-transformed pooled ratio of blood loss with TXA was 0·66 (95 per cent c.i. 0·65 to 0·67; $P < 0·001$), indicating that TXA reduced blood loss by 34 per cent. There was substantial statistical heterogeneity between trials ($I^2 = 83$ per cent). There was heterogeneity in the magnitude of effect by type of surgery, although the extent of the variation was small. All of the subgroup estimates were consistent with a reduction in blood loss, and all but one was statistically significant at the 5 per cent level. TXA had a greater effect on blood loss when

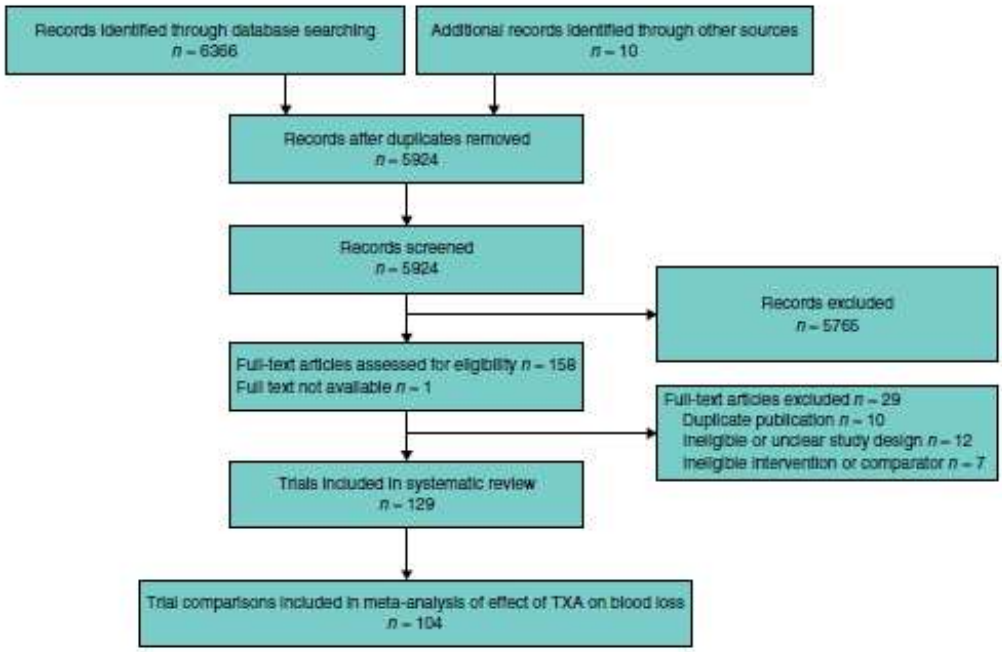

Fig. 1 PRISMA flow diagram for selection of trials. TXA, tranexamic acid

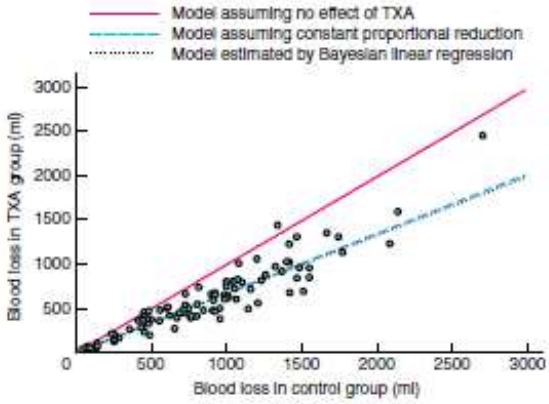

Fig. 2 Mean blood loss in tranexamic acid (TXA) group *versus* control group, with regression lines from models assuming no effect of TXA, a constant proportional reduction, and estimated by Bayesian linear regression

given after incision, although the difference between the preincision and postincision estimates was small. There was heterogeneity in the magnitude of effect by adequacy of allocation concealment. When the analysis was restricted to the 33 adequately concealed trials, TXA reduced blood loss by 30 per cent (effect estimate 0·70, 95 per cent c.i. 0·68 to 0·72; $P < 0·001$). There was no evidence for heterogeneity in the estimated effects of TXA compared with either placebo or a no-intervention control group. The results from random-effects meta-analyses were similar to those of the fixed-effect analyses, and are shown in *Table S2* (supporting information).

A fixed dose was converted to the equivalent milligram per kilogram dose in 21 trials. The total dose of TXA used in the trials ranged from 5·5 to 300 mg/kg. The median dose was 22 mg/kg, with the majority of trials (70 per cent) using a total dose of 30 mg/kg or less. Results from the meta-regression suggested that the effect of TXA on blood loss did not vary over the dose range assessed (coefficient 0·889, 95 per cent c.i. 0·787 to 1·004; $P = 0·059$).

There was no clear asymmetry in the funnel plot (*Fig. 4*).

Discussion

The results of this meta-analysis suggest that TXA reduces surgical blood loss by about one-third. Although the magnitude of the reduction differs by type of surgery and timing of TXA administration, the differences are small and unlikely to be clinically important. A total dose of 1 g is likely to be sufficient for most adults, and there is no evidence to support the use of higher doses.

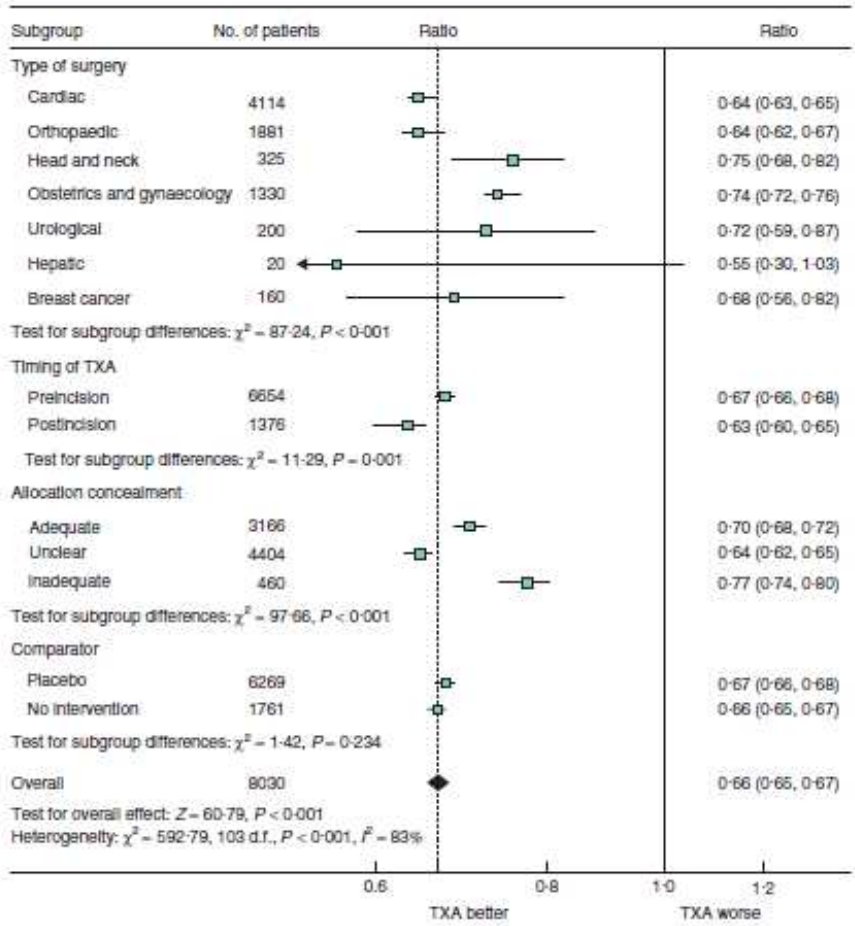

Fig. 3 Forest plot of the effect of tranexamic acid (TXA) on blood loss stratified by type of surgery, timing of TXA administration, adequacy of allocation concealment and type of comparator. A fixed-effect model was used for meta-analysis. Effect estimates are back-transformed ratios of geometric means with 95 per cent confidence intervals. The overall pooled estimate is marked by the diamond and dotted line

The validity of these results depends on the quality of the included trials, and many were of low quality. Less than a third of trials were judged to be at low risk of bias on the basis of allocation concealment. Nevertheless, even when the analysis was restricted to adequately concealed trials, the effect of TXA on blood loss remained large and highly statistically significant. Statistical heterogeneity between trials was substantial and was not explained by type of surgery, trial quality, timing of TXA administration or dose. Differences in the methods used to estimate blood loss, the duration over which blood loss was measured and other aspects of trial quality may explain some of the heterogeneity. The subgroup analyses showed that the effect of TXA on blood loss varied by type of surgery, trial quality and timing of TXA. However, the extent of the variation was small and the clinical importance of such small variations is questionable.

There was no obvious asymmetry in the funnel plot, but reporting bias remains a concern, particularly as about one-fifth of trials were not included in the analysis owing to unsuitable data or inadequate reporting. If many of these or other unpublished trials showed little or no effect of TXA on blood loss, the analysis would have overestimated the treatment effect. However, in consideration of the magnitude and precision of the effect, it is unlikely that any such bias would account for all of the observed effect.

The reduction in bleeding with TXA is almost identical to the reduction in the risk of receiving a blood transfusion

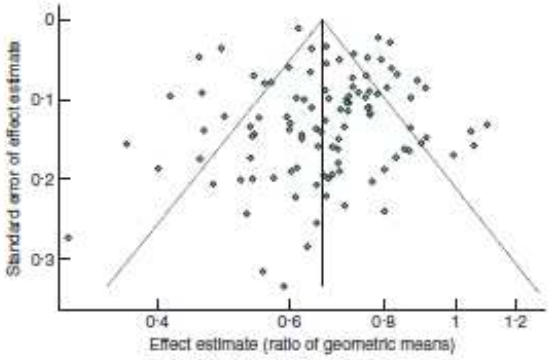

Fig. 4 Funnel plot with pseudo 95 per cent confidence intervals for meta-analysis of the effect of tranexamic acid on blood loss

with TXA, suggesting that, in surgery, transfusion may be closely titrated to blood loss. This may not be the case in injured patients. The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial found that early administration of TXA reduced the risk of death from bleeding by about one-third, but there was no clear reduction in the risk of receiving a blood transfusion[94,95].

Although there is reliable evidence that TXA reduces bleeding and blood transfusion in surgery, its effect on other important outcomes including death and thromboembolic events remains uncertain[1]. There is no evidence that it increases the risk of thromboembolic events, but this is a theoretical concern that may deter some surgeons from using TXA. These uncertainties need to be resolved before TXA can be recommended for routine use in surgery.

The apparent lack of a dose–response relationship across the range of doses examined (5·5–300 mg/kg) has important implications for the use of TXA in surgery. TXA crosses the blood–brain barrier and there is some evidence from observational studies of patients undergoing cardiac surgery that high-dose TXA (100 mg/kg or more) may cause seizures[96,97]. The present results imply that the clinical benefit of TXA on bleeding can be achieved at doses much lower than those associated with such adverse effects. Indeed, a total dose of about 14 mg/kg (or about 1 g in adults) appears to be sufficient for most patients.

Disclosure

The authors declare no conflict of interest.

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Appendix K. Research Paper 2: Further detail of statistical methods

Bayesian model for linear regression of means in the two groups

Ideally the population means for each group in each trial would be used for the regression however, in this case only the sample means were available. According to the Central Limit Theorem, the means of random samples should be normally distributed centred on the population mean. The standard error of the sample mean with the sample variance was estimated using the Student's t distribution as follows.

So: yc[i] ~ Student-T(mc[i] , sec[i], nc[i]) and yt[i] ~ Student-T(mt[i] , set[i], nt[i])

And: sec[i] = sdc[i] / sqrt(nc[i]) and set[i] = sdt[i] / sqrt(nt[i])

Where: 'yc[i]' is sample mean of controls, 'mc[i]' is population mean of controls and 'sec[i]' is standard error of yc[i] estimated with the sample standard deviation sdc[i] and sample size nc[i], all in trial[i]. Also yt[i], mt[i], set[i], sdt[i] and nt[i] have the same meaning for the treatment group in trial[i].

The linear model is: mt[i] <- intercept + slope*mc[i] + e[i]

e[i] ~ dnorm(0, sde[i])

sde[i] <- e0 + e1*mc[i]

Where e[i] is the random error in the regression that is assumed to be distributed normally and independently for each trial. However, as it is not realistic to think of an error of constant standard deviation (sde[i]) the standard deviation was allowed to vary with the mean of the control group.

Interpretation: The 'intercept' is expected to be 0 if there is a constant proportional effect of TXA. The 'slope' is the coefficient that estimates the proportional reduction in blood loss in intervention compared to control group.

Priors: Non informative priors to mc[i], intercept, slope, e0 and e1 were assigned.

Transformation of blood loss data into the logarithmic scale

Ideally, individual patient data would be available and the natural logarithm of the estimated blood loss in each patient is taken and the mean and standard deviation calculated using the transformed data. Because individual patient data were not available, the summary statistics from the trials were used to estimate the log-transformed values.

It was assumed that the variable blood loss (X) followed a log-normal distribution $X \sim LogNormal\ (\mu,\sigma)$, thus $Ln(X) \sim Normal(\mu_L,\sigma_L)$ and the equations linking the means (μ) and standard deviation (σ) of the distributions were:

$$\sigma_L = \sqrt{Ln\left(1+\frac{\sigma^2}{\mu^2}\right)} \quad \text{and} \quad \mu_L = Ln(\mu) - \frac{(\sigma_L)^2}{2}$$

For trials that reported average blood loss as means with standard deviations, the equations above were used to estimate the log means and standard deviations.

Appendix L. Research Paper 2: Characteristics of included trials

Trial	Participants	Intervention and comparator	Risk of bias judgements
Alvarez 2008 Spain	95 patients undergoing knee arthroplasty **TXA group** (n=46): M/F=7/39; mean age(sd)=71(9) **Control group** (n=49): M/F=10/39; mean age(sd)=72(7)	**TXA group**: bolus 10mg/kg before deflation of tourniquet, then infusion 1mg/kg/hr **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data unclear
Armellin 2001 Italy	283 patients undergoing aortic valve replacement **TXA group** (n=143): M/F=71/72; mean age(sd)=65.7(11.7) **Control group** (n=140): M/F=90/50; mean age(sd)=65.9(12.8)	**TXA group**: 2.5g before skin incision, further 2.5g added to pump prime **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data unclear
Auvinen 1987 Finland	76 patients undergoing surgery of the thyroid gland **TXA group** (n=39): M/F=4/35; mean age(sd)=50(16.4) **Control group** (n=37): M/F=2/35; mean age(sd)=51(13.5)	**TXA group**: 0.5g at induction of anaesthesia then 0.5g during each 8h of the intra- and post-op period 24 hrs **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Benoni 1996 Sweden	96 patients undergoing knee arthroplasty **TXA group** (n=43): M/F=13/30; mean age(sd)=76(7) **Control group** (n=43): M/F=10/33; mean age(sd)=74(7)	**TXA group**: 10mg/kg given as slow injection towards end of operation, before deflation of tourniquet **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
Benoni 2001 Sweden	38 patients undergoing hip arthroplasty **TXA group** (n=18): M/F=9/9; mean age(sd)=66(9.5) **Control group** (n=20): M/F=10/10; mean age(sd)=68(9.4)	**TXA group**: 10 mg/kg immediately before operation **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Blauhut 1994 Austria/Switzerland	30 patients undergoing cardiac surgery **TXA group** (n=16): M/F=13/3; mean age(sd)=62.5(2.2) **Control group** (n=14): M/F=11/3; mean age(sd)=62.7(2.6)	**TXA group**: 10 mg/kg 30 mins before skin incision, then 1mg/kg per hr for 10 hr after the beginning of surgery **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data unclear
Bulutcu 2005 Turkey	50 paediatric patients undergoing cardiac surgery **TXA group** (n=25): M/F=15/10; mean age(sd)=4.1(2.0) **Control group** (n=25): M/F=12/13; mean age(sd)=3.8(2.4)	**TXA group**: 100mg/kg after anaesthesia, 100mg/kg in pump prime and 100mg/kg after weaning from CPB until skin closure **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data unclear
Caglar 2008 Turkey	100 patients undergoing myomectomy **TXA group** (n=50): All F; mean age(sd)=34.2(5.5) **Control group** (n=50): All F; mean age(sd)=36.5(2.6)	**TXA group**: Bolus of 10mg/kg during 10 min, 15 mins before incision, then continuous infusion of 1mg/kg/h 10 hrs **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Casati 2004a Italy	51 patients undergoing cardiac surgery **TXA group** (n=26): M/F=24/2; mean age(sd)=64(9) **Control group** (n=25): M/F=21/4; mean age(sd)=60(9)	**TXA group**: Bolus 1g in 20 mins after induction anaesthesia before skin incision then continuous infusion of 400mg/h during operation **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
Casati 2004b Italy	51 patients undergoing cardiac surgery **TXA group** (n=26): M/F=20/6; mean age(sd)=64(12) **Control group** (n=25): M/F=21/4; mean age(sd)=61(11)	**TXA group**: 1g in 20 mins after induction anaesthesia before skin incision then infusion of 400mg/h during operation plus 500mg added to priming **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Chauhan 2003 India	120 paediatric patients undergoing cardiac surgery **TXA group** (n=96): M/F=71/25; mean age(sd)=4.4(3.6) **Control group** (n=24): M/F=20/4; mean age(sd)=4.2(3.3)	**TXA group**: 10mg/kg after anaesthetic induction, 10mg/kg on CPB and 10mg/kg after protamine reversal of heparin **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chauhan 2004a India	100 paediatric patients undergoing cardiac surgery **TXA group** (n=50): M/F=36/14; mean age(sd)=4.1(2.4) **Control group** (n=50): M/F=35/15; mean age(sd)=4.2(2.1)	**TXA group**: 10mg/kg after anaesthetic induction, 10mg/kg on CPB and 10mg/kg after protamine reversal of heparin **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chauhan 2004b India	Paediatric patients undergoing cardiac surgery **TXA group** (n=30): M/F=24/6; mean age(sd)=3.3(2.9) **Control group** (n=30): M/F=20/10; mean age(sd)=4.3(3.3)	**TXA group**: single dose of 50mg/kg given over 30 mins after anaesthetic induction **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chauhan 2004c India	Paediatric patients undergoing cardiac surgery **TXA group** (n=30): M/F=25/5; mean age(sd)=4.2(4.0) **Control group**: as for Chauhan 2004b	**TXA group**: 10mg/kg given over 30 mins after anaesthetic induction, followed by infusion of 1mg/kg for 8 hours **Control group**: as for Chauhan 2004b	• Sequence generation unclear • Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chauhan 2004d	Paediatric patients undergoing cardiac surgery		• Sequence generation unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
India	**TXA group** (n=30): M/F=26/4; mean age(sd)=3.0(4.3) **Control group**: as for Chauhan 2004b	**TXA group**: 10mg/kg given over 30 mins after anaesthetic induction, 10mg/kg on CPB, and 10mg/kg after protamine administration **Control group**: as for Chauhan 2004b	• Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chauhan 2004e India	Paediatric patients undergoing cardiac surgery **TXA group** (n=30): M/F=25/5; mean age(sd)=2.9(5.0) **Control group**: as for Chauhan 2004b	**TXA group**: 20mg/kg after anaesthetic induction and 20mg/kg after protamine **Control group**: as for Chauhan 2004b	• Sequence generation unclear • Allocation concealment high • Blinding unclear • Incomplete outcome data low
Chen 2008 Taiwan	55 patients undergoing head and neck surgery **TXA group** (n=26): M/F=15/11; mean age(sd)=49.8(13.0) **Control group** (n=29): M/F=16/13; mean age(sd)=46.4(14.8)	**TXA group**: Bolus 10mg/kg before incision, then continuous infusion of 1mg/kg/h during the operation **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data high
Choi 2009 Hong Kong	61 patients undergoing head and neck surgery **TXA group** (n=32): M/F=10/22; mean age(sd)=23.9(6.1) **Control group** (n=29): M/F=11/18; mean age(sd)=22.8(4.5)	**TXA group**: 20mg/kg bolus just before surgery **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Claeys 2007 Belgium	40 patients undergoing hip arthroplasty **TXA group** (n=20): M/F=5/15; mean age(sd)=73(8) **Control group** (n=20): M/F=7/13; mean age(sd)=68(11)	**TXA group**: Single pre-op dose of 15mg/kg as slow infusion 15 mins before surgery **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Coffey 1995 USA	30 patients undergoing cardiac surgery **TXA group** (n=16): M/F=5/11; mean age=63.94 **Control group** (n=14): M/F=5/9; mean age=64.75	**TXA group**: Single pre-op dose of 15mg/kg as slow infusion 15 mins before surgery **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
Corbeau 1995 USA	61 patients undergoing cardiac surgery **TXA group** (n=41): M/F=26/15; mean age(sd)=62.46(14.33) **Control group** (n=20): M/F=16/4; mean age(sd)=63(15.59)	**TXA group**: 15 mg/kg between heparin injection and beginning of extracorporeal circulation, 15mg/kg after protamine injection **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data unclear
Crescenti 2011 Italy	200 patients undergoing prostatectomy **TXA group** (n=100): All M; mean age(sd)=64(7.4) **Control group** (n=100): All M; mean age(sd)=64(7.8)	**TXA group**: 500mg, then infusion of 250mg/h during operation **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Dadure 2011 France	39 paediatric patients undergoing head and neck surgery **TXA group** (n=19): M/F=17/2; median age(range)=7 months (4-15) **Control group** (n=20): M/F=17/3; median age(range)=6 months(3-9)	**TXA group**: 15mg/kg over 15 mins after induction of anaesthesia, before skin incision, then continuous infusion of 1ml/kg/hr until skin closure **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Diprose 2005 UK	123 patients undergoing cardiac surgery **TXA group** (n=62): M/F=49/11; median age(range)=65 (40-81) **Control group** (n=61): M/F=52/8; median age(range)=65(32-82)	**TXA group**: 5g IV in 200ml volume at start of surgery **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data high
Durán de la Fuente 2003 Spain	20 paediatric patients undergoing cranial surgery **TXA group** (n=10): M/F=3/7; mean age(sd)=6(1) **Control group** (n=10): M/F=3/7; mean age(sd)=7(3)	**TXA group**: 15mg/kg IV on anaesthetic induction, every 4 hrs during surgery and every 8 hrs for 48 hrs after surgery **Control group**: no TXA	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
Ekback 2000 Sweden	40 patients undergoing hip arthroplasty **TXA group** (n=20): M/F=9/11; mean age(sd)=66.4(9.0) **Control group** (n=20): M/F=11/9; mean age(sd)=65.6(8.8)	**TXA group**: bolus of 10mg/kg before surgical incision, continuous infusion of 1mg/kg/hr during 10 hr started immediately after 1st bolus dose, 2nd bolus dose of 10mg/kg given 3 hr later **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Elwatidy 2008 Saudi Arabia	64 patients undergoing spinal surgery **TXA group** (n=32): M/F=21/11; mean age(sd)=51.56(19.08) **Control group** (n=32): M/F=18/14; mean age(sd)=49.75(21.04)	**TXA group**: loading dose of 2g followed by continuous infusion of 100mg/h during surgery and for 5 hrs after operation **Control group**: placebo	• Sequence generation high • Allocation concealment low • Blinding low • Incomplete outcome data low
Gai 2004 China	180 patients undergoing caesarean section **TXA group** (n=91): All F; mean age(sd)=29.71(4.18) **Control group** (n=89): All F; mean age(sd)=29.75(4.01)	**TXA group**: 1g Iv infused over 5 mins, 10 mins before incision **Control group**: no intervention (standard care)	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Garneti 2004 UK	50 patients undergoing hip arthroplasty **TXA group** (n=25): M/F=NR; mean age(sd)=69.6(11.99) **Control group** (n=25): M/F=NR; mean age(sd)=67.6(11.4)	**TXA group**: 10mg/kg as a bolus at anaesthesia **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Gobbur 2010 India	100 patients undergoing caesarean section **TXA group** (n=50): All F=NR; mean age(sd)=NR **Control group** (n=50): All F; mean age(sd)=NR	**TXA group**: 1g 20 mins before surgery **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
Gohel 2007 India	100 patients undergoing caesarean section **TXA group** (n=50): All F=NR; mean age(sd)=24.30(3.65) **Control group** (n=50): All F; mean age(sd)=24.89(3.99)	**TXA group**: 1g over 5 minutes, 20 mins before incision **Control group**: no intervention (standard care)	• Sequence generation high • Allocation concealment high • Blinding high • Incomplete outcome data low
Goobie 2011 USA	46 paediatric patients undergoing head and neck surgery **TXA group** (n=23): M/F=15/8; mean age(sd)=23 months(19) **Control group** (n=20): M/F=11/9; mean age(sd)=25 months(20)	**TXA group**: after induction of anaesthesia and before skin incision, loading dose of 50mg/kg as infusion over 15 mins, followed by infusion of 5mg/kg/hr **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Greiff 2011 Norway	63 patients undergoing cardiac surgery **TXA group** (n=30): M/F=18/12; mean age(sd)=77(4) **Control group** (n=33): M/F=19/14; mean age(sd)=77(5)	**TXA group**: 10mg/kg bolus injection before surgery, then 1mg/kg/h as infusion during surgery **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data low
Gungorduk 2010 Turkey	660 patients undergoing caesarean section **TXA group** (n=330): All F=18/12; mean age(sd)=26.3(3.5) **Control group** (n=330): All F=19/14; mean age(sd)=26.6(3.6)	**TXA group**: 1g over 5 mins at least 10 mins prior to skin incision **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Hiippala 1995 Finland	29 patients undergoing knee arthroplasty **TXA group** (n=15): M/F=2/12; mean age(range)=70(56-82) **Control group** (n=13): M/F=3/10; mean age(range)=70(63-78)	**TXA group**: 15mg/kg , 2/5 minutes before tourniquet was deflated **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data high
Hiippala 1997	77 patients undergoing knee arthroplasty **TXA group** (n=39):		• Sequence generation unclear unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
Finland	M/F=4/35; mean age(sd)=70(7) **Control group** (n=38): M/F=8/30; mean age(sd)=69(5)	**TXA group**: 15mg/kg just before tourniquet was deflated, further 2 doses of 10mg/kg given during the operation day **Control group**: placebo	• Allocation concealment low • Blinding unclear • Incomplete outcome data
Horrow 1990 USA	38 patients undergoing cardiac surgery **TXA group** (n=18): M/F=NR; mean age(sd)=62(9) **Control group** (n=20): M/F=NR; mean age(sd)=66(10)	**TXA group**: 10 mg/kg infusion over 20 min period followed by infusion of 1mg/kg for 10 hours **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Horrow 1991a USA	81 patients undergoing cardiac surgery **TXA group** (n=37): M/F=NR; mean age(sd)=65(11) **Control group** (n=44): M/F=NR; mean age(sd)=64(10)	**TXA group**: loading dose 10mg/kg over 30 mins after induction of anaesthesia, followed by 12 hr infusion of 1 mg/kg/hr **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Horrow 1991b USA	78 patients undergoing cardiac surgery **TXA group** (n=40): M/F=NR; mean age(sd)=63(9) **Control group** (n=38): M/F=NR; mean age(sd)=63(11)	**TXA group**: loading dose 10mg/kg over 30 mins after induction of anaesthesia, followed by 12 hr infusion of 1 mg/kg/hr + desmopressin **Control group**: placebo + desmopressin	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Horrow 1995a USA	Patients undergoing cardiac surgery **TXA group** (n=24): M/F=18/6; mean age(sd)=67(9.8) **Control group** (n=38): M/F=23/4; mean age(sd)=63(10.4)	**TXA group**: loading dose of 2.5mg/kg after the induction of anaesthesia over a period of 30 mins followed by a 12 hour continuous infusion of 0.25mg/kg/hr **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Horrow 1995b USA	Patients undergoing cardiac surgery **TXA group** (n=22): M/F=19/3; mean age(sd)=61(9.4) **Control group**: as for Horrow 1995a	**TXA group**: loading dose of 5.0mg/kg after the induction of anaesthesia over a period of 30 mins followed by a 12 hour continuous infusion of 0.5mg/kg/hr	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
		Control group: as for Horrow 1995a	
Horrow 1995c USA	Patients undergoing cardiac surgery **TXA group** (n=21): M/F=18/3; mean age(sd)=66(9.2) **Control group**: as for Horrow 1995a	**TXA group**: loading dose of 10mg/kg after the induction of anaesthesia over a period of 30 mins followed by a 1 hr continuous infusion of 1.0mg/kg/hr **Control group**: as for Horrow 1995a	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Horrow 1995d USA	Patients undergoing cardiac surgery **TXA group** (n=21): M/F=18/3; mean age(sd)=66(9.2) **Control group**: as for Horrow 1995a	**TXA group**: loading dose of 20mg/kg after the induction of anaesthesia over a period of 30 mins followed by a 12 hr continuous infusion of 2.0mg/kg/hr **Control group**: as for Horrow 1995a	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Horrow 1995e USA	Patients undergoing cardiac surgery **TXA group** (n=27): M/F=21/6; mean age(sd)=65(10.4) **Control group**: as for Horrow 1995a	**TXA group**: loading dose of 40mg/kg after the induction of anaesthesia over a period of 30 mins followed by a 12 hr continuous infusion of 4.0mg/kg/hr **Control group**: as for Horrow 1995a	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Husted 2003 Denmark	40 patients undergoing hip arthroplasty **TXA group** (n=20): M/F=7/13; mean age=65 **Control group**: (n=20): M/F=6/14; mean age=67	**TXA group**: 10mg/kg bolus followed by continuous infusion of 1mg/kg/hr for 10 hrs **Control group**: as for Horrow 1995a	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Isetta 1993 France	140 patients undergoing cardiac surgery **TXA group** (n=70): M/F=NR; age=NR **Control group**: (n=70):	**TXA group**: 15mg/kg before injection of heparin prior to CPB	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear low

Trial	Participants	Intervention and comparator	Risk of bias judgements
	M/F=NR; age=NR	**Control group**: no intervention (standard care)	• Incomplete outcome data
Jansen 1999 Belgium	42 patients undergoing knee arthroplasty **TXA group** (n=21): M/F=5/16; median age(range)=70.7(62-80) **Control group** (n=21): M/F=3/18; median age(range)=71.0(64-84)	**TXA group**: 15mg/kg 30 min before inflation of the tourniquet and surgery, and again every 8 hrs for 3 days **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Jimenez 2007 Spain	50 patients undergoing cardiac surgery **TXA group** (n=24): M/F=12/12; mean age(95% CI)=66(63-70) **Control group** (n=26): M/F=15/11; mean age(95% CI)=67(62-71)	**TXA group**: 2g pre and post surgery **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data low
Johansson 2005 Sweden	100 patients undergoing hip arthroplasty **TXA group** (n=47): M/F=25/22; mean age(sd)=68(8) **Control group** (n=53): M/F=28/25; mean age(sd)=69(7)	**TXA group**: 15mg/kg before start of the operation **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Kakar 2009 India	50 patients undergoing knee arthroplasty **TXA group** (n=25): M/F=7/18; mean age(sd)=62.78(13.48) **Control group** (n=25): M/F=7/18; mean age(sd)=66.69(5.88)	**TXA group**: 10mg/kg just before tourniquet inflation followed by 1mg/kg/hr until closure of wound **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Karski 1995a Canada	Patients undergoing cardiac surgery **TXA group** (n=49): M/F=NR; mean age(sd)=59(3) **Control group** (n=48): M/F=NR; mean age(sd)=58(2)	**TXA group**: 10g over 20 minutes **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data high

Trial	Participants	Intervention and comparator	Risk of bias judgements
Karski 1995b Canada	Patients undergoing cardiac surgery **TXA group** (n=50): M/F=NR; mean age(sd)=63(1) **Control group**: as for Karski 1995a	**TXA group**: 10g over 20 minutes and another 10g infused over 5 hours **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data high
Karski 2005 Canada	312 patients undergoing cardiac surgery **TXA group** (n=25): M/F=7/18; mean age(sd)=62.78(13.48) **Control group** (n=25): M/F=7/18; mean age(sd)=66.69(5.88)	**TXA group**: 100 mg/kg over 20 minutes after induction of anaesthesia **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Katoh 1997a Japan	Patients undergoing cardiac surgery **TXA group** (n=31): M/F=22/9; mean age(sd)=63.7(1.5) **Control group** (n=31): M/F=22/9; mean age(sd)=64.7(2.1)	**TXA group**: infusion 100mg/kg over 20 mins after induction of anaesthesia and before CPB **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Katoh 1997b Japan	Patients undergoing cardiac surgery **TXA group** (n=31): M/F=21/10; mean age(sd)=62.9(1.7) **Control group**: as for Katoh 1997b	**TXA group**: infusion 100mg/kg over 20 mins after induction of anaesthesia and before CPB and 50mg/kg infused over 20 mins after being weaned from CPB **Control group**: as for Katoh 1997b	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Katsaros 1996 USA	210 patients undergoing cardiac surgery **TXA group** (n=104): M/F=68/36; mean age(sd)=65(0.91) **Control group** (n=106): M/F=80/26; mean age(sd)=63(1.2)	**TXA group**: 10g over 20 mins before incision **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Kazemi 2010 Iran	64 patients undergoing hip arthroplasty **TXA group** (n=32): M/F=23/9; mean age(sd)=46.6(16.2)	**TXA group**: 15mg/kg given 5 mins pre-op **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear low

Trial	Participants	Intervention and comparator	Risk of bias judgements
	Control group (n=32): M/F=20/12; mean age(sd)=45.4(17.2)		• Blinding low • Incomplete outcome data
Kojima 2001 Japan	22 patients undergoing hip arthroplasty **TXA group** (n=11): M/F=6/5; mean age(sd)=56(4) **Control group** (n=11): M/F=8/3; mean age(sd)=60(2)	**TXA group**: bolus 100mg/kg over 20 mins after anaesthesia induction and prior to skin incision **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Kuitunen 2005 Finland	40 patients undergoing cardiac surgery **TXA group** (n=20): M/F=NR; mean age(sd)=63(2) **Control group** (n=20): M/F=NR mean age(sd)=65(2)	**TXA group**: 15mg/kg after induction of anaesthesia then infusion of 15mg/kg until end of surgery and 15mg/kg added to pump prime of CPB circuit **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data low
Kuitunen 2006 Finland	30 patients undergoing cardiac surgery **TXA group** (n=15): M/F=12/3; mean age(sd)=57(16) **Control group** (n=15): M/F=11/4; mean age(sd)=61(11)	**TXA group**: 10 min bolus of 1g in 100ml saline, given after operation **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Leelahanon 2002 Thailand	101 patients undergoing cardiac surgery **TXA group** (n=50): M/F=NR; age=NR **Control group** (n=15): M/F=NR; age=NR	**TXA group**: 1000mg before sternotomy **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Lemay 2004 Canada	39 patients undergoing hip arthroplasty **TXA group** (n=20): M/F=12/8; mean age(sd)=59.7(10.3) **Control group** (n=19): M/F=13/6; mean age(sd)=53.6(12.8)	**TXA group**: 10mg/kg bolus before surgery plus 1mg/kg/hr infusion until wound closure **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
Lin 2011 Taiwan	100 patients undergoing knee arthroplasty **TXA group** (n=50): M/F=6/44; mean age(sd)=69.2(6.3) **Control group** (n=50): M/F=9/41; mean age(sd)=58.3(8.4)	**TXA group**: 10mg/kg before deflation of tourniquet usually at end of wound closure **Control group**: placebo	• Sequence generation high • Allocation concealment high • Blinding unclear • Incomplete outcome data high
MacGillivray 2010a Dubai	Patients undergoing knee arthroplasty **TXA group** (n=20): M/F=7/13; mean age(sd)=69.2(6.3) **Control group** (n=20): M/F=5/15; mean age(sd)=66(7.3)	**TXA group**: 1 dose of 10mg/kg over 10 mins before deflation of tourniquet, 2nd dose of 10mg/kg given 3 hrs later **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
MacGillivray 2010b Dubai	Patients undergoing knee arthroplasty **TXA group** (n=20): M/F=8/12; mean age(sd)=65(4.3) **Control group**: as for MacGillivray 2010a	**TXA group**: 1 dose of 15mg/kg over 10 mins before deflation of tourniquet, 2nd dose of 15mg/kg given 3 hrs later **Control group**: as for MacGillivray 2010a	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Maddali 2007 Oman	222 patients undergoing cardiac surgery **TXA group** (n=111): M/F=80/31; mean age(sd)=57.1(8.9) **Control group** (n=111): M/F=72/39; mean age(sd)=58.2(8.3)	**TXA group**: loading dose of 10mg/kg before incision, then continuous infusion of 1mg/kg/hr until end of CPB **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data low
Mehr-Aein 2007 Iran	66 patients undergoing cardiac surgery **TXA group** (n=33): M/F=NR; mean age(sd)=44(10) **Control group** (n=33): M/F=NR; mean age(sd)=45(10)	**TXA group**: loading dose of 15mg/kg at beginning of surgery, same dose before infusion of heparin at the end of surgery, and after protamine infusion **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Menichetti 1996 Italy	48 patients undergoing cardiac surgery **TXA group** (n=24): M/F=12/12; mean age(sd)=55.2(8.6)		• Sequence generation unclear • Allocation concealment unclear high

Trial	Participants	Intervention and comparator	Risk of bias judgements
	Control group (n=24): M/F=13/11; mean age(sd)=61.0(9.7)	**TXA group**: 10mg/kg bolus then continuous infusion of 3mg/kg/hr plus 10mg/kg in the CPB priming **Control group**: no intervention (standard care)	• Blinding low • Incomplete outcome data
Misfeld 1998 Germany	24 patients undergoing cardiac surgery **TXA group** (n=14): M/F=14/0; mean age(sd)=56(7) **Control group** (n=14): M/F=11/3; mean age(sd)=59(10)	**TXA group**: 10mg/kg as bolus after heparinization then continuous infusion of 1mg/kg/hr over 10 hrs **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding high • Incomplete outcome data low
Molloy 2006 UK	100 patients undergoing knee arthroplasty **TXA group** (n=50): M/F=NR; age=NR **Control group** (n=50): M/F=NR; age=NR	**TXA group**: 500mg 5mins before deflation of tourniquet and repeat dose 3 hrs later **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Moret 2006a Spain	Patients undergoing cardiac surgery **TXA group** (n=70): M/F=NR; age=NR **Control group** (n=70): M/F=NR; age=NR	**TXA group**: 1g bolus after anaesthetic induction then constant infusion of 400mg/h iv until end of surgery and 500mg on bypass **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data unclear
Moret 2006b Spain	Patients undergoing cardiac surgery **TXA group** (n=69): M/F=NR; age=NR **Control group**: as for Moret 2006a	**TXA group**: 30mg/kg bolus after heparin administration **Control group**: as for Moret 2006a	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data unclear
Movafegh 2011 Iran	100 patients undergoing caesarean section **TXA group** (n=50): All F; mean age(sd)=37 (3.4) **Control group** (n=50): All F; mean age(sd)=27.6(4.1)	**TXA group**: 10mg/kg in 200ml saline infused over 10 mins, 20 mins before beginning spinal anaesthesia **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
Murphy 2006 Italy	100 patients undergoing cardiac surgery **TXA group** (n=50): M/F=42/8; mean age(sd)=64.9 (7) **Control group** (n=50): M/F=37/13; mean age(sd)=65.8(8.7)	**TXA group**: 2g as a bolus before sternotomy **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data low
Neilipovitz 2001 Canada	40 adolescent patients undergoing spinal surgery **TXA group** (n=22): M/F=12/10; mean age(sd)=14.1 (2.1) **Control group** (n=18): M/F=5/13; mean age(sd)=13.7(2.5)	**TXA group**: 10mg/kg initial dose then infusion of 1mg/kg/hr until skin closure **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Niskanen 2005 Finland	39 patients undergoing hip arthroplasty **TXA group** (n=19): M/F=6/13; mean age(sd)=66 (9.1) **Control group** (n=20): M/F=7/13; mean age(sd)=65(8.2)	**TXA group**: 3 doses of 10mg/kg, one given over 5-10 mins immediately before operation, next 2 given 8 and 16h after 1st injection **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data unclear
Oertli 1994 Switzerland	160 patients undergoing surgery for breast cancer **TXA group** (n=79): All F; mean age(sd)=58.1 (10.4) **Control group** (n=81): All F; mean age(sd)=59.4(14.6)	**TXA group**: Post-operative administration of 1g every 8 hrs for 5 days **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Orpen 2006 UK	30 patients undergoing knee arthroplasty **TXA group** (n=50): M/F=8/7; mean age(95% CI)=73 (70-80) **Control group** (n=50): M/F=3/11; mean age(95% CI)=69(63-74)	**TXA group**: 15mg/kg at the time that cement mixing commenced **Control group**: placebo	• Sequence generation unclear • Allocation concealment low • Blinding low • Incomplete outcome data unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
Özal 2002 Turkey	100 patients undergoing cardiac surgery **TXA group** (n=15): M/F=35/15; mean age(sd)=59 (4) **Control group** (n=14): M/F=38/12; mean age(sd)=61(7)	**TXA group**: Desmopressin + 10mg/kg loading dose over 30 mins before skin incision then 12 hrs of 1mg/kg/hr **Control group**: Desmopressin only	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Penta de Peppo 1995 Italy	30 patients undergoing cardiac surgery **TXA group** (n=15): M/F=12/3; mean age(sd)=60 (12) **Control group** (n=14): M/F=13/2; mean age(sd)=63(7)	**TXA group**: 10mg/kg within 30 mins of induction of anaesthesia then infusion of 1mg/kg/hr for 10 hrs **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Pfizer 2011 India	80 patients undergoing surgery for long bone fracture **TXA group** (n=40): M/F="mostly male"; age range=18-44 **Control group** (n=40): M/F="mostly male"; age range=18-44	**TXA group**: 15mg/kg 15 mins before surgery, followed by 2nd dose at 3 hrs later and a 3rd dose 3 hrs later **Control group**: no intervention (standard care)	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Pinosky 1997 USA	39 patients undergoing cardiac surgery **TXA group** (n=20): M/F=12/8; mean age(sd)=62.6(2.1) **Control group** (n=19): M/F=15/4; mean age(sd)=60.6(2.5)	**TXA group**: 15mg/kg loading dose then continuous infusion of 1mg/kg/hr for 6 hrs immediately after induction of anaesthesia **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Pleym 2003 Norway	79 patients undergoing cardiac surgery **TXA group** (n=40): M/F=34/6; mean age(sd)=63.6(9.9) **Control group** (n=39): M/F=32/7; mean age(sd)=62.0(9.2)	**TXA group**: 30mg/kg as bolus in injection 5 mins before start of CPB **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Sadeghi 2007 Iran	67 patients undergoing hip arthroplasty **TXA group** (n=32): M/F=3/29; mean age(sd)=51.81(25.7)	**TXA group**: bolus of 15mg/kg at beginning of surgery	• Sequence generation low • Allocation concealment low low

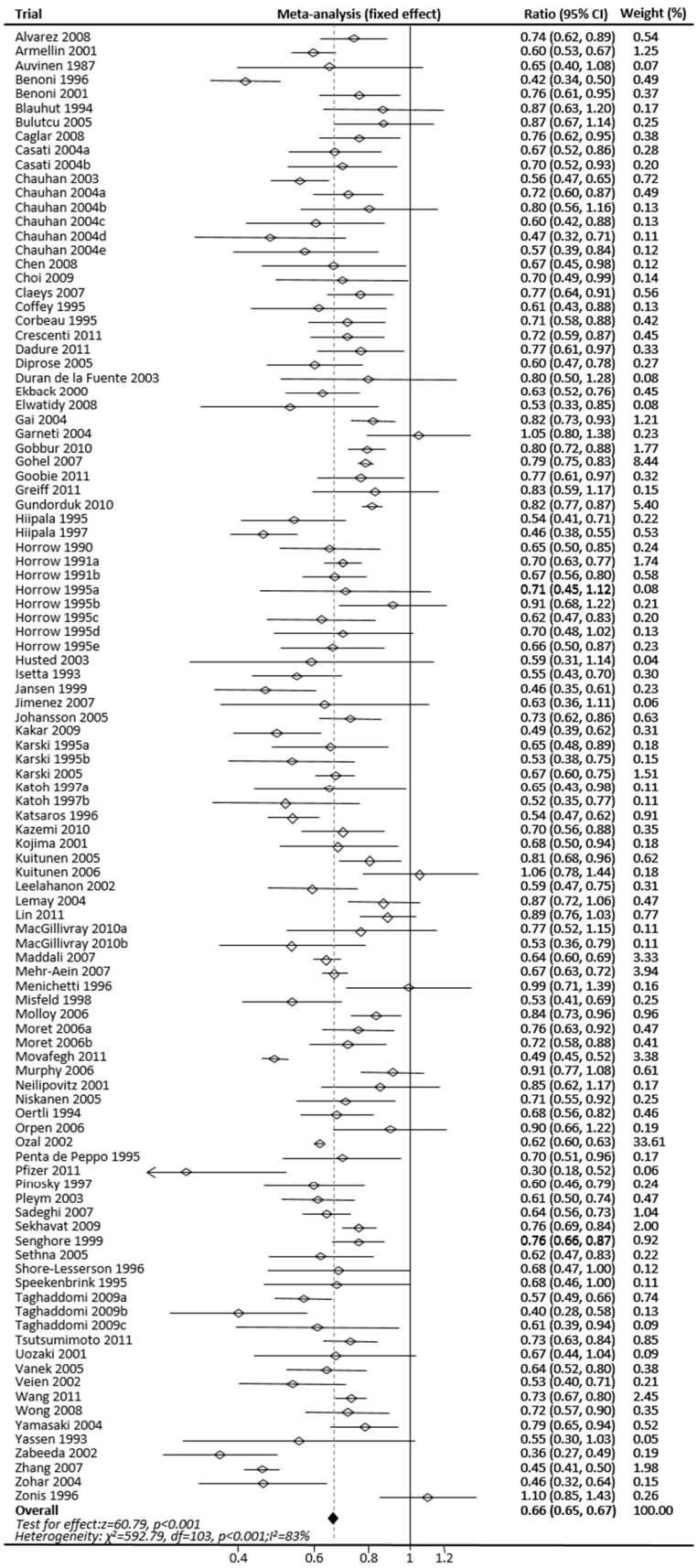
Trial	Participants	Intervention and comparator	Risk of bias judgements
	Control group (n=35): M/F=4/31; mean age(sd)=44.4(26.16)	**Control group**: placebo	• Blinding unclear • Incomplete outcome data
Sekhavat 2009 Iran	90 patients undergoing caesarean section **TXA group** (n=45): All F; mean age(sd)=26.2(4.7) **Control group** (n=45): All F; mean age(sd)=27.1(4.1)	**TXA group**: 10 mins before incision 1g/10mL infused over 5 mins **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Senghore 1999 UK	52 patients undergoing dental surgery **TXA group** (n=45): M/F=8/18; age range=16-39 **Control group** (n=45): M/F=8/18; age range=16-39	**TXA group**: single dose 25mg/kg at induction of anaesthesia **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Sethna 2005 USA	44 adolescent patients undergoing spinal surgery **TXA group** (n=23): M/F=17/6; mean age(sd)=13.6(1.8) **Control group** (n=21): M/F=13/8; mean age(sd)=14.0(2.0)	**TXA group**: 100mg/kg before incision then infusion of 10mg/kg/hr during surgery **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Shore-Lesserson 1996 USA	30 patients undergoing cardiac surgery **TXA group** (n=17): M/F=10/7; mean age(sd)=68(13) **Control group** (n=13): M/F=10/3; mean age(sd)=63(6)	**TXA group**: 20mg/kg at skin incision then infusion of 2mg/kg/hr for duration of operation **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Speekenbrink 1995 The Netherlands	30 patients undergoing cardiac surgery **TXA group** (n=15): M/F=1/14; mean age(sd)=61(11) **Control group** (n=15): M/F=1/14; mean age(sd)=57(12)	**TXA group**: After induction of anaesthesia given bolus of 10mg/kg in 20 mins and infusion of 1mg/kg up to total dose of 1000mg	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
		Control group: no intervention (standard care)	
Taghaddomi 2009a Iran	100 patients undergoing cardiac surgery **TXA group** (n=50): M/F=38/12; mean age(sd)=54.7(10.9) **Control group** (n=50): M/F=34/16; mean age(sd)=60.3(10.2)	**TXA group**: bolus 1g before incision then maintenance dose of 400mg/h during surgery **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Taghaddomi 2009b Iran	40 patients undergoing spinal surgery **TXA group** (n=20): M/F=10/10; mean age(sd)=40.4(7.64) **Control group** (n=20): M/F=9/11; mean age(sd)40.5(12.48)	**TXA group**: 15mg/kg 20-30 mins before skin incision then continued for 0.1mg/kg/min during the operation **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Taghaddomi 2009c Iran	41 patients undergoing spinal surgery **TXA group** (n=20): M/F=15/5; mean age(sd)=68.0(11.0) **Control group** (n=21): M/F=16/4; mean age(sd)=65.8(11.8)	**TXA group**: 15mg/kg, 20-30 mins before skin incision then continued for 0.1mg/kg/min during the operation **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Tsutsumimoto 2011 Japan	40 patients undergoing spinal surgery **TXA group** (n=20): M/F=8/12; mean age(sd)=42.0(17.31) **Control group** (n=20): M/F=9/12; mean age(sd)=42.6(10.42)	**TXA group**: 15mg/kg in 100ml saline over 15 mins before skin incision **Control group**: placebo	• Sequence generation high • Allocation concealment high • Blinding unclear • Incomplete outcome data unclear
Uozaki 2001 Japan	14 patients undergoing cardiac surgery **TXA group** (n=7): M/F=1/5; mean age(sd)=72.3(4.1) **Control group** (n=7): M/F=3/3; mean age(sd)=63.3(5.3)	**TXA group**: 50mg/kg before skin incision and after the start of CPB **Control group**: NR	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low

Trial	Participants	Intervention and comparator	Risk of bias judgements
Vanek 2005 Czech Republic	62 patients undergoing cardiac surgery **TXA group** (n=32): M/F=16/16; mean age(range)=68.4(64.6-72.2) **Control group** (n=32): M/F=22/8; mean age(range)=68.9(65.8-72.0)	**TXA group**: 1g before skin incision then continuous infusion of 200mg/h **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data high
Veien 2002 Denmark	30 patients undergoing cardiac surgery **TXA group** (n=15): M/F=4/11; mean age(sd)=70.5(9.5) **Control group** (n=15): M/F=1/14; mean age(sd)=69.5(9.0)	**TXA group**: 10mg/kg given at conclusion of surgery and again at 3 hrs later **Control group**: no intervention (standard care)	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Wang 2011 China	231 patients undergoing cardiac surgery **TXA group** (n=116): M/F=93/23; mean age(sd)=60.5(8.0) **Control group** (n=115): M/F=102/13; mean age(sd)=60.0(8.5)	**TXA group**: bolus 1g before surgical incision, then infusion 400mg/h during surgery **Control group**: placebo	• Sequence generation low • Allocation concealment unclear • Blinding low • Incomplete outcome data high
Wong 2008 Canada	147 patients undergoing spinal surgery **TXA group** (n=73): M/F=21/52; mean age(sd)=56.8(16.2) **Control group** (n=74): M/F=26/48; mean age(sd)=50.0(16.2)	**TXA group**: bolus of 10mg/kg after induction then maintenance infusion of 1mg/kg/hr until skin closure **Control group**: placebo	• Sequence generation low • Allocation concealment low • Blinding low • Incomplete outcome data unclear
Yamasaki 2004 Japan	40 patients undergoing hip arthroplasty **TXA group** (n=20): M/F=19/1; mean age(sd)=55.5(14.2) **Control group** (n=20): M/F=18/2; mean age(sd)=61.2(6.9)	**TXA group**: 1000mg administered 5 mins before start of operation **Control group**: no intervention (standard care)	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Yassen 1993 UK	20 patients undergoing hepatic surgery **TXA group** (n=10): M/F=5/5; mean age(sd)=44.8(12.2)		• Sequence generation unclear • Allocation concealment unclear unclear

Trial	Participants	Intervention and comparator	Risk of bias judgements
	Control group (n=10): M/F=4/6; mean age(sd)=49.6(14.2)	**TXA group**: 10mg/kg loading dose at start of operation then infusion of 3mg/kg/h until transfer to ITU **Control group**: placebo	• Blinding low • Incomplete outcome data
Zabeeda 2002 Israel	50 patients undergoing cardiac surgery **TXA group** (n=25): M/F=20/5; mean age(sd)=65.6(9) **Control group** (n=25): M/F=18/7; mean age(sd)=65(13)	**TXA group**: 10mg/kg after induction of anaesthesia followed by infusion of 1mg/kg per hr during the operation **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data low
Zhang 2007 China	102 patients undergoing knee arthroplasty **TXA group** (n=51): M/F=NR; mean age(sd)=68.14(9.05) **Control group** (n=51): M/F=NR; mean age(sd)=67.64(8.33)	**TXA group**: 1g infused before deflation of tourniquet, then administration of 1g 3 hrs later **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding unclear • Incomplete outcome data unclear
Zohar 2004 Israel	40 patients undergoing knee arthroplasty **TXA group** (n=20): M/F=6/14; mean age(sd)=73(8) **Control group** (n=20): M/F=7/13; mean age(sd)=73(7)	**TXA group**: 30 mins before limb tourniquet deflated, bolus of 15mg/kg administered over 30 mins then constant infusion of 10mg/kg/hr until 12 hrs after final deflation of limb tourniquet **Control group**: no intervention (standard care)	• Sequence generation low • Allocation concealment unclear • Blinding unclear • Incomplete outcome data low
Zonis 1996 Canada	82 paediatric patients undergoing cardiac surgery **TXA group** (n=40): M/F=19/21; mean age(sd)=62.8 months(58.1) **Control group** (n=42): M/F=21/21; mean age(sd)=52.6 months(51.2)	**TXA group**: single dose 50mg/kg **Control group**: placebo	• Sequence generation unclear • Allocation concealment unclear • Blinding low • Incomplete outcome data high

Appendix M. Research Paper 2: Fixed effects meta-analysis of the effect of tranexamic acid on surgical blood loss (all trials)



Appendix N. Research Paper 2: Results of random effects meta-analysis of the effect of TXA on blood loss stratified by type of surgery, timing of TXA administration, adequacy of allocation concealment and type of comparator

	Ratio* (95% CI) *back-transformed ratio of geometric means	**Test for effect (p value)**
Type of surgery		
Orthopaedic	0.64 (0.58 to 0.70)	<0.0001
Cardiac	0.67 (0.64 to 0.70)	<0.0001
Head & neck	0.75 (0.68 to 0.82)	<0.0001
Obs & gynae	0.74 (0.63 to 0.86)	<0.0001
Urological	0.72 (0.59 to 0.87)	0.001
Breast cancer	0.68 (0.56 to 0.82)	<0.0001
Hepatic	0.55 (0.30 to 1.03)	0.060
Timing		
Pre-incision	0.69 (0.66 to 0.71)	<0.0001
Post-incision	0.64 (0.57 to 0.71)	<0.0001
Allocation concealment		
Yes	0.68 (0.64 to 0.72)	<0.0001
Unclear	0.66 (0.63 to 0.70)	<0.0001
No	0.73 (0.64 to 0.84)	<0.0001
Comparator		
Placebo	0.67 (0.64 to 0.71)	<0.0001
No TXA	0.66 (0.65 to 0.67)	<0.0001
Overall	**0.67 (0.65 to 0.70)**	**<0.0001**
Heterogeneity: χ^2=592.79, df=103, p<0.001;I^2=83%		

Appendix O. Research Paper 3: Retention of copyright/permission to publish

Appendix P. Research paper 3: Published article

Open Access Research

BMJ Open

Exploring redundant research into the effect of tranexamic acid on surgical bleeding: further analysis of a systematic review of randomised controlled trials

Katharine Ker, Ian Roberts

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ABSTRACT

Objectives: We examined whether apparent redundancy in a cumulative meta-analysis of trials is justified by concern about bias, random error or generalisability of the results.

Design: Cumulative meta-analysis, risk of bias assessment, trial sequential analysis, description of study participants over time and a review of rationales for conducting trials.

Data source: 126 randomised trials included in a systematic review assessing of tranexamic acid on blood transfusion in surgery.

Results: The cumulative meta-analysis including all trials shows that the pooled estimate first reached statistical significance after the second trial in 1993. When the analysis was limited to the 38 high-quality trials and adjusted to account for potential systematic and random errors, the uncertainty was resolved after the 22nd trial in 2008. When the analysis was restricted to the two high-quality, prospectively registered trials, the cumulative z-curve crossed p=0.05 but not the monitoring boundary, suggesting an early potentially spurious statistically significant result. As precision of the pooled estimate increased, the number of trials initiated increased, although trial activity appeared to move to other surgery types. Most (62%) reports cited at least one systematic review. Of 118 reports examined, concern about generalisability was the reason for initiating the trial in 60%. Other reasons were to address a question other than the effect on bleeding (26%) and to confirm previously observed results (4%). Unawareness of previous research was apparent in 4% trials, while the rationale was unclear in 3%.

Conclusions: Our results indicate that poor quality is a more important cause of redundant research than the failure to review existing evidence. Concerns about generalisability of results is the main motivation for new trials. Contrary to previous claims, our results suggest that systematic reviews showing treatment effects can stimulate an increase in trial activity rather than reduce it.

Strengths and limitations of this study

- The results are based on data from a comprehensive and up-to-date systematic review of trials assessing the effect of tranexamic acid (TXA) in all surgery types.
- The results challenge the view that the failure to systematically review existing evidence is the main cause of research redundancy.
- The examination of reasons for initiating new trials is based on the rationales given in the trial reports which may not accurately reflect the rationale.
- The results are based on trials of TXA in surgery, and although the extent to which the findings apply to other topics is questionable, similar observations have been made elsewhere.

INTRODUCTION

Results from cumulative meta-analyses are often cited as proof that many researchers fail to systematically review the evidence from existing trials before initiating new trials. For example, a cumulative meta-analysis of aprotinin in cardiac surgery[1] showed that trials were initiated long after the pooled estimates showed a statistically significant effect. Commenting on the paper, Chalmers[2] observed that it "*compellingly demonstrates why all new research—whether basic or applied—should be designed in the light of scientifically defensible syntheses of existing research evidence, and reported setting the new research 'in the light of the totality of the available evidence'*". Similar conclusions have been made on the basis of other cumulative meta-analyses.[3–5]

When the apparently redundant aprotinin trials were conducted, systematic reviews were relatively uncommon and failure to review the previous trials was a plausible

explanation for the redundancy. However, given the increase in published reviews and their easy availability, lack of awareness of what has gone before is nowadays a less credible explanation for redundancy. We found that seemingly redundant trials of the effect of tranexamic acid (TXA) on blood transfusion were conducted even though many of them cited a systematic review concluding that the uncertainty had been resolved.[6] Habre *et al*[7] found that 73% of trials of an anaesthetic intervention cited a systematic review showing that the uncertainty about its effects had been resolved. They also observed that the number of new trials increased after publication of the review and suggested that the strong pressure to publish and the failure of ethics committees to ensure the clinical relevance of new trials could be the main reasons.

We considered two alternative explanations for the apparent redundancy. First, the trialists may be sceptical about the results of even seemingly conclusive reviews. Such scepticism may arise from concerns about systematic or random errors distorting the results. Poor-quality trials can introduce bias and multiple statistical testing as new trials accumulate may increase the risk of false-positive results. Second, even in the absence of substantial bias or random error, there may be a reluctance to generalise trial results to different patient groups. If this were the case, strong evidence of a treatment effect might be expected to lead to more trial activity rather than less, as researchers examine the impact of patient or intervention characteristics on the results.

We used data from a cumulative meta-analysis of trials examining the effect of TXA on blood transfusion in surgery, to explore whether deficiencies in the quality of the evidence justify the continuation of trial activity. We explored the impact of trial quality on effect estimates and used trial sequential analysis to quantify required information sizes and construct monitoring boundaries to assess the risk of random error affecting the cumulative estimate. We examined whether patient characteristics changed over time and the reasons given by the trial investigators for conducting their trial.

METHODS

Systematic review

We extracted data from trials included in our previous systematic review of TXA for surgical bleeding. The methods used to identify trials are described in detail elsewhere.[6] Briefly, we searched for all randomised controlled trials comparing TXA with placebo or a no-treatment control. We searched the Cochrane central register of controlled trials, MEDLINE, EMBASE and the WHO International Clinical Trials Registry Platform, using a combination of subject headings and text words to identify randomised controlled trials of any antifibrinolytic drug (see online supplementary file for MEDLINE search strategy). We updated our searches to May 2014 to incorporate trials published since the original version of the review. Data were extracted on patient characteristics, type of surgery and the number of patients who received a blood transfusion. We used the Cochrane's tool for assessing risk of bias in the included trials.[8] We assessed the risk of bias associated with the method of sequence generation, allocation concealment, blinding and the completeness of outcome data. Trials were rated as being at high, low or unclear risk of bias for each domain. We considered trials with adequate allocation concealment and blinded outcome assessment to be at low risk of bias.

Analysis

Systematic review and meta-analyses

We calculated risk ratios (RRs) and 95% CIs to assess the effect of TXA on blood transfusion. We pooled the data in a fixed-effect cumulative meta-analysis based on date of publication. We conducted separate meta-analysis for all trials, trials at low risk of bias and trials at low risk of bias that had prespecified blood transfusion as outcome on a registration record.

Trial sequential analyses

We used trial sequential analyses (TSA) to examine the reliability of the cumulative meta-analysis. TSA involves calculating the number of participants (ie, information size) required before the result of a meta-analysis can be considered reliable and constructs statistical monitoring boundaries to account for type I and II errors due to multiple testing.[9] We conducted three analyses: (1) all trials, (2) trials at low risk of bias and (3) prospectively registered, low risk of bias trials with blood transfusion as a prespecified outcome. We calculated the required meta-analysis information size assuming a type I error of 5% and 90% power, a baseline event rate of 40% and a relative risk reduction of 15%. We chose a relative risk reduction of 15% as we judged this to represent a minimally clinical important effect. The estimate was adjusted for maximum anticipated heterogeneity of I^2=75%.

We used Microsoft Excel, STATA V.13,[10] RevMan V.5.3[11] and the TSA Software V.0.9 β[12] for the analyses.

To explore the hypothesis that reliable demonstration of a treatment effect leads to an increase in trial activity, we plotted the precision of the pooled effect estimate (described by the SE of the cumulative pooled RR) against the number of new trials initiated (defined as start date of recruitment) per year. We did this both for all trials and for the subset of cardiac surgery trials.

We also plotted the publication date of each trial stratified by surgery type.

We examined trial reports to explore the reasons given for trial initiation and categorised the reasons into main themes.

Finally, we explored how the size and quality of trials changed over time. We compared the mean sample size and the proportion of trials at low risk of bias that were published before and after the Cochrane systematic

review by Henry *et al*.[15] This systematic review was chosen as it was the first and most comprehensive review conducted on the effect of TXA in surgical bleeding. The review was published in October 1999. We allowed for a 5-year time lag for the results of the review to have an impact on published research and compared trials published before and after 1 November 2004.

RESULTS

Systematic review and meta-analyses

We found 126 trials with 12 429 patients of the effect of TXA on blood transfusion in surgery with data suitable for analysis. One hundred and twenty trials (95%) were conducted in a single centre. The median sample size was 79 patients (range 10–660). The trials involved cardiac (n=51), orthopaedic (n=49), obstetric and gynaecological (n=10), cranial (n=9), urological (n=3), hepatic (n=2), vascular (n=1) and abdominal (n=1) procedures. Thirty-eight (30%) trials had adequate allocation concealment and blinded outcome assessment and were considered at low risk of bias. We identified a clinical trial registration record for 24 (19%) trials. Six (5%) trials had been prospectively registered, four (3%) of which had prespecified blood transfusion as an outcome and two of these (2%) were at low risk of bias. Allowing for a 12-month publication time lag, 110 of the 118 (93%) trial reports published as journal articles were published when at least one systematic review was available. Examination of the reference lists showed that 68 (62%) cited one of the available systematic reviews.

Based on all 126 included trials, TXA administration appeared to reduce the risk of receiving a blood transfusion by 38% (pooled RR=0.62; 0.59 to 0.65; p<0.0001). The cumulative estimate was statistically significant (p<0.05) after the second trial (published in August 1993) and remained so thereafter. Based on data from the 38 trials at low risk of bias, TXA appeared to reduce the risk of receiving a blood transfusion by 32% (pooled RR=0.68; 0.63 to 0.73; p<0.001). The cumulative estimate was first statistically significant after the fourth high-quality trial but remained statistically significant after the sixth trial. When the analysis was limited to the two low risk of bias, prospectively registered trials that prespecified blood transfusion as an outcome measure, TXA appeared to reduce the risk of transfusion by 21% (pooled RR=0.79; 0.71 to 0.87; p<0.001).

Trial sequential analyses

Figure 1 shows the results of the TSA. The required information size was estimated at 10 888 patients.

Based on data from all 126 trials, there appears to be strong evidence that TXA reduces the risk of blood transfusion in surgery. The z-curve crosses the monitoring boundary before the heterogeneity-adjusted information size is achieved when the 28th trial was published in March 2001. Prior to this point, there were 26 potentially spurious p values. Since the monitoring boundary was crossed, a further 98 trials have been published.

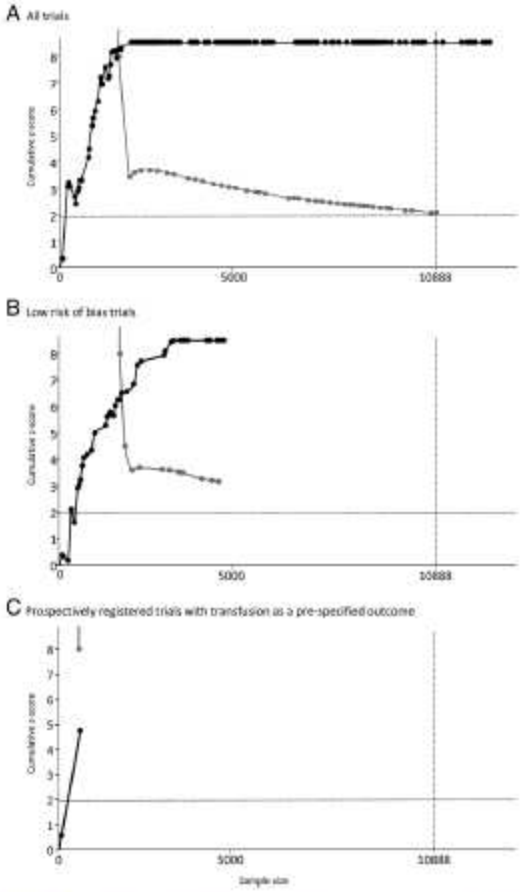

Figure 1 Results of trial sequential analyses for (A) all trials, (B) trials at low risk of bias and (C) low risk of bias trials with transfusion prespecified on prospective registration record. For each analysis an information size is calculated on the basis assuming α=5%, β=10%, control group event rate of 40%, relative risk reduction of 15% and anticipated maximum heterogeneity of I^2=75%. The solid black line illustrates the cumulative z-curve, the solid grey line shows the trial sequential monitoring boundary.

Based on the 38 low risk of bias trials, there appears to be strong evidence that TXA reduces blood transfusion. The z-curve crosses the monitoring boundary after the 22nd high-quality trial published in November 2008. Prior to this point, there were 18 potentially spurious p values. Since the monitoring boundary was crossed, a further 15 high-quality trials have been published.

When the analysis is restricted to the two low risk of bias trials which had prespecified blood transfusion as an outcome, the z-curve does not cross the monitoring

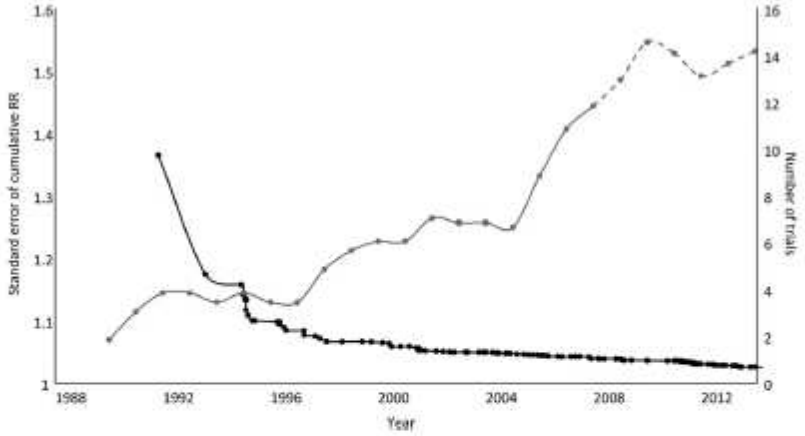

Figure 2 Precision of the cumulative pooled estimates described by the SE of the risk ratios (RRs; left hand axis) and the number of trials (5-year moving averages, right hand axis) initiated per year.

boundary and the heterogeneity-adjusted information size is not achieved. There is one potentially spurious p value.

Figure 2 shows the precision of the cumulative pooled estimate (SE of the log cumulative RR) and the number of trials initiated per year from 1991 to 2014. As the precision of the pooled estimate increases (ie, decrease in the SE), the number of new trials initiated each year also increases. A similar pattern is observed for trials in cardiac surgery (figure 3).

Figure 4 shows a timeline of the publication of the trials, stratified by surgery type. It appears that trials were first conducted in cardiac surgery and shortly afterwards in orthopaedic surgery. Trial activity then expands to other types of surgery namely cranial, urological and gynaecological surgery.

Qualitative review of trial justifications

Eight trials were reported in abstract or summary form only, leaving 118 trials reported in sufficient detail to extract information on the rationale. A summary of the extracted information is shown in table 1. Concerns about the generalisability of the available evidence was used to justify 71 (60%) trials. These trials sought to replicate a previously observed beneficial effect of TXA on surgical bleeding but in a different group of patients, such as those undergoing a different type of surgical procedure. Thirty-one (26%) trials were initiated to answer a different research question to the effect of TXA on bleeding. Most of these trials were conducted to examine the effect of different doses or timings of TXA despite the inclusion of a placebo or no-TXA

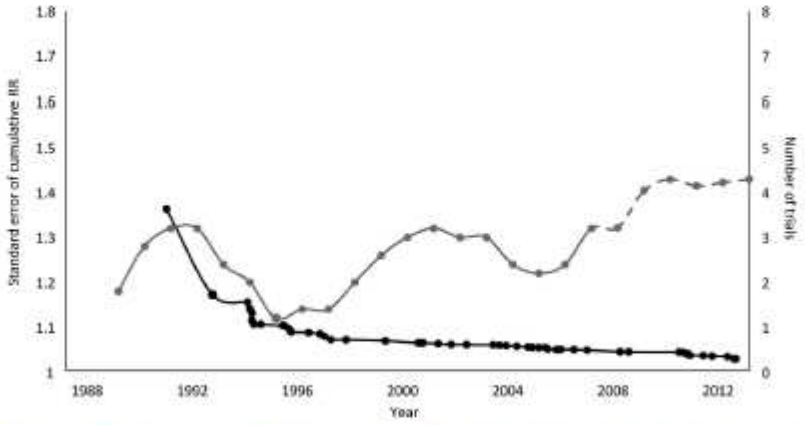

Figure 3 Precision of the cumulative pooled estimates for the effect of tranexamic acid in cardiac surgery described by the SE of the risk ratios (RRs; left hand axis) and the number of trials (5-year moving averages, right hand axis) initiated per year.

Figure 4 Timeline of publication of trials of TXA stratified by type of surgery (TXA, tranexamic acid; O&G, obstetric and gynaecological).

control group. Five (4%) trials appeared to have been conducted because of a failure to synthesise prior evidence. The trial rationale was unclear in 4 (4%) trials.

Comparison of trials conducted before and after publication of the Henry *et al* systematic review

Of the 126 trials, 47 (37%) were published before 1 November 2004 compared with 79 (63%) published afterwards up to May 2014. The average sample size had increased between the two periods (mean±SD, 64±50 vs 119±103; p<0.0001). A larger proportion of trials published after November 2004 were judged to be at low risk of bias for both allocation concealment and blinding (12 (26%) vs 28 (35%); p=0.23).

DISCUSSION

Principal findings

We examined two hypotheses for the redundancy in a cumulative meta-analysis. First, that despite the apparently conclusive results, legitimate concerns about bias and random error justified new trials. We found some support for this. Most trials were small, single centre, low quality and hardly any were prospectively registered. Nevertheless, when only high-quality trials were considered, with steps taken to reduce the risk of false-positive results, there remained strong evidence that TXA reduces transfusion.

Our second hypothesis was that new trials are conducted because of concerns about the generalisability of the results. We found strong support for this. Increasing evidence that TXA decreases the need for blood transfusion resulted in more trial activity and not less. The change in patient characteristics over time and the rationales given by trialists also indicate that generalisability concerns motivated the new trials. That over half of trials cited at least one of the existing systematic reviews suggests that ignorance of the existing evidence does not fully explain ongoing trial activity.

The average sample size of trials has increased, and there is some suggestion that the quality of trials has improved over time.

Strengths and weaknesses

We examined trial reports to find the reasons authors gave for conducting new trials. This process was inevitably subjective and different assessors might have made different judgements. Furthermore, trial reports might not accurately reflect the rationale at trial inception. We did not contact authors, although whether this would have provided more reliable information is uncertain. There are other, non-scientific motivations, such as monetary and academic, for initiating a new trial which would not be publically reported. Nevertheless, the reasons given in trial reports are the openly given justifications that are accepted by the scientific community and are therefore a reasonable focus for review.

Our study was based on clinical trials of TXA in surgery, and the extent to which the results apply to other topics is questionable. However, we have also

Table 1 Summary of reasons for initiating trials of tranexamic acid for surgical bleeding based on information extracted from the final reports

	Failure to synthesise evidence	Confirmatory	Generalisability	Assessing a different research question	Unclear
Trials citing ≥1 available systematic review (n=68)	–	2	51	11	4
Trials not citing an available systematic review (n=42)	2	3	21	16	–
Trials published before a systematic review was available (n=9)	3	–	–	6	–
All trial reports (n=118)	5 (4%)	5 (4%)	72 (61%)	33 (28%)	4 (3%)

found that publication of a systematic review showing strong evidence that TXA reduces mortality in bleeding trauma patients also resulted in increased trial activity rather than less. A 2004 systematic review of TXA in acute traumatic injury[14] found no eligible trials even though TXA was commonly used in other bleeding conditions. The review prompted the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial which included 20 211 bleeding trauma patients and showed that TXA reduces death due to bleeding and all-cause mortality.[15] The subsequently updated review included two trials and reported that the uncertainty had been resolved.[16] Nevertheless, some authors, pointing out that many of the patients in the CRASH-2 trial were recruited from hospitals in Africa, Asia and Latin America, questioned whether the results can be applied in 'modern' trauma care systems[17] and have initiated new clinical trials rather than implementing the results.[18 19] Although subgroup analyses show that the CRASH-2 trial results do not vary by geographical region,[20] two placebo-controlled trials are underway.[14 15] Habre *et al*[7] also found that publication of a conclusive review coincided with increased trial activity and that most new trials cited the conclusive review.

There are other potential explanations for the continuation of trial activity that we have not explored. Habre *et al* suggested that redundant trials of an anaesthetic intervention may have been motivated by the self-interest of researchers wishing to gain more research publications. In relation to our study, trials of the effect of TXA on blood transfusion are relatively easy to conduct, and since a treatment effect is highly likely, it would be an attractive topic for research.

Implications

Our results raise questions about the process of scientific generalisation. If there is strong evidence that TXA reduces bleeding in cardiac and orthopaedic surgery, is it necessary to examine its effect in obstetric surgery? Rothman *et al*[21] argues that the reluctance to generalise results to populations that were not represented in the original research confuses statistical and scientific inference. Statistical inference, the process of using sample information to reach conclusions about the population from which it was drawn, is helped by having a representative sample. However, generalising trial results involves scientific inference, a process of reaching general conclusions about how a treatment works. The main prerequisite for scientific inference is a biological insight into the mechanism of action of the treatment and an awareness of the circumstances that may be relevant to this mechanism. Rather than using statistical reasoning, it is more appropriate to use biological reasoning and ask whether there is any good reason why TXA would work differently in orthopaedic or urological surgery?

A further concern is the number of inappropriately designed trials. This typically concerns trials which aimed to build on the existing knowledge by comparing different doses or timings of TXA, yet opted to include a no-treatment comparison group. The inclusion of a no-treatment comparison group in such trials is wasteful and unethical—failings that implicate both trialists and the ethical review committees approving the trials. In this article, we focus on the potential explanations for trialists' decision to initiate further trials of TXA, yet there is also a question regarding why patients continue to agree to participate in apparently 'redundant' trials in which there is a chance they will forego receiving an effective treatment. We did not attempt to obtain the patient information sheets used in the trials, and there remains an unanswered question regarding the extent to which trial participants are made aware of the existing evidence as part of the consent giving process.

Our results suggest that low-quality trials are a more important cause of 'research waste' than the failure to systematically review the existing evidence. When only high-quality trials are considered, the number of statistically 'redundant' trials was reduced from 98 to 15. Most trial reports clearly indicated an awareness that TXA had been shown to reduce bleeding but sought to examine its effect in different types of surgery. For this reason, more systematic reviews and greater attention to existing reviews will only increase research waste unless determined efforts are made to increase quality in the form of adequately powered trials that are properly randomised with adequate allocation concealment and blinding.

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Contributors KK and IR conceived the study. KK extracted the data and conducted the analyses. KK and IR wrote the manuscript. The final version was approved by both authors. KK is the guarantor.

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Competing interests Ian Roberts is a National Institute for Health Research senior investigator.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Appendix Q. Research Paper 3: MEDLINE (Ovid) search strategy, 1950 to May 2014

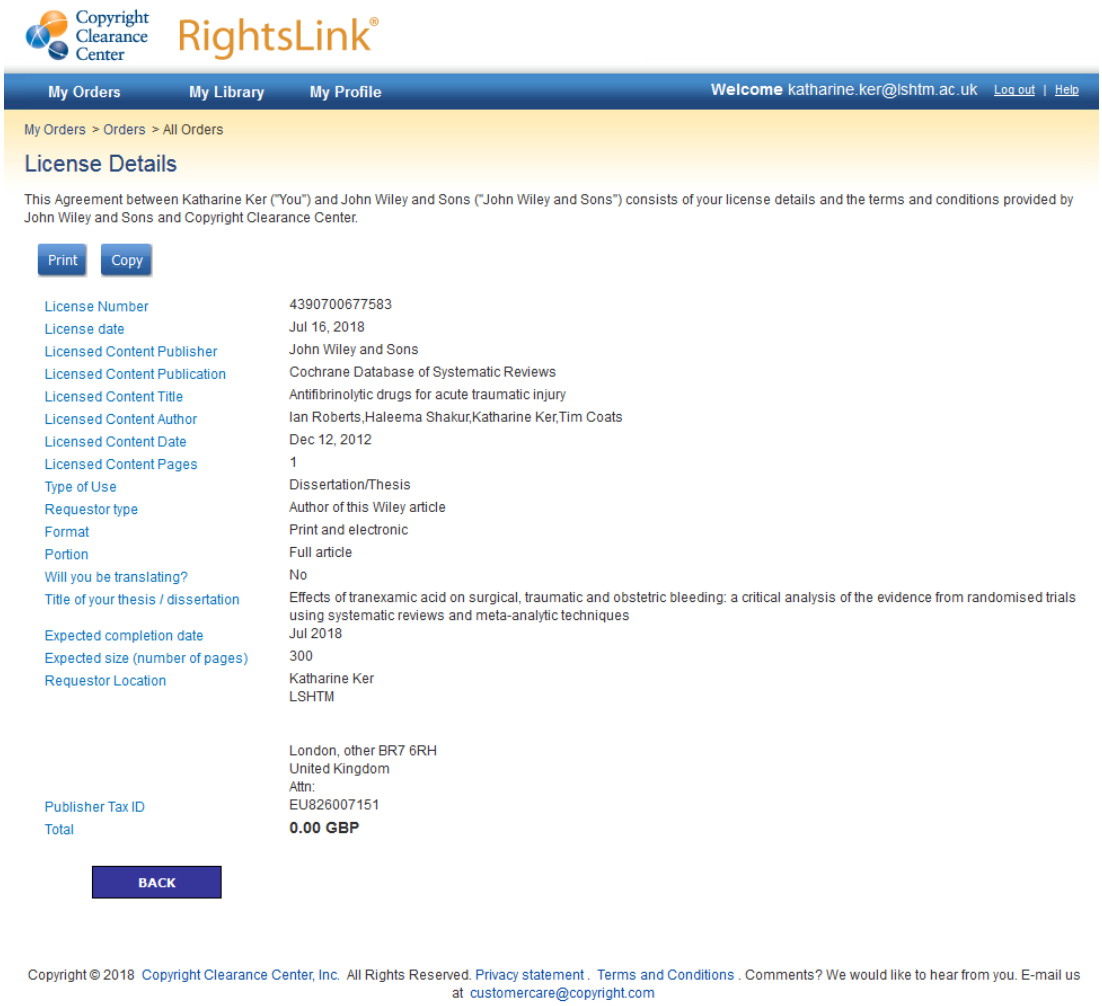
1. exp Antifibrinolytic Agents/
2. (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3. exp Aprotinin/
4. (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5. exp Tranexamic Acid/
6. (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7. exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8. (((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomi?ed.ab,ti.
11. randomized controlled trial.pt.
12. controlled clinical trial.pt.
13. placebo.ab.
14. clinical trials as topic.sh.
15. randomly.ab.
16. trial.ti.

17. 10 or 11 or 12 or 13 or 14 or 15 or 16
18. (animals not (humans and animals)).sh.
19. 17 not 18
20. 9 and 19

Appendix R. Research Paper 3: Results of random effects meta-analysis of the effect of TXA on blood loss stratified by type of surgery, timing of TXA administration, adequacy of allocation concealment and type of comparator

	Ratio* (95% CI) *back-transformed ratio of geometric means	**Test for effect** **(P value)**
Type of surgery		
Orthopaedic	0.64 (0.58 to 0.70)	<0.0001
Cardiac	0.67 (0.64 to 0.70)	<0.0001
Head & neck	0.75 (0.68 to 0.82)	<0.0001
Obs & gynae	0.74 (0.63 to 0.86)	<0.0001
Urological	0.72 (0.59 to 0.87)	0.001
Breast cancer	0.68 (0.56 to 0.82)	<0.0001
Hepatic	0.55 (0.30 to 1.03)	0.060
Timing		
Pre-incision	0.69 (0.66 to 0.71)	<0.0001
Post-incision	0.64 (0.57 to 0.71)	<0.0001
Allocation concealment		
Yes	0.68 (0.64 to 0.72)	<0.0001
Unclear	0.66 (0.63 to 0.70)	<0.0001
No	0.73 (0.64 to 0.84)	<0.0001
Comparator		
Placebo	0.67 (0.64 to 0.71)	<0.0001
No TXA	0.66 (0.65 to 0.67)	<0.0001
Overall	**0.67 (0.65 to 0.70)**	**<0.0001**
Heterogeneity: χ^2=592.79, df=103, p<0.001;I^2=83%		

Appendix S. Research Paper 4: Retention of copyright/permission to publish



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Licensed Content Date	Dec 12, 2012
Licensed Content Pages	1
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Portion	Full article
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BACK

Appendix T. Research Paper 4: Published article

Antifibrinolytic drugs for acute traumatic injury (Review)

Roberts I, Shakur H, Ker K, Coats T, on behalf of the CRASH-2 Trial collaborators

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2012, Issue 12

http://www.thecochranelibrary.com

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TABLE OF CONTENTS

[Intervention Review]

Antifibrinolytic drugs for acute traumatic injury

Ian Roberts[1], Haleema Shakur[2], Katharine Ker[1], Tim Coats[3], on behalf of the CRASH-2 Trial collaborators[2]

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ABSTRACT

Background

Uncontrolled bleeding is an important cause of death in trauma victims. Antifibrinolytic treatment has been shown to reduce blood loss following surgery and may also be effective in reducing blood loss following trauma.

Objectives

To quantify the effects of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

Search methods

We searched the PubMed, Science Citation Index, National Research Register, Zetoc, SIGLE, Global Health, LILACS, and Current Controlled Trials to March 2004 and the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE and EMBASE to July 2010.

Selection criteria

We included all randomised controlled trials of antifibrinolytic agents (aprotinin, tranexamic acid [TXA] and epsilon-aminocaproic acid) following acute traumatic injury.

Data collection and analysis

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches, and contacts with experts, two authors independently selected trials meeting the inclusion criteria.

Main results

Four trials met the inclusion criteria, including 20,548 randomised patients. Two trials with a combined total of 20,451 patients assessed the effects of TXA on mortality: TXA reduced the risk of death by 10% (RR=0.90, 95% CI 0.85 to 0.97; P=0.0035). Data from one trial involving 20,211 patients found that TXA reduced the risk of death due to bleeding by 15% (RR=0.85, 95% CI 0.76 to 0.96; P=0.0077). There was evidence that early treatment (≤3 hours) was more effective than late treatment (>3 hours). There was no evidence that TXA increased the risk of vascular occlusive events or need for surgical intervention. There was no substantial difference in the receipt of blood transfusion between the TXA and placebo groups. The two trials of aprotinin provided no reliable data.

Authors' conclusions

Tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events. TXA should be given as early as possible and within three hours of injury, as treatment later than this is unlikely to be effective. Further trials are needed to determine the effects of TXA in patients with isolated traumatic brain injury.

PLAIN LANGUAGE SUMMARY

Blood-clot promoting drugs for acute traumatic injury

Injury is the second leading cause of death for people aged five to 45 years. Over three million people worldwide die of injuries every year, often because of extensive blood loss. Antifibrinolytic drugs promote blood clotting by preventing blood clots from breaking down. Some examples of antifibrinolytic drugs are aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid. Doctors sometimes give these drugs to patients having surgery to prevent blood loss. They appear to have few complications. These drugs might also stop blood loss in seriously injured patients and, as a result, save lives.

The authors of this review searched for randomised trials assessing the effects of antifibrinolytics in trauma patients. When the review was first done in 2004 the results of the research were inconclusive. Since then, two new trials of TXA, one involving over 20,000 patients, have been completed. The results of this new research show that when given early, TXA reduces the risk of death compared to patients who do not receive TXA without increasing the risk of side events. The review now includes data from 20,548 people who took part in four trials.

Two small trials of aprotinin were also found although they provided no reliable data.

The authors conclude that TXA can safely reduce death in bleeding trauma patients. They suggest that future trials should explore the effects of TXA in patients with traumatic brain injury with no other trauma.

BACKGROUND

Description of the condition

For people aged five to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma (Murray 1996), many after reaching hospital. Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths in some settings (Sauaia 1995). Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding (BTF 2000).

Clotting helps to maintain the integrity of the circulatory system after vascular injury, whether traumatic or surgical in origin (Lawson 2004). Major surgery and trauma trigger similar haemostatic responses and the consequent massive blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma in any patient, is stimulation of clot breakdown (fibrinolysis) which may become pathological (hyper-fibrinolysis) in some cases. Antifibrinolytic agents have been shown to reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, without apparently increasing the risk of post-operative complications.

Description of the intervention

Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss. A recent systematic review (Henry 2011) of randomised controlled trials of antifibrinolytics (mainly aprotinin or tranexamic acid [TXA]) in elective surgical patients showed that antifibrinolytics reduced the numbers needing transfusion by one third, reduced the volume needed per transfusion by one unit, and halved the need for further surgery to control bleeding. These differences were all statistically significant at the $P<0.01$ level. Specifically, aprotinin reduced the rate of blood transfusion by 34% (relative risk [RR] 0.66; 95% confidence interval [CI] 0.60 to 0.72) and TXA by 39% (RR 0.61; 95% CI 0.53 to 0.70). Aprotinin use saved 1.02 units of red blood cells (RBCs) (95% CI 0.79 to 1.26) in those requiring transfusion,

and TXA use saved 0.87 units (95% CI 0.53 to 1.20). There was a non-significant reduction in mortality with both aprotinin (RR–0.81; 95% CI 0.63 to 1.06) and TXA (RR–0.60; 95% CI 0.33 to 1.10).

How the intervention might work

Because the coagulation abnormalities that occur after injury are similar to those after surgery, it is possible that antifibrinolytic agents might also reduce blood loss and mortality following trauma. A simple and widely practicable intervention that reduced blood loss following trauma might prevent tens of thousands of premature deaths. A reduction in the need for transfusion would also have important public health implications. Blood is a scarce and expensive resource and major concerns remain about the risk of transfusion-transmitted infection. Trauma is particularly common in parts of the world where the safety of blood transfusion cannot be assured. A recent study in Uganda estimated the population-attributable fraction of HIV acquisition as a result of blood transfusion to be around two percent (Kiwanuka 2004) although some estimates are much higher (Heymann 1992).

OBJECTIVES

To quantify the effect of antifibrinolytic drugs on mortality, vascular occlusive events, surgical intervention and receipt of blood transfusion after acute traumatic injury.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT), as per the following definition.

RCT: A study involving at least one intervention and one control treatment, concurrent enrolment and follow-up of the intervention and control groups, and in which the interventions to be tested are selected by a random process, such as the use of a random numbers table (coin flips are also acceptable). If the study author(s) state explicitly (usually by using some variant of the term 'random' to describe the allocation procedure used) that the groups compared in the trial were established by random allocation, then the trial is classified as an 'RCT'.

Types of participants

People of any age following acute traumatic injury.

Types of interventions

The interventions considered are the antifibrinolytic agents: aprotinin, tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA).

Types of outcome measures

Primary outcomes

- Mortality at the end of the follow up.

Secondary outcomes

- Number of patients experiencing an adverse event, specifically vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis or pulmonary embolism).
- Number of patients undergoing surgical intervention.
- Number of patients receiving blood transfusion.
- Volume of blood transfused (units).

Search methods for identification of studies

Searches were not restricted by date, language or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group's Specialised Register (searched July 2010)
- Cochrane Central Register of Controlled Trials Issue 3, 2010 (*The Cochrane Library*)
- MEDLINE (1966 to July week 2, 2010)
- PubMed (searched March 17, 2004)
- EMBASE (1980 to week 28, July 2010)
- Science Citation Index (searched March 17, 2004)
- National Research Register (issue 1, 2004)
- Zetoc (searched March 17, 2004)
- SIGLE (searched March 17, 2004)
- Global Health (searched March 17, 2004)
- LILACS (searched March 17, 2004)
- Current Controlled Trials (searched March 17, 2004)

The search strategies used in the latest update are listed in full in Appendix 1.

Searching other resources

All references in the identified trials and background papers were checked and study authors contacted to identify relevant published and unpublished data. Pharmaceutical companies were contacted in 2004 to obtain information on ongoing trials.

Data collection and analysis

Selection of studies

The titles and abstracts identified in the electronic searches were screened by two independent authors to identify studies that had the potential to meet the inclusion criteria. The full reports of all such studies were obtained. From the results of the screened electronic searches, bibliographic searches and contacts with experts, two authors independently selected trials meeting the inclusion criteria. There were no disagreements on study inclusion.

Data extraction and management

Two authors independently extracted information on the following: number of randomised participants, types of participants and types of interventions. The outcome data sought were: numbers of deaths in each group, numbers with vascular occlusive events, numbers requiring surgical intervention, and the amount of blood transfused. Information on loss to follow-up, blinding, and whether an intention-to-treat analysis was performed was also extracted. The authors were not blinded to the authors or journal when doing this. Results were compared and differences would have been resolved by discussion had there been any. Where there was insufficient information in the published report, we attempted to contact the authors for clarification.

Assessment of risk of bias in included studies

Two authors assessed the risk of bias for allocation concealment. Each trial was assessed as being at high, low or unclear risk of bias according to the criteria presented in Higgins 2008.

Assessment of heterogeneity

The presence of heterogeneity of the observed treatment effects were assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity; substantial heterogeneity is considered to exist when I^2 >50% (Higgins 2008). The following were specified a-priori as factors that could explain any observed heterogeneity: adequacy of allocation concealment; injury severity based on the injury severity score (an ISS of greater than or equal to 16 defines the severely injured strata); and according to whether the study population included predominantly blunt or penetrating trauma.

Assessment of reporting biases

We planned to investigate the presence of reporting (publication) bias using funnel plots, however there were too few included studies to enable meaningful analysis.

Data synthesis

Risk ratios (RR) and 95% confidence intervals (95% CI) were calculated. The risk ratio was chosen because it is more readily applied to the clinical situation. For transfusion volumes, the mean difference (MD) in the units of blood transfused were calculated with 95% CI.

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses to explore whether effect sizes vary according to the type of antifibrinolytic agent and the dosing regimen. However there were too few trials for such analyses.

RESULTS

Description of studies

Searches conducted in April 2004 identified a total of 819 records. These were screened by two authors and the full texts of nine potentially eligible reports were obtained for closer examination. Of the nine potentially eligible reports, two trials met the inclusion criteria. Two further trials were identified in an updated search conducted in July 2010. In summary, four randomised controlled trials including 20,548 randomised patients have been identified as meeting the inclusion criteria and are included in this review.

Tranexamic acid

Two trials compared TXA with placebo in trauma patients. The CRASH-2 2010 recruited 20,211 trauma patients with, or at risk of, significant haemorrhage. A trial in Thailand (Yutthakasemsunt 2010) recruited 240 trauma patients with moderate to severe traumatic brain injury. As of November 2012, the Thai trial Yutthakasemsunt 2010 was only available as an abstract with publication of the full trial report pending. The trial has been included based on the data reported in the abstract. The full trial data will be incorporated into this systematic review once the full trial report is available.

Aprotinin

Two trials compared the effects of aprotinin with placebo in trauma patients. One trial (Auer 1979) involved 20 patients with severe head injury, and one (McMichan 1982) involved 77 patients with a combination of hypovolaemic shock and major fractures of either the lower limb, pelvis or both.

See 'Characteristics of included studies' for further details.

Risk of bias in included studies

The CRASH-2 2010 trial was judged to be at low risk of bias. It was a large randomised controlled trial involving 20,211 adult trauma patients who were randomly allocated to receive TXA or placebo. TXA and placebo were packaged in identical ampoules. Hospitals with reliable telephone access used a telephone randomisation service, hospitals without used a local pack system; allocation concealment was adequate. Participants and trial staff were blinded to treatment allocation. Over 99% of patients were followed up.

There was insufficient information presented in the abstract to assess the risk of bias of the trial by Yutthakasemsunt 2010.

The trial by Auer 1979 was described as double blind. The adequacy of allocation concealment was unclear. However, after randomly allocating the first 20 patients, five patients were added to the aprotinin group. Because it was not possible to separate the outcome data for the 20 randomised and the five non-randomised patients, this study provided no useable outcome data.

In the randomised controlled trial by McMichan 1982 the aprotinin and placebo were prepared in "similar ampoules". All ampoules were in boxes of 50, with a code number assigned to each box. The nature of the content of the ampoules was not known to any of the investigators nor to the attending physicians. The codes were not broken until the end of the study. There were seven post-randomisation exclusions from the study in which there were three deaths. These three deaths were excluded because they occurred within the first 24 hours (it is not clear whether or not this was specified in the study protocol). Three patients refused the trial investigations, and one patient was transferred to another hospital for specialist treatment of quadriplegia and later died.

Effects of interventions

Tranexamic acid versus placebo

Mortality

Both the CRASH-2 2010 trial and the trial by Yutthakasemsunt 2010 reported mortality data.

All-cause mortality was significantly reduced with tranexamic acid (pooled risk ratio (RR) 0.90, 95% CI 0.85 to 0.97; P=0.003; Analysis 1.1). There was no evidence of statistical heterogeneity (Chi^2=0.77, df=1 (P=0.38); I^2=0%).

The CRASH-2 2010 also presented mortality data by cause. The risk of death due to bleeding and myocardial infarction were significantly reduced with TXA. There were no statistically significant differences in the risk of death from other causes:

- Bleeding: RR 0.85, 95% CI 0.76 to 0.96; P=0.0077
- Myocardial infarction: RR 0.32, 95% CI 0.14 to 0.75; P=0.0053
- Vascular occlusion: RR 0.69, 95% CI 0.44 to 1.07; P=0.096
- Stroke: RR 1.60, 95% CI 0.52 to 4.89; P=0.40
- Pulmonary embolism: RR 0.86, 95% CI 0.46 to 1.61; P=0.63
- Multi-organ failure: RR 0.90, 95% CI 0.75 to 1.08; P=0.25
- Head injury: RR 0.97, 95% CI 0.87 to 1.08; P=0.60
- 'Other' causes: RR 0.94, 95% CI 0.74 to 1.20; P=0.63

Although not prespecified subgroup analyses of this review, the effects of TXA on death due to bleeding by time to treatment, severity of haemorrhage, Glasgow coma score, and type of injury were assessed in the CRASH-2 trial (CRASH-2 2011). The results are presented below.

Analysis of the risk of death due to bleeding indicated that the effect of TXA varied by time to treatment. Treatment within one hour of injury was associated with a 32% relative reduction in risk of death due to bleeding (RR 0.68, 95% CI 0.57 to 0.82; P<0.0001) and treatment between 1 and 3 hours after injury was associated with a 21% reduction (RR 0.79, 95% CI 0.64 to 0.97; P=0.03). Treatment with TXA after three hours of injury was associated with a 44% relative increase in risk of death due to bleeding (RR 1.44, 95% CI 1.12 to 1.84; P=0.004). Test for subgroup differences: Chi^2=23.51, P<0.00001.

There was no evidence that the effect of TXA on death due to bleeding varied by the severity of haemorrhage, Glasgow coma score, or type of injury:

- Severity of haemorrhage (as assessed by systolic blood pressure): >89 mm Hg (RR 0.88, 95% CI 0.71 to 1.10); 76-89 (RR 1.01, 95% CI 0.79 to 1.30); ≤75 (RR 0.81, 95% CI 0.69 to 0.95). Test for subgroup differences: Chi^2=2.24, P=0.33.
- Glasgow coma score: severe (RR 0.92, 95% CI 0.76 to 1.13); moderate (RR 0.77, 95% CI 0.59 to 0.99); mild (RR 0.86, 95% CI 0.72 to 1.02). Test for subgroup differences: Chi^2=1.28, P=0.53.
- Type of injury: blunt (RR 0.89, 95% CI 0.77 to 1.04); penetrating (RR 0.79, 95% CI 0.66 to 0.96). Test for subgroup differences: Chi^2=0.92, P=0.34.

Vascular occlusive events

The CRASH-2 2010 trial reported data on vascular occlusive events. There was no difference in the risk of experiencing one

or more vascular occlusive events (fatal or non-fatal: myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) between the TXA and placebo groups (RR 0.84, 95% CI 0.68 to 1.02; P=0.084). TXA reduced the risk of myocardial infarction (RR 0.64, 95% CI 0.42 to 0.97; P=0.035). There was no difference in the risk of stroke (RR 0.86, 95% CI 0.61 to 1.23; P=0.42), pulmonary embolism (RR 1.01, 95% CI 0.73 to 1.41; P=0.93) or deep vein thrombosis (RR 0.98, 95% CI 0.63 to 1.51; P=0.91).

Surgical intervention

Data from the CRASH-2 2010 trial suggest that there is no statistically significant difference in the risk of receiving one or more surgical interventions (neurosurgery, chest, abdominal or pelvic surgery) (RR 1.00, 95% CI 0.97 to 1.03; P=0.79) Analysis 1.2.

Receipt of blood transfusion

Of the patients allocated to TXA in the CRASH-2 2010 trial, 5067 (50.4%) received a blood product transfusion versus 5160 (51.3%) of the patients allocated to placebo (RR 0.98, 95% CI 0.96 to 1.01; P=0.21) Analysis 1.3. There was no difference in the average number of blood units transfused (MD -0.17; 95% CI -0.39 to 0.05; P=0.13) Analysis 1.4.

Aprotinin versus placebo

The study by Auer 1979, with 20 randomised patients, provided no useable outcome data for the reasons outlined above. The study by McMichan 1982, with 77 randomised patients (seven post-randomisation exclusions), was reported in four separate reports (Rosengarten 1977; Rosengarten 1979 and McMichan 1977 in 'included studies' reference McMichan 1982).

Mortality

McMichan 1982 reported mortality data: there was no difference in the risk of death between the aprotinin or placebo groups (RR 0.14, 95% CI 0.01 to 2.67; P=0.19) Analysis 2.1.

Vascular occlusive events

Data on vascular occlusive events were not reported.

Surgical intervention

McMichan 1982 reported data on the number of patients undergoing a surgical intervention: there was no difference between the aprotinin or placebo groups (RR 1.07, 95% CI 0.87 to 1.33; P=0.53) Analysis 2.2.

Receipt of blood transfusion

Data on the number of patients receiving a blood transfusion were not reported. The volume of blood transfused was reported, there was no difference between groups (MD -0.40 units; 95% CI -0.91, 0.11; P=0.12) Analysis 2.3.

DISCUSSION

Summary of main results

Tranexamic acid reduces all-cause mortality in bleeding trauma patients, with no apparent increase in the risk of vascular occlusive events. This conclusion is based on the results of the CRASH-2 2010 trial which recruited 20,211 bleeding trauma patients from 274 hospitals in 40 countries.

Overall completeness and applicability of evidence

The large numbers of patients in a wide range of different health care settings around the world studied in the CRASH-2 2010 trial help the result to be widely generalised. The treatment is effective in patients with blunt and penetrating trauma. Because TXA is inexpensive and easy to administer, it could readily be added to the normal medical and surgical management of bleeding trauma patients in hospitals around the world.

Each year, worldwide, about four million people die as a result of traumatic injuries and violence. Approximately 1.6 million of these deaths occur in hospital and about one third of these deaths (480,000) are from haemorrhage. The CRASH-2 2010 trial has shown that TXA reduces mortality from haemorrhage by about one sixth. If this widely practicable intervention was used worldwide in the treatment of bleeding trauma patients, it could prevent over 70,000 deaths each year (see Table 1).

Many trauma patients suffer a brain injury. Traumatic brain injury (TBI) is commonly accompanied by intracranial bleeding which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and regardless of location, haemorrhage size is strongly correlated with outcome. If TXA reduced intracranial bleeding after isolated TBI then this could improve patient outcomes. Although, many of the bleeding trauma patients included in the CRASH-2 2010 trial also suffered a brain injury, it is possible that the effects of TXA may differ in patients with isolated TBI. The trial by Yutthakasemsunt 2010 provides some promising evidence for the beneficial effect of TXA on mortality in patients with isolated TBI: however, further evidence is required from larger trials which also assess the effect on disability.

There is no evidence for the effect of aprotinin for trauma.

Quality of the evidence

The quality of the evidence supporting the use of tranexamic acid for trauma is high. The findings of this review are based primarily on the results of the CRASH-2 2010 trial. This was a large, high quality randomised trial with low risk of bias. Sequence generation was appropriately randomised, allocation was concealed and participants, trial personnel and outcome assessors were all blinded. Furthermore, there were minimal missing data with over 99% of patients followed up.

Potential biases in the review process

This systematic review addresses a focused research question and uses pre-defined inclusion criteria and methodology to select and appraise eligible trials.

As with all systematic reviews, the possibility of publication bias should be considered as a potential threat to validity. However, in light of our extensive and sensitive searching we believe that the risk of such a bias affecting the results is minimal.

Agreements and disagreements with other studies or reviews

A systematic review of randomised trials assessing the effects of TXA in patients undergoing elective surgery has been conducted (Henry 2011). This review found that compared to control, TXA reduced the need for blood transfusion without any apparent increase in the risk of adverse events. Unlike the Henry 2011 review, we found no evidence of any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. One possible explanation is that in the CRASH-2 2010 trial, following the loading dose, TXA was infused over a period of eight hours, whereas decisions about transfusion are made very soon after hospital admission. The absence of any large effect on blood transfusion may also reflect the difficulty of accurately estimating blood loss in trauma patients when assessing the need for transfusion. Finally, the absence of any substantial reduction in transfusion requirements in patients treated with TXA acid may reflect the fact that there were fewer deaths in patients allocated to TXA acid than to placebo and patients who survive as a result of TXA administration would have had a greater opportunity to receive a blood transfusion (competing risks).

AUTHORS' CONCLUSIONS

Implications for practice

Tranexamic acid (TXA) safely reduces mortality in bleeding trauma patients. As there is evidence that the effect on death due to bleeding depends on the time interval between the injury and treatment, TXA should be given as early as possible and within three hours of the injury as treatment later than this is unlikely to be effective.

Implications for research

The knowledge that TXA safely reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations where bleeding can be life threatening or disabling and further research is warranted to explore this potential. Randomised trials involving patients with isolated traumatic brain injury that assess both mortality and disability outcomes are required before TXA can be recommended for use in these patients. The ongoing CRASH-3 trial with a planned sample size of 10,000 patients with traumatic brain injury, will contribute to resolving the uncertainty about the effects of TXA in this group.

ACKNOWLEDGEMENTS

Many thanks to Vasiliy Vlassov for help with translation.

We also thank Karen Blackhall for designing and conducting the electronic searches.

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* *Indicates the major publication for the study*

Appendix U. Research Paper 4: Search strategies

Cochrane Injuries Group Specialised Register (searched July 2010)

(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren) or (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA) or (aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan)

Cochrane Central Register of Controlled Trials 2010, Issue 3 (**The Cochrane Library*****)***

#1 MeSH descriptor Antifibrinolytic Agents explode all trees
#2 (anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin*):ab,ti or ((plasmin or fibrinolysis) near3 inhibitor*):ab,ti
#3 MeSH descriptor Aprotinin explode all trees
#4 (Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren or midran):ab,ti or ((Kunitz near3 inhibitor*) or (pancrea* near3 antitrypsin) or (pancrea* near3 trypsin next inhibitor*)):ab,ti
#5 MeSH descriptor Tranexamic Acid explode all trees
#6 (tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino

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Appendix V. Research Paper 4: Characteristics of included studies

Auer 1979		
Methods	Probable RCT: "Twenty patients were included in a double-blind study; nine patients were treated with Trasylol. Eleven received a placebo drug." Five additional (non-randomly allocated) patients were added to the study and received aprotinin treatment. These patients were not separated out in the analysis.	
Participants	Patients with severe head injury who had remained comatose for seven days. Most of them had clinical brain stem signs.	
Interventions	Aprotinin group: 500,000 IE initially thereafter 200,000 IV every four hours	
Outcomes	Death. Range of biochemical end points.	
Notes	Notes Because it was not possible to separate the 5 non-randomised patients from the 20 probably randomised patients, this study provides no useable outcome data	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear.

CRASH-2 2010	
Methods	RCT: Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Participants and study staff were blind to treatment allocation
Participants	20,211 adult (>16 years) trauma patients with, or at risk of, significant bleeding
Interventions	Tranexamic acid group: loading dose 1g over 10 minutes then infusion of 1g over 8 hours Matching placebo.
Outcomes	Death. Vascular occlusive events.

	Blood transfusion requirements. Disability.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	TXA and placebo were packaged in identical ampoules. Hospitals with a reliable telephone access used a telephone randomisation service, hospitals without used a local pack system

McMichan 1982	
Methods	RCT: Aprotinin and placebo were supplied in identical coded ampoules. Ampoules were in boxes of 50 with a code number assigned to each box. These numbers were randomised in groups of 20 and each batch was assigned in numerical order. The codes were not broken until the end of the study. Patients excluded after randomisation were those who died within the first 24 hours or refused continuing investigation.
Participants	Patients with a combination of hypovolaemic shock and major fractures of the lower limb and or pelvis. Patients seen 12 or more hours after injury and those with major head or chest injuries were excluded.
Interventions	Aprotinin group: 500,000 Kallikrein Inhibitor Units (KIU) IV statim followed by 300,000 KIU at 6-hour intervals for 96 hours.
Outcomes	Death. Mean blood transfusion. Respiratory function.
Notes	77 patients were randomised but there were 7 post-randomisation exclusions. Among the 7 excluded patients, there were 3 deaths within the first 24 hours of injury. One patient was

	transferred to another hospital because of quadriplegia and died later, and three patients refused investigation. It was noted in the results that the data on transfusion requirement was found to have a non-normal distribution. Nevertheless, the mean and standard deviation were presented.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Aprotinin and placebo were prepared in "similar ampoules". All ampoules were in boxes of 50, with a code number assigned to each box. The nature of the content of the ampoules was not known to any of the investigators nor to the attending physicians. The codes were not broken until the end of the study

Yutthakasemsunt 2010		
Methods	RCT	
Participants	240 adults patients (>16 years) with moderate to severe traumatic brain injury (Glasgow Coma Scale 4 to 12) within 8 hours of injury	
Interventions	Tranexamic acid group: 2g. Matching placebo.	
Outcomes	Death. Progressive intracranial haemorrhage. Disability (GOS). Thromboembolic events.	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

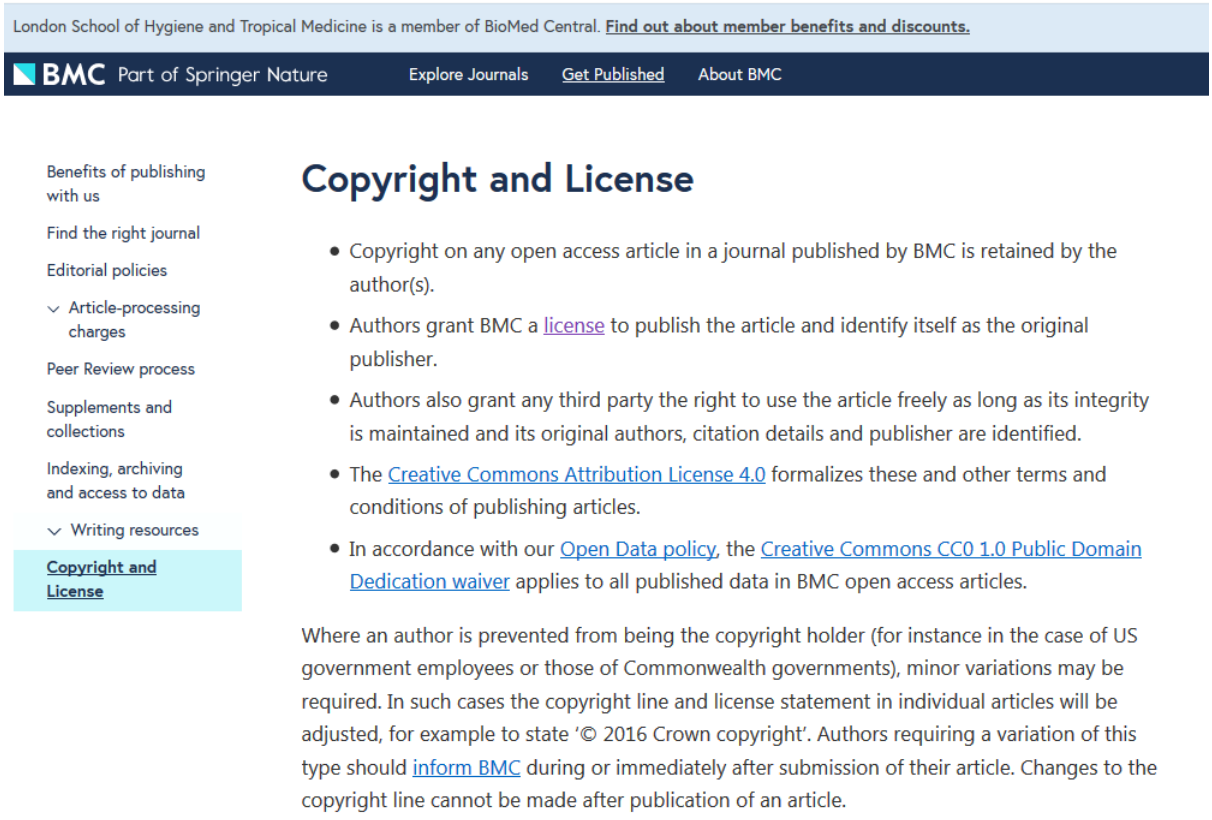
Appendix W. Research Paper 4: Characteristics of excluded studies

Study	**Reason for exclusion**
Gierhake 1971	Types of patients: general surgery patients not trauma.
Husted 2003	Types of patients: orthopaedic patients not trauma.
Klobow 1977a	Types of interventions: trasylol compared with heparin.
Klobow 1977b	Types of interventions: trasylol compared with heparin.
Kuiian 1999	Types of studies: After Dr Vasiliy Vlassov, Director of the Russian Branch of the Nordic Cochrane Centre kindly translated the methods section it was clear that this study was not randomised
Loew 1970	Types of studies: alternation used not random allocation.
Nissen 1989	Types of studies: review article not randomised controlled trial
Schneider 1976	Types of studies: randomisation in this trial was by allocating patients to the treatment group according to the day of admission. However, this procedure was subverted for large numbers (813) of patients in which case the study cannot be considered to be a randomised controlled trial

Appendix X. Research Paper 4: Characteristics of ongoing studies

CRASH-3	
Trial name or title	Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3)
Methods	Large, international, randomised, placebo controlled trial.
Participants	Adults with traumatic brain injury, who are within eight hours of injury, with any intracranial bleeding on CT scan or who have a GCS of 12 or less, and have no significant extra-cranial haemorrhage, are eligible for inclusion, except those for whom antifibrinolytic agents are thought to be clearly indicated or clearly contraindicated
Interventions	Loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given as soon as possible after randomisation. Maintenance dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) given after the loading dose is finished
Outcomes	Primary outcome is death in hospital within 28 days of injury. Secondary outcomes are vascular occlusive events (myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis), stroke, disability, seizures, neurosurgical intervention, days in intensive care, other adverse events
Starting date	July 2012
Contact information	crash@Lshtm.ac.uk
Notes	Current Controlled Trials ISRCTN15088122; Clinicaltrials.gov NCT01402882 The JP Moulton Charitable Trust, UK, is funding the run-in costs for the trial and up to 500 patients' recruitment. Full funding is being sought from public funding organisations for the main trial

Appendix Y. Research Paper 5: Retention of copyright/permission to publish



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Appendix Z. Research Paper 4: Published article

Ker et al. BMC Emergency Medicine 2012, 12:3
http://www.biomedcentral.com/1471-227X/12/3

BMC Emergency Medicine

RESEARCH ARTICLE Open Access

Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial

Katharine Ker*, Junko Kiriya, Pablo Perel, Phil Edwards, Haleema Shakur and Ian Roberts

Abstract

Background: The CRASH-2 trial showed that early administration of tranexamic acid (TXA) safely reduces mortality in bleeding in trauma patients. Based on data from the CRASH-2 trial, global mortality data and a systematic literature review, we estimated the number of premature deaths that might be averted every year worldwide through the use of TXA.

Methods: We used CRASH-2 trial data to examine the effect of TXA on death due to bleeding by geographical region. We used WHO mortality data (2008) and data from a systematic review of the literature to estimate the annual number of in-hospital trauma deaths due to bleeding. We then used the relative risk estimates from the CRASH-2 trial to estimate the number of premature deaths that could be averted if all hospitalised bleeding trauma patients received TXA within one hour of injury, and within three hours of injury. Sensitivity analyses were used to explore the effect of uncertainty in the parameter estimates and the assumptions made in the model.

Results: There is no evidence that the effect of TXA on death due to bleeding varies by geographical region (heterogeneity $p = 0.70$). Based on WHO data and our systematic literature review, we estimate that each year worldwide there are approximately 400,000 in-hospital trauma deaths due to bleeding. If patients received TXA within one hour of injury then approximately 128,000 (uncertainty range [UR] ≈ 72,000 to 172,000) deaths might be averted. If patients received TXA within three hours of injury then approximately 112,000 (UR ≈ 68,000 to 148,000) deaths might be averted. Country specific estimates show that the largest numbers of deaths averted would be in India and China.

Conclusions: The use of TXA in the treatment of traumatic bleeding has the potential to prevent many premature deaths every year. A large proportion of the potential health gains are in low and middle income countries.

Background

Trauma is a leading cause of death and disability. Each year, worldwide, an estimated 5.8 million people die as a result of trauma [1], many after reaching hospital. Among trauma patients who survive to reach hospital, bleeding is a common cause of death, accounting for around 40% of in-hospital trauma deaths [2].

The CRASH-2 trial was an international randomised controlled trial of the early administration of tranexamic acid (TXA) to bleeding trauma patients. The trial recruited 20,211 patients from 274 hospitals in 40 countries. The results show that TXA reduces mortality in trauma patients with or at risk of bleeding, with no apparent increase in side effects [3]. If given within three hours of injury, TXA reduces the risk of death due to bleeding by about a third [4]. TXA administration has been shown to be highly cost-effective in high, middle or low income countries [5]. On the basis of the

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results of the CRASH-2 trial, TXA has been included on the WHO Essential Medicines List [6].

Since publication of the trial results, TXA has been included into trauma care guidelines in many high income countries. In March 2010, the British Army incorporated TXA into combat care treatment protocols [7] and in July 2011 the UK NHS ambulance service agreed that TXA would be given to all adults and teenagers who suffer major injury in the UK. In 2011, the US Army reviewed the evidence from the CRASH-2 trial and included TXA into its trauma treatment protocols. However, bearing in mind that 90% of trauma deaths are in low and middle income countries [8], the potential of TXA to reduce premature mortality is likely to be much greater in these settings. An estimation of the number of deaths that could be averted through the use of TXA for in traumatic haemorrhage would allow better targeting of dissemination and implementation activities. In this study we used data from the CRASH-2 trial, WHO mortality database and a systematic review of the recent literature, to estimate the potential number of deaths that could be averted through the early administration of TXA to bleeding trauma patients.

Methods

Estimation of effect of TXA on death due to bleeding by geographical region

We used individual patient data from the CRASH-2 trial to assess the extent to which the effect of TXA on death due to bleeding varied according to geographical region. Hospitals participating in the CRASH-2 trial were grouped into four geographical regions: (1) Africa, (2) Asia, (3) Europe, Australia, North America, and (4) Central & South America. Heterogeneity in treatment effect by geographical region was assessed by a χ^2 test. We pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $p < 0.001$), the overall risk ratio (RR) would be considered to be the most reliable guide to the approximate RRs in all regions.

Estimation of number of in-hospital trauma deaths due to bleeding per year

The number of in-hospital trauma deaths that are due to bleeding and thus potentially avoidable through the early administration of TXA was estimated in three steps.

First, we obtained estimates of the number of trauma deaths (N_T) by country. Since the risk of death due to bleeding may vary according to type of injury (i.e. blunt or penetrating) [9], we classified deaths as being a result of blunt trauma (N_{BT}) or penetrating trauma (N_{PT}). Second, we obtained data on the proportion of trauma deaths that occur in hospital (P_H). The numbers of in-hospital blunt trauma deaths ($N_{H,\ BT}$) and in-hospital penetrating trauma deaths ($N_{H,\ PT}$) were then estimated according to the following equations:

$$N_{H,BT} = N_{BT} \times P_H$$
$$N_{H,PT} = N_{PT} \times P_H$$

Third, we obtained data on proportion of in-hospital blunt trauma deaths caused by bleeding ($P_{H,\ BT,\ BL}$) and the proportion of in-hospital penetrating trauma deaths caused by bleeding ($P_{H,\ PT,\ BL}$). Using these estimates we derived the number of in-hospital trauma deaths caused by bleeding ($N_{H,\ T,\ BL}$) as follows;

$$N_{H,T,BL} = (N_{H,BT} \times P_{H,BT,BL}) + (N_{H,PT} \times P_{H,PT,BL})$$

The number of premature deaths potentially averted by TXA was then estimated by applying the relative risk reduction from the CRASH-2 trial to the number of in-hospital deaths due to bleeding as follows:

$$\text{Premature deaths averted} = N_{H,T,BL} \times (1 - RR)$$

Data sources

Data from the WHO, the CRASH-2 trial and a systematic review of literature published since 2004 were used to parameterise the equations. The number of trauma deaths for each country, were obtained from the WHO for the year 2008, the most recent year for which data were available. Blunt trauma deaths were estimated by adding the number of deaths from road traffic crashes, falls and other unintentional injuries. Penetrating trauma deaths were estimated by adding the number of deaths from violence and war. Deaths from drowning, poisoning, self-inflicted injuries or burns were not included as these injuries are not usually associated with life-threatening bleeding. Estimates of the proportion of trauma deaths that are in-hospital and the proportion caused by bleeding were based on data from the CRASH-2 trial and from studies identified through a systematic review.

Systematic review methods

We searched for studies containing original data describing the epidemiology of trauma deaths. We searched MEDLINE, EMBASE and Cab Abstracts on 2 March 2011 using a combination of subject headings and key words based on the following terms; injuries, trauma, mortality, death, fatality, burden, epidemiology. We searched the internet and checked the reference lists of eligible articles. The searches were not restricted by language or publication status. To improve the applicability of the extracted data to the current patterns in trauma death epidemiology, we limited our search to studies published since 2004.

Record screening, full text review and data extraction were performed independently by two authors (KK and JK), with any disagreements resolved through discussion. Data were extracted on study design, setting, sample size, the proportions of deaths occurring in hospital and due to bleeding, using a pre-designed form. Studies that did not provide data on any of the parameters of interest were excluded.

To obtain a summary estimate for each parameter, the study proportions were transformed according to the Freeman Tukey variant of the arcsine square root transformed proportions to correct for over-dispersion [10]. Pooled proportions were calculated as the back-transformation of the weighted mean of the transformed proportions using the random effects model [11].

Data analysis

For each country, the number of in-hospital trauma deaths due to bleeding was calculated by applying the corresponding estimated proportions to the mortality data, as described above. For the primary analysis, the relative risk reduction from the CRASH-2 trial was applied to estimate the number of premature deaths that could be averted (1) if all patients received TXA within one hour of injury, and (2) if all patients received TXA within three hours of injury. The numbers of deaths averted in each country were combined to give an overall global estimate. To identify the countries with the greatest potential for benefit from TXA, countries were ranked in order of the estimated number of premature deaths averted.

To investigate the impact on the results of uncertainty in the parameter estimates used in the modelling, a number of sensitivity analyses were conducted. First, the analysis was repeated using the lower and upper bounds of the 95% confidence intervals for the parameter estimates to explore the effect of parameter uncertainty. Second, we repeated the analysis using the relative risk estimate for all-cause mortality rather than death due to bleeding. This analysis was conducted to take account of the possibility that some patients who do not die from bleeding because of TXA administration would nevertheless die of other causes such multi-organ failure or brain injury. Third, we repeated the analyses using the relative risk estimate for all-cause mortality with TXA when given at any time within eight hours of injury. Although, previously published subgroup analyses show that early treatment is more effective it is possible that treatment within three hours is not possible in some settings.

For each estimate, to reflect statistical uncertainty around the relative risks of TXA, an uncertainty range was estimated by calculating the numbers of deaths averted based on the 95% confidence intervals for the relative risks. The analyses were conducted using Microsoft Excel and STATA 11 (TX: StataCorp LP) software.

Results

Estimation of the effect of TXA on death due to bleeding by geographical region

Figure 1 shows the effect of TXA given within three hours of injury on death due to bleeding by geographical region. There was no evidence for heterogeneity in the effect of TXA by region ($\chi^2 = 1.445$; $p = 0.70$). The overall RRs for the effect of TXA on death due to bleeding when given within one hour (RR = 0.68; 95% CI 0.57 to 0.82) and within three hours (RR = 0.72; 95% CI 0.63 to 0.83) of injury were therefore taken as the most reliable guide as to the approximate RRs in all regions, and were used to estimate the number of deaths that could be averted with TXA.

Estimation of the annual number of in-hospital trauma deaths due to bleeding

We identified 18 studies, described in 17 reports [12-28], which presented data on the parameters of interest and were included in the systematic review. Studies were conducted in 13 countries; USA, Canada, UK, Australia, Brazil, Denmark, Norway, Mozambique, South Africa, Italy, France, Spain and India. In addition, we obtained data collected as part of the CRASH-2 trial, which recruited patients from hospitals in 40 countries throughout the world. The study selection process is summarised in Figure 2. Data extracted from the studies are summarised in Additional File 1.

Fourteen studies [13-15,17,19-27] involving 24,831 trauma deaths provided data on the proportion of deaths occurring in-hospital; the pooled proportion was 44% (95% CI 33 to 56%). Five studies [3,12,16,18,28] involving 9684 deaths presented data on the proportion of blunt trauma deaths due to haemorrhage; the pooled proportion was 18% (95% CI 13 to 23%). Four studies [3,12,16,28] involving 2256 deaths presented data on the proportion of penetrating trauma deaths due to

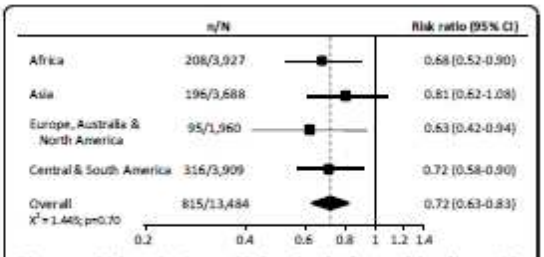

Figure 1 Risk ratio (95% CI) for death due to bleeding with TXA given within three hours of injury, overall and by geographical region.

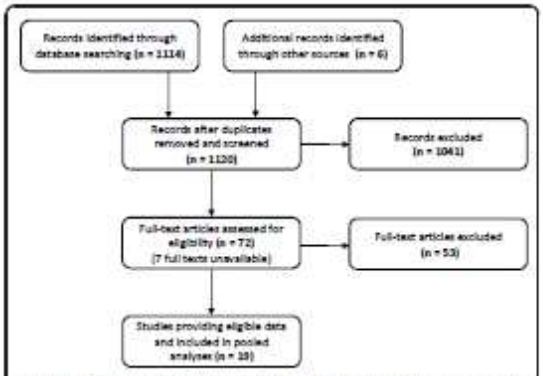

Figure 2 Flow diagram of the study selection process for systematic review.

haemorrhage; the pooled proportion was 55% (95% CI 49 to 62%).

After applying these parameter estimates to the WHO data, we estimate that worldwide every year approximately 400,000 trauma patients die in-hospital from bleeding. If all of these patients receive TXA within one hour of injury the about 128,000 (uncertainty range [UR] ≈ 72,000 to 172,000) deaths could be averted. If all of these patients receive TXA within three hours of injury about 112,000 (UR ≈ 68,000 to 148,000) deaths could be averted. The global distribution of number of premature deaths averted by TXA when administered within three hours of injury is shown in Figure 3.

Results for the countries where more than 1000 deaths could be averted are shown in Table 1. The largest numbers of deaths from haemorrhage and consequently the largest numbers of deaths averted are in Asia. The largest numbers of premature deaths averted are in India (*TXA ≤ 1 hr* ≈ 19,000; *TXA ≤ 3 hrs* ≈ 16,500) and China (*TXA ≤ 1 hr* ≈ 17,000; *TXA ≤ 3 hrs* ≈ 15,000). When ranked by the number of premature deaths potentially averted, nine of the top ten countries are low or middle income, the exception being the USA where approximately 4,000 and 3,500 deaths would be averted by TXA given within one hour and three hours of injury, respectively.

Sensitivity analyses

When the analyses were repeated using the values of the lower and upper 95% CIs of the pooled parameter estimates, the global number of deaths averted ranged from approximately 76,000 to 198,000 if TXA is given within one hour of injury and from 67,000 to 173,000 if given with three hours of injury. When the analysis was carried out using the relative risk estimate for all-cause mortality if TXA is given within one hour (RR = 0.87; 0.78 to 0.97) and within three hours (RR = 0.87; 0.80 to 0.94) of injury, the number of premature deaths averted was 52,000 (TXA ≤ 1 hr ≈ 12,000 to 88,000; TXA ≤ 3 hrs ≈ 24,000 to 80,000). When the analysis was repeated using relative risk estimate for death due to bleeding when TXA is given at any time within eight hours of injury (RR = 0.85; 0.76 to 0.96), the number of premature deaths averted was 60,000 (UR ≈ 16,000 to 96,000). Finally, using the relative risk estimate for all-cause mortality when TXA is given within eight hours of injury (RR = 0.91; 0.85 to 0.97), an estimated 36,000 (UR ≈ 12,000 to 60,000) premature deaths could be averted.

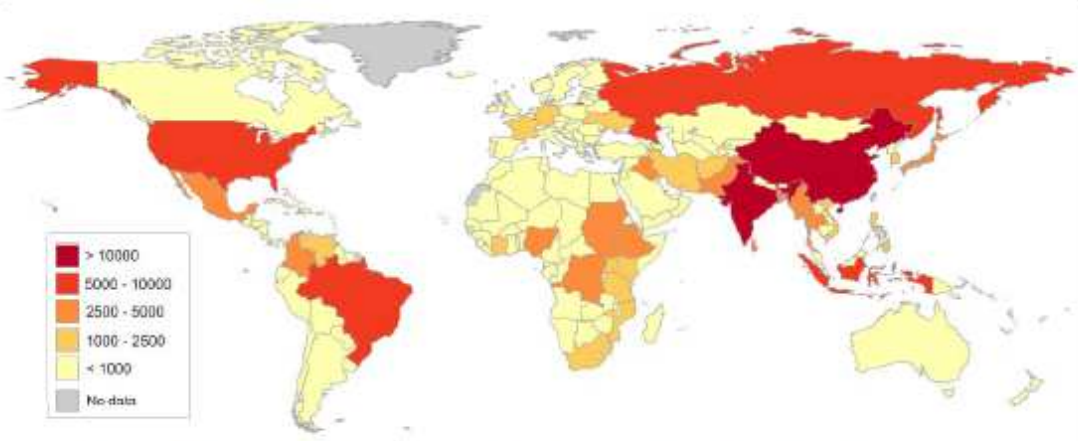

Figure 3 Global distribution of number of deaths averted with TXA administration within three hours of injury.

Table 1 Estimated number of premature trauma deaths averted by TXA per year

	In-hospital trauma deaths from bleeding	Deaths averted TXA ≤ 1 hour	Deaths averted TXA ≤ 3 hours
Worldwide	400,467	128,149	112,131
Countries with > 1000 deaths averted			
India	58,801	18,816	16,464
China	54,241	17,357	15,187
Brazil	19,187	6,140	5,372
Russian Federation	16,731	5,354	4,685
Myanmar	13,193	4,222	3,694
Iraq	12,786	4,091	3,580
USA	12,489	3,996	3,497
Indonesia	11,033	3,531	3,089
DR Congo	9,373	2,999	2,624
Sri Lanka	8,979	2,873	2,514
Pakistan	8,770	2,806	2,456
Ethiopia	8,768	2,806	2,455
Nigeria	8,258	2,643	2,312
Colombia	7,348	2,352	2,058
Sudan	7,292	2,334	2,042
Bangladesh	7,210	2,307	2,019
Mexico	7,059	2,259	1,976
Philippines	6,119	1,958	1,713
Thailand	5,572	1,783	1,560
Afghanistan	4,774	1,528	1,337
Uganda	4,620	1,478	1,294
South Africa	4,245	1,359	1,189
Venezuela	4,172	1,335	1,168
Kenya	4,029	1,289	1,128
Tanzania	3,969	1,270	1,111
Iran	3,921	1,255	1,098

Discussion

Based on WHO mortality data and a systematic review of the literature we estimate that there are about 400,000 in-hospital deaths from bleeding each year worldwide. If all hospitalised bleeding trauma patients could be treated with TXA within an hour of injury then up to 128,000 of these premature deaths could be averted. If they could be treated within three hours of injury then up to 112,000 premature deaths could averted. Although there is considerable uncertainty in the estimates even the most conservative suggest that tens of thousands of deaths could be averted every year.

We found no compelling evidence that the effect of TXA on death due to bleeding varies by geographical region. Our conclusion is based on a statistical test of interaction which is considered to be the most appropriate way to evaluate subgroup effects [29]. As recommended by methodologists, we pre-specified that unless there was strong evidence against the null hypothesis of homogeneity of effects (i.e. $p < 0.001$), that the overall risk ratio (RR) would be considered to be the most reliable guide to the approximate RRs in all regions. We found no statistical basis to reject the null hypothesis.

The data sources used to parameterise the model are subject to a number of limitations which may have affected our results. First, although the WHO database provides the best available country-level mortality data, poor coverage and coding of mortality registration systems may affect the accuracy of the number of trauma deaths for some countries. Second, our classification of trauma deaths into blunt or penetrating trauma based on the cause of death categories in the WHO data was somewhat arbitrary and would have resulted in some misclassification. However, in the absence of accurate country-specific data, we judged that this approach would provide the most reliable estimates. Third, due to the absence of country-specific data for the proportions of deaths occurring in hospital and the proportion of deaths caused by haemorrhage, we chose to apply average global estimates. We were therefore unable to incorporate between-country variations in these parameter estimates into our analysis. Nevertheless, our estimates were derived from a systematic review of the recent

literature and data from the CRASH-2 trial, and thus represent the most accurate estimates available. We also performed sensitivity analyses to assess the impact of uncertainty around the parameter estimates.

Since many deaths from self-inflicted injuries are not usually associated with life-threatening haemorrhage (e.g. self-poisoning, hanging) we excluded this category to avoid over-estimating the number of deaths due to bleeding. However, this is likely to have led to the exclusion of some self-inflicted deaths that were associated with haemorrhage, in which case we may have underestimated the potential of TXA administration.

Our analysis was based on a number of assumptions. We have assumed that there was no use of TXA as a treatment for traumatic bleeding prior to publication of the CRASH-2 trial results. It is possible that a small proportion of the trauma deaths in our sample did receive TXA prior to their death, which may over-estimate the number of deaths averted. However, given that any such prior use of TXA would have been minimal it is unlikely to have greatly affected our overall estimates.

The objective of our analysis was to estimate the potential number of deaths that could be averted assuming TXA use under optimal conditions, that is, when administered appropriately and within three hours of injury, to all eligible bleeding trauma patients. It is unrealistic that such conditions are consistently and fully achieved in clinical practice. For example, the opportunity to treat some eligible patients will be missed and errors in the dose used or its administration may reduce the beneficial effect of TXA.

We assumed that the results of the CRASH-2 trial could be extrapolated to all hospitalised bleeding trauma patients. The CRASH-2 trial used clinical criteria to recruit a large number of patients from 274 hospitals in 40 countries, which helps the results to be generalised widely. Whilst we acknowledge that the underlying risk of death will vary in different settings, this does not necessarily imply that that the relative effect will vary. Indeed, relative effects are often remarkably homogeneous despite differences in underlying risk. This is supported by empirical evidence from a range of trials in which the relative effects are constant across variations in baseline risk [30]. Furthermore, there is no reason to suppose that the mechanism of action of TXA would vary in different populations. However, we acknowledge that the appropriateness of such extrapolation is a matter of judgement.

A further assumption is that all trauma patients reached hospital in time to receive early treatment with TXA; that is either within one hour or within three hours of injury. Such a time frame is unlikely to be realistic in many settings where long distances and other logistical difficulties may delay arrival at hospital. For this reason we performed sensitivity analyses based on the relative effect of TXA from a more conservative estimate of time-to-treatment of within eight hours of injury, the results of which still suggest that up to 60,000 deaths could be averted. Besides, there is reason to predict that time between injury and treatment would be shorter in clinical practice than in the CRASH-2 trial as delays caused by consent procedures would be avoided [31].

In applying the RR of death due to bleeding in our primary analysis we assumed that all deaths in this group would be avoided. However, it is possible that whilst TXA may prevent death due to bleeding, some patients would die from other causes instead. If this is the case, then our primary analysis would over-estimate the number of death averted. To address this we performed a sensitivity analysis in which the effect of TXA on all-cause mortality was used. Even using this smaller relative reduction, up to 50,000 deaths could be averted.

We restricted our analysis to the potential benefit of in-hospital use of TXA. However, our parameter estimate of the proportion of in-hospital trauma deaths indicates that most trauma deaths occur before arrival at hospital. TXA is a practicable treatment suitable for use in a range of health-care settings, including pre-hospital. If TXA was used in the pre-hospital setting then many more premature deaths might be averted.

Conclusions

Our analysis shows the potential of TXA to reduce trauma deaths worldwide. Realisation of this potential is likely to require further efforts in dissemination and implementation, particularly in low and middle income settings.

Additional material

Additional file 1: Summary of data extracted from studies included in systematic review.

Acknowledgements

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Authors' contributions

KK, JK and IR designed the study. KK, JK and PP obtained the data and conducted all analyses with advice from PE and IR. KK wrote the paper with input from all other authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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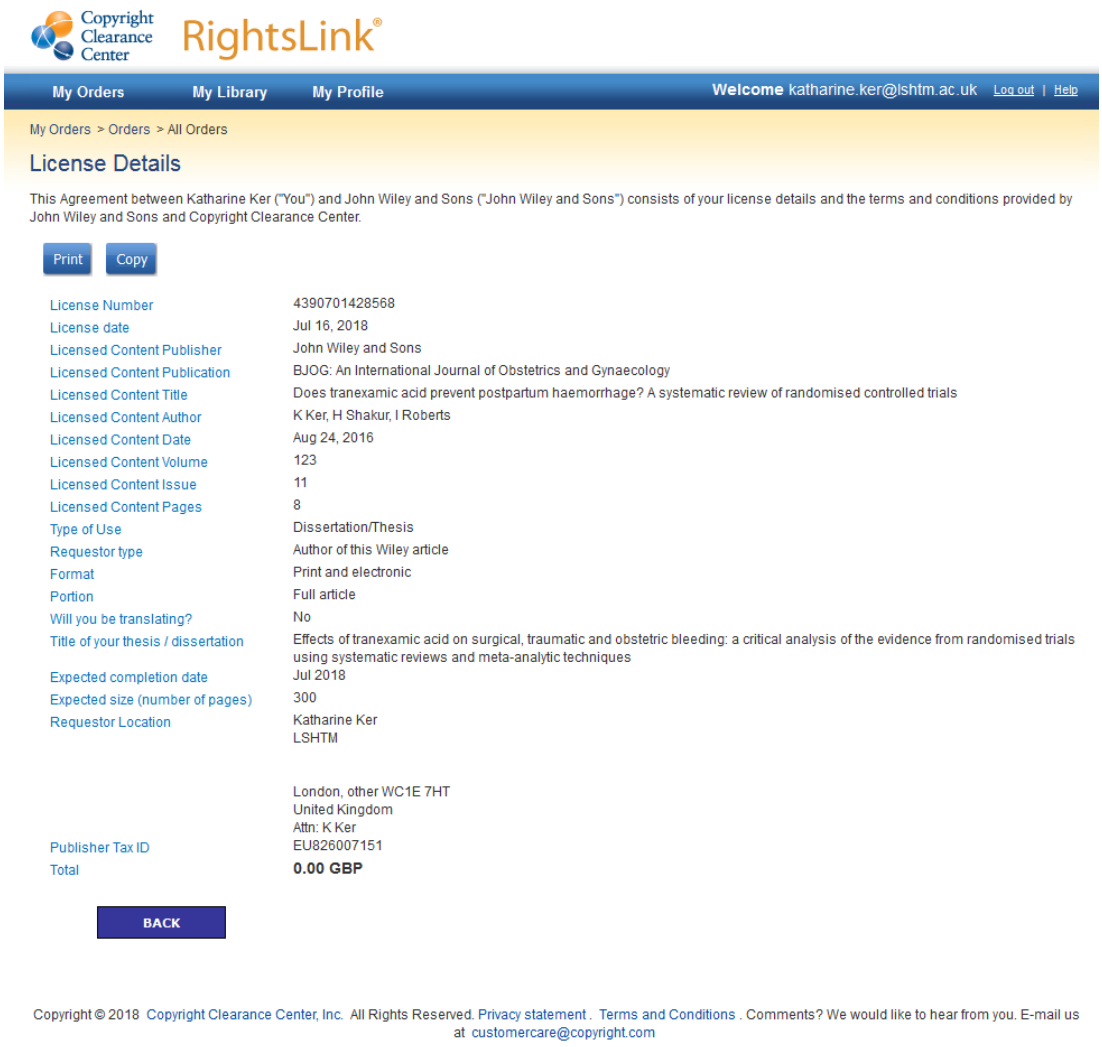
Appendix AA. Research Paper 5: Summary of data extracted from studies included in systematic review

Author, year	Country	Design	Deaths (n)	Deaths occurring in-hospital (n)	Blunt trauma deaths due to haemorrhage (n)	Penetrating trauma deaths due to haemorrhage (n)
Boulanger 2007	USA	Trauma-registry based study; 2000-2004	7362	-	19.6	56.3
CRASH-2 2010	Worldwide	Randomised controlled trial; 2005-2010	1618*	-	28.2	59.6
Demetriades 2004	USA	Trauma-registry based study; 1993-2002	2648	33.4	-	-
Demetriades 2005	USA	Trauma registry and emergency medical services records based study; Jan 2000-Dec 2002	4151	79.6	-	-
Di Barolomeo 2004	Italy	Prospective population-based study; March 1998-Feb 1999	286	37.8	-	-
Dutton 2010	USA	Trauma-registry based study; July 1996-June 2008	2327	-	18.5	46.6
Evans 2010	Australia	Prospective study of autopsies reports and medical records; Feb 2005-Jan 2006	175	61.1	-	-
Gilroy 2005	UK	Retrospective study of in-hospital deaths; 2001	94**	-	13.8	-

Author, year	Country	Design	Deaths (n)	Deaths occurring in-hospital (n)	Blunt trauma deaths due to haemorrhage (n)	Penetrating trauma deaths due to haemorrhage (n)
Gomez de Segura Nieva 2009a	Spain	Prospective study of severe multiple injury patients; April 2001-March 2002	165	27.3	-	-
Gomez de Segura Nieva 2009b	France	Prospective study of severe multiple injury patients; April 2001-March 2002	151	33.8	-	-
Gomez 2010	Canada	Retrospective population-based study; 2002-2003	3486	46.2	-	-
Masella 2008	Brazil	Retrospective population based study; Jan 2000 – Dec 2001	787	43.1	-	-
Meel 2004	South Africa	Retrospective study of medico-legal autopsies; 1997-1998	274	25.9	-	-
Meisler 2010	Denmark	Prospective population based study; 2006	2068	41.7	-	-
Nizamo 2006	Mozambique	Respective review of registered deaths; 2000	1135	38.8	-	-
Potenza 2004	USA	Retrospective population based study; 1987-1997	14,767	27.9	-	-
Singh 2008	India	Retrospective study of autopsy reports; Jan 2001-Dec 2003	344	75.8	-	-

Author, year	Country	Design	Deaths (n)	Deaths occurring in-hospital (n)	Blunt trauma deaths due to haemorrhage (n)	Penetrating trauma deaths due to haemorrhage (n)
Soreide 2007	Norway	Retrospective review of autopsy reports; 1996-2004	260	48.1	-	-
Tien 2007	Canada	Retrospective study of in-hospital deaths; 1999-2003	558	-	8.5	61.6

Appendix BB. Research Paper 6: Retention of copyright/permission to publish



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Appendix CC. Research Paper 6: Published article

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Systematic review

Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials

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Background Postpartum haemorrhage is the leading cause of maternal mortality. Tranexamic acid (TXA) reduces surgical haemorrhage and the risk of death in bleeding trauma patients.

Objectives To assess the effects of TXA on risk of postpartum haemorrhage and other clinically relevant outcomes.

Search strategy We searched the MEDLINE, CENTRAL, EMBASE, PubMed, ClinicalTrials.gov and WHO ICTRP electronic databases to May 2015.

Selection criteria Randomised controlled trials comparing TXA with no TXA or placebo in women giving birth vaginally or by caesarean section.

Data collection and analysis Two authors extracted data and assessed the risk of bias for each trial. Because of data concerns we did not conduct a meta-analysis.

Main results We found 26 trials including a total of 4191 women. Examination of the trial reports raised concerns about the quality of the data. Eight trial reports contained identical or similar text and there were important data inconsistencies in several trials. Two trials did not have ethics committee approval. Meta-analysis of baseline variables suggested that randomisation was inadequate in many trials.

Conclusions There is no reliable evidence that TXA prevents postpartum haemorrhage during childbirth. Many of the trials conducted to date are small, low quality and contain serious flaws.

Keywords Postpartum haemorrhage, systematic review, tranexamic acid.

Tweetable abstract No evidence that TXA prevents postpartum haemorrhage. Existing trials are unreliable, with serious flaws.

Please cite this paper as: Ker K, Shakur H, Roberts I. Does tranexamic acid prevent postpartum haemorrhage? A systematic review of randomised controlled trials. BJOG 2016;123:1745–1752.

Introduction

Postpartum haemorrhage (PPH), one of the most common obstetric emergencies, occurs in about 10% of deliveries.[1] It is the leading cause of maternal mortality worldwide, responsible for about 50 000 deaths each year.[2] Because hysterectomy is sometimes carried out to control the bleeding, PPH deprives thousands of women of their ability to bear children. Anaemia is another important consequence that limits a mother's well-being and her ability to work and care for children.[3]

Tranexamic acid (TXA) reduces bleeding by inhibiting the breakdown of fibrin blood clots. The WOMAN trial is currently evaluating the effect of TXA on death and hysterectomy in women with established PPH.[4] However, for many women, treatment of PPH is too late. Over one-third of pregnant women in the world are anaemic and many are severely anaemic.[5] In these women, even moderate bleeding can be life-threatening and, by worsening their anaemia, can cause disabling fatigue that limits their ability to care for themselves and their baby.[6] TXA given at the time of delivery could prevent severe postpartum bleeding. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth.[7]

We conducted a systematic review of randomised controlled trials to assess the effects of TXA on the risk of postpartum haemorrhage and other clinically relevant outcomes.

Methods

We specified the methods in advanced and registered the review on PROSPERO (CRD42015020670).

Selection criteria and search strategy

We searched for randomised controlled trials comparing TXA with no TXA or a placebo in women delivering vaginally or by caesarean section. The primary outcome was the number of women with a clinical diagnosis of postpartum haemorrhage. Trials of TXA for the treatment of established postpartum haemorrhage were not eligible. Secondary outcomes were death, blood loss, blood transfusion, thromboembolic events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism), surgical intervention, maternal well-being and quality of life, and adverse events in baby.

Eligible trials were identified from a register of randomised controlled trials of anti-fibrinolytic drugs maintained by the London School of Hygiene & Medicine Clinical Trials Unit (LSHTM CTU). The register contains records of trials identified through searches of MEDLINE, CENTRAL, EMBASE, PubMed, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform. Each database was searched using a combination of subject headings and keywords (Appendix S1). In addition, we checked reference lists of relevant articles and searched the internet using the Google search engine for further potentially eligible trials. The searches were run to 13 May 2015 and were not restricted by date, language or publication status.

Procedures

One author screened the titles and abstracts of the search output to identify potentially eligible trials. The full text of these reports was then retrieved and assessed for eligibility. Data on the number of participants, type of delivery, dose and timing of TXA, type of comparator and outcome data were extracted by two authors using a form developed specifically for the review. We used the Cochrane Collaboration tool for assessing the risk of bias. The risk of bias assessments was based on the information presented in the trial report.[8] We assessed the sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting as being at low, high or unclear risk of bias for each trial.

Statistical analysis

For dichotomous outcomes, we calculated risk ratios and 95% confidence intervals. For continuous outcomes, we calculated the mean difference and 95% confidence interval. However, for blood loss, we estimated the proportional change in blood loss with TXA. Full details of the method used are described elsewhere.[9] In brief, we expressed the change in blood loss with TXA as a proportion of the blood loss in the control group. As estimates of average blood loss are not normally distributed, we transformed blood loss data into a logarithmic scale and conducted the analysis using the transformed values. A meta-analysis of the differences in means using the transformed data on blood loss corresponds to a meta-analysis of the ratio of the geometric means on the original scale. The estimates were back-transformed to give the blood loss ratios and 95% confidence intervals on the original scale. If sufficiently homogeneous in terms of patients, intervention and outcome measurement, we planned to pool the trial data using the fixed effect model.

We planned to conduct subgroup analyses to examine whether the effect of TXA on the risk of PPH varied according to whether the women were anaemic at baseline (anaemic = Hb <11 g/dl and non-anaemic = Hb ≥11 g/dl). We also planned a sensitivity analysis restricted to trials at low risk of bias for allocation concealment. Analyses were carried out using STATA version 13 and REVMAN version 5.3.5. We reported the review in accordance with the PRISMA Statement (Table S1).

Results

Trial characteristics

We identified 31 reports[10–40] describing 26 trials involving a total of 4191 women (Figure S1). The trial reports were published between 2001 and 2015. Five trials were Master's degree projects that were later published in medical journals. Two trials were reported as conference abstracts only.

The characteristics of the included trials are shown in Table S2. The median sample size was 120 (min–max = 74–740). They were conducted in China ($n = 3$), Egypt ($n = 2$), India ($n = 9$), Iran ($n = 5$), Malaysia ($n = 1$), Pakistan ($n = 2$), Turkey ($n = 3$) and Ukraine ($n = 1$). All but one were single-centre trials. Twenty-two trials assessed the effect of TXA in women giving birth by caesarean section and four in women giving birth vaginally. One trial was restricted to anaemic women (Hb 7–10 g/dl).

TXA was given within 30 minutes prior to incision in all of the caesarean delivery trials except for one in which TXA was administered at delivery of anterior shoulder. Of the four trials involving vaginal delivery, TXA was given at delivery of anterior shoulder in three and at delivery of the placenta in one. The TXA dose ranged from 0.5 to 1 g. TXA was compared with placebo in 13 trials and with a no-TXA group in 13 trials.

The number of patients allocated to each group was not reported in one trial and so the data could not be used. The frequency of PPH was reported in 13 (50%) trials, blood loss in 24 (92%), thromboembolic events in 16 (62%), death in six (23%), surgical intervention in five (19%), and blood transfusion in 10 (38%). None of the trials collected data on maternal well-being or quality of life.

Risk of bias

A summary of the risk of judgements is shown in Figure S2. The method used to generate the allocation sequence was

adequate in eight trials and inadequate in four. The remaining 14 trials did not describe the method used and so the risk was unclear. Allocation concealment was adequate in four, inadequate in seven, and unclear in 15 trials. Blinding was adequate in 11 trials, inadequate in 13, and unclear in two trials. There were no missing outcome data in four trials (low risk of bias). However, there were post-randomisation exclusions in three trials (high risk of bias). For the remaining 19 trials, insufficient information was reported to judge the risk of bias from missing outcome data. In the one trial that was prospectively registered, comparison of prespecified and reported outcomes suggested selective outcome reporting. We could not determine the risk of bias from selective outcome reporting for the remaining trials, which were either retrospectively registered ($n = 5$) or not registered ($n = 20$).

Data reliability

Several reports raised concerns about the data and prompted further investigations. Eight reports contained sections of identical or very similar text despite purporting to be different trials (Table S3), in addition, many of the results sections contained discrepancies and other errors. We therefore sought further information from the authors of all trial reports to reassure ourselves about the reliability of the data. We identified contact information for as many authors as possible. Each author was contacted and asked to provide the dates when the first and last patients were randomised; a copy of the ethics committee approval; and the anonymised individual patient data. Where possible we also contacted the ethics committee for confirmation of their approval.

We received responses for 13 (50%) trials (Table S4). One author declined to provide the information requested. Authors of nine trials confirmed recruitment dates, one did not have a record of the dates, and one did not include this information in the response. We received a copy of the ethics approval for 10 trials, one of which was granted after the start of recruitment. Two trials did not receive ethics approval. In one case, an author explained that the trial was undertaken for a student thesis and formal approval from the ethics committee was not required (this was confirmed in a separate response from the ethics committee). In the other, although the trial report stated that ethics approval had been obtained, the author stated this was not in fact the case. This was confirmed by the ethics committee, who said that they had no record of the trial. No explanation was offered as to why approval was not obtained.

Seven of the 13 trials for which we received a response sent individual patient data. The authors of two trials did not respond to this part of our request and one author of two trials explained that he was unable to send us the data due to the theft of the laptop on which the data for both trials were stored.

We then explored the success of the randomisation process by conducting meta-analyses of selected baseline variables. As recommended by Clark et al.[41] we meta-analysed age as well as baseline haemoglobin (Hb), which we identified as another relevant prognostic covariate. The premise of this analysis is that if the trials are properly randomised, there will be no heterogeneity, i.e. $I^2 = 0\%$ and any difference in baseline variables will be minimal and the result of random error.[41] Figures S3 and S4 show the results of the meta-analyses of age and baseline Hb. There was no heterogeneity ($I^2 = 0\%$) observed for age. However, there was a statistically significant difference between groups suggesting that women allocated to the TXA group were younger than those in the control ($P = 0.01$), although this difference was not observed when the analysis was restricted to adequately concealed trials ($P = 0.59$). There was substantial heterogeneity between trials for baseline Hb ($I^2 = 67\%$) and a statistically significant difference between groups indicating that women allocated to the TXA group had a lower Hb at baseline than those in the control ($P = 0.02$). Substantial heterogeneity remained when the analysis was restricted to adequately concealed trials ($I^2 = 62\%$), although the difference in Hb between groups was no longer statistically significant ($P = 0.79$).

Data analysis

Although the patients, interventions and outcomes were sufficiently homogeneous to pool the data, because of our concerns about trial quality and data reliability we did not conduct a meta-analysis. However, effect estimates and 95% CIs were calculated and presented as Forest plots (Figures 1–3). We stratified the trials according to whether the final report contained similar text. Thirteen trials presented data on the number of women who developed postpartum haemorrhage. There was variation in the threshold used to diagnose PPH. Four trials applied the usual definition of blood loss ≥1000 ml after caesarean delivery or ≥500 ml after vaginal delivery. The remaining trials used other, lower thresholds, including ≥500 ml after caesarean delivery or ≥400 ml after vaginal delivery. Because none of the trials were prospectively registered, we cannot discount the possibility that the selection of these thresholds was *post hoc* and data-driven. In all trials, fewer women in the TXA group developed PPH than in the control group.

Twenty-four trials presented data on average blood loss in both groups. All of the effect estimates are consistent with less blood loss in the TXA group; the difference is statistically significant in all but one trial. There is notable variation in the magnitude of the effect estimates.

Nine trials reported blood transfusion data. There were no events in two trials. In all of the remaining seven trials,

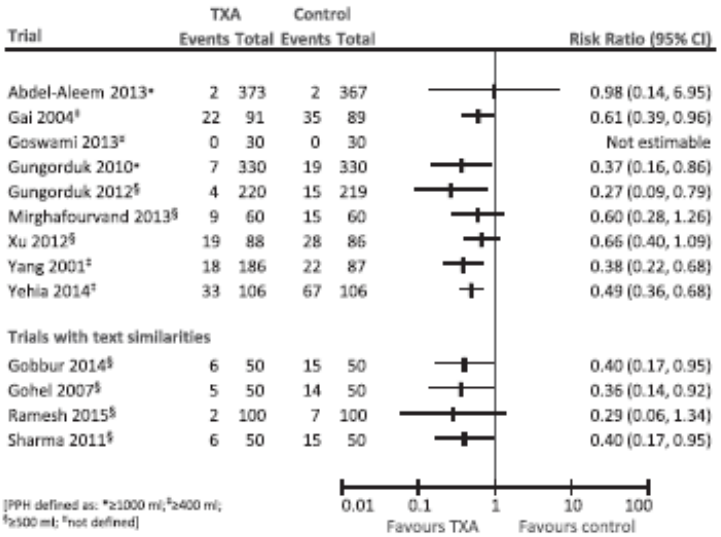

Figure 1. Results of trials assessing the effect of TXA on postpartum haemorrhage.

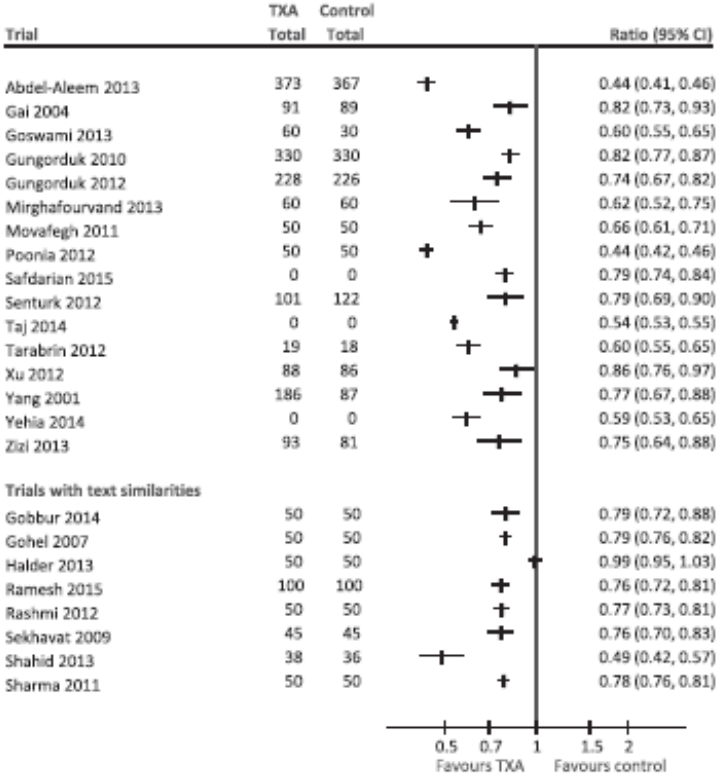

Figure 2. Results of trials assessing the effect of TXA on blood loss.

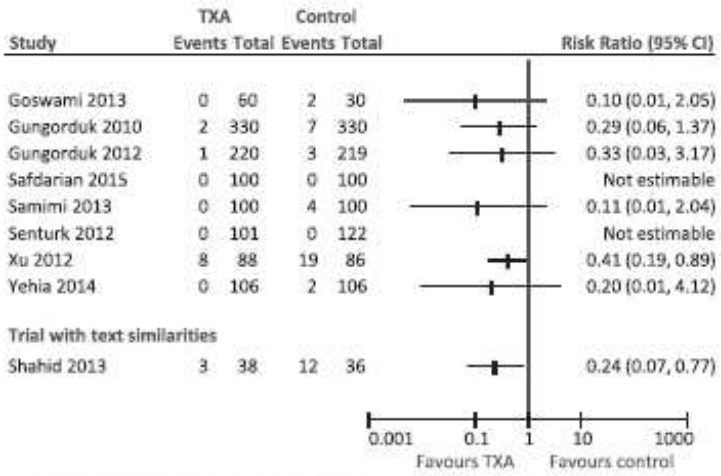

Figure 3. Results of trials assessing the effect of TXA on blood transfusion.

fewer women in the TXA group received a blood transfusion than those in the control group. There were no deaths, surgical interventions, or cases of myocardial infarction, stroke or pulmonary embolism in any of the trials reporting these outcomes. In one trial, four women suffered a deep vein thrombosis, there was no difference in risk between the groups (TXA 2/88 versus control 2/86; RR = 0.98, 95% CI 0.14–6.78).

Discussion

Main findings

Worldwide, over 10 million women experience a postpartum haemorrhage each year. About 50 000 women die, many more lose their ability to bear children, and hundreds of thousands suffer debilitating fatigue from anaemia. TXA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients.[42,43] It is therefore unsurprising that there is interest in its role in the prevention of postpartum haemorrhage. However, our review shows that most trials of TXA are small, low quality, single-centre studies. We found that many trial reports shared similar or identical text, and contained important errors or inconsistencies. Two trials were conducted without ethics committee approval and only one was prospectively registered.

Strengths and limitations

Due to concerns about data quality and reliability we did not conduct a meta-analysis. When examined separately, the results of the individual trials were largely consistent with evidence from surgical bleeding, with most reporting less bleeding with TXA. However, the criteria used to diagnose PPH varied between trials and the absence of blinded outcome assessment in many trials may have introduced bias. Also, because the trials are too small to assess the effect of TXA on maternal health outcomes and none measured maternal well-being, the clinical importance of any reduction in bleeding is uncertain.

Most systematic reviews assume that trial reports provide an accurate description of the methods and results. However, after finding that eight trials contained identical text and that some of the trial results were also similar, we were obliged to question this assumption. We therefore asked the authors of all trials to provide dates of recruitment, a copy of the ethics committee approval, and the anonymised individual patient data in an attempt to assess their reliability. We received a response for only half of the included trials and less than half of these provided all the information requested. Moreover, the meta-analysis of baseline variables suggests that the randomisation process was inadequate in many trials. Although our review aimed to include only randomised controlled trials, many of the included trials were not properly randomised and were imbalanced for key prognostic variables.

Interpretation (in the light of other evidence)

Other systematic reviews have assessed the effect of TXA on obstetric bleeding.[44–46] However, ours is the first to describe the scale and nature of deficiencies in the evidence that go beyond the standard risk of bias assessment. Unless these deficiencies are brought to the attention of the maternal health community, treatment decisions could be based on unsound evidence, putting women at risk. Indeed, some of the trials have already informed the WHO

recommendations on the use of TXA for the treatment of postpartum haemorrhage.

As well as highlighting the poor quality of trial research in this area, the process of conducting this review has brought to our attention the lack of guidance on how systematic reviewers should deal with trial quality concerns that go beyond those assessed by the standard risk of bias approach.

Furthermore, because we were unwilling to ignore these concerns, we devised our own approach to investigating them. We do not claim that our approach is the best and we welcome ideas on more effective ways to deal with similar situations in the future.

Conclusions

Although reducing maternal mortality has been a development goal for 15 years, this review suggests that in some areas the quantity and quality of the research needed to support this humanitarian aspiration is inadequate and is not commensurate with the level of political ambition. We do not doubt that most of the included trials were conducted in good faith with the patients' interests in mind. However, a problem of such global health importance requires a strategic response from professional research teams rather than the efforts of concerned clinicians at a single hospital. Large, high quality, multi-centre trials with endpoints that matter to women are urgently needed.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

KK, IR and HS designed the study. KK screened the search output and extracted data with assistance from HS. KK carried out the analyses. KK wrote the manuscript with contributions from IR and HS. The final version was approved by all authors.

Details of ethics approval

Not required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram of the selection of trials.

Figure S2. Summary of the risk of bias judgements for each methodological quality domain ('L' = Low, 'U' = unclear, 'H' = High).

Figure S3. Forest plots showing the difference in age between women allocated to the TXA group and those allocated to the control group.

Figure S4. Forest plots showing the difference in haemoglobin between women allocated to the TXA group and those allocated to the control group.

Table S1. PRISMA Checklist.

Table S2. Characteristics of included trials.

Table S3. Selected extracts from eight included trials containing identical or similar text.

Table S4. Summary of response to review authors' requests for additional trial information.

Appendix S1. MEDLINE (Ovid) search strategy. ■

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Appendix DD. Research Paper 6: MEDLINE (Ovid) search strategy

1	exp Antifibrinolytic Agents/
2	(anti-fibrinolytic* or antifibrinolytic* or antifibrinolysin* or anti-fibrinolysin* or antiplasmin* or anti-plasmin* or ((plasmin or fibrinolysis) adj3 inhibitor*)).ab,ti.
3	exp Aprotinin/
4	(Aprotinin* or kallikrein-trypsin inactivator* or bovine kunitz pancreatic trypsin inhibitor* or bovine pancreatic trypsin inhibitor* or basic pancreatic trypsin inhibitor* or BPTI or contrykal or kontrykal or kontrikal or contrical or dilmintal or iniprol or zymofren or traskolan or antilysin or pulmin or amicar or caprocid or epsamon or epsikapron or antilysin or iniprol or kontrikal or kontrykal or pulmin* or Trasylol or Antilysin Spofa or rp?9921 or antagosan or antilysin or antilysine or apronitin* or apronitrine or bayer a?128 or bovine pancreatic secretory trypsin inhibitor* or contrycal or frey inhibitor* or gordox or kallikrein trypsin inhibitor* or kazal type trypsin inhibitor* or (Kunitz adj3 inhibitor*) or midran or (pancrea* adj2 antitrypsin) or (pancrea* adj2 trypsin inhibitor*) or riker?52g or rp?9921or tracylol or trascolan or trasilol or traskolan or trazylol or zymofren or zymophren).ab,ti.
5	exp Tranexamic Acid/
6	(tranexamic or Cyclohexanecarboxylic Acid* or Methylamine* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or kabi 2161 or transamin* or exacyl or amchafibrin or anvitoff or spotof or cyklokapron or ugurol oramino methylcyclohexane carboxylate or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or anvitoff or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or exacyl or frenolyse or hexacapron or hexakapron or tranex or TXA).ab,ti.
7	exp Aminocaproic Acids/ or exp 6-Aminocaproic Acid/
8	(((aminocaproic or amino?caproic or aminohexanoic or amino?hexanoic or epsilon-aminocaproic or E-aminocaproic) adj2 acid*) or epsikapron or cy-116 or cy116 or epsamon or amicar or caprocid or lederle or Aminocaproic or aminohexanoic or amino caproic or amino n hexanoic or acikaprin or afibrin or capracid or capramol or caprogel or caprolest or caprolisine or caprolysin or capromol or cl 10304 or EACA or eaca roche or ecapron or ekaprol or epsamon or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or tachostyptan).ab,ti.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	randomi?ed.ab,ti.
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	placebo.ab.
14	clinical trials as topic.sh.
15	randomly.ab.
16	trial.ti.
17	10 or 11 or 12 or 13 or 14 or 15 or 16
18	(animals not (humans and animals)).sh.
19	17 not 18
20	9 and 19

Appendix EE. Research Paper 6: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page[x]
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S1

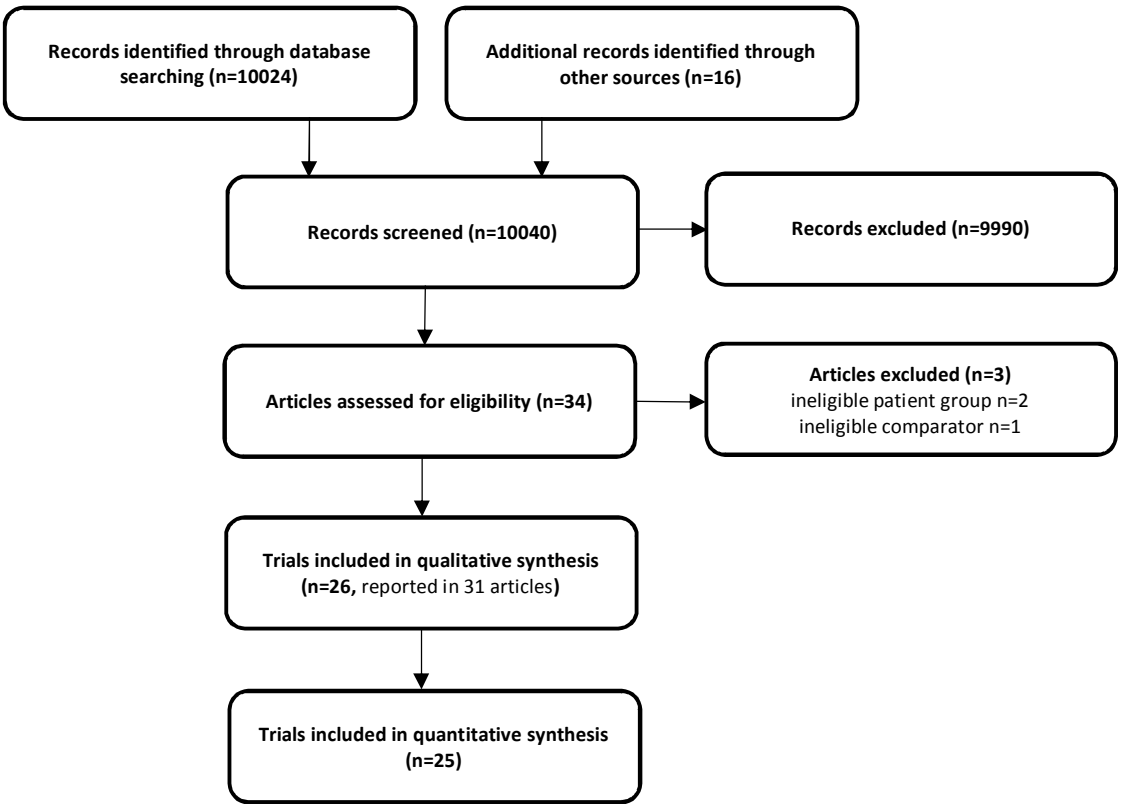
[x]Corresponds to page numbers within the manuscript submitted to the journal

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	5-6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7, Table S3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7, Figure S2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, Figures 1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Appendix FF. Research Paper 6: Flow diagram of the selection of trials



Appendix GG. Research Paper 6: Characteristics of included trials.

Trial	Participants	Intervention and comparator	Outcomes
Abdel-Aleem 2013 Single-centre, Egypt	740 women delivering by **caesarean section** **TXA group** (n=373) Age mean(sd)= 26.62(5.05) Baseline Hb<11g/dL=55% **Control group** (n=367) Age mean(sd)=26.34(5.16) Baseline Hb<11g/dL=46%	**TXA group** 1g IV given over 10 mins before incision **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥1000ml) Blood loss Thromboembolic events Surgical intervention Death
Gai 2004 Multi-centre, China	180 women delivering by **caesarean section** **TXA group** (n=91) Age mean(sd)=29.71(4.18) Baseline Hb=NR **Control group** (n=89) Age mean(sd)=29.75(4.01) Baseline Hb=NR	**TXA group** 1g IV over 5 mins, 10 mins before incision **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥400ml) Blood loss Thromboembolic events
Gobbur 2014 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age mean(sd)=23.62(3.43) Baseline Hb=NR **Control group** (n=50) Age mean(sd)=24.5(3.98) Baseline Hb=NR	**TXA group** 1g IV 20 mins before incision **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss Thromboembolic events

Trial	Participants	Intervention and comparator	Outcomes
Gohel 2007 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age mean(sd)=24.30(3.65) Baseline Hb=NR **Control group** (n=50) Age mean(sd)=24.89(3.99) Baseline Hb=NR	**TXA group** 1g IV over 5 mins, 20 mins before incision **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss Thromboembolic events
Goswami 2013 Single-centre, India	90 women delivering by **caesarean section** **TXA group 1*** (n=30) Age mean(sd)=23.6(2.5) **TXA group 2*** (n=30) Age mean(sd)=22.8(2.2) **Control group** (n=30) Age mean(sd)=24.3(2.6) All women were anaemic at baseline (Hb 7-10g/dL) [*combined for purpose of this review]	**TXA group 1** 10mg/kg IV 20 mins before incision **TXA group 2** 15mg/kg IV 20 mins before incision **Control group** Placebo All groups received oxytocin	Postpartum haemorrhage (not defined) Blood loss Thromboembolic events Blood transfusion
Gungorduk 2010 Single-centre, Turkey	660 women delivering by **caesarean section** **TXA group** (n=330) Age mean(sd)=26.3(3.5) Baseline Hb mean(sd)=11.4(0.8)g/dL **Control group** (n=330) Age mean(sd)=26.6(3.6) Baseline Hb mean(sd)=11.3(0.6)g/dL	**TXA group** 1g IV over 5 mins, 10 mins before incision **Control group** Placebo Both groups received oxytocin	Postpartum haemorrhage (≥1000ml) Blood loss Thromboembolic events Surgical intervention Death Blood transfusion
Gungorduk 2012 Single-centre, Turkey	454 women delivering **vaginally** **TXA group** (n=228) Age mean(sd)=27.9(4.9) Baseline Hb mean(sd)=9.9(1.4)g/dL **Control group** (n=226) Age mean(sd)=27.6(4.8) Baseline Hb mean(sd)=9.3(0.9)g/dL	**TXA group** 1g IV at delivery of anterior shoulder **Control group** Placebo Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss Thromboembolic events Surgical intervention Death Blood transfusion

Trial	Participants	Intervention and comparator	Outcomes
Halder 2013 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age mean(sd)=26.06(2.51) Baseline Hb=NR **Control group** (n=50) Age mean(sd)=26.04(2.50) Baseline Hb=NR	**TXA group** 1g 30 mins before incision **Control group** No TXA Both groups received oxytocin	Blood loss Thromboembolic events
Mirghafourvand 2015 Single-centre, Iran	120 women delivering **vaginally** **TXA group** (n=60) Age mean(sd)=26.2(4.8) Baseline Hb mean(sd)=12.9(0.9)g/dL **Control group** (n=60) Age mean(sd)=26.1(4.9) Baseline Hb mean(sd)=13.0(0.9)g/dL	**TXA group** 1g IV at delivery of anterior shoulder **Control group** Placebo Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss
Movafegh 2011 Single-centre, Iran	100 women delivering by caesarean section **TXA group** (n=50) Age mean(sd)=27.0(3.4) Baseline Hb mean(sd)=12.5(1.4)g/dL **Control group** (n=50) Age mean(sd)=27.6(4.1) Baseline Hb mean(sd)=12.8(1.0)g/dL	**TXA group** 10mg/kg IV over 10 mins, 20 mins before anaesthesia **Control group** Placebo Both groups received oxytocin	Blood loss Thromboembolic events
Poonia 2012 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age=NR Baseline Hb mean(sd)=10.2(0.73)g/dL **Control group** (n=50) Age=NR Baseline Hb mean(sd)=10.1(0.91)g/dL	**TXA group** 1g IV given 10 mins before incision **Control group** No TXA Both groups received oxytocin	Blood loss

Trial	Participants	Intervention and comparator	Outcomes
Ramani 2014 Single-centre, India	120 women delivering by **caesarean section** **TXA group** (n=NR) Age mean(sd)=24.9(3.9) Baseline Hb mean(sd)=10.5(1.15)g/dL **Control group** (n=NR) Age mean(sd)=24.4(3.7) Baseline Hb mean(sd)=10.1(2.14)g/dL	**TXA group** 1g IV prior to incision plus 2nd 500mg dose at end of CS if bleeding continued **Control group** No TXA Both groups received oxytocin	No useable outcome data (number allocated to each group NR).
Ramesh 2015 Single-centre, India	200 women delivering by **caesarean section** **TXA group** (n=100) Age mean(sd)=23.62(3.43) Baseline Hb mean(sd)=10.84(0.75)g/dL **Control group** (n=100) Age mean(sd)=24.5(3.89) Baseline Hb mean(sd)=11.4(0.89)g/dL	**TXA group** 1g IV given 10 mins before incision **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss Thromboembolic events
Rashmi 2012 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age mean(sd)=25.7(3.7) Baseline Hb=NR **Control group** (n=50) Age mean(sd)=25.1(4.73) Baseline Hb=NR	**TXA group** 1g IV over 5 mins, 30 mins before incision **Control group** No TXA Both groups received oxytocin	Blood loss Thromboembolic events
Safdarian 2015 Single-centre, Iran	200 women delivering by **caesarean section** **TXA group** (n=100) Age mean(sd)=26.3(5.97) Baseline Hb mean(sd)=11.96(1.00)g/dL **Control group** (n=100) Age mean(sd)=26.83(6.31) Baseline Hb mean(sd)=12.28(1.26)g/dL	**TXA group** 10mg/kg IV 20 mins before incision **Control group** Placebo Both groups received oxytocin	Blood loss Blood transfusion

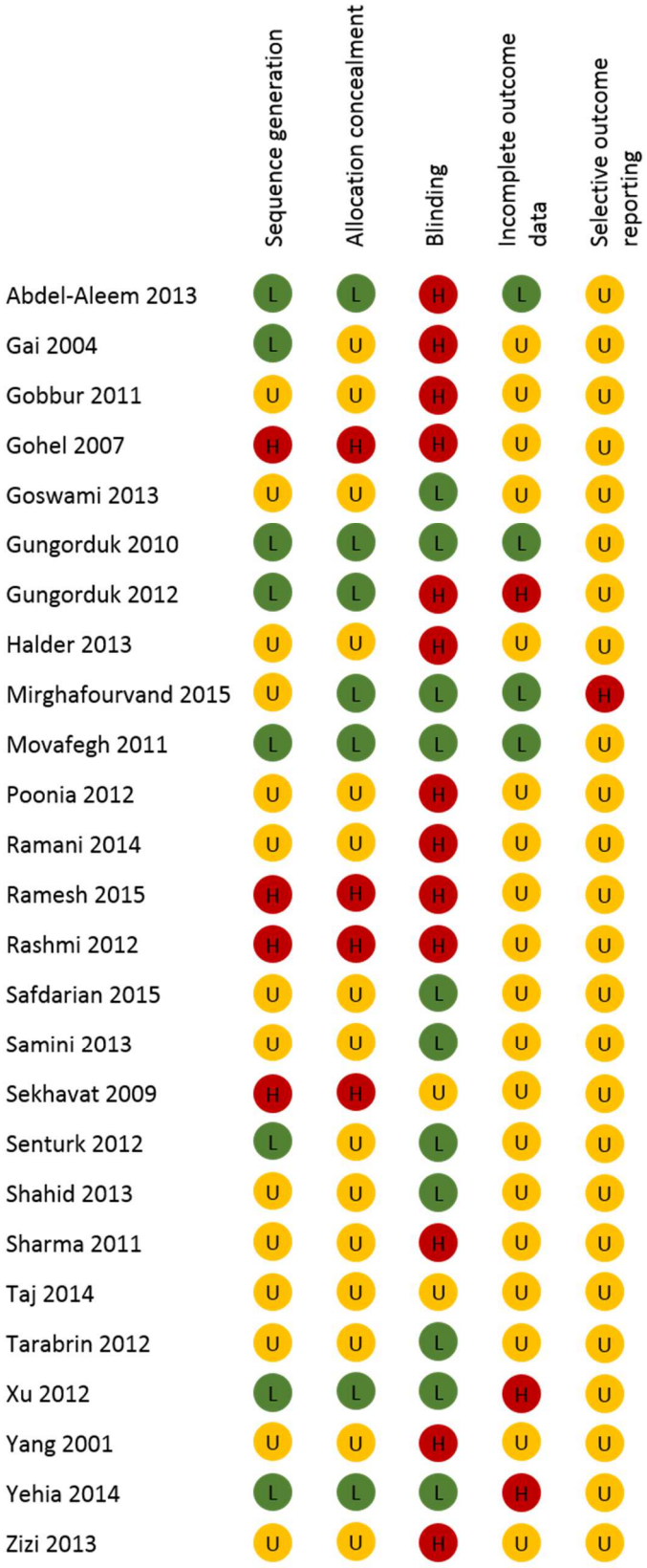
Trial	Participants	Intervention and comparator	Outcomes
Samini 2003 Single-centre, Iran	200 women delivering **vaginally** **TXA group** (n=100) Age(sd)=23.93(4.29) Baseline Hb mean(sd)=12.73(0.9) **Control group** (n=100) Age(sd)=24.28(4.82) Baseline Hb mean(sd)=12.92(1.51)	**TXA group** 1g IV given at placental delivery **Control group** Placebo Both groups received oxytocin	Surgical intervention Death Blood transfusion
Sekhavat 2009 Single-centre, Iran	90 women delivering by **caesarean section** **TXA group** (n=45) Age(sd)=26.2(4.7) Baseline Hb mean(sd)=13.6(1.4)g/dL **Control group** (n=45) Age(sd)=27.1(4.1) Baseline Hb mean(sd)=14.0(1.9)g/dL	**TXA group** 1g IV over 5 mins, 10 mins before incision **Control group** Placebo Both groups received oxytocin	Blood loss Thromboembolic events
Senturk 2012 Single-centre, Turkey	223 women delivering by **caesarean section** **TXA group** (n=101) Age mean(sd)=30.2(6.83) Baseline Hb mean(sd)=11.66(1.02)g/dL **Control group** (n=122) Age mean(sd)=29.22(6.93) Baseline Hb mean(sd)=11.86(1.32)g/dL	**TXA group** 1g IV over 5 mins, 10 mins before incision **Control group** Placebo Both groups received oxytocin	Blood loss Thromboembolic events (DVT, PE) Surgical intervention Death Blood transfusion
Shahid 2012 Single-centre, Pakistan	74 women delivering by **caesarean section** **TXA group** (n=38) Age mean(sd)=24.18(3.93) Baseline Hb mean(sd)=9.76(0.85)g/dL **Control group** (n=36) Age mean(sd)=24.89(4.16) Baseline Hb mean(sd)=9.88(1.26)g/dL	**TXA group** 1g IV 10 mins before incision **Control group** Placebo Both groups received oxytocin	Blood loss Thromboembolic events Blood transfusion

Trial	Participants	Intervention and comparator	Outcomes
Sharma 2011 Single-centre, India	100 women delivering by **caesarean section** **TXA group** (n=50) Age mean(sd)=25.63(3.72) Baseline Hb=NR **Control group** (n=50) Age mean(sd)=25.88(3.89) Baseline Hb=NR	**TXA group** 1g IV immediately before CS **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥500ml) Blood loss
Taj 2014 Single-centre, Pakistan	120 women delivering by **caesarean section** **TXA group** (n=60) Age mean(sd)=23.56(3.82) Baseline Hb=NR **Control group** (n=60) Age mean(sd)=24.18(3.47) Baseline Hb=NR	**TXA group** 1g IV 20 mins before incision **Control group** Placebo	Blood loss Thromboembolic events Blood transfusion
Tarabrin 2012[1, 21, 21, 21, 2] Single-centre, Ukraine	37 women delivering by **caesarean section** **TXA group** (n=19) Age=NR Baseline Hb=NR **Control group** (n=18) Age=NR Baseline Hb=NR	**TXA group** 10mg/kg IV 30 mins before incision **Control group** Placebo	Blood loss Thromboembolic events
Xu 2012 Single-centre, China	176 women delivering by **caesarean section** **TXA group** (n=88) Age mean(sd)=26.7(3.7) Baseline Hb mean(sd)=12.4(1.3)g/dL **Control group** (n=86) Age mean (sd)=27.1(4.1) Baseline Hb mean(sd)=12.6(1.2)g/dL	**TXA group** 10mg/kg IV 10-20 mins before incision **Control group** Placebo	Postpartum haemorrhage (≥500ml) Blood loss Thromboembolic events (DVT) Death Blood transfusion

Trial	Participants	Intervention and comparator	Outcomes
Yang 2001 Single-centre, China	400 women delivering **vaginally** **TXA group 1*** (n=94) Age mean(sd)=27.6(2.9) Baseline Hb=NR **TXA group 2*** (n=92) Age mean(sd)=27.0(2.6) Baseline Hb=NR **Control group** (n=87) Age mean(sd)=28.0(2.6) Baseline Hb=NR [*combined for purpose of this review]	**TXA group 1** 1g IV after delivery of shoulders **TXA group 2** 0.5g IV after delivery of shoulders **Control group** No TXA All groups received oxytocin	Postpartum haemorrhage (≥400ml) Blood loss
Yehia 2014 Single-centre, Egypt	223 women delivering by **caesarean section** **TXA group** (n=106) Age mean(sd)=28.4(4.9) Baseline Hb mean(sd)=11.8(1.5)g/dL **Control group** (n=106) Age mean (sd)=28.6(4.7) Baseline Hb mean(sd)=11.9(1.2)g/dL	**TXA group** 1g IV at induction of anaesthesia **Control group** No TXA Both groups received oxytocin	Postpartum haemorrhage (≥400ml) Blood loss Thromboembolic events Blood transfusion
Zizi 2013 Single-centre, Malaysia	174 women delivering by caesarean section **TXA group** (n=93) Age mean(sd)=NR Baseline Hb=NR **Control group** (n=81) Age mean(sd)=NR Baseline Hb=NR	**TXA group** 1g IV given immediately before incision **Control group** No TXA	Blood loss

TXA=tranexamic acid
sd=standard deviation
Hb=haemoglobin
NR=not reported

Appendix HH. Research Paper 6: Summary of the risk of bias judgement for each methodological quality domain ('L' = Low, 'U' = unclear, 'H' = High)



Appendix II. Research Paper 6: Selected extracts from eight included trials containing identical or similar text.

[Gai *et al* was the first trial to be published.]

Gai 2004	Gobbur 2014	Gohel 2005	Halder 2014	Ramesh 2015	Rashmi 2012	Sekhavat 2009	Shahid 2013	Sharma 2011
Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-center, randomized trial.	**Efficacy of tranexamic acid in reducing blood loss during lower segment caesarean section.**	**Efficacy of tranexamic acid in decreasing blood loss during and after cesarean section: A randomized case controlled prospective study.**	**Tranexamic acid used before caesarean section reduces blood loss based on pre- and postoperative haemoglobin level: a case-control study**	**Efficacy of tranexamic acid in decreasing blood loss during and after caesarean section: a randamized case controlled prospective study**	**Role of Tranexamic acid in reducing blood loss during and after cesarean section: A randomized case control prospective study.**	**Efficacy of tranexamic acid in reducing blood loss after cesarean section.**	**Tranexamic acid in decreasing blood loss during and after caesarean section**	**Efficacy of tranexamic acid in decreasing blood loss during and after caesarean section**
Caesarian section (CS) rates have increased to as high as 40–50% in many areas of China.	Cesarean section rates have increased to as high as 25 - 30% in many areas of the world.1	Cesarean section (CS) rates have increased to as high as 25 to 30% in many areas of the world1.	Caesarean section (CS) rates have increased all over India.	Cesarean section (CS) rates have increased to as high as 25 to 30 % in many areas of the world. (1)	Cesarean Section (CS) rates have increased to as high as 25-30% in many areas of the world1.	Cesarean section (CS) rate has increased to as high as 25 to 30% in many areas of the world [1].	Caesarean section (CS) rates have increased to as high as 25-30% in many areas of the world.	
Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is hemorrhaging, which can be life threatening. In order to reduce maternal mortality and morbidity caused by bleeding, it is important to reduce the extent	Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is primary or secondary hemorrhage. In order to reduce maternal mortality and morbidity caused by bleeding it is important to reduce the maternal bleeding during and after	Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is primary or secondary postpartum hemorrhage (20%). It leads to increased maternal mortality and morbidity. In order to reduce maternal mortality and morbidity caused		Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is primary or secondary postpartum hemorrhage (20%). It leads to increased maternal mortality and morbidity. In order to reduce maternal mortality and morbidity caused	Delivery by cesarean section can cause more complication than normal vaginal delivery and one of the most common complication is primary or secondary postpartum hemorrhage (20%)1. It leads to increased maternal mortality and morbidity. In order to reduce maternal mortality and morbidity caused	Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is postpartum bleeding, which can be life-threatening. To reduce maternal mortality and morbidity caused by bleeding, it is important to reduce the extent of bleeding	Delivery by CS can cause more complications than normal vaginal delivery and one of the most common complications is primary or secondary postpartum haemorrhage (20%).3 Obstetric haemorrhage can be life threatening, therefore, to reduce the morbidity and mortality due to	The incidence of complications is much higher as compared with normal vaginal delivery. Out of these complications primary and secondary postpartum haemorrhage is most common. It leads to increased maternal

of bleeding during and after CS.	lower segment cesarean section.1	by bleeding, it is important to reduce the amount of bleeding during and after lower segment cesarean section (LSCS) 1.		by bleeding, it is important to reduce the amount of bleeding during and after lower segment cesarean section (LSCS).1	by bleeding, it is important to reduce the amount of bleeding during lower segment cesarean section.	during and after CS [2].	obstetric haemorrhaging we need to reduce the bleeding at caesarean sections.	morbidity and mortality. Effect of this complication is reduced by reducing the amount of blood loss during and after cesarean section.
Tranexamic acid is an inhibitor of fibrinolysis.	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on the plasminogen molecules.3,4	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules 2.	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules 1.	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules.3,4	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules 2.	Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of the lysine binding sites on plasminogen molecules [5].	Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that exerts its anti-fibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules.	Tranexamic acid (a synthetic derivative of the amino acid lysine) is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin.
It has been routinely used for many years to reduce hemorrhaging during and after surgical procedures [1] such as coronary artery bypass, scoliosis surgery, and knee arthroplasty.	Intravenous administration of the tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery etc	Intravenous administration of tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery, orthotopic liver transplantation, total hip or knee arthroplasty, and urinary tract surgery 3,4.	Intravenous administration of tranexamic acid has been routinely used for many years to reduce haemorrhage during and after surgical procedures.	Intravenous administration of tranexamic acid has been routinely used for many years to reduce haemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery, orthotopic liver transplantation, total hip or knee arthroplasty, and urinary tract surgery.	Intravenous administration of tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, oral surgeries2.	It has been routinely used for many years to reduce hemorrhage during and after surgical procedures, such as coronary artery bypass, scoliosis surgery and knee arthroplasty.	It has been in used for many years for reducing the blood loss in surgeries like, cardiac surgery with cardiopulmonary bypass, orthotopic liver transplantation, transurethral prostatic surgery, total hip/knee arthroplasty, or urinary tract surgery,4…	
It has been shown to be very useful for reducing blood loss	Tranexamic acid has been shown to be very useful in	Tranexamic acid has been shown to be very useful in	Tranexamic acid has been shown to be very useful in	Tranexamic acid has been shown to be very useful in	Tranexamic acid has been shown to be very useful in	It has been shown to be very useful for reducing blood loss	TXA has been shown to be very useful in reducing blood loss	

and blood transfusion, but there has been no report on preventing blood loss at CS.	reducing blood loss and incidence of blood transfusion in these surgeries.*	reducing blood loss and incidence of blood transfusion in these surgeries.	reducing blood loss and incidence of blood transfusion in these surgeries[2].	reducing blood loss and incidence of blood transfusion in these surgeries.	reducing blood loss and incidence of blood transfusions in these surgeries 2.	and blood transfusion [6].	and incidence of blood transfusion in these surgeries…	
In this study, the efficacy and safety of tranexamic acid was investigated in the management of CS.	In this study the efficacy of tranexamic acid in reducing the blood loss during and after LSCS…	In this study, the efficacy and safety of tranexamic acid in the reducing the blood loss during and after LSCS was investigated.	In this study, the efficacy and safety of tranexamic acid was studied in reducing blood loss during and after CS...	In this study, the efficacy of tranexamic acid in the reducing the blood loss during and after LSCS was investigated.	In this study the efficacy and safety of tranexaminc acid in reducing blood loss during cesarean section is investigated.	In this study, the efficacy and safety of tranexamic acid in reducing blood loss after CS was investigated.	In this study, the aim was to determine the efficacy and safety of TXA in reducing the blood loss during and after LSCS.	
A multi-center, prospective, randomized, case-controlled clinical trial…	It is prospective randomized case control study…	This is a prospective randomized case controlled study.	This is a prospective randomised case-control study.	A randomized, case controlled, prospective study…	This is a prospective randomized case controlled study.	A prospective, randomised, case-controlled clinical trial…	It was a prospectively conducted randomized double-blind placebo controlled study…	The present study in a prospective randomized case controlled study.
	The study group comprise 50 subjects who received tranexamic acid and 50 subjects who did not receive tranexamic acid formed the control group.	One hundred subjects were enrolled in the study. In 50 subjects tranexamic acid was given immediately before LSCS and the blood loss was compared with that in 50 others to whom tranexamic acid was not given		100 women comprised study group – subject who received tranexamic acid, & 100 women comprised control group – subject who did not received tranexamic acid.	One hundred subjects are enrolled in the study. In fifty subjects tranexamic acid is given immediately before Lower Segment Cesarean Section (LSCS) and the blood loss is compared with that in 50 others to whom tranexamic acid was not given.	The women were randomly allocated into two groups: study group (n = 45) receiving tranexamic acid and control group (n = 45) receiving placebo.		
Inclusion criteria Term primipara with a singleton delivered by CS. Regular perinatal care. Adherence to research regulations.	**Inclusion criteria** 1. Full term primigravida or multigravida with singleton pregnancy delivered by CS. 2. Normal or abnormal presentation	Full term primiparas / multiparas with singleton pregnancy being delivered by LSCS were included in the study…	Full term primiparas with singleton pregnancy and have regular antenatal check-up being delivered by lower segment caesarean section (LSCS) were included in the study…	**Inclusion criteria :** • Term primipara with a singleton delivered by CS • Regular perinatal care • Adherence to research regulations • Informed consent obtained.	**Inclusion Criteria** All singleton pregnancies being delivered by LSCS	We enrolled only nuliparas because of risk of multiparity for uterine inertia after delivery.	Full term primipara / multiparas (parity not more than two) with the singleton pregnancy being delivered by LSCS were included in the study.	Subjects with full term primipara and multipara with single pregnancy being delivered by cesarean section were included in this study…

Informed consent obtained.								
Exclusion criteria Severe medical and surgical complications involving the heart, liver or kidney, brain disease and blood disorders. Allergy to tranexamic acid. History of thrombo-embolic disorders. Abnormal placenta: such as placenta-previa, placenta-abruptio, placental adhesion caused by repeated artificial abortions. Severe pregnancy complications, such as severe preeclampsia. Multiple pregnancies, macrosomia, polyhydramnios. Complication with myoma.	**Exclusion criteria** 1 Medical or surgical problem involving heart, liver and kidney disease 2 Allergy to tranexamic acid 3 H/O thrombo embolic disorder 4 Abnormal placenta such as placenta previa, placenta aburption, pregnancy complication such as pre-eclampsia 5 Multiple pregnancy, macrosomia and polyhydraminos 6 Complication with myoma 7 Any blood dyscrasia*	…while subjects having medical and problems involving the heart, liver, kidney and brain and having blood disorders were excluded from the study. Subjects having allergy to tranexamic acid, history of thromboembolic disorders, abnormal placentation, severe pre-eclampsia, multiple pregnancy, macrosomia, polyhydromnios and those requiring blood transfusion due to anemia were also excluded from the study.	… while mothers having medical and surgical problems involving the heart, liver, kidney and having blood disorders were excluded from the study.	**Exclusion criteria :** • Severe medical and surgical complications including the heart, liver and kidney, brain disease and blood disorders. • Allergy to tranexamic acid. • History of thromboembolic disorders. • Abnormal placenta : such as placenta previa, placenta abruption, placental adhesions caused by repeated artificial abortions. • Severe pregnancy complications such as severe pre-eclampsia. • Multiple pregnancies, macrosomia, poly hydromnios • Complication with myoma.	**Exclusion Criteria:** Blood disorders, renal insufficiency, liver disorders, polyhydramnios, multiple gestation, imminent ecclampsia, ecclampsia, severe anemia, known hypersensitivity to drugs.	Women with severe medical and surgical disorders, having blood disorders and anemia, allergy to tranexamic acid, history of thrombo-embolic disorders, abnormal placenta such as placenta-previa, placenta-abruptia and pregnancy complications such as severe preeclampsia, multiple pregnancies, macrosomia, polyhydramnios and those requiring blood transfusion were excluded.	Subjects having medical problems involving the heart, liver, kidney, brain and having blood disorders were excluded from the study. Subjects having allergy to TXA, history of thromboembolic disorders, abnormal placentation, severe pre-eclampsia, multiple pregnancy, macrosomia, polyhydromnios and those requiring blood transfusion due to anaemia were also excluded from the study.	…and subjects with medical disorders and having blood disorders were excluded from this study. Subjects with a history of thromboembolic disorders, hypersensitivity to tranexamic acid, multiple pregnancy, polyhydromnios and those with anemia requiring blood transfusion were also excluded from this study.
Vital signs: heart rate (HR), respiratory rate (RR), blood pressure (BP) were checked immediately after placental delivery,	1. Vital sign – BP, RR and heart rate were measured immediately after placental delivery and 1and 2 hours after birth respectively*	Heart rate, respiratory rate and blood pressure were checked and noted before the surgery, immediately after placental delivery and	Heart rate, respiratory rate and blood pressure were checked and noted before the surgery, immediately after the operation and 1 and 2 hours after birth.	1. Vital signs : Heart rate (HR) : Respiratory rate (RR), Blood pressure (BP), were checked immediately after placental delivery and	Vital signs (PR, RR, BP) are checked and noted before surgery, immediately after delivery of the placenta 1 hour, 2 hour after birth respectively.	Vital signs (heart rate, blood pressure and respiratory rate) were checked and noted before operation, immediately after placental delivery and		The vital parameters (blood pressure, heart rate and respiratory rate) were checked and noted before the

and 1 and 2 h after birth, respectively.		1 and 2 hours after birth, respectively.		1 and 2 hour after birth respectively.		1 and 2 h after birth, respectively.		surgery, immediately after placental delivery and 1 and 2 hrs after birth of the neonate.
Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine-binding locus of the plasminogen and plasmin molecules, thereby preventing the binding of plasminogen and plasmin to the fibrin substrate. Tranexamic acid also inhibits the conversion of plasminogen to plasmin by the plasminogen activators [2]. It has been used in the treatment of bleeding for many years.	Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine binding locus of the plasminogen and plasmin molecules, thereby preventing the binding of the plasminogen and plasmin to the fibrin substrate. Tranexamic acid also inhibits conversion of plasminogen to plasmin by plasminogen activators.3,4	Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine binding locus of the plasminogen & plasmin molecules, thereby preventing the binding of plasminogen & plasmin to the fibrin substrate. Tranexamic acid also inhibits conversion of plasminogen to plasmin by plasminogen activators. It has been used in the treatment of bleeding for many years. (3,4)*	Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine binding locus of the plasminogen and plasmin molecules. It also inhibits the conversion of plasminogen to plasmin by the plasminogen activators.	Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine binding locus of the plasminogen & plasmin molecules, thereby preventing the binding of plasminogen & plasmin to the fibrin substrate. Tranexamic acid also inhibits conversion of plasminogen to plasmin by plasminogen activators. It has been used in the treatment of bleeding for many years.3,4		Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine-binding locus of the plasminogen and plasmin molecules, thereby preventing the binding of plasminogen and plasmin to the fibrin substrate. Tranexamic acid also inhibits the conversion of plasminogen to plasmin by the plasminogen activators [10]. It has been used in the treatment of bleeding for many years.	Tranexamic acid exerts its antifibrinolytic effect by blocking the lysine-binding locus of the plasminogen and plasmin molecules, thereby preventing the binding of plasminogen and plasmin to the fibrin substrate. TXA also inhibits the conversion of plasminogen to plasmin by the plasminogen activators.	

During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products (FDP) increase due to activation of the fibrinolytic system. This activation can last up to 6–10 h postpartum, causing more bleeding. It was because of this activation of the fibrinolytic system that we decided to use tranexamic acid in this trial.	During placental delivery fibrinogen and fibrin are rapidly degraded whereas plasminogen activators and fibrin degradation products (FDP) increase due to activation of the fibrinolytic system. This activation can last upto 6-10 hours post-partum causing more bleeding. It was because of this activation of the fibrinolytic system that we decided to use tranexamic acid the trial.	During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products (FDP) increase due to activation of the fibrinolytic system. This activation can last up to 6-10 hours postpartum, causing more bleeding 5. It was because of this activation of the fibrinolytic system that we decided to use tranexamic acid in this trial.	During placental delivery there is activation of the fibrinolytic system resulting in rapid degradation of fibrinogen and fibrin. Also there is increase in plasminogen activators and fibrin degradation products (FDP). This activation can last up to 6 to 10 hours postpartum. This is one of the cause of bleeding in the postpartum period.	During placental delivery, fibrinogen & fibrin are rapidly degraded, whereas plasminogen activators & fibrin degradation products (FDP) increase due to activation of fibrinolytic system. This activation can last up to 6-10 hrs postpartum, causing more bleeding. It was because of this activation of fibrinolytic system that we decided to use tranexamic acid in this trial.	During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and FDP increase due to activation of fibrinolytic system1. This activation can last up to 6-10 hours postpartum causing more bleeding 1. It was because of this activation of the fibrinolytic system that we decided to use tranexamic acid.1	During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products increase due to activation of the fibrinolytic system. This activation can last up to 6–10 h postpartum; causing more bleeding. According to this activation of the fibrinolytic system, we decided to use tranexamic acid in this trial.	During placental delivery, fibrinogen and fibrin are rapidly degraded, whereas plasminogen activators and fibrin degradation products (FDP) increase due to activation of the fibrinolytic system. This activation can last up to 6 – 10 hours postpartum, causing more bleeding, which can be taken care of by anti-fibrinolytic agents.	At the time of placental delivery there is activation of the fibrinolytic system which leads to rapid degradation of fibrinogen and fibrin. There is also an increase in plasminogen activators and fibrin degradation products (FDP). This activation can last up to 6-10 hours postpartum, causing more bleeding. As we known that tranexamic acid acts as an Antifibrinolytic agent, so in this study we used tranexamic acid to reduce post LSCS bleeding.
Our study showed that tranexamic acid significantly reduces bleeding from placental delivery to 2 h postpartum.	Our study showed that tranexamic acid significantly reduces bleeding from the time of placental delivery to 2 hours postpartum in LSCS. Results show that study group patients had mean blood loss of 360.9ml ± 110.3 as	This study showed that tranexamic acid significantly redues bleeding from time of placental delivery to 2 hours postpartum in LSCS (P=0.001). This study shows significant decrease in the incidene of > 500 mL blood loss in the		Our study showed that tranexamic acid significantly reduces bleeding from time of placental delivery to 2 hrs postpartum in LSCS. Results show that study group patients had mean blood loss	The study shows that tranexamic acid significantly reduced the bleeding from placental delivery to 2hr postpartum in LSCS ($p < 0.001$).	Our study showed that tranexamic acid significantly reduces bleeding after cesarean section. The study group's total blood loss was significantly less than control group.	This study was a double blind placebo controlled trial which showed that TXA significantly reduced bleeding from the time of placental delivery to two hours postpartum in LSCS. This study shows significant decrease in	During this study we found that the amount of blood loss is very much reduced from the time of placental delivery to 2 hours postpartum in lower segment

	standard deviation, while control group patients had mean blood loss of 443ml ± 88.552 as standard deviation. Thus, there is reduction in blood loss by about 20% & was found to be statistically highly significant (p value= 0.000).*	study group as compare to control group (P-0.049).		of 362.70ml ± 110.3 as standard deviation, while control group patients had mean blood loss of 476.70ml ±88.552 as standard deviation. Thus, there is reduction in blood loss by about 30% & was found to be statistically highly significant (p value= 0.001).			the bleeding volume in TXA group as compared with the placebo group.	caesarean section (Table 3).
	Similar study carried out by Ming-Ying Gai, Lian-Fang Wu and co-workers5 in China showed blood loss reduction by 30% as compared to control group and also reduced the incidence of postpartum hemorrhage by 25.7%. These results co related well with our study. Zheng SR, Yang HX et al.6 showed similar results.	Similar study carried out by Ming-ying Gai et al 5 in China showed that tranexamic acid significantly reduces bleeding from the time of placental delivery to 2 hours post partum. The study showed significant decrease in the incidence of > 500 ml blood loss in the study group as compared to control group (P-0.029). Zheng et al 6, showed similar results after vaginal delivery.		Similar study carried out by Ming-ying Gai, Lian-fang Wu & coworkers (28) in China showed that tranexamic acid significantly reduces bleeding from the time of placental delivery to 2 hrs postpartum. The study group showed total blood loss reduction by 30% as compared to control group. Tranexamic acid also reduced the incidence of postpartum hemmorhage by 25.7% in the study group (22 cases Vs 35 cases in the study & controlled group respectively) (P value was 0.029). These results	Similar study carried on by Gohel Mayur et al.1 and Ming Ying Gai et al. showed similar results. In the study by Ming Ying et al.3, Gohel Mayur et al. the drug was administered between 10 – 20 minutes here in present study it was administered 30 minutes before and hence the amount of bleeding from placental delivery to end of LSCS is significantly reduced. It also reduced the amount of PPH between the two groups but not statistically significant.		Similar study carried out in India by Mayur et al.8 showed comparable results reducing the blood loss in the study group. Another study carried out by Ming-Ying et al., in China showed that TXA significantly reduces bleeding from the time of placental delivery to the end of caesarean section, which was 351 mL in the study group while 440 mL in the control group.15 Zheng et al. showed similar results after vaginal delivery; there was significantly less blood loss in the TXA group (243 mL) when compared to those who receive no	

				correlated well with our study. Zheng SR, Yang HX, et al81 showed similar results.			treatment (309 mL).16	
The incidence of thrombosis during pregnancy and peuperium is 5–6 times higher than that in the general population [4]. When the anti-fibrinolytic drug tranexamic acid is administered, the increased risk of thrombosis should be considered, especially in the CS postpartum population.	The incidence of thrombosis during pregnancy &puerperium is 5-6 times higher than that in general population. When the antifibrinolytic drug tranexamic acid is administered, increased risk of thrombosis should be considered, especially in the LSCS postpartum population. In our study, not a single patient developed signs of thrombosis.	The incidence of thrombosis during pregnancy and puerperium is 5-6 times higher then that in the general population 7. When the antifibrinolytic drug tranexamic acid is administered, the increased risk of post partum thrombosis after LSCS should be considered. In the present study, not a single patient developed thrombosis…		The incidence of thrombosis during pregnancy & puerperium is 5-6 times higher than that in the general population. When the anti fibrinolytic drug tranexamic acid is administered, the increased risk of thrombosis should be considered, especially in the LSCS postpartum population. In our study, not a single patient developed signs of thrombosis.	The incidence of thrombosis during pregnancy and puerperium is 5-6 times higher than that in the general population. When the antifibrinolytic drug tranexamic acid is administered the increased risk of postpartum thrombosis after LSCS should be considered. In the present study not a single patient developed thrombosis…	The incidence of thrombosis during pregnancy and peuperium is 5–6 times higher than that in the general population [11]; when the antifibrinolytic drug tranexamic acid is administered, the increased risk of thrombosis should be considered, especially in the CS postpartum population….		
All data demonstrated that tranexamic acid can be used safely without increasing the occurrence of thrombosis, but we still need more cases to be observed for the occurrence of thrombosis.	Tranexamic acid significantly reduces the amount of blood loss during & after the LSCS**.** Its use is not associated with increased risk of adverse drug reaction like nausea, vomiting, diarrhoea or thrombosis. Tranexamic acid can be used safely during LSCS to reduce the blood loss.	Tranexamic acid significantly reduced the amount of blood loss during and after the lower segment cesarean section and its use was not associated with any side effects and.or complication like thrombosis. Thus, tranexamic acid can be used safely and effectively in subjects undergoing LSCS.		1) Tranexamic acid significantly reduced the amount of blood loss during & after the lower segment cesarean section. 2) Its use was not associated with any adverse drug reaction like nausea, vomiting, diarrhea or thrombosis. Fetal outcome as evaluated by apgar score was not adversely affected by use of tranexamic acid.	Tranexamic acid significantly reduced the amount of blood loss during and after LSCS with no significant side effects. Thus tranexamic acid can be safely and effectively used in subjects undergoing LSCS.	All data demonstrated that tranexamic acid can be used safely to reduce bleeding after CS and its use was not associated with any side effects or complications. Thus, tranexamic acid can be used safely and effectively to reduce bleeding resulting from CS, but we still need more cases to be observed for the	Tranexamic acid significantly reduced the amount of blood loss during the lower segment caesarean section, but it did not significantly reduced the blood loss after the caesarean section. Its use was not associated with any side effects and or complication like thrombosis. Thus, TXA can be used safely and effectively	Tranexamic acid significantly reduces the amount of blood loss during and after the lower segment caesarean section. The use of tranexamic acid was not associated with any side effects or complication like thrombosis, nausea,

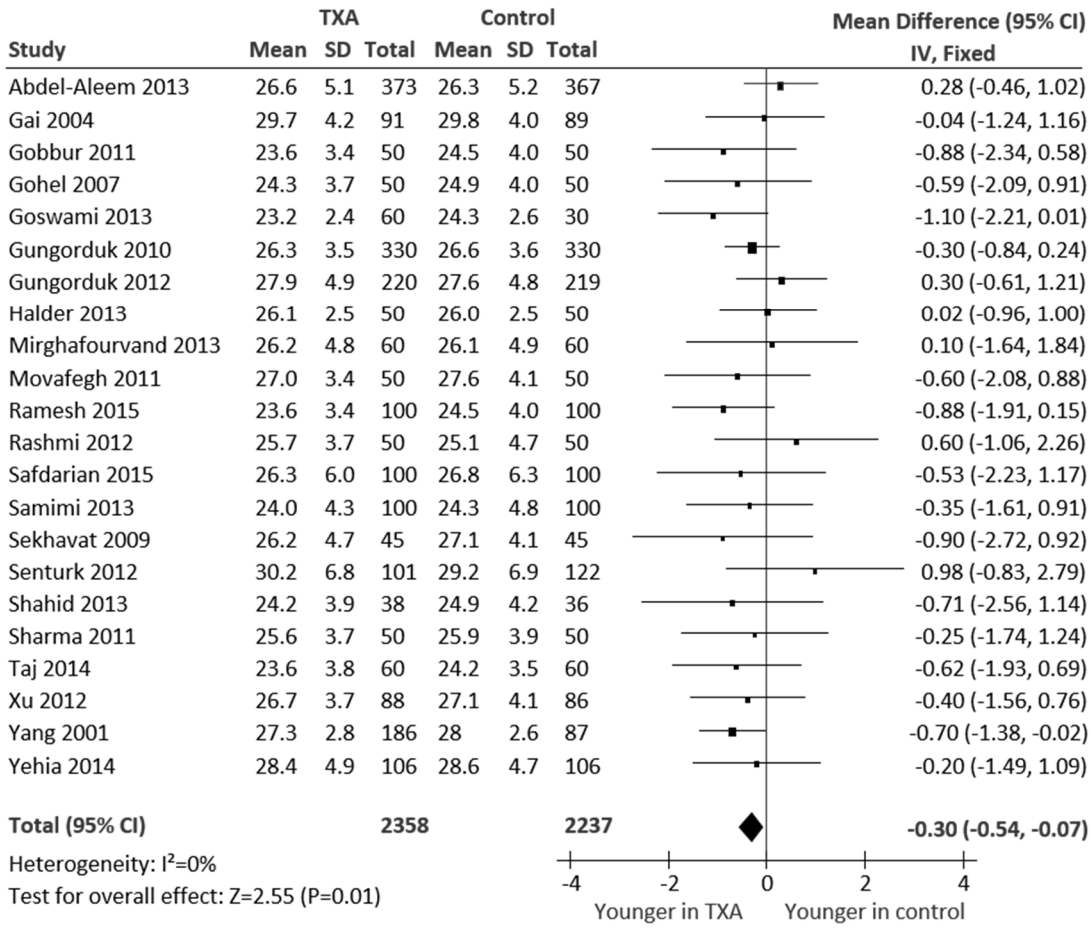
				3) Tranexamic acid can be used safely in subjects with lower caesarean section.		occurrence of thrombosis.	in subjects undergoing LSCS.	vomiting and diarrhea.

Appendix JJ. Research Paper 6: Summary of response to review authors' requests for additional trial information.

Trial	Date 1st randomised	Date last randomised	Copy of ethics approval received?	Trial data sent?	Notes
Abdel-Aleem 2013	03/08/2011	01/12/2011	Y	Y	
Gai 2004					No response
Gobbur 2014			Y		Response from ethics committee (no response from authors)
Gohel 2007	03/08/2004	25/07/2005	N*	Y	*Author response: *"This study was carried out as a thesis of the first author Dr Mayur Gohel who was a post-graduate student in the department at that time. At the point in time when this study was carried out, according to the local guidelines, conducting a study for thesis purpose required just an information to the ethics committee and not a formal approval. Hence we are unable to provide you with an approval letter from the ethics committee."* (This was confirmed in response from the ethics committee)
Goswami 2013	*	*	Y	Y	*Author response: "*we did not keep any record of the exact dates of the cases done, i can only say that the study was conducted between November, 2009 to 2011"*[sic]
Gungorduk 2010	01/06/2009	30/09/2009	Y	N*	*Author response: *"Dear Sir; Thank you for your email. I sent the all information within 5 day. I am on holiday now. Unfortunately, last year (22-june-2013) my computers and hard disk was stolen therefore, I can not sent the patients data. A police burgary report was attached. I am very sorry about this topic."* [sic]

Gungorduk 2012	01/03/2011	31/08/2011	Y	see above	see above
Halder 2013					No response
Mirghafourvand 2015	12/08/2012	13/11/2012	Y	N	
Movafegh 2011					No response
Poonia 2012					No response
Ramani 2014	07/03/2013	29/05/2013	Y	N	
Ramesh 2015					No response
Rashmi 2012					Author response: *"Sir, The work has been actually undertaken after proper clearance. And details of the same are available with the competent authority. We don't want to be get disturbed as I discussed with our main author. Excuse us..Bye."* [sic]
Safdarian 2015					No response
Samimi 2013	21/11/2012	16/03/2013	Y	Y	No response
Sekhavat 2009					No response
Senturk 2012			Y	Y	
Shahid 2013	20/03/2009	28/04/2011	N*	Y	*Response from ethics committee: *"After detailed scrutiny of our records I regret to inform you that no such approval was given by the Institutional Review Board of Dow University of Health Sciences."*
Sharma 2011					No response
Taj 2014					No response
Tarabrin 2012					No response
Xu 2012					No response
Yang 2011					No response
Yehia 2014			Y*	Y	*Approval dated approximately 3 months after start of recruitment.
Zizi 2013					No response

Appendix KK. Research Paper 6: Forest plots showing the difference in age between women allocated to the TXA group and those allocated to the control group.



Appendix LL. Research Paper 6: Forest plots showing the difference in haemoglobin between women allocated to the TXA group and those allocated to the control group.