RESEARCH ARTICLE

REVISED Effect of early tranexamic acid treatment on fatigue in patients with mild traumatic brain injury: data from the CRASH-3 clinical trial [version 3; peer review: 2 approved, 1 not approved]

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Abstract

Background

Each year world-wide about 65 million people sustain a mild traumatic brain injury (mTBI). Fatigue is a common and distressing symptom after mTBI. We examine the effect of tranexamic acid (TXA) on fatigue in patients with mTBI using data from the CRASH-3 trial.

Methods

The CRASH-3 trial randomised 9,202 patients with traumatic brain injury and no significant extracranial bleeding to receive TXA or placebo within 3 hours of injury. The primary outcome was death from head injury within 28 days of injury. The methods and results are presented elsewhere. Fatigue was recorded as “None”, “Moderate” or “Extreme.” This study examines the effect of TXA on extreme fatigue in the 2,632 patients with mTBI (Glasgow Coma Scale [GCS] score≥13). Our analyses were not prespecified.

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Results

Our study primary outcome, extreme fatigue, was reported for 10 (0.8%) of 1,328 patients receiving TXA and 19 (1.5%) of 1,288 patients receiving placebo (risk ratio [RR]=0.51, 95% confidence interval [CI] 0.24-1.09). Death within 28 days of injury was reported for 34 (2.6%) of 1,328 patients receiving TXA versus 47 (3.6%) of 1,288 patients receiving placebo (RR=0.70, 95% CI 0.45-1.08). Among patients allocated to TXA, 44 (3.3%) patients either died or reported extreme fatigue versus 66 (5.1%) patients among those allocated to placebo (RR=0.65, 95% CI 0.44-0.94). This composite outcome is disproportionately influenced by deaths which account for 74% (81 from 110) of events.

Conclusions

We found no evidence that tranexamic acid reduces fatigue in patients with mTBI. Given, 1) our analyses were not prespecified, 2) our outcome measure is not based on a validated fatigue severity scale, and 3) TBI patients can suffer from hospital-induced delirium, which hinders clinician assessment, these results need to be replicated in another study.

Registration

ISRCTN (ISRCTN15088122, 19/07/2011), ClinicalTrials.gov (NCT01402882, 26/07/2011), EudraCT (2011-003669-14, 25/07/2011), Pan African Clinical Trial Registry (PACTR20121000441277, 30/10/2012).

Keywords
Traumatic Brain Injury, Ttranexamic Acid, Fatigue, CRASH-3 trial, Randomised Controlled Trial, IntracranialHaemorrhage

Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 2**

This new version:

1) Highlights the biological significance of our results.

2) Makes a case for assessing fatigue at hospital discharge.

3) Consolidates our last 2 paragraphs into 1.

Any further responses from the reviewers can be found at the end of the article

Introduction

Each year, world-wide about 65 million people experience a mild traumatic brain injury (mTBI)[1]. The most common causes are falls and road traffic crashes[2]. With an increasing and ageing world population the number of people suffering mTBI is expected to rise.

Tranexamic acid reduces bleeding by inhibiting blood clot breakdown. The CRASH-2 trial[3] showed that giving tranexamic acid within 3 hours of injury reduces deaths due to bleeding in trauma patients. This raised the hope that tranexamic acid might reduce traumatic brain injury (TBI) deaths. Intracranial bleeding is common after TBI and causes death and disability. The CRASH-3 trial[4] was a large randomised trial of the effect of tranexamic acid on death and disability in patients with TBI. The primary outcome was head injury death. The results were published in 2019. The risk of head injury death was 12.5% in the TXA group versus 14.0% in the placebo group (risk ratio [RR] = 0.89, 95% confidence interval [CI] 0.80–1.00). The reduction was greater in patients with mild and moderate head injury (RR = 0.78, 95% CI 0.64–0.95) than in severe head injury (RR = 0.99, 95% CI 0.91–1.07). The effect of tranexamic acid on disability was assessed by comparing the Disability Rating Scale (DRS)[5] score in the tranexamic acid and placebo group. The mean DRS scores were similar in the tranexamic acid and placebo groups.

Fatigue is defined as overwhelming tiredness not relieved by sleep or rest and is a common and distressing symptom in patients with mTBI[6]. Over one third of mTBI patients have fatigue six months after injury[6]. TBI related fatigue has a detrimental effect on patients' quality of life[7,8] and TBI patents who report fatigue are at increased risk of anxiety and depression[9–11]. When planning the CRASH-3 trial, we discussed the proposed outcome measures with patient representatives who specifically requested that fatigue was included as an outcome.

Intracranial bleeding appears to increase the risk of fatigue. A recent prospective cohort study[12] found that mTBI patients with intracranial bleeding on computerised tomography (CT) or magnetic resonance imaging (MRI) scans were significantly more likely to experience fatigue compared to those without intracranial bleeding. Early tranexamic acid treatment may reduce intracranial bleeding in TBI patients. It therefore seems plausible that timely tranexamic acid treatment might reduce fatigue in mTBI patients. We examine the effect of tranexamic acid on fatigue in mTBI patients in the CRASH-3 trial.

Methods

The CRASH-3 trial is registered at ISRCTN (ISRCTN15088122), ClinicalTrials.gov (NCT01402882), EudraCT (2011-003669-14), and the Pan African Clinical Trial Registry (PACTR20121000441277). This article is reported in line with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[13].

The background to the CRASH-3 trial, the methods, baseline characteristics and main results were previously reported[4,14,15]. Briefly, CRASH-3 trial participants were adults with TBI, who had a Glasgow Coma Scale (GCS) score $\leq$ 12 or any intracranial bleeding on CT scan and no significant extracranial bleeding. Patients were recruited from 175 hospitals in 20 countries. The primary outcome was head injury related in hospital death within 28 days of injury in patients treated within 3 hours of injury. Between July 2012 and January 2019, 12,737 patients with TBI were randomly allocated to receive tranexamic acid or placebo, of whom 9,202 patients were treated within 3 hours. This analysis focusses on the 2,632 mTBI patients who had a GCS score of between 13 and 15 and intracranial bleeding on CT scan who were treated within 3 hours of injury.

The trial treatment was 1g of tranexamic acid administered intravenously over 10 minutes followed by a 1g maintenance dose administered intravenously over 8 hours. Patients were allocated a treatment pack identifiable by a unique number. These unique numbers (randomisation codes) were prepared by an independent statistician from Sealed Envelope (UK) Ltd. Packs were equally likely to contain tranexamic acid or placebo. Once patients had been deemed suitable for trial entry, and baseline details obtained, they were designated the lowest numbered treatment pack remaining from a box of 8 packs. Each pack contained four ampoules of either 500g of tranexamic acid or placebo (0.9% sodium chloride), a 100ml bag of 0.9% sodium chloride (to be used for infusing the loading dose), a syringe with needle, stickers containing the randomisation number (to be attached to patient records, trial forms and saline bags) and a document of instructions for clinicians. Tranexamic acid and placebo treatment packs, labels and ampoules were identical. Patients, clinicians and trial coordinating centre staff were blinded to treatment allocation. Once a patient had been designated a treatment pack, providing the ampoules contained in that pack were not broken, they were considered to be randomised into the trial.

Fatigue was assessed by a clinician and recorded as "None", "Moderate" or "Extreme". Patient fatigue was recorded either at discharge or in hospital after 28 days of injury if the patient had not already been discharged. The statistical analysis plan[15] prespecified that we would report the effect of tranexamic acid on fatigue by estimating the risk ratio of being in the extreme fatigue category. We considered that the extreme category of fatigue would be less susceptible to misclassification bias and a better measure of the disabling patient fatigue that many mTBI patients experience.

We selected mTBI patients for this study motivated by a recent cohort study[12] which reported an association between

intracranial findings on a CT or MRI scan and fatigue in mTBI patients. Severely injured patients are likely to suffer the effects of pathophysiological processes other than intracranial bleeding which tranexamic acid is unlikely to affect. Deaths and fatigue caused by these processes are likely to bias our treatment effect estimates towards the null.

We report risk ratios and 95% confidence intervals for the effect of early tranexamic acid treatment on extreme fatigue which is our study primary outcome. As a secondary outcome we report death within 28 days of injury. As an additional secondary outcome, we report the composite outcome "death or extreme fatigue" to highlight the potential benefits early tranexamic acid treatment may provide mTBI patients. This composite outcome is consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 guidelines' "Composite strategy" for handling intercurrent events[16]. Patients with missing outcome data were excluded from our analysis. All analyses were performed in R version 4.1.1.

Ethical approval and consent to participate

Most patients with TBI are unable to provide informed consent to participate in a clinical trial due to the nature of their injury. In the CRASH-3 trial, consent was sought from the patient's relative or a legal representative unless no such representative was available, in which case the study proceeded with the agreement of two clinicians. If the patient regained capacity, they were told about the trial and written consent was sought to continue participation. If either the patient or their representative declined consent, participation was stopped. If patients were included in the trial but did not regain capacity, consent was sought from a relative or legal representative. We adhered to the requirements of the local and national ethics committees. The trial received a favourable opinion by London School of Hygiene & Tropical Medicine observational/interventions research ethics committee on 17 November 2011 (LSHTM ethics ref: 6060).

Results

The CRASH-3 trial randomised 2,632 patients with a GCS 13-15 to receive tranexamic acid or placebo within 3 hours of injury. Outcome data were collected for 2,616 patients of whom 1,328 received tranexamic acid and 1,288 received placebo (Figure 1). Baseline characteristics of the trial participants are shown in Table 1.

A total of 29 (1.1%) patients had extreme fatigue and 81 (3.1%) patients died within 28 days of injury. There were 110 (4.2%) patients who either died or experienced extreme fatigue. The mean age (standard deviation [SD]) of study participants was 45 (20) years. The mean (SD) age of participants with extreme fatigue was 61 (20) years. Extreme fatigue was reported for 6 (1.0%) of 618 women and 23 (1.2%) of 1998 men. Extreme fatigue was reported for 8 (0.5%) of 1687 patients in low to middle income countries and 21 (2.3%) of 929 patients in high income countries. The effects of tranexamic acid on extreme fatigue, death within 28 days of injury, and the composite outcome of extreme fatigue or death are shown in Figure 1. Extreme fatigue was reported for 10 (0.8%) out of 1,328 patients in the tranexamic acid group and 19 (1.5%) out of 1,288 patients in the placebo group (RR=0.51, 95% CI: 0.24-1.09). For death within 28 days of injury, 34 (2.6%) out of 1,328 patients died in the tranexamic acid group versus 47 (3.6%) out of 1,288 patients from the placebo group (RR=0.70, 95% CI: 0.45-1.08). The risk of the composite outcome of extreme fatigue or death was reduced by 35% in patients treated with tranexamic acid. There were 44 (3.3%) patients with this outcome among the 1,328 patients allocated to the tranexamic acid group compared with 66 (5.1%) patients among the 1,288 patients allocated to the placebo group (RR=0.65, 95% CI: 0.44-0.94). This composite outcome is disproportionately

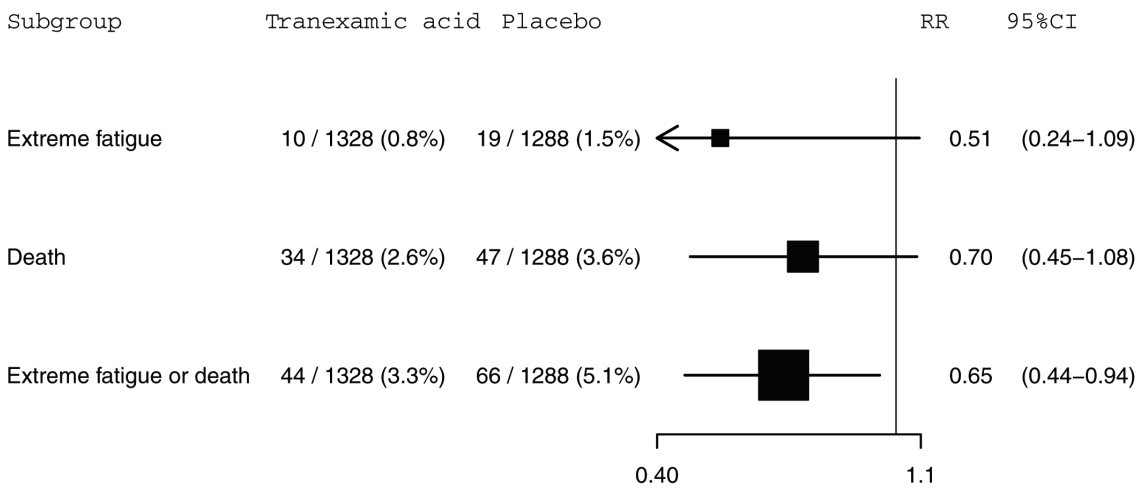

Figure 1. The effect of tranexamic acid on extreme fatigue, death within 28 days of injury and extreme fatigue or death within 28 days of injury for CRASH-3 trial participants with mild traumatic brain injury who were randomised within 3 hours of injury. N=2616. RR=risk ratio; CI=confidence interval.

Table 1. Baseline characteristics before randomisation for CRASH-3 trial participants with mild traumatic brain injury who were randomised within 3 hours of injury. TXA=tranexamic acid; SD=standard deviation.

	TXA (N=1335)		Placebo (N=1297)	
	n	%	n	%
Sex				
Men	1039	77.8%	974	75.1%
Woman	296	22.2%	323	24.9%
Age at randomisation (years)				
Mean (SD)	44.4	20.3	45.3	20.0
16–24	271	20.3%	235	18.1%
25–34	259	19.4%	236	18.2%
35–44	194	14.5%	211	16.3%
45–54	189	14.2%	195	15.0%
55+	422	31.6%	420	32.4%
Time since injury (h)				
Mean (SD)	2.0	0.7	2.0	0.7
≤1	184	13.8%	199	15.3%
1–2	559	41.9%	543	41.9%
2–3	592	44.3%	555	42.8%
Systolic blood pressure (mm Hg)				
0–89	11	0.8%	7	0.5%
90–119	408	30.6%	394	30.4%
120–139	492	36.9%	488	37.7%
140+	421	31.5%	405	31.2%
Unknown	3	0.2%	3	0.2%
Glasgow Coma Scale score				
13	297	22.2%	312	24.0%
14	526	39.4%	458	35.3%
15	484	36.3%	492	38.0%
Unknown	28	2.1%	35	2.7%
Pupil reaction				
Both React	1288	96.5%	1249	96.3%
One Reacts	33	2.5%	28	2.2%
None React	4	0.3%	3	0.2%
Unable to assess	10	0.7%	17	1.3%

influenced by deaths which account for 74% (81 from 110) of events. Excluding the 63 patients with a missing GCS score from our analysis left these effect estimates and confidence intervals (Figure 2) almost entirely unchanged.

Discussion

Our study found no evidence that tranexamic acid reduced fatigue in patients with mTBI. Our analysis was not pre-specified, the precision of the estimates was low and our outcome measure is not based on a validated fatigue scale. In addition, TBI patients are prone to hospital-induced delirium which will hinder clinician assessment of fatigue. A larger trial is needed to test the hypothesis that early tranexamic acid treatment reduces fatigue in mTBI patients.

Ours is the first trial to examine the effect of tranexamic acid on fatigue in mild TBI patients. The study was randomised and placebo controlled with a large sample size and minimal loss to follow up. However, our study has important limitations. Although we planned to examine the impact of TXA treatment on extreme fatigue, the focus on mild TBI was not pre-specified but stimulated by the observation from the CRASH-3 intracranial bleeding mechanistic study[17] that patients with less severe TBI may have less intracranial bleeding at baseline and so there is more potential to prevent bleeding. Patients with more severe TBI either have extensive intracranial bleeding at baseline or other intracranial pathologies that are not affected by TXA. On the other hand, because clinicians underestimated time to treatment[18] some mild TBI patients may have been treated beyond 3 hours of injury with reduced potential to prevent bleeding. Inaccuracy in time to treatment may have biased the estimated treatment effects of tranexamic acid towards the null. The CRASH-3 trial assessed fatigue via a three-point scale which hasn't been validated. We acknowledge this is a significant limitation with our study. Ideally, fatigue would be measured using a validated scoring system such as the 9 item Fatigue Severity Scale (FSS). Other studies have found that around 30% of all mTBI patients experience fatigue[12,19–22]. We cannot rule out clinicians underreporting extreme fatigue. However, this misclassification of our outcome variable would be expected to bias our results towards the null. Our study primary outcome extreme fatigue is measured at a single timepoint. Although patients in the CRASH-3 trial were only followed to hospital discharge, early fatigue has been shown to predict more long term post-concussive symptoms[20]. This measure is an imperfect proxy for the disabling long-term fatigue many mTBI patients experience. Some patients with our outcome will eventually recover while others without the outcome will later experience fatigue.

Intracranial bleeding in mTBI patients is associated with an increased risk of fatigue. Saksvik[12] used data from the Trondheim mild traumatic brain injury [mTBI] follow-up study to compare fatigue in patients with complicated (intracranial findings on a CT or MRI scan) and uncomplicated mTBI. Fatigue was assessed using the FSS questionnaire[19,23]. Patients were monitored for fatigue at 2 weeks, 3 months and 12 months. The percentage of patients with fatigue was higher at every time point for the complicated mTBI group compared to the uncomplicated group. Although the association may be confounded by injury severity, in the light of our results, the possibility that intracranial bleeding is causally related to fatigue and might be prevented by TXA treatment deserves further consideration.

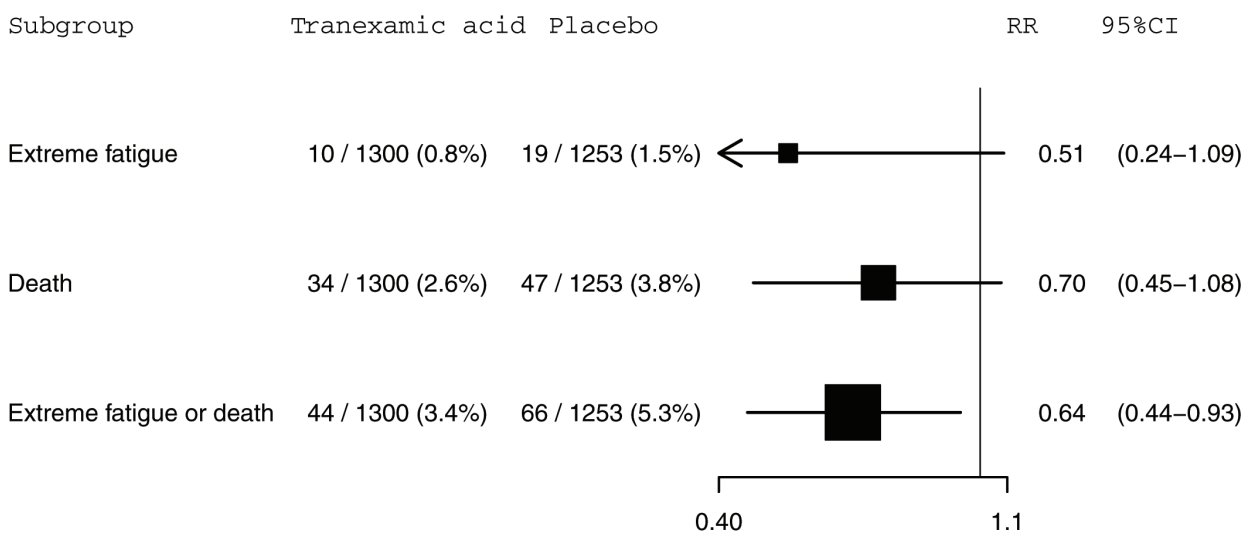

Figure 2. The effect of tranexamic acid on extreme fatigue, death within 28 days of injury and extreme fatigue or death within 28 days of injury for CRASH-3 trial participants with mild traumatic brain injury excluding patients with a missing GCS score who were randomised within 3 hours of injury. N=2553. RR=risk ratio; CI=confidence interval.

The pathophysiology of fatigue after mild TBI is uncertain[24]. Central fatigue after mild TBI may be associated with lesions to specific brain structures, particularly those in the limbic system involved in attention, concentration and executive function[25]. It is hypothesised that deficits in these processes are interpreted as mental fatigue. For example, Vanier at al recently showed that asymmetry of limbic system structures after mild TBI is associated with the persistence of cognitive symptoms[25]. However, if it is proven that tranexamic reduces fatigue after mild TBI this would suggest a role for inflammation and there are some small cohort studies that show increased levels of pro-inflammatory cytokines in patients with severe fatigue after haemorrhagic stroke[26].

Tranexamic acid substantially reduces blood loss in surgery[27]. The CRASH-2 trial[3] showed that prompt tranexamic acid treatment reduces death due to bleeding in trauma patients. The CRASH-3 trial showed that early treatment with tranexamic acid is safe and reduces head injury deaths in mild and moderately injured TBI patients, potentially by reducing intracranial bleeding[28]. We were unable to demonstrate that tranexamic acid prevents fatigue in mTBI patients. Further randomised controlled trials investigating the effect of early tranexamic acid treatment on disability and death in mTBI patients are needed.

Data availability

Underlying data

Individual de-identified patient data from the CRASH-3 trial is available from the The Free Bank of Injury and Emergency Research Data (freeBIRD) website: https://freebird.lshtm.ac.uk/.

LSHTM CTU regulations require an account to be created before data can be accessed. Our registration process only requires an email address and takes less than five minutes.

Extended data

The CRASH-3 trial protocol is available at https://freebird.lshtm.ac.uk/.

The protocol includes the information patients were given before trial enrolment and also the patient consent form.

Reporting guidelines

Zenodo: CONSORT checklist for 'Effect of early tranexamic acid treatment on fatigue in patients with mild traumatic brain injury: data from the CRASH-3 clinical trial.' https://doi.org/10.5281/zenodo.5730383[13].

Acknowledgements

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Open Peer Review

Current Peer Review Status: ✔ ✘ ✔

Version 3

Reviewer Report 04 November 2024

https://doi.org/10.21956/wellcomeopenres.25699.r108273

✔ **Vincenzo Menditto**
Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy

I think that the authors have addressed the concerns I raised in my peer review report appropriately.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Emergency and internal medicine. Mild traumatic brain injury. Pulmonary embolism. Anticoagulant therapy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 15 October 2024

https://doi.org/10.21956/wellcomeopenres.25368.r102425

? **Vincenzo Menditto**
Azienda Ospedaliero Universitaria delle Marche, Ancona, Italy

This study examined the effect of early TXA on fatigue and death in patients with a mild traumatic brain and any intracranial bleeding on the CT scan during the CRASH-3 Trial. This focus was not

pre specified. The authors didn't use a validated fatigue scale and this outcome was assessed either at discharge or in hospital after 28 days of injury if the patient had not already been discharged. Extreme fatigue or death was reported in 3.3% of TXA treated patients vs 5.1% in the placebo group, but this composite outcome is disproportionately influenced by deaths.

The conclusions are drawn adequately supported by the results and discussed citing the current literature. However, the major concern is the biological significance of the results. I suggest to add in the discussion some sentences about the biological background of the findings the authors found in this work. Moreover, the authors should explain why they choose a so early outcome's timing. So, pertinent articles would be cited, almost the following article:
Vanier C, Santhanam P, Rochester N, Carter L, Lim M, Kilani A, Venkatesh S, Azad S, Knoblauch T, Surti T, Brown C, Sanchez JR, Ma L, Parikh S, Germin L, Fazzini E, Snyder TH. Symptom Persistence Relates to Volume and Asymmetry of the Limbic System after Mild Traumatic Brain Injury. J Clin Med. 2024 Aug 30;13(17):5154. doi: 10.3390/jcm13175154. PMID: 39274367; PMCID: PMC11396354.

I suggest checking at page 7 the following: “Tranexamic acid substantially reduces blood loss in surgery. The CRASH-2 trial3 showed that prompt tranexamic acid treatment reduces death due to bleeding in trauma patients. The CRASH-3 trial showed that early treatment with tranexamic acid reduces head injury deaths in mild and moderately injured TBI patients, potentially by reducing intracranial bleeding.
Previous studies have shown that tranexamic acid is safe and reduces head injury-related deaths in TBI patients if given within 3 hours of injury.”
Perhaps, they didn’t add a lot to the text.

No other comments.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Emergency and internal medicine. Mild traumatic brain injury. Pulmonary embolism. Anticoagulant therapy.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Oct 2024

Raoul Mansukhani

Dear Dr Menditto Thank you for reviewing our article. We have made the following changes guided by your comments:
"However, the major concern is the biological significance of the results. I suggest to add in the discussion some sentences about the biological background of the findings the authors found in this work. Moreover, the authors should explain why they choose a so early outcome's timing. So, pertinent articles would be cited, almost the following article:
Vanier C, Santhanam P, Rochester N, Carter L, Lim M, Kilani A, Venkatesh S, Azad S, Knoblauch T, Surti T, Brown C, Sanchez JR, Ma L, Parikh S, Germin L, Fazzini E, Snyder TH. Symptom Persistence Relates to Volume and Asymmetry of the Limbic System after Mild Traumatic Brain Injury. J Clin Med. 2024 Aug 30;13(17):5154. doi: 10.3390/jcm13175154. PMID: 39274367; PMCID: PMC11396354."
Response: We have added the following to the discussion:
The pathophysiology of fatigue after mild TBI is uncertain. Central fatigue after mild TBI may be associated with lesions to specific brain structures, particularly those in the limbic system involved in attention, concentration and executive function. It is hypothesised that deficits in these processes are interpreted as mental fatigue. For example, Vanier at al recently showed that asymmetry of limbic system structures after mild TBI is associated with the persistence of cognitive symptoms. However, if it is proven that tranexamic reduces fatigue after mild TBI this would suggest a role for inflammation and there are some small cohort studies that show increased levels of pro-inflammatory cytokines in patients with severe fatigue after haemorrhagic stroke. We have also added the sentence: Although patients in the CRASH-3 trial were only followed to hospital discharge, early fatigue has been shown to predict more long term post-concussive symptoms. Note the next two sentances in our discussion highlight limitations in our outcome measure.

"I suggest checking at page 7 the following: “Tranexamic acid substantially reduces blood loss in surgery. The CRASH-2 trial showed that prompt tranexamic acid treatment reduces death due to bleeding in trauma patients. The CRASH-3 trial showed that early treatment with tranexamic acid reduces head injury deaths in mild and moderately injured TBI patients, potentially by reducing intracranial bleeding.

Previous studies have shown that tranexamic acid is safe and reduces head injury-related deaths in TBI patients if given within 3 hours of injury."
Response: We have consolidate our last two paragraphs into one which now reads: "Tranexamic acid substantially reduces blood loss in surgery. The CRASH-2 trial showed that prompt tranexamic acid treatment reduces death due to bleeding in trauma patients. The CRASH-3 trial showed that early treatment with tranexamic acid is safe and reduces head injury deaths in mild and moderately injured TBI patients, potentially by reducing intracranial bleeding. We were unable to demonstrate that tranexamic acid prevents fatigue in mTBI patients. Further randomised controlled trials investigating the effect of early tranexamic acid treatment on disability and death in mTBI patients are needed." Would you be able to appove our article?
Yours sincerely
Raoul Mansukhani
Research fellow in medical statistic

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 12 August 2024

https://doi.org/10.21956/wellcomeopenres.19261.r86356

Christie Fritz
Harvard Medical School, Boston, Massachusetts, USA

Thank you for the opportunity to review "Effect of early tranexamic acid treatment on fatigue in patients with mild traumatic brain injury: data from the CRASH-3 clinical trial". The authors present an original submission in which they evaluated the effect of TXA in TBI patients on fatigue and death.

The research behind TXA and fatigue as a surrogate for disability in significant head injuries has not been completely studied and this study attempts to utilize the existing CRASH 3 data and perform a subgroup analysis.

General comments:

I suggest the authors define mTBI in their introduction.

This study has a few significant issues that are concerning:

- Outcome measure: fatigue was assessed only by the clinician so isn't the patient centered outcome that we may necessarily hope for. Also, fatigue was measured either at hospital discharge (not as useful, since the hospital is a difficult place to measure fatigue at discharge), or at 28 days after injury while still inpatient. Hospital delirium would appear to be a significant factor in this, and I'm concerned this is not as useful a marker/outcome, especially as a patient centered marker.

- They posit that severely injured patients are more likely to suffer effects from blood and would be less likely to benefit from TXA, but do not supply adequate references to make this assertion.

- I have significant issues with the "composite outcome" of extreme fatigue or death. The authors didn't seem to get the results they were looking for with "Extreme fatigue" (only 1.1% of patients, most studies they say cite around 30%) in the GCS greater than or equal to 13 group so they added in death as an endpoint. There are more (34) patients with death as an outcome than extreme fatigue (10) in the treatment arm and I'm concerned that it is the significance of death, not fatigue that are driving these outcomes, since either alone is not significant. These seem to be disparate outcomes that shouldn't be logically grouped together.

- I'd also say that their discussion "suggesting" that TXA may reduce the risk of extreme fatigue is not borne out. Their CI crosses 1 and is not statistically significant in either of their analyses. I was also surprised that their first table, which they note were for patients with GCS of 13 or greater included those with no GCS recorded, which is not well explained.

- They also state "crash 3 trial showed that early treatment with TXA reduces head injury deaths in TBI patients, almost certainly by reducing intracranial bleeding" which may be an overstatement of the conclusions of that paper.

- My biggest concern is their "composite outcome" of death or extreme fatigue.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: EMS, Emergency Medicine, Protocol Development

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 27 Aug 2024

Raoul Mansukhani

Dear Dr Fritz,

Thank you for your comments which we have used to improve our article. When we were developing the CRASH-3 trial protocol we asked patient groups for their input. Their main suggestion was that we conduct an analysis of the impact of the trial treatment on fatigue because extreme fatigue is the symptom that patients find particularly troubling. We do not want to make any claim that is not supported by the data but we do feel an obligation to publish the results as promised. We accept that we may have overstated the potential of TXA to reduce this outcome.

Please see below for our responses:

Comment 1: Outcome measure: fatigue was assessed only by the clinician so isn't the patient centered outcome that we may necessarily hope for. Also, fatigue was measured either at hospital discharge (not as useful, since the hospital is a difficult place to measure fatigue at discharge), or at 28 days after injury while still inpatient. Hospital delirium would appear to be a significant factor in this, and I'm concerned this is not as useful a marker/outcome, especially as a patient centered marker.
Response: We've changed the abstract conclusions to read: Given, 1) our analyses were not prespecified, 2) our outcome measure is not based on a validated fatigue severity scale, and 3) TBI patients can suffer from hospital-induced delirium, which hinders clinician assessment, these results need to be replicated in another study. We have added the following to the discussion: Our analysis was not prespecified, the precision of the estimates was low and our outcome measure is not based on a validated fatigue scale. In addition, TBI patients are prone to hospital-induced delirium which will hinder clinician assessment of fatigue. A larger trial is needed to test the hypothesis that early tranexamic acid treatment reduces fatigue in mTBI patients. ..... The CRASH-3 trial assessed fatigue via a three-point scale which hasn't been validated. We acknowledge this is a significant limitation with our study. Ideally, fatigue would be measured using a validated scoring system such as the 9 item Fatigue Severity Scale (FSS). We have removed the next sentence: However, studies that use more elaborate scoring systems with long questionnaires tend to have fewer participants and this would increase random error. Misclassification of an outcome variable usually biases towards the null.

Comment 2: They posit that severely injured patients are more likely to suffer effects from blood and would be less likely to benefit from TXA, but do not supply adequate references to make this assertion.
Response: *I*n the discussion we have changed the sentence in the discussion: Although we planned to examine the impact of TXA treatment on extreme fatigue, the focus on mild TBI was not pre-specified but stimulated by the observation from the CRASH-3 intracranial bleeding mechanistic study[17] that patients with less severe TBI may have less intracranial bleeding at baseline and so there is more potential to prevent bleeding.

Comment 3: I have significant issues with the "composite outcome" of extreme fatigue or death. The authors didn't seem to get the results they were looking for with "Extreme fatigue" (only 1.1% of patients, most studies they say cite around 30%) in the GCS greater than or equal to 13 group so they added in death as an endpoint. There are more (34) patients with death as an outcome than extreme fatigue (10) in the treatment arm and I'm concerned that it is the significance of death, not fatigue that are driving these outcomes, since either alone is not significant. These seem to be disparate outcomes that shouldn't be logically grouped together.
Response: We have added the following to our methods: This composite outcome is consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 guidelines' "Composite strategy" for handling intercurrent events. We have added the following sentence to the results section of the abstract: This composite outcome is disproportionately influenced by deaths which account for 74% (81 from 110) of events. We added the following sentence to the results section: This composite outcome is disproportionately influenced by deaths which account for 74 % (81 from 110) of events. We have also changed the conclusions of our study based on extreme fatigue alone rather the composite outcome of extreme fatigue and death. (See our response to comment 4 below)

Comment 4: I'd also say that their discussion "suggesting" that TXA may reduce the risk of extreme fatigue is not borne out. Their CI crosses 1 and is not statistically significant in either of their analyses. I was also surprised that their first table, which they note were for patients with GCS of 13 or greater included those with no GCS recorded, which is not well explained. **Response:** We have changed the abstract conclusions to read: We found no evidence that tranexamic acid reduces fatigue in patients with mTBI. We changed the first sentence in our discussion to read:
Our study found no evidence that tranexamic acid reduced fatigue in patients with mTBI. We replaced the sentence: The results of this study suggest that promptly treating mTBI patients with tranexamic acid may reduce risk of fatigue. With We were unable to demonstrate that tranexamic acid prevents fatigue in mTBI patients.

Comment 5: They also state "crash 3 trial showed that early treatment with TXA reduces head injury deaths in TBI patients, almost certainly by reducing intracranial bleeding" which may be an overstatement of the conclusions of that paper.
Response: We have changed our discussion to read: The CRASH-3 trial showed that early treatment with tranexamic acid reduces head injury deaths in mild and moderately injured TBI patients, potentially by reducing intracranial bleeding.

Comment 6: My biggest concern is their "composite outcome" of death or extreme fatigue.
Response: We believe we have addressed this in points 3 and 4 above. I do hope you will be able to approve our article.
Yours Sincerely
Raoul Mansukhani
Research fellow in medical statistics

Competing Interests: No competing interests were disclosed.

Reviewer Report 11 May 2024

https://doi.org/10.21956/wellcomeopenres.19261.r76923

Kim Kirby
University of the West of England,, Bristol, UK

This study sought to investigate the effect of early tranexamic acid on fatigue in patients with a mild traumatic brain injury during the CRASH-3 Trial. This focus on fatigue on mild traumatic brain injury was not pre specified. CRASH-3 recruited patients with a GCS less than or equal to 12 or with intracranial bleeding on the CT scan and no significant extracranial bleeding. Patients were randomly allocated to TXA or placebo. In CRASH-3 there were 2,632 patients with a mild traumatic brain injury who had a GCS score of between 13 and 15 and intracranial bleeding on the CT scan and these patients were the focus of this study. Fatigue was assessed and recorded by a clinician and the analysis plan estimated the risk ratio of being in the extreme fatigue category. In the study 4.2% of patients either died, or experienced extreme fatigue. Extreme fatigue was 0.8% TXA v 1.5% placebo.

This report is well written. It is clearly and accurately presented and easy to understand. The authors adequately address the study limitations (focus on mTBI not prespecified, use of a 3 point scale to measure fatigue, clinician report of fatigue, requirement for a larger adequately powered trial). I have no revisions to suggest.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Prehospital research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.