Colloids versus crystalloids for fluid resuscitation in critically ill patients (Review)

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[Intervention Review]

Colloids versus crystalloids for fluid resuscitation in critically ill patients

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ABSTRACT

Background

Colloid solutions are widely used in fluid resuscitation of critically ill patients. There are several choices of colloid and there is ongoing debate about the relative effectiveness of colloids compared to crystalloid fluids.

Objectives

To assess the effects of colloids compared to crystalloids for fluid resuscitation in critically ill patients.

Search methods

We searched the Cochrane Injuries Group Specialised Register (searched 16 March 2012), the Cochrane Central Register of Controlled Trials 2011, issue 3 (*The Cochrane Library*), MEDLINE (Ovid) 1946 to March 2012, EMBASE (Ovid) 1980 to March 2012, ISI Web of Science: Science Citation Index Expanded (1970 to March 2012), ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to March 2012), PubMed (searched 16 March 2012), www.clinical trials.gov and www.controlled-trials.com. We also searched the bibliographies of relevant studies and review articles.

Selection criteria

Randomised controlled trials (RCTs) of colloids compared to crystalloids, in patients requiring volume replacement. We excluded cross-over trials and trials in pregnant women and neonates.

Data collection and analysis

Two review authors independently extracted data and rated quality of allocation concealment. We analysed trials with a 'double-intervention', such as those comparing colloid in hypertonic crystalloid to isotonic crystalloid, separately. We stratified the analysis according to colloid type and quality of allocation concealment.

Main results

We identified 74 eligible trials; 66 of these presented mortality data.

Colloids compared to crystalloids

Albumin or plasma protein fraction - 24 trials reported data on mortality, including a total of 9920 patients. The pooled risk ratio (RR) from these trials was 1.01 (95% confidence interval (CI) 0.93 to 1.10). When we excluded the trial with poor-quality

allocation concealment, pooled RR was 1.00 (95% CI 0.92 to 1.09). ***Hydroxyethyl starch*** - 21 trials compared hydroxyethyl starch with crystalloids and included 1385 patients. The pooled RR was 1.10 (95% CI 0.91 to 1.32). ***Modified gelatin*** - 11 trials compared modified gelatin with crystalloid and included 506 patients. The pooled RR was 0.91 (95% CI 0.49 to 1.72). (When the trials by Boldt et al were removed from the three preceding analyses, the results were unchanged.) ***Dextran*** - nine trials compared dextran with a crystalloid and included 834 patients. The pooled RR was 1.24 (95% CI 0.94 to 1.65).

Colloids in hypertonic crystalloid compared to isotonic crystalloid

Nine trials compared dextran in hypertonic crystalloid with isotonic crystalloid, including 1985 randomised participants. Pooled RR was 0.91 (95% CI 0.71 to 1.06).

Authors' conclusions

There is no evidence from RCTs that resuscitation with colloids reduces the risk of death, compared to resuscitation with crystalloids, in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and as they are more expensive than crystalloids, it is hard to see how their continued use in these patients can be justified outside the context of RCTs.

PLAIN LANGUAGE SUMMARY

Are colloids more effective than crystalloids in reducing mortality in people who are critically ill or injured?

Trauma, burns or surgery can cause people to lose large amounts of blood. Fluid replacement, giving fluids intravenously (into a vein) to replace lost blood, is used to try to maintain blood pressure and reduce the risk of dying. Blood products, non-blood products or combinations are used, including colloid or crystalloid solutions. Colloids are increasingly used but they are more expensive than crystalloids. This review of trials found no evidence that colloids reduce the risk of dying compared with crystalloids.

BACKGROUND

Fluid resuscitation for hypovolaemia is a mainstay of the medical management of critically ill patients, whether as a result of trauma, burns, major surgery or sepsis. Although some studies (Bickell 1994) have suggested that the timing of volume replacement deserves careful consideration, when it comes to selecting the resuscitation fluid, clinicians are faced with a range of options. At one level the choice is between a colloid or crystalloid solution. Colloids are widely used, having been recommended in a number of resuscitation guidelines and intensive care management algorithms (Armstrong 1994; Vermeulen 1995).

The US Hospital Consortium Guidelines recommend that colloids are used in haemorrhagic shock prior to the availability of blood products, and in non-haemorrhagic shock following an initial crystalloid infusion. However, a 1995 survey of US academic health centres found that the use of colloids far exceeded even the Hospital Consortium recommendations (Yim 1995). Surveys of burn care in the US (Fakhry 1995) and in Australia (Victorian DUAC 1991) found that the use of colloids for resuscitation varied without a set pattern.

The choice of fluid has considerable cost implications. Volume replacement with colloids is considerably more expensive than with crystalloids. Clinical studies have shown that colloids and crystalloids have different effects on a range of important physiological parameters. Because of these differences, all-cause mortality is arguably the most clinically relevant outcome measure in randomised trials comparing the two fluid types.

Why it is important to do this review

Although there have been previous meta-analyses of mortality in randomised trials comparing colloids and crystalloids (Bisonni 1991; Velanovich 1989), neither of these satisfy the criteria that have been proposed for scientific overviews (Oxman 1994), and they predate most of the trials that have been conducted using synthetic colloids, and hypertonic crystalloid solutions. The purpose of this systematic review is to identify and synthesise all available unconfounded evidence of the effect on mortality in critically ill patients of colloids compared to crystalloids for volume replacement.

OBJECTIVES

To assess the effects on mortality of using colloids compared to crystalloids, during fluid resuscitation in critically ill patients.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled trials in which participants were randomised to treatment groups (colloid or control) on the basis of random allocation. As the comparison between fluid type was in terms of effects on mortality, we excluded randomised cross-over trials.

Types of participants

Critically ill patients (excluding neonates and pregnant women) who required volume replacement. We included patients who were critically ill as a result of trauma, burns, undergoing surgery, or had other critical conditions such as complications of sepsis.
We excluded preoperative elective surgical patients.

Types of interventions

We considered the following colloids: dextran 70, hydroxyethyl starches, modified gelatins, albumin or plasma protein fraction.
There is overlap between albumin given for volume replacement and albumin given as a nutritional supplement, and many patients with a critical illness have low serum albumin. Where the trial was of total parenteral nutrition with or without albumin, we excluded it. We included trials where the albumin was given as part of volume replacement guided by colloid osmotic pressure or albumin levels.
The control group received crystalloid (isotonic or hypertonic) for fluid replacement. We included trials in which both groups received blood.
We excluded trials of fluids used for other purposes. For example, we excluded trials of pre-loading in preparation for elective surgery, and trials in patients undergoing fluid loading before cardiopulmonary bypass.

Types of outcome measures

The principal outcome measure was mortality from all causes, assessed at the end of the follow-up period scheduled for each trial.

Search methods for identification of studies

We did not restrict the search for trials by date, language or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched 16 March 2012);
- the Cochrane Central Register of Controlled Trials 2011, issue 3 (*The Cochrane Library*);
- MEDLINE (Ovid) 1946 to March, Week 1, 2012;
- EMBASE (Ovid) 1980 to March 2012;
- ISI Web of Science: Science Citation Index Expanded (1970 to March 2012);
- ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to March 2012);
- PubMed (searched 16 March 2012);
- National Research Register (2006, Issue 4).

All search strategies are listed in full in Appendix 1.

Searching other resources

We searched the reference lists of all relevant papers and published review articles. We also contacted known trialists to identify any further studies that we may have missed. We searched the online trials registers www.clinical trials.gov and www.controlled-trials.com for published and unpublished studies.

Data collection and analysis

The Injuries Group Trials Search Coordinator ran the electronic database searches, collated the results and removed duplicates before passing the list of citations to the lead review author (PP) for screening.

Selection of studies

Two review authors independently examined the list of citations for eligibility. We obtained full-text copies of all relevant records and independently assessed whether each met the pre-defined inclusion criteria. We resolved disagreement by discussion.

Assessment of risk of bias in included studies

We scored allocation concealment as described by Higgins 2011, assigning 'high risk of bias' to poorest quality and 'low risk of bias' to best quality (the presence of solutions in identical containers was only taken to mean adequate concealment if the fluid containers were used sequentially).

- Low risk of bias = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).
- Unclear = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories.
- High risk of bias = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

We collected but did not score information on blinding and loss to follow-up.

Data synthesis

As a result of comments on the previous version of this review, we have stratified trials by type of fluid rather than type of original injury.

We calculated risk ratios (RRs) and 95% confidence intervals (CI) for each study using a fixed-effect model. We then inspected each comparison visually for evidence of heterogeneity and performed a Chi^2 test. If there was no evidence of heterogeneity (visually or with a P value < 0.1) the trials were pooled within each type of fluid, but not combined between type of fluid.

Sensitivity analysis

We then excluded trials with allocation concealment judged as inadequate and repeated the calculations.

The editorial group is aware that a clinical trial by Professor Joachim Boldt has been found to have been fabricated (Boldt 2009). As the editors who revealed this fabrication point out (Reinhart 2011; Shafer 2011), this casts some doubt on the veracity of other studies by the same author. All Cochrane Injuries Group reviews that include studies by this author have therefore been edited to show the results with this author's trials included and excluded. Readers can now judge the potential impact of trials by this author on the conclusions of the review.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

We identified 74 trials meeting the inclusion criteria for study design, participants and interventions. We were able to obtain mortality data for 66 of these. We have reported details of the included trials in the 'Characteristics of included studies' table.

Reasons for exclusion of trials were: the use of a cross-over design, testing a resuscitation algorithm, giving the control group oral fluids, the intervention being directed to the maintenance of serum albumin levels, for haemodilution, for fluid loading and for the reduction of intracranial pressure (see 'Characteristics of excluded studies' table).

Of the 66 trials with data on deaths, the quality of allocation concealment was adequate in 13 trials and unclear in most of the others.

There were 65 comparisons of colloids and crystalloids (add-on colloid), 12 comparisons of colloid in hypertonic crystalloid with isotonic crystalloid and three comparisons of colloid with hypertonic crystalloid.

Risk of bias in included studies

In general, the design of studies was not well reported. This is reflected in the number of unclear scores given for allocation concealment. We also collected information on blinding and loss to follow-up. Blinding was not well reported and loss to follow-up was generally small. The characteristics for each trial are listed in the 'Characteristics of included studies' table.

Effects of interventions

Colloids compared to crystalloids

Albumin or plasma protein fraction

Twenty-four trials reported data on mortality, including a total of 9920 patients. The pooled RR was 1.01 (95% CI 0.93 to 1.10). When trials by Boldt were removed, the results were unchanged (RR 1.01; 95% CI 0.93 to 1.10). When we excluded the trial with poor-quality allocation concealment (Lucas 1978), pooled RR was 1.00 (95% CI 0.92 to 1.09).

Hydroxyethyl starch

Twenty-one trials compared hydroxyethyl starch with crystalloids, including a total of 1385 randomised patients. The pooled RR was 1.10 (95% CI 0.91 to 1.32). When trials by Boldt were removed, the results were unchanged.

Modified gelatin

Eleven trials compared modified gelatin with crystalloid, including a total of 506 randomised patients. The pooled RR was 0.91 (95% CI 0.49 to 1.72). When trials by Boldt were removed, the results were unchanged.

Dextran

Nine trials compared dextran with a crystalloid, including a total of 834 randomised patients. The pooled RR was 1.24 (95% CI 0.94 to 1.65).

Colloids in hypertonic crystalloid compared to isotonic crystalloid

One trial compared albumin and hypertonic saline with isotonic crystalloid. The RR of death was 0.50 (95% CI 0.06 to 4.33). One trial compared 6% hydroxyethyl starch 130/0.4 and hypertonic saline with Ringer's lactate. The RR of death was 0.25 (95% CI 0.03 to 2.15).

Nine trials compared dextran in hypertonic crystalloid with isotonic crystalloid, including 1879 randomised patients. The pooled RR was 0.91 (95% CI 0.79 to 1.06).

Colloids in isotonic crystalloid compared to hypertonic crystalloid

Three trials compared colloids in isotonic crystalloid with hypertonic crystalloid. In two of these, where the colloid was either gelatin or starch, there were no deaths in either group. In the remaining trial, with 38 patients, there was a RR of death of 7.00 (95% CI 0.39 to 126.93) for use of colloid, based on three deaths in the treatment group and none in the control group.

Sensitivity analysis

When all trials authored by Professor Boldt (Boldt 1986; Boldt 1993; Boldt 2001; Lang 2001; Lang 2003) were excluded conclusions remain unchanged.

DISCUSSION

This systematic review synthesises the evidence from RCTs comparing colloid and crystalloid fluid resuscitation across a wide variety of clinical conditions. The review has been updated and extensively revised to take into account the comments made since it was first published. In particular, several commentators pointed out that it is inappropriate to combine effect estimates from studies of different colloids. For example, it was argued that large molecular weight colloids such as hydroxyethyl starch may be better retained in the vascular compartment than albumin and gelatins, and would therefore be more likely to show a favourable effect on mortality (Gosling 1998). In response to these concerns, the review has been stratified by type of colloid. However, the pooled RRs fail to show a mortality benefit for resuscitation with any type of colloid.

There was a trend towards a favourable effect on mortality for colloids in hypertonic crystalloid, compared to isotonic crystalloids. Nevertheless, the results are compatible with the play of chance.

Common to all meta-analyses, this systematic review may have included studies whose interventions and patient characteristics are sufficiently incomparable that the calculation of a summary effect measure may be questioned. The resuscitation regimen differed between trials. Some trials randomised participants to an initial quantity of colloid or crystalloid, and then proceeded with some form of standard resuscitation for all participants. Other trials resuscitated with the allocated fluid to pre-determined end points, either resuscitation end points, or in the case of trauma, until corrective surgery. In addition, the type of colloid or crystalloid, the concentration, and the protocol to determine the quantity of fluid varied. Despite these differences, all participants were in need of volume replacement, and we believe that this variation in the intervention would have an impact on the size of the effect, rather than on its direction.

As regards the effects of albumin versus crystalloid, most of the information (as indicated by the weighting in the meta-analysis) was provided by the SAFE (Saline versus Albumin Fluid Evaluation) trial (SAFE 2004). The SAFE trial used central randomisation with a minimisation algorithm to ensure balance on known potential confounders. Blinding was assured through the use of specially designed masking cartons and specially designed and manufactured administration sets. The trial authors report that the effectiveness of the blinding was confirmed in a formal study before the trial was initiated. In brief, this was a well-conducted, high-quality trial. There were 726 deaths (20.9%) in the albumin-treated group and 729 deaths (21.1%) in the saline-treated group (RR of death 0.99; 95% CI 0.91 to 1.09). Although even this large trial was unable to confirm or refute the possibility of a modest benefit or harm from albumin, it has provided some reassurance that any hazard from albumin, if indeed there is any, is unlikely to be as extreme as was suggested by the results from the previously published (now here updated) meta-analysis of much smaller trials. The pooled RR for death with albumin in this updated meta-analysis is now 1.02 (95% CI 0.93 to 1.11). It is important to note that the effect estimate from the SAFE trial is entirely consistent with the results of previous trials of albumin in hypovolaemia and there is no significant heterogeneity (I^2 = 0%, P = 0.46).

The results of this updated meta-analysis have important policy implications. There is still no evidence that colloids are superior to crystalloids as a treatment for intravascular volume resuscitation in critically ill patients. Importantly, the SAFE trial also provided no evidence of any other clinical advantages from using albumin. It also debunked the belief, from pathophysiological inference, that very large volumes of crystalloid must be administered to reach the same resuscitation end points as can be achieved using much smaller volumes of colloid. In the SAFE trial, the ratio of albumin administered to saline administered was approximately 1:1.4. Col-

loids, in particular albumin, are considerably more expensive than crystalloids, and albumin is a blood product and so carries at least a theoretical infectious disease risk. The economic opportunity cost of ongoing colloid use, particularly albumin use, is likely to be considerable and for this reason its ongoing use in this context is unjustified.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from RCTs that resuscitation with colloids, instead of crystalloids, reduces the risk of death in patients with trauma, burns or following surgery. As colloids are not associated with an improvement in survival, and further, colloids are considerably more expensive than crystalloids, it is hard to see how their continued use outside the context of RCTs in subsets of patients of particular concern, can be justified.

Implications for research

Future trials may need to concentrate on specific subgroups of patients to identify people who may benefit from colloids rather than crystalloids.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Boldt 1986

Methods	RCT, using sealed opaque envelopes Information on allocation concealment was obtained on contact with the authors Blinding and loss to follow-up not mentioned
Participants	55 patients undergoing elective aorta-coronary bypass surgery Exclusion criteria: ejection fraction < 50% and LVEDP > 15 mmHg
Interventions	1. 300 mL 20% Human albumin solution (n = 15) 2. 500 mL 3% HES (n = 13) 3. 500 mL 3.5% Gelatin (n = 14) 4. No colloid (n = 13)
Outcomes	Haemodynamic variables were measured Deaths not reported
Notes	Follow-up until discharge from ICU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Boldt 1993

Methods	RCT, allocation concealment by sealed opaque envelopes (information from author) Blinding and loss to follow-up not mentioned
Participants	75 males undergoing elective aortocoronary bypass grafting, who had a pulmonary capillary WP < 5 mmHg after induction of anaesthesia
Interventions	1. 5% Albumin (n = 15) 2. 6% HES, mean molecular weight 450,000 (n = 15) 3. 6% HES, mean molecular weight 200,000 (n = 15) 4. 3.5% Gelatin (n = 15) 5. No colloid (n = 15) Fluid used through operation and on intensive care postoperatively
Outcomes	Deaths not reported, author confirmed there were no deaths
Notes	Follow-up to 1 day

Boldt 1993 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Boldt 2001

Methods	RCT, using a closed-envelope system
Participants	100 patients undergoing major abdominal surgery
Interventions	1. Ringer's lactate (n = 25) 2. 6% HES, mean molecular weight 200 kDa, degree of substitution 0.5 (n = 25) 3. 6% HES, mean molecular weight 130 kDa, degree of substitution 0.4 (n = 25) 4. 4% Modified fluid gelatin, molecular weight 35 kDa (n = 25)
Outcomes	Deaths Orthostatic problems Haemodynamics and laboratory data Fluid input and output Costs
Notes	Follow-up period unclear

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Boutros 1979

Methods	RCT ("randomly divided"), method of allocation concealment not described Blinding not mentioned No loss to follow-up
Participants	24 people undergoing major operative procedures on the abdominal aorta
Interventions	1. Albumin in 5% dextrose (n = 7) 2. 5% Dextrose and Ringer's lactate (n = 8) 3. 5% Dextrose in 0.45% saline (n = 9) Allocated fluids were used on admission to ICU, following surgery, guided by PAWP. Whole blood also given if clinically needed
Outcomes	Deaths reported

Boutros 1979 (*Continued*)

Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Bowser-Wallace 1986

Methods	Quasi-RCT, allocation by alternation Blinding not mentioned No loss to follow-up	
Participants	Admitted for burns of 30% or more Age range 5 months to 21 years Excluded if already given more than half calculated daily requirement before reaching hospital	
Interventions	1. 2 mL/kg/%burn Ringer's lactate over 24 hours, then 0.5 mL plasmanate/kg/%burn over 24 hours plus 5% dextrose (n = 19) 2. 2 mL/kg/%burn hypertonic lactated saline over 24 hours, then 0.6 mL/kg/%burn hypertonic lactated saline over 24 hours plus oral Haldane's solution (n = 19) IV fluids stopped at 48 hours (n = 19)	
Outcomes	Deaths reported Fluid and electrolytes given, weight, haematocrit	
Notes	Follow-up to 5 days	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Brunkhorst 2008

Methods	Multicentre, RCT Blinding not mentioned Use of a 2 x 2 factorial, open label study design	
Participants	Critically ill patients with severe sepsis or septic shock of at least 18 years of age. Excluded if onset of symptoms commenced > 24 hours before admission to the ICU, if the symptoms commenced > 12 hours after onset in the ICU or if patient had received more than 1000 mL of HES in the 24 hours before randomisation	

Brunkhorst 2008 (*Continued*)

Interventions		
Outcomes	Deaths reported at 28 and 90 days. 90-day mortality rate was cited as it marked the end of the follow-up period	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Bulger 2011

Methods	Double-blind RCT	
Participants	15 years or older with hypovolaemic shock (< 70 mmHg SBP or SBP 71 mmHg to < 90 mmHg and HR < 108 bpm	
Interventions	1. 7.5% saline per 6% dextran (n = 220) 2. 0.9% saline (n = 376)	
Outcomes	Primary outcome: 28-day survival Secondary outcomes: fluid and blood requirements, ARDS, MODS and nosocomial infections	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	All care providers, investigators and patients remained blinded to the treatment assignment

Chavez-Negrete 1991

Methods	RCT, allocation by "random numbers" Blinding not mentioned No loss to follow-up
Participants	Adults admitted to an emergency department with acute GI haemorrhage, SBP $\leq$ 90 mmHg for up to 1 hour and normal ECG Excluded if pregnant or had renal, cardiac or neurological disease

Chavez-Negrete 1991 (*Continued*)

Interventions	1. Initial infusion of 250 mL 7.5% saline/6% dextran 60 given IV (16 patients) or intraosseous (n = 10) 2. Initial IV infusion of 250 mL Ringer's lactate (n = 23) Resuscitation continued with red cells, 0.9% saline and dextran 40 according to clinical judgement
Outcomes	Death Haemodynamic variables
Notes	Follow-up to 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Cifra 2003

Methods	Quasi-RCT (allocation by alternation), allocation concealment not reported Blinding not reported No loss to follow-up
Participants	27 children with dengue shock syndrome Exclusion criteria included: other severe infection, protein-deficient abnormalities, bleeding diathesis, patients who have been given multiple plasma substitutes
Interventions	1. 6% Haes-Steril (n = 11) 2. Ringer's lactate (n = 16) 1 patient from group 1 and 3 patients from group 2 were excluded because they needed inotropic support and multiple plasma substitute
Outcomes	Duration of control of shock Recurrence of shock Length of ICU stay Death not reported as an outcome but they reported that 4 patients died
Notes	Length of follow-up not reported but all outcomes were in hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not used

Cooper 2006

Methods	Multicentre unblinded controlled trial with stratified block randomisation by centre and mortality prediction at enrolment
Participants	Patients with cutaneous thermal burns of at least 20% TBSA within 12 hours of injury
Interventions	1. Ringer lactate and 5% albumin (n = 19) 2. Ringer lactate (n = 23)
Outcomes	Primary outcome was MODS Mortality was reported
Notes	The trial was suspended due to slow enrolment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Patients were allocated to study groups with stratified randomisation with a computer-generated randomisation list and sequentially numbered sealed, opaque envelopes

Dawidson 1991

Methods	RCT, allocation by drawing a card from a deck Blinding not mentioned No loss to follow-up
Participants	Adults undergoing elective abdominal aortic surgery No exclusions mentioned
Interventions	1. 3% Dextran 70 in Ringer's lactate (n = 10) 2. IV Ringer's lactate (n = 10) Fluid used during and for 24 hours after operation, guided by haemodynamic variables
Outcomes	Death Volume transfused, weight change, haemodynamic variables
Notes	Follow-up to discharge from hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate

Dehne 2001

Methods	RCT, allocation by sealed envelope assignment
Participants	60 male patients (of ASA physical status 1 or 2) scheduled for middle ear surgery
Interventions	1. Ringer's lactate solution (n = 15) 2. 6% HES: molecular weight 200 kDa, degree of substitution 0.5 (n = 15) 3. 6% HES: molecular weight 200 kDa, degree of substitution 0.60 to 0.66 (n = 15) 4. 6% HES: molecular weight 450 kDa, degree of substitution 0.7 (n = 15)
Outcomes	Deaths not stated but 'all' patients discharged 10 to 14 days after surgery; therefore no deaths Central venous pressure Urine output Blood osmolality Urine osmolality
Notes	Follow-up 2 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Du 2011

Methods	Randomised controlled study
Participants	Participants had confirmed diagnosis of severe acute pancreatitis. Patients were included within 72 hours after the onset of symptoms
Interventions	1. 6% HES 130/0.4 (n = 20) 2. Ringer's lactate (n = 21)
Outcomes	Primary outcome was intra-abdominal pressure. They also reported in-hospital mortality, organ complications, inflammatory markers and fluid requirement
Notes	Patients were excluded if they died within 72 hours after admission

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Dubin 2010

Methods	RCT	
Participants	Patients with severe sepsis	
Interventions	1. 6% HES 130/0.4 (n = 12) 2. Normal saline (n = 13)	
Outcomes	Sublingual microcirculation	
Notes	Data on mortality are not clear from the report	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	sealed enveloped were used

Eleftheriadis 1995

Methods	Patients "randomizedly distributed" Blinding not mentioned Unable to assess loss to follow-up	
Participants	Participants were undergoing coronary artery bypass surgery	
Interventions	1. 6% HES 2. 3.5% Gelatin 3. Ringer's lactate Allocated fluid was used in the postoperative period only guided by mean arterial pressure	
Outcomes	Deaths were not reported Haemodynamic variables	
Notes	Follow-up period unspecified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Ernest 1999

Methods	RCT, allocation concealment not described No blinding No loss to follow-up mentioned	
Participants	Patients with a clinical diagnosis of sepsis	
Interventions	1. 5% Albumin (n = 9) 2. 0.9% Saline (n = 9) Volume of infusion guided by PAWP	
Outcomes	Haemodynamic variables and volume measurements Deaths not reported	
Notes	Follow-up to immediately after infusion	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Evans 1996

Methods	Quasi-randomised trial, allocation by day of the week Blinding not mentioned No loss to follow-up	
Participants	Aged ≥ 16 years, admitted with trauma to an emergency centre within 2 hours after injury, only crystalloid as a pre-hospital infusion Excluded if had underlying illness likely to affect clotting	
Interventions	1. IV Haemaccel (n = 11) 2. IV Ringer's lactate (n = 14) Fluid was used until vital signs were stable	
Outcomes	Deaths from author Clotting variables	
Notes	Follow-up period unspecified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Evans 2003

Methods	RCT, allocation concealment not reported Blinding methods not reported Loss to follow-up not reported
Participants	55 patients undergoing primary unilateral total hip replacement Exclusion criteria: pre-existing defect in platelet function or on aspirin that could not be stopped for 2 weeks prior to the operation
Interventions	1. 4.5% Albumin (n = 13) 2. Gelofusine (n = 14) 3. Haemaccel (n = 14) 4. 0.9% Saline (n = 14)
Outcomes	Haemostatic parameters Death not reported
Notes	Length of follow-up not reported but all outcomes were in-hospital

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Fries 2004

Methods	RCT, patients "randomly" received crystalloid or colloids Method of allocation concealment not reported Blinding not reported Loss to follow-up not reported
Participants	60 patients undergoing knee replacement surgery Exclusion criteria: contraindication for regional anaesthesia, known allergies or haemostatic disorders
Interventions	1. HES (n = 20) 2. Modified gelatin (n = 20) 3. Ringer's solution (n = 20) Groups 1 and 2 also received a basis of Ringer's solution infusion
Outcomes	Coagulation parameters Death not reported
Notes	Length of follow-up not reported but all outcomes were in-hospital measures

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Allocation concealment (selection bias)	Unclear risk	Unclear

Gallagher 1985

Methods	RCT, method of allocation concealment not described. Author contacted - allocation concealment by computerised system - patient details were entered before treatment assignment was revealed Blinding not mentioned No loss to follow-up
Participants	Patients after coronary artery bypass graft surgery Exclusion criteria: patients with significant left main coronary artery stenosis, poor left ventricular function or poor pulmonary function
Interventions	1. IV 5% albumin (n = 5) 2. IV 6% HES (n = 5) 3. IV Ringer's lactate (n = 5) Fluid used from admission to ICU post operation, guided by PAWP. RBC given if needed
Outcomes	Deaths were not reported. Author contacted and confirmed that there were no deaths in any group Haemodynamic data
Notes	Follow-up to 1 day

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Goodwin 1983

Methods	RCT, assigned by "random numbers table", method of allocation concealment unclear Blinding not mentioned No loss to follow-up
Participants	79 previously healthy young adults admitted with burns No exclusion criteria reported
Interventions	1. 2.5% Albumin in Ringer's lactate (n = 40) 2. Ringer's lactate (n = 39) Fluids on day 1 guided by haemodynamic variable. On day 2, given at 0.3 to 0.5 mL/kg/%burn, then 5% dextrose

Goodwin 1983 (*Continued*)

Outcomes	Deaths reported Pulmonary oedema Infections	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Grundmann 1982

Methods	RCT, method of allocation concealment unclear Blinding not mentioned No loss to follow-up	
Participants	20 people undergoing partial gastrectomy The average age was 50 years (range 19 to 84 years) No exclusion criteria reported	
Interventions	1. Colloid group received human albumin solution (n = 14) 2. Details of crystalloid were not reported (n = 6) Allocated fluid was continued for 4 days after operation	
Outcomes	Deaths reported Volumes of fluid given Haemodynamic variables	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Guo 2003

Methods	RCT, allocation concealment not reported Blinding not reported No loss to follow-up reported	
Participants	42 patients undergoing elective cytoreductive surgery for ovarian cancer Exclusion criteria: preoperative anaemia, allergic response to HES or perioperative administration of cardiovascular agents	

Guo 2003 (*Continued*)

	2 patients randomised but excluded because of use of cardiovascular agents	
Interventions	1. Ringer's lactate (n = 20) 2. 6% HES (n = 20)	
Outcomes	Splanchnic perfusion Death not reported but in results authors mentioned that "all patients were discharged"	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Hall 1978

Methods	Quasi-RCT (participants were stratified by age, extent of burn and aetiology, and then allocated by alternation) Blinding not mentioned No loss to follow-up	
Participants	Burns covering > 10% of the body surface (for children), and > 15% of the body surface (for adults) No exclusions mentioned	
Interventions	1. 120 mL/%burn IV 6% dextran 70 in 0.9% saline over 48 hours plus oral water or IV 5% dextrose for 'metabolic requirements' (n = 86) 2. 4 mL/kg/%burn IV Ringer's lactate over 24 hours, then 10% of initial body weight of fluid over 24 hours plus oral water (n = 86)	
Outcomes	Death Fluid given, haemodynamic variables	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Hartmann 1993

Methods	RCT, method of allocation unclear Blinding not mentioned No loss to follow-up
Participants	Adults undergoing major abdominal surgery Exclusion criteria: cardiorespiratory dysfunction, uraemia, diabetes, taking steroids, anticoagulants or diuretics
Interventions	1. IV Dextran 70 in saline (concentration not given) with 2.5% dextrose (n = 15) 2. IV Saline (concentration not given) with 2.5% dextrose (n = 14) Both groups given red cells, plasma, dextran 70 and crystalloids during the operation as decided by the clinician. Postoperative fluids according to the trial group guided by tissue oxygen tension to the end of resuscitation
Outcomes	Death not reported Fluid given, haemodynamic variables
Notes	Follow-up to 7 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

James 2011

Methods	RCT Double-blind
Participants	Patients with blunt or penetrating trauma requiring more than 3 L volume resuscitation (blunt and penetrating trauma patients were randomised separately)
Interventions	1. HES 130/0.4, penetrating trauma (n = 36) 2. 0.9% Saline, penetrating trauma (n = 34) 3. HES 130/0.4, blunt trauma (n = 22) 4. 0.9% Saline, blunt trauma (n = 23)
Outcomes	Primary outcomes were the volumes of first fluid needed in the first 24 hours, and normal GI function by day 5
Notes	Although mortality at 30 days was a safety measure, the authors did not report data on mortality for each group

Risk of bias

Bias	Authors' judgement	Support for judgement

James 2011 (*Continued*)

Allocation concealment (selection bias)	Low risk	Plastic bags with concealed label were randomly selected and placed sequentially in a warming cabinet

Jelenko 1978

Methods	RCT, method of allocation concealment unclear Blinding not mentioned No loss to follow-up
Participants	19 people with burns covering more than 20% of body surface
Interventions	1. 12.5% Albumin in hypertonic saline (240 mEq/L sodium, 120 mEq/L chloride, 120 mEq/L lactate) (n = 7) 2. Hypertonic saline (240 mEq/L sodium, 120 mEq/L chloride, 120 mEq/L lactate) (n = 5) 3. Ringer's lactate (n = 7) Allocated fluid was used, guided by haemodynamic variables, to the end of resuscitation
Outcomes	Deaths reported Haemodynamic variables
Notes	Follow-up to end of resuscitation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Karanko 1987

Methods	RCT, description of allocation procedure unclear Blinding not mentioned No loss to follow-up
Participants	32 adult men scheduled for coronary artery bypass surgery Exclusion criteria: LVEF < 40%, abnormal lung function
Interventions	1. 6% Dextran 70 (n = 14) 2. Ringer's lactate (n = 18) Allocated fluid was used to the end of resuscitation
Outcomes	Deaths reported Haemodynamic variables Pulmonary oedema

Karanko 1987 (*Continued*)

Notes	Follow-up 2 weeks	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Lang 2001

Methods	RCT, using a closed-envelope system	
Participants	42 patients scheduled for elective major abdominal surgery	
Interventions	1. Ringer's lactate (n = 21) 2. 6% HES, molecular weight 139 kDa, degree of substitution 0.4 (n = 21)	
Outcomes	Deaths Haemodynamics and laboratory data Tissue oxygenation Volume input and output	
Notes	Follow-up period unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Lang 2003

Methods	RCT, allocation concealment not clearly reported ("closed envelope system") Blinding method not reported ("...treatment in the ICU was performed by physicians who were blinded to the study")
Participants	36 patients undergoing elective major abdominal surgery Exclusion criteria: myocardial failure, renal insufficiency, severe pulmonary disease, liver dysfunction, diabetes mellitus, steroid therapy, pre-existing viral or bacterial infection and known allergic reactions to starch preparations
Interventions	1. 6% HES (n = 18) 2. Ringer's lactate (n = 18) Additional crystalloid solutions were supplied to equalise insensible fluid loss or as a solvent for drugs in group 1

Lang 2003 (*Continued*)

Outcomes	Pro- and anti-inflammatory cytokines All patients survived	
Notes	Length of follow-up not reported but all outcomes were in-hospital measures	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Ley 1990

Methods	RCT, method of allocation concealment unclear Assessment of chest x-ray blinded No loss to follow-up	
Participants	21 people undergoing coronary artery bypass grafting or valve surgery	
Interventions	1. 6% Hetastarch up to 1.5 L then 5% plasma protein fraction (n = 11) 2. 0.9% Saline (n = 10) Allocated fluid was used for postoperative fluid resuscitation	
Outcomes	Deaths were not reported Pulmonary and peripheral oedema Haemodynamic variables	
Notes	Follow-up to discharge	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Lowe 1977

Methods	RCT, allocation by sealed envelopes Blinding not mentioned No loss to follow-up	
Participants	Participants with serious trauma	
Interventions	1. 25% Albumin in Ringer's lactate (n = 77) 2. Ringer's lactate (n = 94) Allocated fluid was used throughout the pre- and intraoperative period	

Lowe 1977 (*Continued*)

Outcomes	Deaths reported	
Notes	Follow-up to 5 days postoperatively. Data on the 30 participants with chest injuries who were left out of the Lowe 1977 report, but included in Moss 1981, have been included in the meta-analysis	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Lu 2012

Methods	Randomised controlled study	
Participants	42 patients with septic shock	
Interventions	1. Ringer's lactate (n = 20) 2. HES 130/0.4 (n = 22)	
Outcomes	Mortality, fluid replacement, use of vasoactive drugs and inflammatory markers	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Lucas 1978

Methods	RCT, randomisation was based on the last digit of each patient's case number
Participants	52 seriously injured patients
Interventions	1. Standard resuscitation regimen ('balanced electrolyte', blood, fresh frozen plasma) plus salt-poor albumin, maximum 150 g during surgery and 150 g/day for the next 5 days (n = 27) 2. Standard resuscitation regimen as above (n = 25)
Outcomes	Deaths reported in some patients
Notes	In the final report of 94 randomised patients deaths were not reported. However, in this preliminary report of 52 injured patients deaths were reported

Lucas 1978 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Maitland 2005

Methods	RCT, open label, random allocation was assigned by the use of sealed cards No loss to follow-up
Participants	159 children with severe malaria and metabolic acidosis Exclusion criteria: pulmonary oedema, oedematous malnutrition or papilloedema
Interventions	Severe acidosis 1. 4.5% Albumin (n = 23) 2. 0.9% Saline (n = 26) Moderate acidosis 1. 4.5% Albumin (n = 33) 2. 0.9% Saline (n = 35) 3. Control (n = 33)
Outcomes	Reduction in base deficit Neurological sequelae Death reported
Notes	Length of follow-up not reported but all outcomes were in-hospital measures

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Maitland 2011

Methods	2 stratum multicentre open, RCT
Participants	Children aged between 60 days and 12 years, with severe febrile illness, randomly assigned within 2 strata (stratum A was children with severe febrile illness and impaired perfusion but without severe hypotension; stratum B was children with severe hypotension)
Interventions	Children were randomly allocated to rapid volume replacement over the course of 1 hour with either: 1. 20 mL 5% Human albumin solution per kg body weight (n = 1063) 2. 20 mL 0.9% Saline solution per kg body weight (n = 1063)

Maitland 2011 (*Continued*)

Outcomes	Mortality at 4 weeks after randomisation	
Notes	Children (n = 1044) assigned to no treatment were not included in the analysis	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Trial numbers kept inside opaque, sealed envelopes. Opened in numerical order by clinician

Mattox 1991

Methods	Quasi-randomised, allocation by alternation Double-blind 2 patients excluded from the analysis as code of fluid lost	
Participants	Participants were pre-hospital trauma victims attended to by emergency personnel within 1 hour of injury, with SBP $\leq$ 90 mmHg, $\geq$ 16 years. 72% of participants had sustained penetrating trauma	
Interventions	1. 250 mL Dextran 70 in 7.5% saline (n = 211) 2. 250 mL Ringer's lactate, saline or plasmalyte (n = 211) Allocated fluid was for initial pre-hospital resuscitation only	
Outcomes	Deaths reported	
Notes	Follow-up to hospital discharge or transfer	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Mazher 1998

Methods	Patients "randomized" Blinding of carers by use of pharmacy-prepared solutions No loss to follow-up
Participants	Patients undergoing elective coronary artery surgery Exclusion criteria: age > 75 years, ejection fraction < 35%, creatinine > 135 μmol/L, ACE inhibitors

Mazher 1998 (*Continued*)

Interventions	1. 5 mL/kg Polygeline (n = 10) 2. 5 mL/kg 7.2% Saline (n = 10) Allocated fluid given postoperatively over 1 hour. All patients subsequently receive polygeline and RBCs
Outcomes	Haemodynamic variables Death
Notes	Follow-up to discharge from ICU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

McIntyre 2008

Methods	A feasibility RCT
Participants	Patients with early septic shock defined with at least 2 systemic inflammatory response syndrome criteria, infectious source and persistent hypotension after > 1 L of crystalloid fluid
Interventions	1. Normal saline (n = 19) 2. Pentastarch (n = 21)
Outcomes	Primary outcomes were feasibility measures for the pilot RCT. ICU and 28-day mortality were also reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Only the designated research pharmacist at each institution was aware of the treatment allocation for individual patients. Study fluids were prepared and blinded ahead of time by the site research pharmacist

McNulty 1993

Methods	RCT, method of allocation concealment not described Blinding not mentioned No loss to follow-up
Participants	Patients following elective cardiopulmonary bypass
Interventions	1. 5% Albumin and cell-saved blood (n = 14) 2. Plasmalyte and cell-saved blood (n = 14) Allocated fluid used as part of fluid volume replacement
Outcomes	Deaths not reported Study was designed to look at the effect of protein infusion on the accuracy of a haematocrit measuring device
Notes	Length of follow-up unspecified

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Metildi 1984

Methods	RCT Blinding not mentioned No loss to follow-up
Participants	Participants were admissions to an ICU and a trauma unit with ARDS and established pulmonary failure. Included both trauma and non-trauma patients
Interventions	1. 5% Salt-poor albumin (n = 20) 2. Ringer's lactate (n = 26) Allocated fluid was used throughout resuscitation, and if an operation was required the allocated fluid was used for volume replacement before and during the operation
Outcomes	Deaths reported Haemodynamic variables
Notes	Follow-up to discharge

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Modig 1983

Methods	Quasi-RCT, allocation by admission date Blinding not mentioned No loss to follow-up
Participants	Participants were trauma admissions to an emergency department with SBP < 70 mmHg. Age range 20 to 58 years
Interventions	1. Dextran 70 in Ringer's lactate (n = 12) 2. Ringer's lactate (n = 11) Allocated fluids were given as the initial resuscitation fluid on admission to the emergency department, and continued as needed until after the 6th day when major reconstructive surgery was undertaken
Outcomes	Deaths reported Development of ARDS
Notes	Follow-up to definitive reconstructive surgery

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate

Moretti 2003

Methods	RCT, allocation concealment method not clearly reported ("Patients randomized...by using a closed-envelope technique") Blinding method not clearly reported ("Researchers were unaware of the patient's randomization") No loss to follow-up
Participants	90 adult patients undergoing major elective general, gynaecological, orthopaedic or urological surgery with an anticipated blood loss > 500 mL Exclusion criteria: age < 16 years, coagulopathy, renal or hepatic dysfunction and congestive heart failure
Interventions	1. Hetastarch-normal saline (n = 30) 2. Hetastarch-balanced salt (n = 30) 3. Ringer's lactate (n = 30)
Outcomes	Postoperative nausea and vomiting Death not reported
Notes	Follow-up to discharge

Risk of bias

Moretti 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Nagy 1993

Methods	RCT, contact with author showed it was an open-label study Blinding not mentioned No loss to follow-up
Participants	Participants were adult admissions to a trauma unit, with measurable SBP < 90 mmHg
Interventions	1. Pentastarch in 0.9% saline (n = 21) 2. Ringer's lactate (n = 20) Allocated fluid was used throughout resuscitation with the exception that colloid patients received a maximum 4 L of pentastarch, after which Ringer's lactate was given
Outcomes	Deaths were not reported Haemodynamic variables
Notes	Follow-up to discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate

Ngo 2001

Methods	RCT, opaque envelopes containing only treatment pack number
Participants	230 children with dengue shock syndrome
Interventions	1. Dextran 70 (n = 55) 2. 3% Gelatin (n = 56) 3. Ringer's lactate (n = 55) 4. 'Normal' saline (n = 56)
Outcomes	Initial pulse recovery time Occurrence of timing and subsequent episodes of shock Decrease in haematocrit Volume of fluid administered until recovery Complications No deaths in any group

Ngo 2001 (*Continued*)

Notes	Follow-up period unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Nielsen 1985

Methods	RCT, method of allocation concealment not described Blinding not mentioned No loss to follow-up	
Participants	26 patients admitted for reconstructive surgery of the abdominal aorta	
Interventions	1. Whole blood, crystalloid plus 80 g albumin on the day of the operation, and 20 g/day for the next 3 days. Albumin given as 100 mL 20% human albumin solution (n = 13) 2. Whole blood and crystalloid, type not specified (n = 13)	
Outcomes	Deaths not reported Author when contacted confirmed that there were no deaths in either group	
Notes	Length of follow-up 4 days	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Pockaj 1994

Methods	RCT, allocation concealment unclear Blinding not mentioned Loss to follow-up: 18/54 in colloid group, 13/53 in saline group	
Participants	Participants required fluid resuscitation as a result of vascular leak syndrome associated with interleukin-2 therapy for metastatic cancer	
Interventions	1. 250 mL Bolus of 5% albumin in saline (n = 36 reported) 2. 250 mL Bolus of 0.9% normal saline (n = 40 reported) Boluses guided by haemodynamic variables. Both groups also received 0.45% saline with 10 mmol/L KCl	

Pockaj 1994 (*Continued*)

Outcomes	Deaths Toxic effects of chemotherapy Haemodynamic variables
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Prien 1990

Methods	RCT Blinding not mentioned No loss to follow-up
Participants	Participants were undergoing modified Whipple's operation
Interventions	1. 10% HES in 0.9% saline plus plasma protein fraction if requirements > 20 mL/kg (n = 6) 2. 20% human albumin solution (n = 6) 3. Ringer's lactate (n = 6) Allocated fluid was administered intraoperatively only
Outcomes	Deaths Intestinal oedema formation
Notes	Follow-up period was unspecified

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Rackow 1983

Methods	RCT, allocation concealment unclear Blinding not mentioned No loss to follow-up
Participants	Participants were aged 54 to 97 years, and had any 1 of the following pre-determined indicators of shock: SBP $\leq$ 90 mmHg, cardiac index < 2.2 L/minute/m^2, serum arterial lactate > 18 mg/dL and WP < 15 mmHg

Rackow 1983 (*Continued*)

Interventions	1. 6% HES (n = 9) 2. 5% Albumin (n = 9) 3. 0.9% Saline (n = 8) Allocated fluid was given as needed until the end of resuscitation	
Outcomes	Deaths reported Fluid balance	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Rocha e Silva 1994

Methods	RCT	
Participants	Participants were admissions to the emergency department, with SBP $\leq$ 90 mmHg and $\geq$ 16 years of age	
Interventions	1. 6% Dextran 70 in 7.5% saline 2. Ringer's lactate Allocated fluid was used for the first IV infusion only	
Outcomes	Death was the main outcome measure, but the data are unpublished	
Notes	Follow-up to 30 days. By April 1994, 125 patients had been entered into the study	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

SAFE 2004

Methods	RCT. Randomisation by minimisation algorithm accessed through secure website
Participants	Patients aged $\geq$ 18 years admitted to closed multidisciplinary ICUs in 16 tertiary hospitals in Australia over 19-month period
Interventions	1. 4% Albumin (Albumex, CSL) (n = 3499) 2. Normal saline (n = 3501)

SAFE 2004 (*Continued*)

Outcomes	Death Patients with new single- or multiple-organ failure Mean number of days: in ICU, in hospital, on mechanical ventilation, on renal replacement therapy	
Notes	Follow-up to 28 days	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Shah 1977

Methods	RCT, allocation by sealed envelope Blinding not mentioned No loss to follow-up	
Participants	Patients with severe, multiple trauma and SBP < 90 mmHg. All patients were adults and both sexes were included	
Interventions	1. 5% Salt-poor albumin in Ringer's lactate (n = 9) 2. Ringer's lactate (n = 11) Volume infused guided by physiological parameters	
Outcomes	Death reported Haemodynamic variables	
Notes	Length of follow-up not stated	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Shires 1983

Methods	Patients 'assigned randomly' Blinding not mentioned No loss to follow-up	
Participants	People undergoing aortic reconstruction surgery No exclusion criteria mentioned	

Shires 1983 (*Continued*)

Interventions	1. Plasmanate (n = 9) 2. Ringer's lactate (n = 9) Allocated fluid used guided by haemodynamic variables until the first postoperative morning. All patients then received 0.45% saline	
Outcomes	Pulmonary oedema Haemodynamic variables Death	
Notes	Follow-up to 2 days postoperative	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Sirieix 1999

Methods	Patients "randomly assigned" Blinding not described 2 patients excluded after randomisation due to arrhythmias on giving the fluid (both in hypertonic saline group)	
Participants	Patients undergoing mitral valve repair Exclusion criteria: LVEF < 0.4, systolic PAP > 50 mmHg, coagulation disorders, creatinine > 150 mmoL/L, electrolyte imbalance, diabetes, previous atrial fibrillation lasting > 1 year	
Interventions	1. 250 mL 7.2% Hypertonic saline, 6% HES (n = 8) 2. 250 mL 7.2% Hypertonic saline (n = 10) 3. 250 mL 6% HES (n = 8) Fluid given over 15 minutes, 1 hour after admission to postoperative ICU	
Outcomes	Haemodynamic variables Deaths reported Side effects (severe hypotension: 1 patient in group 1 and 2 patients in group 2; arrhythmias: 1 patient in group 1, 3 patients in group 2 and 1 patient in group 3)	
Notes	Follow-up to discharge from hospital (all within 10 days)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Skillman 1975

Methods	RCT, allocation concealment unclear Blinding not mentioned No loss to follow-up
Participants	Participants were undergoing elective abdominal reconstructive surgery
Interventions	1. 25% Salt-poor albumin 1 g/kg and 5% albumin 1 L (n = 7) 2. Ringer's lactate Allocated fluid was given intraoperatively. All patients received crystalloids only for pre-loading before surgery
Outcomes	Deaths were not reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Tollofsrud 1995

Methods	RCT, allocation by sealed envelopes Blinding not mentioned No loss to follow-up
Participants	Participants were adults in need of volume replacement during and after coronary artery bypass surgery
Interventions	1. Haemaccel (n = 10) 2. Dextran 70 (n = 10) 3. Albumin 40 (n = 10) 4. Ringer's lactate (n = 10) Allocated fluid was used throughout resuscitation
Outcomes	Deaths reported Fluid balance
Notes	Follow-up to 48 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Tollofsrud 1998

Methods	RCT, allocation by sealed envelope Described as double blind No loss to follow-up mentioned
Participants	Patients with 3 vessel coronary artery disease undergoing elective coronary artery surgery Exclusion criteria: LVEF < 0.4, ventricular aneurysm, significant arrhythmia, diabetes, renal failure, lung disease
Interventions	1. 4 mL/kg of 75 mg/mL hypertonic saline in dextran 70 60 mg/mL over 30 minutes (n = 10) 2. Same volume and rate of isotonic saline (n = 10) Fluid given just after surgery while still in operating theatre. Ringer's lactate for additional fluid
Outcomes	Fluid balance Haemodynamic variables Deaths not reported
Notes	Follow-up to 48 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Upadhyay 2004

Methods	Open-label randomised trial, allocation by sealed envelope No loss to follow-up mentioned
Participants	60 patients with septic shock aged 1 month to 12 years Exclusion criteria: age < 1 month, multiorgan failure and immunodeficiency states
Interventions	1. Normal saline (n = 31) 2. Polymer from degraded gelatin in saline (n = 29)
Outcomes	Haemodynamic data Death reported
Notes	Length of follow-up not reported but all outcomes were in-hospital measures

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Vassar 1990

Methods	RCT, allocation concealment unclear Double-blind study (solutions prepared in identical containers) No loss to follow-up
Participants	Participants were emergency department admissions with trauma and SBP < 80 mmHg and ≥ 18 years of age Exclusion criteria: pregnant women and people with pre-existing cardiac, hepatic or renal disease
Interventions	1. 6% Dextran 70 in 7.5% saline (n = 23) 2. Ringer's lactate (n = 24) Allocated fluids were given as the initial resuscitation in the emergency department. Additional isotonic crystalloids (Ringer's lactate) were given as needed
Outcomes	Deaths reported Haemodynamic variables
Notes	Follow-up to hospital discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Vassar 1991

Methods	RCT, allocation by randomised sequence of coded containers Double-blind study No loss to follow-up
Participants	Participants were pre-hospital trauma cases undergoing helicopter transport to an emergency centre, with SBP ≤ 100 mmHg and ≥ 18 years Exclusion criteria: pre-existing cardiac renal, hepatic or neurological disease; peripheral oedema
Interventions	1. 4.2% Dextran 70 in 7.5% saline or 6% dextran 70 in 7.5% saline (n = 83) 2. Ringer's lactate (n = 83) Fluids were given as the initial resuscitation fluid in the pre-hospital setting. Supplemental isotonic fluids were given at the discretion of the flight nurses
Outcomes	Deaths reported Haemodynamic variables
Notes	Follow-up to discharge. Allocation was to 4.2% dextran 70, to 6% dextran 70, or to crystalloid; for the calculation of the summary effect measure, the 2 dextran groups were combined

Vassar 1991 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Vassar 1993a

Methods	RCT, allocation concealed by random sequence of identical containers Double-blind study 36 people excluded post randomisation as deemed not to have met eligibility criteria No loss to follow-up
Participants	Participants, who were undergoing ambulance transport to an emergency centre, SBP $\leq$ 90 mmHg, $\geq$ 18 years Exclusion criteria: asystolic; undergoing CPR; lack sinus complex on ECG; > 2 hours after trauma; pregnant; pre-existing seizures; bleeding disorder; hepatic, cardiac or renal disease
Interventions	1. 6% Dextran 70 in 7.5% saline (n = 89) 2. 7.5% Saline (n = 85) 3. 0.9% Saline (n = 84) Participants received 250 mL of the allocated fluid in the pre-hospital setting. Additional isotonic crystalloids were given as needed
Outcomes	Deaths reported Haemodynamic variables Trauma scores
Notes	Follow-up was to discharge from hospital

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Vassar 1993b

Methods	RCT, allocation concealed by sequential use of coded identical containers Double-blind study 39/233 patients excluded as deemed not to meet eligibility criteria, unclear from which groups
Participants	Participants were pre-hospital trauma cases undergoing helicopter transport to an emergency centre, SBP $\leq$ 100 mmHg, $\geq$ 18 years Exclusion criteria: asystolic; undergoing CPR; lack sinus complex on ECG; > 2 hours after trauma; pregnant; pre-existing seizures; bleeding disorder; hepatic, cardiac or renal disease

Vassar 1993b (*Continued*)

Interventions	1. 12% Dextran 70 in 7.5% saline (n = 49) 2. 6% Dextran 70 in 7.5% saline (n = 50) 3. 7.5% Saline (n = 50) 4. Ringer's lactate (n = 45) Participants received 250 mL of the allocated fluid in the pre-hospital setting. Additional isotonic crystalloids were given as needed	
Outcomes	Deaths reported Haemodynamic variables Trauma scores and neurological outcome scores	
Notes	Follow-up to hospital discharge	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate

Verheij 2006

Methods	RCT, allocation concealment by "the sealed envelope method" Blinding method not reported No loss to follow-up	
Participants	67 patients with presumed hypovolaemia after cardiac and major vascular surgery Exclusion criteria: age > 79 years and known anaphylactoid reaction to colloids	
Interventions	1. Saline (n = 16) 2. Gelatin (n = 16) 3. HES (n = 16) 4. Albumin (n = 16)	
Outcomes	Haemodynamic data Death not reported	
Notes	Length of follow-up not reported but all outcomes were in-hospital measures	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Virgilio 1979

Methods	Allocation "by random number" Blinding not mentioned No loss to follow-up
Participants	Participants were undergoing abdominal aortic surgery
Interventions	1. 5% Albumin (n = 15) 2. Ringer's lactate (n = 14) Allocated fluid was used during operation for maintenance of pre-defined physiological parameters, and the resuscitation was continued with the allocated fluid until the day following the operation. This was followed by 5% dextrose in half-normal saline, with potassium chloride as needed
Outcomes	Deaths reported
Notes	Follow-up 2.5 weeks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Wahba 1996

Methods	Patients "randomly allocated" Blinding not mentioned 2 patients excluded as they required reoperation for bleeding
Participants	22 adults in need of volume replacement following coronary artery bypass surgery Exclusion criteria: abnormal left ventricular function, platelet active medication or heparin
Interventions	1. Haemaccel (n = 10) 2. Ringer's lactate (n = 10) Allocated fluid was used from the time of admission to ICU following operation, to the end of resuscitation
Outcomes	Deaths reported Pulmonary oedema
Notes	Follow-up to discharge

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Wills 2005

Methods	RCT, allocation concealed by specially prepared cardboard containers Method of blinding not mentioned No loss to follow-up
Participants	512 children with dengue shock syndrome aged 2 to 15 years
Interventions	Children with immoderately severe shock were randomised to the 3 interventions 1. Ringer's lactate (n = 128) 2. 6% Dextran 70 (n = 126) 3. 6% HES 200/0.5 (n = 129) Children with severe shock were randomised only to either of the 2 colloids interventions: 1. 6% Dextran 70 (n = 67) 2. 6% HES 200/0.5 (n = 62)
Outcomes	Requirement for supplemental intervention with rescue colloid Time taken to achieve initial cardiovascular stability Time taken to achieve sustained cardiovascular stability Volume required Change in haematocrit Days in hospital 1 death reported but not specified in which group
Notes	Length of follow-up not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate

Woittiez 1997

Methods	RCT, allocation concealment by sealed opaque envelopes No information on blinding or loss to follow-up
Participants	60 patients who had developed hypoalbuminaemia (< 20 g/L) after major surgery 2 patients died after randomisation and before treatment started. They were excluded from the analysis
Interventions	1. Saline (500 mL/24 hours) (n = 16) 2. 20% Albumin (300 mL/24 hours) (n = 15) 3. 10% HES (500 mL/24 hours) for 3 days (n = 27) Aim was to restore COP
Outcomes	Changes in fluid balance, serum albumin, COP and clinical signs of oedema were followed daily Death rates supplied by the author

Woittiez 1997 (*Continued*)

Notes	Length of follow-up unspecified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Wu 2001

Methods	RCT. No details given of randomisation method	
Participants	41 adolescent or adult patients in emergency department suffering from shock	
Interventions	1. 4% Modified fluid gelatin: succinated gelatin 40 g/L, sodium chloride 7 g/L, sodium hydroxide 1.36 g/L (n = 18) 2. Ringer's lactate (n = 16)	
Outcomes	Death Haemodynamic variables	
Notes	Not intention-to-treat: 5 patients who received blood transfusion and 2 who had surgery within the first hour of resuscitation were dropped from the analysis Length of follow-up not clear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Younes 1992

Methods	Randomised "in a double blind fashion" Blinding by use of similar bottles No loss to follow-up
Participants	Participants were emergency department admissions, SBP < 80 mmHg, ≥ 19 years Exclusion criteria: pregnant, pre-existing cardiac or metabolic disease
Interventions	1. 6% Dextran 70 in 7.5% saline (n = 35) 2. 7.5% Saline (n = 35) 3. 0.9% Saline (n = 35) Allocated fluid was for initial bolus of 250 mL, followed by isotonic crystalloids as needed

Younes 1992 (*Continued*)

Outcomes	Deaths reported Fluid balance	
Notes	Follow-up to discharge from hospital	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Younes 1994

Methods	Trial conducted in a "double blind randomised fashion" Blinding by use of coded, identical containers	
Participants	Participants were trauma admissions to the emergency department requiring treatment for haemorrhagic hypovolaemia; all were over 15 years old Exclusion criteria: pregnant, cardiac or renal failure, cardiac arrest on arrival	
Interventions	1. 6% Dextran 70 in 7.5% saline (n = 101) 2. 0.9% Saline (n = 111) Allocated fluid was for the first IV infusion only	
Outcomes	Deaths reported Complications	
Notes	Follow-up period was 30 days	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Younes 1998

Methods	RCT, allocation by sealed envelope Blinding not mentioned No apparent loss to follow-up
Participants	Trauma patients SBP < 90 mmHg admitted to the emergency department, with no previous treatment
Interventions	1. 10% Pentastarch (n = 12) 2. 0.9% Saline (n = 11) Fluid given in 250 mL boluses until systolic blood pressure > 100 mmHg

Younes 1998 (*Continued*)

Outcomes	Deaths reported No complications reported in either group	
Notes	Follow-up to 24 hours	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Zetterstrom 1981a

Methods	The patients were randomly divided into 2 groups Allocation concealment was by sealed opaque envelopes (information supplied by study author) Blinding not mentioned No loss to follow-up	
Participants	Adults undergoing elective major abdominal surgery	
Interventions	1. Standard volume replacement regimen (1 L dextran 70 then up to 4 units of RBC with electrolyte, then whole blood or RBC with plasma; postoperative patients were given crystalloids and whole blood) plus 20% human albumin solution 100 mL at end of operation, 200 mL to 300 mL on same day, then 200 mL on first postoperative day, then 100 mL for next 3 days (n = 15) 2. Standard volume replacement regimen (as above) (n = 15)	
Outcomes	Deaths reported Haemodynamic variables	
Notes	Length of follow-up unspecified	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear

Zetterstrom 1981b

Methods	Patients were randomly divided into 2 groups Allocation concealment was by sealed opaque envelopes (information supplied by study author) Blinding not mentioned No loss to follow-up
Participants	18 patients who had undergone elective abdominal aortic surgery No exclusions mentioned
Interventions	1. 5% Human albumin solution (n = 9) 2. Ringer's lactate solution (n = 9) Administration guided by pulmonary arterial occlusion pressure
Outcomes	Deaths reported Haemodynamic variables
Notes	Follow-up to discharge from hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

Zhu 2011

Methods	RCT
Participants	135 participants with severe sepsis
Interventions	1. 7.5% Hypertonic saline plus 6% HES 130/0.4 (n = 45) 2. Ringer's lactate plus 6% HES 130/0.4 (n = 45) 3. Ringer's lactate (n = 45)
Outcomes	Biomarkers, fluid requirements, and MODS. Mortality was also reported
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear

ACE: angiotensin-converting enzyme; ARDS: adult respiratory distress syndrome; ASA: American Society of Anesthesiologists; bpm: beats per minute; COP: colloid osmotic pressure; CPR: cardiopulmonary resuscitation; GI: gastrointestinal; HES: hydroxyethyl starch; HR: heart rate; ICU: intensive care unit; IV: intravenous; LVEDP: left ventricular end diastolic pressure; LVEF: left ventricular

ejection fraction; MODS: multiple organ dysfunction score; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; RBC: red blood cell; RCT: randomised controlled trial; SBP: systolic blood pressure; TBSA: total body surface area; WP: wedge pressure.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Artru 1989	Intervention to control intracranial pressure not directed at fluid resuscitation
Bocanegra 1966	Study contained 2 quasi-randomised comparisons of colloid with glucose and plasma/saline with saline. In both studies, the control solution was only given IV if the patient was in coma or shock. It was therefore not a reasonable comparison of colloid and crystalloid
Boldt 1996	All groups received some colloid
Boldt 2007	Comparison was not between colloids and crystalloids, rather 2 different colloid solutions
Bothner 1998	Participants were having minor elective surgery, therefore not considered to be critically ill
Breheme 1993	Intervention directed at haemodilution, not at volume replacement
Bueno R 2004	The participants had elective surgery
Chin 2006	Participants were undergoing elective surgery, therefore not considered to be critically ill
Golub 1994	Albumin given solely as a nutritional supplement
Goslinga 1992	Intervention directed at haemodilution, not volume replacement
Green 2008	Article is a review
Greenhalgh 1995	Intervention directed at the maintenance of serum albumin levels, not for volume replacement
Hauser 1980	Cross-over trial
Ko 2007	Comparison of crystalloids and colloids as pre-loading solutions
Krasheninnikov 2007	Not an RCT
Lagonidis 1995	Intervention was pre-loading for coronary artery bypass surgery
Lange 2011	Article was a review
Lobo 2008	Experiment conducted on rabbits
Marhofer 1999	Trial of fluid for pre-loading before spinal anaesthesia

(*Continued*)

Mittermayr 2007	Patients were undergoing elective surgery
Mittermayr 2008	Outcome was the change in concentration of tissue-type plasminogen activator
Morrison 2011	Study evaluated the effect of hypertonic saline in patients with blunt head injury
Niemi 2008	Solutions were used for pump priming
Nilsson 1980	Albumin given as a nutritional supplement
Oliviera 2002	The participants had sepsis
Paton-Gay 2007	The outcome was non-relevant to comparing crystalloids and colloids
Paul 2003	The participants had elective surgery
Rehm 2001	2 colloids (albumin and hetastarch) compared
Steinberg 1989	Cross-over trial
Tiryakioglu 2008	Patients were undergoing elective surgery and not considered critically ill. Also, the solutions were used as priming solutions
Tseng 2008	Crystalloid and colloid treatment was not randomised
Valetova 2007	Patients were randomised depending upon their treatment not prior to treatment
van der Heijden 2009	The report did not provide separate data for the 3 arms that received colloids (gelatin 4%, hydroxyethyl starch 6% and albumin 5%)
Vercueil 2006	Article is a review
Wilkes 2001	1 group received saline plus hetastarch, the other received 'balanced' fluid plus hetastarch. Thus, each group received both a colloid and a crystalloid. This conflicts with the purpose our review, which compares patients who had 1 of these with patients who had the other
Woods 1993	This quasi-randomised trial looked at albumin supplementation in postoperative patients, with the aim of maintaining the serum albumin. Since the main aim of giving albumin was not to replace volume, the study was excluded

Characteristics of ongoing studies *[ordered by study ID]*

CHEST Trial

Trial name or title	Crystalloid Versus Hydroxyethyl Starch Trials (CHEST)
Methods	Multicentre phase 3 RCT of fluid resuscitation
Participants	7000 patients in ICU requiring fluid resuscitation
Interventions	1. 6% HES (130/0.4) 2. Saline
Outcomes	90 days all-cause mortality
Starting date	December 2009
Contact information	John A Myburgh, The George Institute, Sydney, New South Wales, Australia
Notes	NCT00935168

RASP trial

Trial name or title	Lactated Ringer Versus Albumin in Early Sepsis Therapy (RASP)
Methods	RCT
Participants	360 patients with severe sepsis or septic shock
Interventions	1. Ringer's lactate 2. 4% Albumin
Outcomes	28 days all-cause mortality
Starting date	May 2012
Contact information	Juliano P Almeida, Cancer Institute of Sao Paulo, School of Medicine, University of Sao Paulo
Notes	NCT01337934

The 6S trial

Trial name or title	Scandinavian Starch for Severe Sepsis/Septic Shock Trial (6S)
Methods	Multicentre, randomised, double-blinded trial with concealed allocation
Participants	800 patients with severe sepsis in 30 Scandinavian ICUs

The 6S trial (*Continued*)

Interventions	1. 6% HES 130/0.4 in Ringer's acetate 2. Ringer's acetate
Outcomes	The composite end point of 90-day mortality or end-stage kidney failure is the primary outcome measure
Starting date	December 2009
Contact information	Anders Perner, ICU, Rigshospitalet, University of Copenhagen
Notes	NCT00962156

HES: hydroxyethyl starch; ICU: intensive care unit; RCT: randomised controlled trial.