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[Intervention Review]

Colloid solutions for fluid resuscitation

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ABSTRACT

Background

Colloids are widely used in the replacement of fluid volume. However, doubts remain as to which colloid is best. Different colloids vary in their molecular weight and therefore in the length of time they remain in the circulatory system. Because of this, and their other characteristics, they may differ in their safety and efficacy.

Objectives

To compare the effects of different colloid solutions in patients thought to need volume replacement.

Search methods

We searched the Cochrane Injuries Specialised Register (searched 1 December 2011), the Cochrane Central Register of Controlled Trials 2011, issue 4 (*The Cochrane Library*); MEDLINE (Ovid) (1948 to November Week 3 2011); EMBASE (Ovid) (1974 to 2011 Week 47); ISI Web of Science: Science Citation Index Expanded (1970 to 1 December 2011); ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to 1 December 2011); CINAHL (EBSCO) (1982 to 1 December 2011); National Research Register (2007, Issue 1) and PubMed (searched 1 December 2011). Bibliographies of trials retrieved were searched, and for the initial version of the review drug companies manufacturing colloids were contacted for information (1999).

Selection criteria

Randomised controlled trials comparing colloid solutions in critically ill and surgical patients thought to need volume replacement.

Data collection and analysis

Two review authors independently extracted the data and assessed the quality of the trials. The outcomes sought were death, amount of whole blood transfused, and incidence of adverse reactions.

Main results

Eighty-six trials, with a total of 5,484 participants, met the inclusion criteria. Quality of allocation concealment was judged to be adequate in 33 trials and poor or uncertain in the rest.

Deaths were reported in 57 trials. For albumin or plasma protein fraction (PPF) versus hydroxyethyl starch (HES) 31 trials (n = 1719) reported mortality. The pooled relative risk (RR) was 1.06 (95% confidence interval (CI) 0.86 to 1.31). When the trials by Boldt were removed from the analysis the pooled RR was 0.90 (95% CI 0.68 to 1.20). For albumin or PPF versus gelatin, nine trials (n = 824) reported mortality. The RR was 0.89 (95% CI 0.65 to 1.21). Removing the study by Boldt from the analysis did not change the RR or CIs. For albumin or PPF versus dextran four trials (n = 360) reported mortality. The RR was 3.75 (95% CI 0.42 to 33.09). For gelatin versus HES 22 trials (n = 1612) reported

mortality and the RR was 1.02 (95% CI 0.84 to 1.26). When the trials by Boldt were removed from the analysis the pooled RR was 1.03 (95% CI 0.84 to 1.27). RR was not estimable in the gelatin versus dextran and HES versus dextran groups.

Forty-one trials recorded the amount of blood transfused; however, quantitative analysis was not possible due to skewness and variable reporting. Twenty-four trials recorded adverse reactions, with two studies reporting possible adverse reactions to gel and one to HES.

Authors' conclusions

From this review, there is no evidence that one colloid solution is more effective or safe than any other, although the CIs were wide and do not exclude clinically significant differences between colloids. Larger trials of fluid therapy are needed if clinically significant differences in mortality are to be detected or excluded.

PLAIN LANGUAGE SUMMARY

Are particular types of colloid solution safer for replacing blood fluids than others?

When a person is bleeding heavily, the loss of fluid volume in their veins can lead to shock, so they need fluid resuscitation. Colloids and crystalloids are two types of solutions used to replace lost blood fluid (plasma). They include blood and synthetic products. Both colloids and crystalloids appear to be similarly effective at resuscitation. There are different types of colloids and these may have different effects. However, the review of trials found there is not enough evidence to be sure that any particular colloid is safer than any other.

BACKGROUND

Colloids are used as plasma substitutes for short-term replacement of fluid volume while the cause of the problem is being addressed (e.g. stopping bleeding). These solutions can be blood products (human albumin solution, plasma protein fraction (PPF)) or synthetic products (modified gelatins, dextrans, etherified starches). Colloid solutions are widely used in fluid resuscitation (Yim 1995) and they have been recommended in a number of resuscitation guidelines and intensive care management algorithms (Armstrong 1994; Vermeulen 1995). Previous systematic reviews have suggested that colloids are no more effective than crystalloids in reducing mortality (Perel 2012; Roberts 2011). Despite this, colloid solutions are still widely used as they are thought to remain in the intravascular space for longer than crystalloids and, therefore, be more effective in maintaining osmotic pressure.

It is plausible that colloids may vary in their safety and effectiveness. Different colloids vary in the length of time they remain in the circulatory system. It may be that some low-to-medium molecular weight colloids (e.g. gelatins and albumin) are more likely to leak into the interstitial space (Traylor 1996), whereas some larger molecular weight hydroxyethyl starches (HES) are retained for longer (Boldt 1996). In addition it is thought that some colloids may affect coagulation or cause other adverse effects.

This review examines direct comparisons of the different colloid solutions in randomised trials to complement the earlier reviews on colloids compared to crystalloids (Perel 2012) and human albumin (Roberts 2011).

OBJECTIVES

To quantify the relative effects on mortality of different colloid solutions in critically ill and surgical patients requiring volume replacement, by examining direct comparisons of colloid solutions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Patients clinically assessed as requiring volume replacement or maintenance of colloid osmotic pressure.

Administration of fluid for preoperative haemodilution or volume loading, during plasma exchange, for priming extracorporeal circuits or following paracentesis are excluded.

Types of interventions

The colloid solutions considered are human albumin solutions, PPF, modified gelatins, dextran 70, or etherified starch solutions.

Trials of other blood products not used primarily for volume replacement (e.g. fresh frozen plasma (FFP), pooled serum) were excluded.

The review compares the administration of any regimens of different classes of colloids with each other.

Types of outcome measures

The primary outcome measure was mortality from any cause at the end of the study period.

We also attempted to find data on incidence of adverse reactions, allergies or anaphylactic shock, and the amount of blood (whole blood or red blood cells) transfused in each group. Some of the synthetic colloids may have anticoagulant properties and, therefore, we felt that some measure of blood loss or haemorrhage was important. However, as blood loss is vulnerable to measurement error, we decided to use the amount of blood products transfused as an outcome measure.

Intermediate physiological outcomes were not used for several reasons. These were that they are subject to intra- and inter-observer variation, they have no face value to patients and relatives, and the ones seen as appropriate are not stable over time. Also there would need to exist a strong predictive relationship between the variable and mortality.

Search methods for identification of studies

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

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Specialised Register (searched 1 Dec 2011);
- the Cochrane Central Register of Controlled Trials (2011, issue 4, *The Cochrane Library*);
- MEDLINE (Ovid) (1948 to November Week 3 2011);
- EMBASE (Ovid) (1974 to 2011 Week 47);
- ISI Web of Science: Science Citation Index Expanded (1970 to 1 December 2011);
- ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to 1 December 2011);
- CINAHL (EBSCO) (1982 to 1 December 2011);
- PubMed (ncbi.nlm.nih.gov/sites/entrez/) (searched 1 December 2011 limit-Humans, published in the last 90 days);
- National Research Register (issue 1, 2007);
- Zetoc (searched 23 March 2007).

Full search strategies are listed in Appendix 1.

Searching other resources

We searched the bibliographies of the retrieved trials and contacted drug companies manufacturing colloids for information. For the original version of the review in 1999 we also identified trials by using the searches undertaken for the pre-existing review of colloids versus crystalloids (Perel 2012), which included BIDS Index to Scientific and Technical Proceedings, drawing on the handsearching of 29 international journals and the proceedings of several international meetings on fluid resuscitation, and checking the reference lists of the trials found. There were no language restrictions in any of the searches.

To identify unpublished trials we searched the register of the Medical Editors' Trial Amnesty and we contacted the UK Medicines Control Agency.

For the first version of the review (published 1999) we also contacted the medical directors of the following companies, which all manufacture colloids:

- Alpha Therapeutic UK Limited (Albutein),
- American Critical Care McGraw (Hespan),
- Bayer (Plasbumin),
- Baxter (Gentran),
- Bio Products Laboratory (Zenalb),
- Cambridge Laboratories (Rheomacrodex),
- Centeon Ltd (Albuminar),
- CIS UK Ltd,
- CP (Lomodex),
- Common Services Agency,
- Consolidated (Gelofusine),
- DuPont (Hespan),
- Fresenius (eloHAES and HAES-Steril),
- Geistlich Sons Ltd (Hespan and Pentaspan),
- Hoechst (Haemaccel),
- Mallinckrodt Medical GMBH (Infoson),
- Nycomed, Oxford Nutrition (Elohes),
- Pharmacia and Upjohn Ltd (Rheomacrodex),
- Sorin Biomedica Diagnostics Spa.

Data collection and analysis

The Injuries Group Trials Search Co-ordinator ran the electronic database searches, collated the results, and removed duplicates before sending them to the review authors for screening.

Selection of studies

One review author examined the search results for reports of possibly relevant trials and these reports were then retrieved in full. Two review authors applied the selection criteria independently to the trial reports, resolving disagreements by discussion.

Data extraction and management

Two review authors independently extracted information on the following:

- method of allocation concealment,
- number of randomised patients,
- type of participants,
- the interventions,
- outcome data (numbers of deaths, volume of blood transfused, and incidence of adverse or allergic reactions).

The review authors were not blinded to the trial authors or journal when doing this, as the value of this has not been established (Berlin 1997). Results were compared and any differences resolved by discussion. Where there was insufficient information in the published report, we attempted to contact the trial authors for clarification.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Higgins 2011), two review authors scored this quality on the scale used by Higgins 2011 as shown below, assigning 'high risk of bias' to poorest quality and 'low risk of bias' to best quality:

- low risk of bias = trials deemed to have taken adequate measures to conceal allocation (i.e. central randomisation; numbered or coded bottles or containers; drugs prepared by the pharmacy; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment);
- unclear risk of bias = 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).

Where the method used to conceal allocation was not clearly reported, the trial author was contacted, if possible, for clarification. We then compared the scores allocated and resolved differences by discussion.

Data synthesis

The following comparisons were made:

- albumin or PPF versus etherified starch,
- albumin or PPF versus modified gelatin,
- albumin or PPF versus dextran 70,
- modified gelatin versus etherified starch,
- modified gelatin versus dextran 70,
- etherified starch versus dextran 70.

For each trial we calculated the risk ratio (RR) of death and 95% confidence interval (CI), such that a RR of more than 1 indicates a higher risk of death in the first group named.

We examined the groups of trials for statistical evidence of heterogeneity using Chi^2 and I^2 tests. If there was no obvious heterogeneity on visual inspection or statistical testing, we calculated pooled RRs and 95% CIs using a fixed-effects model.

We assessed the skewness of continuous data by checking the mean and standard deviation (if available). If the standard deviation is more than twice the mean for data with a finite end point (such as 0 in the case of bleeding), the data are likely to be skewed and it is inappropriate to apply parametric tests (Altman 1996). This is because the mean is unlikely to be a good measure of central tendency. If parametric tests could not be applied, we tabulated the data.

Sensitivity analysis

We examined the effect of excluding trials judged to have inadequate (scoring 'high risk of bias') allocation concealment in a sensitivity analysis.

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 pointed 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

For more detailed descriptions of individual studies, see 'Characteristics of included studies'.

Eighty-six studies met the inclusion criteria, with a total of 5488 participants. The earliest trial was from 1980 and the most recent from 2011. From the drug companies that we contacted in 1999, we were sent information by Baxter Healthcare Ltd, CIS UK Ltd, Fresenius Ltd, Hoechst and Pharmacia. No new trials were identified from the information sent to us.

The trials included the following comparisons.

Albumin or PPF versus starch (50 trials with 2458 participants in these groups)

Arellano 2005; Boldt 1986; Boldt 1993a; Boldt 1995; Boldt 1996a; Boldt 1996b; Boldt 1996c; Boldt 1998; Brock 1995; Brutocao 1996; Claes 1992; Diehl 1982; Dolecek 2009; Falk 1988; Friedman 2008; Fulachier 1994; Gahr 1981; Gallagher 1985; Gold 1990; Gondos 2010; Haas 2007; Hausdorfer 1986; Hecht-Dolnik 2009; Hiippala 1995; Huskisson 1993; Jones 2004; Kirklin 1984; London 1989; Mastroianni 1994; Moggio 1983; Mukhtar 2009; Munoz 1980; Munsch 1988; Niemi 2006; Prien 1990; Rackow 1983; Rackow 1989; Reine 2008; Rosencher 1992; Schramko 2009; Shatney 1983; Standl 2008; Veneman 2004; Verheij 2006; Vogt 1994; Vogt 1996; Vogt 1999; von Sommoggy 1990; Woittiez 1997; Yang 2011.

Albumin or PPF versus dextran (six trials with 410 participants in these groups)

Hedstrand 1987; Hiippala 1995; Jones 2004; Karanko 1987; Lisander 1996; Tollofsrud 1995.

Albumin or PPF versus gelatin (14 trials with 1152 participants in these groups)

Boldt 1986; Du Gres 1989; Evans 2003; Gondos 2010; Haas 2007; Huang 2005; Huskisson 1993; Karanko 1987; Niemi 2006; Stockwell 1992; Stoddart 1996; Tollofsrud 1995; Verheij 2006; Wahba 1996.

Starch versus gelatin (26 trials with 1883 participants in these groups)

Allison 1999; Asfar 2000; Beards 1994; Berard 1995; Beyer 1997; Boldt 1986; Boldt 2000; Boldt 2001; Carli 2000; Dytkowska 1998; Godet 2008; Gondos 2010; Haas 2007; Huskisson 1993; Inal 2010; Jin 2010; Mahmood 2007; Molnar 2004; Niemi 2006, Ooi 2009; Rittoo 2004; Schortgen 2001; Schramko 2010; Van der Linden 2004; Van der Linden 2005; Volta 2007.

Starch versus dextran (one trial with 30 participants in these groups)

Hiippala 1995.

Dextran versus gelatin (three trials with 82 participants in these groups)

Gombocz 2007; Karanko 1987; Tollofsrud 1995.

The trials involved patients with hypovolaemia, sepsis, trauma, and patients who had undergone surgery.

The trials tended to report surrogate outcomes such as haemodynamic variables. Data on death were obtainable from 57 trials. Information on the amount of blood or FFP transfused was available in 41 trials. However, the data were reported in a variety of different ways that made combining the data in a meta-analysis unfeasible.

Inclusion and exclusion criteria varied, but many of the studies excluded patients with previous adverse reactions to colloids, clotting problems, or renal disease.

Risk of bias in included studies

Using the criteria defined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) the quality of allocation concealment was judged to be adequate (at low risk of bias) in 33 trials, unclear in 42 trials, and inadequate (at high risk of bias) in 10 trials. Where the method of allocation concealment was unclear, we attempted to contact all of the trialists and we obtained information from 16 of them. However, due to the lack of reported information on the process of randomisation and allocation concealment, we were unable to assess the quality in many of the trials properly.

Thirteen trials mentioned that some form of blinding was used. In nine, some, or all, of the staff giving treatment were blinded, in six those giving postoperative care were blinded, in two the outcome assessors were blinded, and in one the statisticians performing the analysis were blinded to treatment group.

Effects of interventions

Mortality

Of the 86 trials identified, 41 reported mortality data. Information on death was obtained from a further 16 trials by contact with the trial authors. We, therefore, had data on death from 57 trials.

Albumin or PPF versus HES

Thirty-one trials (1719 participants) reported mortality data. The pooled RR was 1.06 (95% CI 0.86 to 1.31). When the trials by Boldt (Boldt 1993a; Boldt 1995; Boldt 1996a; Boldt 1996b; Boldt 1996c; Boldt 1998; Boldt 2006a) were removed from the analysis the pooled RR was 0.97 (95% CI 0.70 to 1.35).

Albumin or PPF versus gelatin

Nine trials (824 participants) reported mortality but only three of those trials had any deaths. The RR was 0.89 (95% CI 0.65 to 1.21). The Boldt trial included in this analysis had no events (Boldt 1993a), and therefore contributed no data to the analysis.

Albumin or PPF versus dextran

Four trials (360 participants) reported mortality and were included in the meta-analysis. Only one of these reported any deaths (Hedstrand 1987). The RR was 3.75 (95% CI 0.42 to 33.09).

Gelatin versus HES

Twenty-two studies (1612 participants) reported mortality and the pooled RR was 1.02 (95% CI 0.84 to 1.26). The effect was unchanged with removal of the six trials by Boldt (Boldt 1993a; Boldt 2000;

Boldt 2001; Haisch 2001c; Haisch 2001c; Huttner 2000a) (RR 1.00; 95% CI 0.80 to 1.25).

Gelatin versus dextran 70

There were three trials (82 participants) that reported mortality. There were no deaths so the RR was not estimable.

HES versus dextran 70

No trials reported mortality.

Amount of blood transfused

Forty-five trials recorded the amount of blood or FFP transfused. As the data were reported in various ways, often lacking a measure of variation, and was also skewed we did not attempt a quantitative synthesis. These data can be seen in the 'other data' tables.

Adverse events

Twenty-four trials reported the incidence of adverse or allergic reactions or anaphylactic shock. The majority reported that there were no such incidents. However, one study (Akech 2006) reported a possible adverse reaction to gelatin (Gelufusine) and one (Godet 2008) reported two possible adverse reactions in the HES group and one in the gelatin group.

Sensitivity analysis

The effect of excluding trials judged to have inadequate or unclear allocation concealment was examined in a subgroup analysis. This made no significant difference to the results (albumin or PPF versus HES: pooled RR 1.08; 95% CI 0.86 to 1.36; albumin or PPF versus gelatin pooled RR 0.92; 95% CI 0.47 to 1.81; gelatin versus HES pooled RR 1.10; 95% CI 0.84 to 1.44).

There was also no significant difference when the trials by Boldt were removed from the analysis (albumin or PPF versus HES pooled RR 0.90 (95% CI 0.68 to 1.20), albumin or PPF vs gelatin 0.92 (0.47, 1.81), gelatin versus HES 1.03 (0.84, 1.27).

Removing both the trials with inadequate allocation concealment and the trials by Boldt from the albumin or PPF versus HES analysis gave a pooled effect of RR 0.88 (95% CI 0.63 to 1.24). The RR for gelatin versus HES was 1.12 (95% CI 0.85 to 1.47).

DISCUSSION

Despite finding 90 trials we cannot make any conclusions about the relative effectiveness of different colloid solutions. Previous systematic reviews have suggested that colloids are no more effective than crystalloids in reducing mortality (Perel 2012; Roberts 2011), but there are too few data available to show in direct comparisons whether any of the colloids are safer or more effective than another. The CIs are wide and do not exclude clinically significant differences between colloids.

Mortality was selected as the main outcome measure in this systematic review for several reasons. In the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients, and data on death are reported in many of the studies. Furthermore, one might expect that mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes. The use of a pathophysiological end point as a surrogate for an adverse outcome assumes a direct relationship between the two, an assumption that may sometimes be inappropriate. Finally, when trials collect data on a number of physiological end points, there is the potential for bias due to the selective publication of end points showing striking treatment effects.

There was wide variation in the participants, intervention regimens, and the length of follow-up. The length of follow-up was not reported in many of the studies. Where it is reported it ranges from a matter of hours to months, which may explain a high proportion of the heterogeneity in overall event rates. The effect of these factors was not examined in a sensitivity analysis, as there was felt to be insufficient data to justify examining subgroups.

Many of the trials were small, and some had been done some time ago. Although older trials will not necessarily be of poorer quality, it may be that treatment protocols have subsequently altered making these trials less relevant to current clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

Previous reviews have not shown a benefit of colloids over crystalloids for volume replacement (Perel 2012; Roberts 2011).

This review does not provide any evidence that one colloid is safer than another, but does not rule out clinically significant differences.

Implications for research

Trials of fluid therapy need to be larger in order to exclude clinically significant differences between colloids in patient relevant outcomes. However, trials should probably first address the question of whether colloids are any more effective than crystalloid solutions.

Use of surrogate outcomes, such as physiological measurements, should be discouraged unless there is a strong relationship with outcomes of interest to patients and relatives.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akech 2006

Methods	Randomised design. Fluid interventions allocated sequentially in blocks of 10 ITT analysis
Participants	88 children over 3 months of age with severe malaria complicated by metabolic acidosis. Inclusion criteria: severe malaria, metabolic acidosis, and clinical feature of shock. Excluded if had pulmonary oedema, oedematous malnutrition, or papilloedema
Interventions	1) 4% Modified gelatin (n = 44) 2) 4.5% Albumin (n = 44)
Outcomes	Death Resolution of shock and acidosis Neurological sequelae at discharge Adverse events
Notes	Intervention arms not blinded

Risk of bias

Bias	Authors' judgement	Support for judgement

Akech 2006 *(Continued)*

Allocation concealment (selection bias)	High risk	Inadequate. Authors report that allocation of intervention was not concealed

Allison 1999

Methods	Randomised controlled trial. Randomisation was based on date of admission Analysis not ITT
Participants	45 patients with blunt trauma who required colloid infusion. Patients were excluded if they were less than 12 years old, did not require admission to the ITU, died within 24 hours, were pregnant or in renal failure 8 gelatin and 6 HES patients excluded after randomisation
Interventions	1) HES (200/0.45 Pentaspan) (n = 24) 2) Gelatin (Gelofusine) (n = 21) After 24 hours, colloid administration was at the discretion of the clinician
Outcomes	Death Glasgow coma score Volumes of blood and platelets infused Haematological parameters
Notes	Data were collected until the patient left the ITU or for a maximum of 5 days. Main outcome of interest was capillary leak

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	High risk	Inadequate. Randomisation was based on date of admission (on even dates patients received HES)

Arellano 2005

Methods	Randomised controlled trial. All participants, healthcare workers, and study personnel blinded to allocation
Participants	50 adults undergoing surgical ablation of oropharyngeal cancer with free flap reconstruction (mean age 55 years). Exclusion criteria - ASA Physical Status Classification 3-4, cardiac insufficiency, pancreatitis, severe hepatic dysfunction, renal dysfunction, anaemia, coagulation abnormalities, ingestion of NSAID, or ASA within 10 days of surgery and previous major head and neck surgery with free flap reconstruction
Interventions	1) 5% HA (n = 25) 2) HES 264/0.45 (n = 25) CVP was maintained between 7 mmHg and 10 mmHg
Outcomes	Clinical indices of coagulation Number of units of blood transfused
Notes	Follow-up 24 hours. 1 patient in each group did not complete the study because planned surgical procedure was abandoned

Arellano 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Study colloids placed in masked container by nurse not involved in other aspects of trial

Asfar 2000

Methods	Randomised controlled trial
Participants	34 septic, hypovolaemic, ventilated, and haemodynamically controlled patients Inclusion criteria: patients aged over 16 years, systolic arterial pressure higher than 90 mmHg and hypovolaemia defined by PAOP of 12 mmHg or less Patients were excluded if they had an overt haemodynamic, ventilatory, or acid base status instability. Sepsis was identified by either positive bacterial blood cultures, bronchoalveolar lavage, or clinical evidence of infection
Interventions	1) 6% HES (n = 16) 2) 4% MFG (n = 18)
Outcomes	Death Haemodynamic variables
Notes	Follow-up 1 hour. 2 patients in the HES group were excluded because they experienced haemodynamic instability. The final analysis was made on remaining 16 patients. Information on allocation concealment obtained from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation using sequentially numbered sealed opaque envelopes

Beards 1994

Methods	Randomised controlled trial
Participants	28 patients with hypovolaemia, mechanically ventilated for concurrent acute respiratory failure. Patients fulfilled the following inclusion criteria: age >16 years, body weight between 50 kg and 85 kg, MAP < 80 mmHg (or 30 mmHg less than previously recorded); PAOP < 10 mmHg with oliguria (i.e. urine output < 15 mL/hour)
Interventions	1) Rapid infusion of 500 mL MFG (n = 15) 2) Rapid infusion of 500 mL hetastarch (n = 13)
Outcomes	Death Haemodynamic variables Oxygen variables
Notes	Follow-up 30 minutes for haemodynamic variables and until discharge for deaths. Information on allocation concealment was obtained on contact with the study author

Beards 1994 *(Continued)*

Risk of bias

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

Berard 1995

Methods	Randomised controlled trial. Blinding not mentioned
Participants	319 patients in a resuscitation service receiving medical (gastrointestinal haemorrhage) and surgical cases. Patients were excluded if they had had a prior allergic reaction
Interventions	1) Gelatin (n = 153) 2) HES (n = 146) The prescribers chose the quantity of colloid, guided by normal practice
Outcomes	Death Amount of colloid and RBCs given Cost
Notes	20 patients lost to follow-up, no explanation given. Follow-up to discharge. Information on method of randomisation was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. 'A set of 200 tickets (type 1) and another set of 200 tickets (type 2) were mixed in a box. One ticket was drawn at random for each patient'

Beyer 1997

Methods	Randomised controlled trial. No blinding
Participants	48 patients undergoing major elective hip surgery with an expected blood loss of > 1000 mL. Exclusion criteria were Hb concentration 11 g/dL or less; heart failure and coronary artery disease; MI within the past 6 months; hypertension (> 180 mmHg systolic); impaired renal function; pregnancy; known hypersensitivity to HES or gelatin; patient taking drugs that may specifically affect blood viscosity, diuresis, or clotting
Interventions	1) 3% MFG (n = 22) 2) 6% HES (n = 19) Both groups also given RL. Fluids administered according to haemodynamic and clinical parameters
Outcomes	Death (information on death was obtained by contact with the study author) Haemodynamic variables Packed cell volume, Hb, clotting times Incidence of allergic reactions
Notes	7 patients were lost to follow-up but only 5 were accounted for. Information on method of allocation concealment was obtained by contact with the author

Beyer 1997 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation was by a list of random numbers read by someone not entering patients into the trial (closed list)

Boldt 1986

Methods	Randomised controlled trial, using sealed opaque envelopes Information on allocation concealment was obtained on contact with the study authors Blinding not mentioned Loss to follow-up not mentioned
Participants	55 patients undergoing elective aortocoronary bypass surgery Exclusion criteria were ejection fraction < 50% and LVEDP >15 mmHg
Interventions	1) 500 mL 20% HA (n = 15) 2) 500 mL 3% HES (n = 13) 3) 500 mL 3.5% Gelatin (n = 14) A fourth group received no colloid (n = 13)
Outcomes	Haemodynamic variables Incidence of anaphylactic shock Amount blood transfused
Notes	Follow-up until discharge from ICU

Risk of bias

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

Boldt 1993a

Methods	Randomised controlled trial
Participants	75 men undergoing elective aortocoronary bypass grafting, who had a PCWP of < 5 mmHg after induction of anaesthesia
Interventions	1) HA 5% (n = 15) 2) 6% HES, HMW (n = 15) 3) 6% HES, LMW (n = 15) 4) Gelatin 3.5% (n = 15) 5) No additional volume
Outcomes	Death (information obtained on contact with author) Haemodynamic variables
Notes	Follow-up 1 day. Information on allocation was obtained on contact with study author

Boldt 1993a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation by sequentially numbered sealed opaque envelopes

Boldt 1995

Methods	Randomised controlled trial. Blinding of outcome assessors not mentioned
Participants	30 consecutive trauma patients (injury severity score > 15) and 30 consecutive septic patients who underwent major surgery. Exclusions: patients suffering from renal failure requiring haemofiltration, severe liver dysfunction or coagulation abnormalities in their history were excluded as were patients who were receiving aspirin or other cyclooxygenase inhibitors
Interventions	1) 10% HES, LMW (15 trauma patients and 15 sepsis patients) 2) 20% HA (15 trauma patients and 15 sepsis patients) Fluid was given to maintain CVP and PCWP between 12 mmHg and 16 mmHg
Outcomes	Death Haemodynamic variables
Notes	Follow-up at 5 days Deaths were reported within the study period and later (time not specified). Information on allocation concealment was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Boldt 1996a

Methods	Randomised controlled trial. Outcome assessors blinded to treatment
Participants	30 trauma patients and 30 patients with from sepsis secondary to major general surgery. Exclusions were patients with renal impairment, liver insufficiency, disseminated intravascular coagulation, or septic shock
Interventions	1) 10% HES (n = 30) 2) 20% HA solution (n = 30) All patients also received RL Volume therapy was given to maintain PCWP between 12 mmHg and 18 mmHg
Outcomes	Death Haemodynamic variables
Notes	Follow-up at 5 days and at discharge from ICU

Boldt 1996a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation by sequentially numbered sealed opaque envelopes

Boldt 1996b

Methods	Randomised controlled trial. The doctors giving the fluid were blinded to the solution but blinding of outcome assessors not mentioned. Loss to follow-up not reported
Participants	45 consecutive trauma patients transferred to the surgical ICU. Inclusion criteria: injury severity score of > 15 points All patients were haemodynamically stable before being admitted to the study
Interventions	1) 10% HES (n = 15) 2) 20% HA (n = 15) 3) Unspecified volume therapy regimen (n = 15) The allocated solution was given to maintain CVP and or PAWP between 12 mmHg and 18 mmHg
Outcomes	Death Haemodynamic variables Circulating adhesion molecules
Notes	Deaths were reported within the study period and later (left ITU). Information on allocation concealment was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Boldt 1996c

Methods	Randomised controlled trial. Outcome variables were collected by an investigator who was blinded to the treatment. Loss to follow-up not reported
Participants	56 patients from the surgical ICU. 28 patients with an injury severity score > 15 and 28 patients with sepsis secondary to major surgery. Patients with renal insufficiency, urine output < 20 mL/hour, severe liver dysfunction, or disseminated intravascular coagulation were excluded
Interventions	1) 10% HES, LMW (14 trauma patients, 14 sepsis patients) 2) 20% HA (14 trauma patients, 14 sepsis patients) Fluid was infused to maintain PCWP at 10 mmHg to 15 mmHg
Outcomes	Death Haemodynamic variables
Notes	Follow-up 5 days Deaths were reported within the study period and later (time not specified)

Boldt 1996c *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Boldt 1998

Methods	Randomised controlled trial. Blinding of outcome assessors not mentioned Loss to follow-up not mentioned
Participants	150 traumatised patients (injury severity score >15) and 150 postoperative patients with sepsis. Patients suffering from renal failure, severe liver insufficiency, or with major coagulation abnormalities were not included
Interventions	1) 10% HES, LMW (n = 150) 2) 20% HA (n = 150) Both for 5 days to maintain the PAWP between 12 Torr and 15 Torr
Outcomes	Death Haemodynamic variables Organ function Coagulation
Notes	Deaths were reported within the study period and after the study period (time not specified). Information on allocation concealment was obtained on contact with the authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Boldt 2000

Methods	Randomised controlled trial
Participants	150 patients undergoing major abdominal surgery
Interventions	1) 6% HES, LMW (n = 50) 2) 6% HES, MMW (n = 50) 3) 3% MFG (n = 50) To keep MAP > 70 mmHg and CVP between 10 mmHg and 14 mmHg Volume was given perioperatively until the morning of the first postoperative day. For each hour of surgery 500 mL to 800 mL of crystalloids was routinely infused
Outcomes	Death Haemodynamic variables Blood loss Blood transfused

Boldt 2000 *(Continued)*

	Cost
Notes	Follow-up 1 postoperative day. Deaths recorded after study period. Information on allocation concealment was obtained on contact with the study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Boldt 2001

Methods	Randomised controlled trial. Volume therapy was done by doctors who did not know the aim of the study
Participants	75 patients undergoing major abdominal surgery Volume was administered to keep the CVP between 8 mmHg and 12 mmHg
Interventions	1) 6% HES (n = 25) 2) 6% HES (n = 25) 3) 4% MFG (n = 25) All groups also received 500 mL of RL for each hour of surgery
Outcomes	Death Haemodynamic variables Blood loss Blood units transfused
Notes	There were no deaths in the study period (until first follow-up on first postoperative day. Deaths until discharge

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. 'Closed envelope system'

Brock 1995

Methods	Randomised controlled trial
Participants	21 patients who had undergone cardiac surgery
Interventions	1) 10% HES 200/0.5 in 7.2% saline (n = 7) 2) 5% HA (n = 7) 3) 6% HES in 0.9% saline (n = 7)
Outcomes	Death (data obtained on contact with study author) Haemodynamic variables

Brock 1995 *(Continued)*

Notes	Data on allocation concealment was obtained on contact with the study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Allocation by list of random numbers read by someone entering patients into the trial (open list)

Brutocao 1996

Methods	Randomised double-blind controlled trial with pharmacy-controlled randomisation
Participants	38 children aged 1 year or more who were undergoing surgical repair of a congenital heart disease. Exclusion criteria included amrinone therapy, renal disease, coagulopathy, or a known bleeding diathesis
Interventions	1) 5% Albumin (n = 18) 2) 6% HES (n = 20) Volume expansion was administered as clinically indicated to maintain adequate CVP, perfusion, and urine output. The total amount of colloid therapy was determined by care providers blinded to the randomisation
Outcomes	Death (information on death was obtained on contact with the study authors) Haemodynamic variables Coagulation variables
Notes	Follow-up until discharge from hospital 9 children excluded post randomisation because they did not require colloid. Information on allocation concealment was obtained on contact with the study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Pharmacy-controlled randomisation

Carli 2000

Methods	Randomised controlled trial. Not ITT analysis
Participants	164 trauma patients. Patients were included if their SBP was < 100 mmHg, associated with signs of hypoperfusion
Interventions	1) HES (Hesteril 6%) (n = 85) 2) Gelatin (Plasmion) (n = 79)
Outcomes	Glasgow coma score Haemodynamic variables Units of blood transfused Adverse reaction
Notes	There were 13 deaths from heart failure but these patients were excluded from the final analysis

Carli 2000 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. 'Each centre received instructions from the coordinating Institute on the treatment to give the patient'

Claes 1992

Methods	Randomised controlled trial Blinding not mentioned No loss to follow-up
Participants	20 patients undergoing brain tumour surgery and 20 patients undergoing transabdominal hysterectomy. Exclusion criteria: pre-existing coagulopathies, abnormal preoperative coagulation screening tests, intake of drugs affecting haemostasis within 2 weeks preoperatively, and liver or kidney dysfunction
Interventions	1000 mL of fluid for volume replacement, as 1) 6% HES (n = 19) 2) 5% HA solution in 0.9% saline (n = 21)
Outcomes	Haemodynamic variables Coagulation variables
Notes	Follow-up 48 postoperative hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation or allocation

Diehl 1982

Methods	Randomised controlled trial Blinding not mentioned No loss to follow-up
Participants	60 patients undergoing coronary artery bypass
Interventions	1) 6% HES (n = 27) 2) 5% Albumin (n = 33) for volume expansion during the first 24 hours postoperatively. Neither hetastarch nor albumin was used intraoperatively or in the pump prime
Outcomes	Death Coagulation data Haemodynamic variables
Notes	Follow-up 7 postoperative days

Diehl 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Patients were allocated to groups according to their hospital identification number

Dolecek 2009

Methods	Randomised controlled trial, randomised according to computer-generated randomisation list
Participants	56 patients with severe sepsis. Patients were included if they were 18 years or older and developed severe sepsis. Exclusion criteria: severe coagulopathy, pregnant, cardiac failure, acute renal failure, aortal aneurysm, severe aortal regurgitation or dysrhythmia
Interventions	1) 20% Albumin (n = 30) 2) 6% HES (n = 26)
Outcomes	Death Haemodynamic variables
Notes	Follow-up 28 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Sealed opaque sequentially numbered envelopes (information obtained from authors)

Du Gres 1989

Methods	Randomised controlled trial Blinding not mentioned No loss to follow-up
Participants	30 patients post cardiac surgery. Patients were included if they were haemodynamically stable, were without serious 'rhythm' problems, had MAP < 90 mmHg, mean pulmonary artery pressure < 20 mmHg and CVP < 10 mmHg. Patients excluded if they needed blood transfusion, had a haematocrit < 28% or Hb < 9 g/100 mL
Interventions	1) 4% HA (n = 15) 2) Haemaccel (n = 15)
Outcomes	Haemodynamic parameters
Notes	Follow-up 4 hours

Risk of bias

Bias	Authors' judgement	Support for judgement

Du Gres 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation

Dytkowska 1998

Methods	Randomised controlled trial
Participants	40 patients post cardiac surgery. Patients were excluded if they had co-existing cardiogenic shock, renal failure with creatinine level > 3.0 mg, or severe clotting disorders
Interventions	1) 200/0 HAES 6% (n = 20) 2) Gelafundin (n = 20) Colloids were administered to patients with diagnosed symptoms of hypovolaemia, during the first 24 hours postoperatively. Infusion rate was adjusted to patients needs but it did not exceed 1000 mL/hour
Outcomes	Haemodynamic parameters Biochemical parameters Adverse reactions
Notes	Follow-up 2 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation

Evans 2003

Methods	Randomised controlled trial Treatment blinded (fluid set up by independent operator and covered with opaque black bag)
Participants	55 patients undergoing unilateral cemented hip replacement Exclusion criteria: cardiac insufficiency, renal insufficiency, altered liver function, preoperative anaemia, preoperative coagulation abnormalities, chronic use of corticosteroids and diuretics
Interventions	1) 4.5% HA (n = 13) 2) 4% Gelosulfine (n = 14) 3) Haemacel (n = 14) 2 L of fluid was infused during the operative period A fourth group received normal saline (n = 14)
Outcomes	Haemodynamic variables Total blood loss
Notes	Follow-up before surgery, at the end of the surgery, and 2 hours postoperatively

Risk of bias

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

Evans 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear - 'sealed envelopes'

Falk 1988

Methods	Randomised controlled trial Blinding not mentioned No loss to follow-up
Participants	12 patients with septic shock. Patients were excluded from the study if the pretreatment PAWP > 10 mmHg
Interventions	1) 250 mL of 5% Albumin (n = 6) 2) 250 mL of 6% HES (n = 6) Given every 15 minutes until the PAWP was increased to 15 mmHg. The test infusion was then continued at 100 mL/hour to maintain PAWP at 15 mmHg for the next 24 hours
Outcomes	Haemodynamic variables Clotting variables
Notes	Follow-up 24 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation

Friedman 2008

Methods	Randomised controlled trial
Participants	34 haemodynamically stable adults with sepsis and suspected hypovolaemia. Exclusion criteria: pregnancy, terminal state, PAOP > 12 mmHg, serum creatinine concentration > 3 mg/dL, severe coagulation abnormalities, history of allergy to any IV fluid
Interventions	1) 400 mL 10% HES (n=11) 2) 400 mL 6% HES (n=10) 3) 4% HA (n=13) All over 40 minutes
Outcomes	Haemodynamic variables
Notes	Follow-up 160 minutes. No data on mortality or blood transfused

Risk of bias

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

Friedman 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear - sealed, opaque envelope assignment (does not say if sequentially numbered)

Fries 2004

Methods	Randomised controlled trial Treatment not blinded
Participants	60 patients undergoing primary knee replacement surgery Exclusion criteria: contraindications for regional anaesthesia and puncture of the radial artery, any known allergies, primary and secondary haemostatic disorder
Interventions	1) 4% Gelofusine (n = 20) 2) 6% HES (n = 20) A third group received RL Before administrating spinal anaesthesia all patients received 500 mL RL. All patient intraoperatively
Outcomes	Haemodynamic variables
Notes	Follow-up 2 hours postoperatively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation or allocation

Fulachier 1994

Methods	Randomised controlled trial Blinding not mentioned No loss to follow-up
Participants	16 patients undergoing cardiac surgery (8 were undergoing valve replacement and 8 undergoing coronary bypass). Patients were excluded if they were > 80 years of age, < 18 years of age, had been included in other studies, had received colloids in the month preceding surgery, had coagulation abnormalities, or who were undergoing inotropic treatment
Interventions	1) 500 mL OF 4% solution of HA in RL (n = 8) 2) 500 mL of HES (n = 8) until starting cardiopulmonary bypass
Outcomes	Haemodynamic variables
Notes	Follow-up 30 minutes

Risk of bias

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

Fulachier 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation or allocation

Gahr 1981

Methods	Randomised controlled trial. No information given on method of randomisation No loss to follow-up
Participants	20 patients with hypovolaemia following abdominal surgery for malignoma
Interventions	1) 500 mL HES 450/0.7 (n = 10) 2) 500 mL HA 5% (n = 10) during the first 24 hours after the operation
Outcomes	Haemodynamic parameters Coagulation data
Notes	Follow-up 6 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of randomisation or allocation

Gallagher 1985

Methods	Randomised controlled trial
Participants	10 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) 5% Albumin (n = 5) 2) 6% HES (n = 5)
Outcomes	Death (data on deaths from study author) Haemodynamic data
Notes	Follow-up 1 day. Data on allocation obtained on contact with author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Adequate. Computerised system - patient details were entered before treatment assignment was revealed

Godet 2008

Methods	Randomised controlled trial. Computer-generated random list with randomisation in balanced blocks
Participants	65 patients aged 18 years and over with renal dysfunction undergoing abdominal aortic surgery. Exclusion criteria: endovascular aortic surgery, preoperative serum creatinine > 250 µmol/L, history or present diagnosis of severe hepatic insufficiency or coagulation disorders, dialysis, anuria, and post-transplant surgery
Interventions	1) 6% HES (n = 32) 2) 3% Gelatin (n = 33)
Outcomes	Death Haemodynamic variables Renal safety (serum creatinine) Adverse events
Notes	Follow-up at 6 days and 3 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Investigator received a set of envelopes. Envelope only opened when the patient arrived at pre-induction anaesthesia room

Gold 1990

Methods	Randomised controlled trial Colloid solution was blinded by covering with foil No loss to follow-up
Participants	40 surgical patients undergoing AAA surgery
Interventions	1) 1 g/kg Albumin 5% solution (n = 20) 2) 1 g/kg Hetastarch 6% solution (n = 20)
Outcomes	Death (data on death was obtained on contact with the author) Haemodynamic and coagulation variables
Notes	Follow-up not specified. Information on allocation concealment was obtained by contact with the author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Randomisation by alternation

Gombocz 2007

Methods	Randomised double-blind study (does not specify who was blinded)
Participants	40 patients undergoing coronary bypass surgery or aortic valve replacement. Exclusion criteria: 'redo' operation, hepatic disease, renal dysfunction, immunological disease, steroid treatment, intake of aspirin or other cyclooxygenase inhibitor within 7 days of surgery, known allergy to volume expanders used in the study
Interventions	1) 5.5% Gelatin (n = 20) 2) 6% Dextran 70 (n = 20)
Outcomes	Death Haemodynamic variables Blood transfused
Notes	Final follow-up 44 hours

Risk of bias

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

Gondos 2010

Methods	Randomised controlled study
Participants	200 postoperative haemodynamically stable hypovolaemic patients needing intensive care treatment because of general health status. Exclusion criteria: aged < 18 years, active bleeding or shock, severe pulmonary oedema, known uraemia, anaphylactic reaction to colloid fluids, and life expectancy less than 24 hours
Interventions	1) 4% Gelatin (n = 50) 2) 6% HES (n = 50) 2) 5% HA (n = 50) A fourth group were given LR (n = 50)
Outcomes	Death Haemodynamic variables Length of ICU stay
Notes	Final follow-up 10th postoperative day. Additional information on allocation obtained from study author

Risk of bias

Bias	Authors' judgement	Support for judgement

Gondos 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Adequate - 'randomised by blinded envelope technique - each centre had got 20 closed, opaque envelopes which were sequentially numbered'

Haas 2007

Methods	Randomised controlled trial. Computer-generated randomisation list
Participants	42 children undergoing surgery (including craniofacial surgery, tumour resection and abdominal surgery and needing colloid replacement. Exclusion criteria: prematurity; emergency surgery; history of hereditary or acquired coagulopathy including renal, hepatic, and bone marrow disease
Interventions	1) 4% Modified gelatin (n = 14) 2) 5% Albumin (n = 14) 3) 6% HES (n = 14)
Outcomes	Haemodynamic variables
Notes	Length of follow-up not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of allocation concealment

Hausdorfer 1986

Methods	Randomised controlled trial. No information given on method of randomisation
Participants	30 children undergoing major surgery. During about 3 hours of surgery, the patients lost up to 15% of blood volume
Interventions	1) HA 5% (n = 15) 2) HES 6% (n = 15) with 14 mL/kg body weight each
Outcomes	Haemodynamic variables
Notes	Follow-up 24 hours postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Hecht-Dolnik 2009

Methods	Randomised controlled trial. Block randomisation with 8 patients in each block. Attending intensivists were blinded to randomisation
Participants	156 patients undergoing off-pump coronary artery bypass grafting. Exclusion criteria: history of cardiac surgery, primary bleeding disorders, end-stage renal disease, and pregnant patients
Interventions	1) 6% HES (n = 78) 2) 5% HA (n = 78)
Outcomes	Death PRBC transfused Haemodynamic variables
Notes	4 patients excluded after randomisation because they were converted to on-pump surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. 'Sealed envelopes, attending anaesthetist opened the envelope linked to the patient's study number in the operating room when the procedure was underway'

Hedstrand 1987

Methods	Randomised controlled trial. No information given on method of randomisation Postoperative care staff were blinded No loss to follow-up
Participants	275 patients undergoing major surgery. Patients were excluded if they were known to have decreased serum albumin levels or expected to sustain plasma loss, or had pronounced cardiovascular disease
Interventions	1) PPF (n = 142) 2) Dextran (n = 133)
Outcomes	Volume transfused Complication rates Serum albumin Deaths
Notes	Follow-up 1 month

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Hiippala 1995

Methods	Randomised controlled trial. No information given on method of randomisation Blinding not mentioned 3 patients lost to follow-up (explanation given)
Participants	60 patients undergoing major abdominal or urological surgery. Patients who had used platelet-inhibiting drugs or had a diagnosed haemostatic defect were excluded
Interventions	1) 3% Dextrose (n = 15) 2) 4% HES (n = 15) 3) 6% HES (n = 15) 4) 5% Albumin (n = 15)
Outcomes	Haemodynamic variables Clotting variables Blood loss
Notes	Follow-up 3 days postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Huang 2005

Methods	Randomised controlled trial No information given on blinding
Participants	20 patients with burns over 40% of total body surface area admitted 4 to 8 hours after injury
Interventions	1) PPF (n = 9) 2) Gelofusine (n = 11) In a third control group patients did not receive fluid resuscitation
Outcomes	Haemodynamic variables
Notes	Follow-up 48 hours No relevant outcome data

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Huskisson 1993

Methods	Randomised controlled trial. No information given on method of randomisation
Participants	27 children returning to the ICU following hypothermic open heart surgery

Huskisson 1993 *(Continued)*

Interventions	1) Albumin 2) Gelatin 3) Hetastarch
Outcomes	Haemodynamic variables
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Inal 2010

Methods	Randomised controlled trial
Participants	30 hypovolaemic patients admitted to ICU. Exclusion criteria: pregnancy, haemodynamic instability, heart failure, renal failure, liver failure, known or suspected brain death
Interventions	1) 3.5% Polygeline (n = 15) 2) 6% HES (n = 15)
Outcomes	Death Haemodynamic variables Liver function Length of ICU stay
Notes	Follow-up 30 minutes

Risk of bias

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

Jin 2010

Methods	Randomised controlled trial
Participants	36 patients undergoing surgery for gastric cancer. Exclusion criteria: cardiac or renal insufficiency, or both; altered liver function; preoperative anaemia or coagulation abnormality, or both; colloid allergy; use of anticoagulants or antiplatelets
Interventions	1) 6% HES (n = 12) 2) 4% Modified gelatin (n = 12)

Jin 2010 *(Continued)*

	3) RL (n = 12)
Outcomes	Haemodynamic variables Adverse events
Notes	Follow-up 4 hours

Risk of bias

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

Jones 2004

Methods	Randomised controlled trial. Surgeons blinded to the fluid administered although the anaesthetist was aware of the fluid administered to a given patient
Participants	40 adults scheduled to undergo radical retropubic prostatomy Exclusion criteria: coagulation disorder, platelet count < 100,000/mm^3, preoperative Hb < 12 g/dL, if anticoagulant therapy within 10 days of the surgery, aspirin or NSAID use < 10 days before surgery or if they had documented allergy to any of the IV fluids used in the protocol
Interventions	1) 5% HA (n = 10) 2) 6% Dextran 70 (n = 10) 3) 6% HES (n = 10) A fourth group received RL Haemodilution was done with the target of 9 g/dL All patients underwent moderate haemodilution to a target of Hb 9 g/dL
Outcomes	Haemodynamic variables Blood loss and units transfused
Notes	Follow-up 3 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Karanko 1987

Methods	Randomised controlled trial. Patients were randomised in blocks of 4 Blinding not mentioned No loss to follow-up
Participants	48 patients who had undergone coronary bypass surgery 20 hours earlier
Interventions	1) 4% PPF (n = 15) 2) 6% Dextran 70 (n = 10)

Karanko 1987 *(Continued)*

	3) 5.5% Oxypolygelatin (n = 12) A fourth group (not randomly selected) acted as a control (n = 11)
Outcomes	Death (data on death was obtained on contact with the author Haemodynamic variables
Notes	Follow-up 28 hours. Information on allocation was obtained on contact with the author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Paper was put into a hat and taken out by an independent person

Kirklin 1984

Methods	Randomised controlled trial. No information given on method of randomisation Blinding not mentioned No loss to follow-up
Participants	30 patients undergoing coronary artery operations. Patients were excluded if they had undergone previous cardiac operations, if they had severe coagulopathies, anaemia, or CRF
Interventions	1) 6% HES (n = 15) 2) 5% Albumin (n = 15) Both fluids infused over 24 hours to maintain left arterial pressure between 6 mmHg and 12 mmHg and cardiac index > 2.0 L/minute/m^2
Outcomes	Death Haemodynamic and coagulation variables Adverse reactions
Notes	Follow-up until discharge from ICU 34 patients were originally included in the trial but data from 4 of them was not included in the final analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation concealment

Lisander 1996

Methods	Randomised controlled trial No loss to follow-up Blinding not mentioned
Participants	40 patients undergoing revision hip arthroplasty
Interventions	1) Albumin 40 g/L (n = 20) 2) Dextran 70 60 g/L (n = 20)

Lisander 1996 *(Continued)*

	Patients all received enoxaparin 40 mg/day
Outcomes	Death (data obtained from contact with study author) External blood loss Red cell balance Packed cell volume
Notes	Follow-up until discharge from hospital. Information on allocation concealment was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

London 1989

Methods	Randomised controlled trial. No information given on method of randomisation Blinding not mentioned No loss to follow-up
Participants	93 male cardiac surgical patients. Patients were excluded from the study if they had a significant coagulopathy or were anaemic (haematocrit value < 30%)
Interventions	1) 10% Pentastarch in 0.9% saline (n = 50) 2) 5% HA in 0.9% saline (n = 44) to provide volume expansion during the first 24 hours after cardiac operations
Outcomes	Haemodynamic variables Coagulation variables Death Length of stay
Notes	1 patient was treated twice with an 8-month interval. Follow-up until discharge from hospital

Risk of bias

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

Mahmood 2007

Methods	Randomised controlled trial. Randomisation by blocks of 6 using random number table. The study was not double blind but person analysing data was blind to study group. ITT analysis
Participants	62 patients undergoing elective infrarenal AAA surgery. Exclusion criteria: preoperative serum creatinine of more than 177 µmol/L and left ventricular ejection fraction < 40%. Also juxtarenal aneurysms and patients who had had a renal transplant
Interventions	1) HES 200/0.62 (n = 21)

Mahmood 2007 *(Continued)*

	2) HES 130/0.4 (n = 21) 3) Gelatin (n = 20)
Outcomes	Haemodynamic variables Deaths Red cells infused
Notes	Follow-up 5 days, but all-cause mortality reported for 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate 'sealed envelops allocating the fluid type' were opened on the morning of surgery. Recruitment, randomisation, and concealment were carried out by the trial coordinator

Mastroianni 1994

Methods	Randomised controlled trial. No information given on method of randomisation Blinding not mentioned
Participants	34 patients undergoing open heart surgery were enrolled
Interventions	1) 10% Pentastarch. (n = 12) 2) 5% Albumin (n = 17)
Outcomes	Deaths Haemodynamics variables Clotting variables Pulmonary oedema
Notes	Follow-up 7 days 4 patients in the pentastarch group, and 1 patient in the albumin group were excluded after randomisation

Risk of bias

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

Mittermayr 2007

Methods	Randomised controlled trial. Computer-generated randomisation list
Participants	66 patients undergoing major orthopaedic surgery (5 excluded from analysis because of pathological baseline measurements of fibrinogen and platelets)
Interventions	1) Gelatin (n = 21)

Mittermayr 2007 *(Continued)*

	2) HES (n = 19) A third group (n = 21) received RL
Outcomes	Haemodynamic variables RBCs transfused
Notes	-

Risk of bias

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

Moggio 1983

Methods	Randomised controlled trial No loss to follow-up Blinding not mentioned
Participants	47 postoperative open heart surgery patients. Operations performed included coronary revascularisation, valve operations, and combined coronary and valve procedures. Patients with pre-existing hepatic or renal disease were not eligible for the study
Interventions	1) 5% Albumin in 0.9% saline (n = 23) 2) 6% HES in 0.9% saline (n = 24)
Outcomes	Haemodynamic variables Clotting variables
Notes	Follow-up not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Randomised according to the last digit of their hospital identification numbers

Molnar 2004

Methods	Randomised controlled trial Blinding unclear
Participants	30 hypovolaemic patients with ITBVI < 850 in septic shock with ALI Exclusion criteria: CVS failure (NYHA class IV), chronic respiratory failure (chronic hypoxia, hypercapnia) requiring renal replacement therapy, chronic liver failure or those with diabetes mellitus or with known aortic aneurysm
Interventions	1) 6% HES (n = 15) 2) 4% GEL (n = 15)

Molnar 2004 *(Continued)*

	250 mL/15-minute boluses (max 1000 mL) were given until the end point ITBVI > 900 mL/m^2
Outcomes	Death Haemodynamic variables
Notes	Follow-up 60 minutes after the end point was reached. Follow-up for deaths was not clear

Risk of bias

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

Mukhtar 2009

Methods	Randomised controlled trial
Participants	40 patients undergoing living donor liver transplantation. Exclusion criteria: retransplantation, history of previous upper abdominal surgery, portal vein thrombosis, < 18 years old, primary renal dysfunction
Interventions	1) 5% HA (n = 20) 2) 6% HES (n = 20)
Outcomes	Death Haemodynamic variables Renal function
Notes	Final follow-up 4 days postoperatively. Mortality given for 2 weeks postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear 'sealed envelope' (does not say if opaque or sequentially numbered)

Munoz 1980

Methods	Randomised controlled trial Blinding not mentioned No mention of loss to follow-up
Participants	14 patients with shock due to haemorrhage or sepsis
Interventions	1) HES (Hespan) 2) 5% Albumin Number in each group not reported
Outcomes	Haemodynamic variables

Munoz 1980 *(Continued)*

Notes	Follow-up 4 hours post infusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of allocation

Munsch 1988

Methods	Randomised controlled trial. No information given on method of randomisation Blinding not mentioned No loss to follow-up
Participants	40 consecutive patients undergoing elective coronary artery bypass graft surgery
Interventions	1) HES 6% (n = 20) 2) PPF (n = 20) as their postoperative volume expander
Outcomes	Haemodynamic variables Clotting variables Death Adverse reactions
Notes	Follow-up 7 postoperative days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on method of allocation

Niemi 2006

Methods	Randomised controlled trial Blinding not clear
Participants	45 patients post cardiac surgery Exclusion criteria: preoperative coagulation disorders; renal or hepatic failure; or taking medication with coumarin anticoagulants, heparin, salicylic acids, or a combination within the previous 5 days
Interventions	1) 4% HA (n = 15) 2) 4% Gelatine (n = 15) 3) 6% HES (n = 15)
Outcomes	Death (data on death obtained on contact with the author) Clotting variables Blood transfused
Notes	Follow-up 1 postoperative day

Niemi 2006 *(Continued)*

	54 patients gave consent but 9 later excluded

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. Allocation by closed envelope (not enough information provided to classify as adequate)

Ooi 2009

Methods	Randomised single-blind controlled study
Participants	90 patients undergoing coronary artery bypass surgery. Exclusion criteria: repeat coronary artery bypass, congestive heart failure, recent antiplatelet therapy, coagulopathy, renal dysfunction, liver dysfunction, history of pancreatitis, and known hypersensitivity to HES
Interventions	1) 6% HES (n = 45) 2) 4% Gelatin (n = 45)
Outcomes	Death PRBCs transfused Postoperative bleeding and renal function
Notes	Follow-up 1, 2, and 4 postoperative days. Final follow-up at 4 weeks. Information on allocation concealment obtained from study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate 'sealed envelopes' - on contact study author confirmed that envelopes opaque and sequentially numbered

Prien 1990

Methods	Randomised controlled trial Blinding not mentioned Loss to follow-up not mentioned
Participants	18 patients undergoing modified Whipple's operation (hemipancreato-duodenectomy). Patients were eligible for the study if there was an absence of major organ dysfunction and serum protein, sodium, glucose, blood urea nitrogen, haematocrit, aPTT and PT times, and platelet times were within normal limits. Specific exclusion criteria included compensated myocardial insufficiency, chronic hypertension, chronic obstructive airways disease, and insulin-dependent diabetes mellitus
Interventions	1) 10% HES (n = 6) 2) 20% HA (n = 6) A third group were given RL (n = 6) All given as a volume replacement solution, which was given to maintain CVP at the preoperative level
Outcomes	Death (data on death was obtained on contact with the study author)

Prien 1990 *(Continued)*

	Haemodynamic variables Clotting variables
Notes	Follow-up unspecified Study was intraoperative

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information on allocation

Rackow 1983

Methods	Randomised controlled trial Blinding not mentioned
Participants	18 patients with hypovolaemic and septic shock. Patients were excluded if they were < 18 years of age, considered to be in a terminal state, or had a significant coagulopathy
Interventions	1) Albumin (n = 9) 2) HES (n = 9) Patients received 250 mL of the treatment fluid every 15 minutes as a fluid challenge. The fluid challenge ended when the WP equalled 15 mmHg. Thereafter the treatment fluid was given in sufficient quantities to maintain the WP at 15 mmHg for the next 24 hours, at which point the study was completed
Outcomes	Death Haemodynamic variables Respiratory variables
Notes	Deaths given for study period and for length of hospital stay. Survival until discharge was used for the mortality data for this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information on allocation

Rackow 1989

Methods	Randomised controlled trial No loss to follow-up Blinding not mentioned
Participants	20 patients with severe sepsis and systemic hypoperfusion. Patients were excluded from the study if they were < 21 years of age, pregnant, considered to be terminal, or they manifested spontaneous bleeding
Interventions	1) 5% Albumin (n = 10) 2) 10% HES (pentastarch) (n = 10)

Rackow 1989 *(Continued)*

	Each group received 250 mL of the treatment fluid every 15 minutes until either the WP was 15 mmHg or less or a maximum volume of 2000 mL of study colloid was infused
Outcomes	Death Haemodynamic variables Clotting variables Allergic reactions
Notes	Follow-up unspecified

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information on allocation

Reine 2008

Methods	Randomised controlled trial. Computerised randomisation
Participants	38 patients undergoing major orthopaedic, gastrointestinal, or gynaecological surgery
Interventions	1) 20% HA (n = 19) 2) 6% HES (n = 19)
Outcomes	Haemodynamic variables Changes in albumin binding capacity
Notes	Final follow-up first postoperative day (approximately 22 hours)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate, 'randomisation process was handled by the hospital's office for clinical research'

Rittoo 2004

Methods	Randomised controlled trial Blinding-not clear
Participants	40 patients undergoing AAA surgery Exclusion criteria: ejection fraction of < 40% with poor pulmonary function with microalbuminuria and a creatinine concentration of > 150 µmol/L
Interventions	1) 6% HES (n = 20) 2) 4% Gelosulfine (n = 20) All patients received crystalloid. Colloid infused to maintain stable heart rate, CVP 8 cmH_2O to 10 cmH_2O and steady MAP and urine output of

Rittoo 2004 *(Continued)*

	> 40 mL/hour
Outcomes	Lung function Adverse events
Notes	Follow-up 24 hours

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. Allocation by sealed envelopes (not enough information provided to classify as adequate)

Rosencher 1992

Methods	Randomised controlled trial No mention of blinding Loss to follow-up not mentioned
Participants	32 patients undergoing total hip replacement
Interventions	1) 4% Albumin (n = 16) 2) LMW HES (n = 16)
Outcomes	Death (data obtained on contact with study author) Bleeding Clotting variables
Notes	Follow-up 5 postoperative days. Information on allocation concealment was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered, sealed, opaque envelopes

Schortgen 2001

Methods	Randomised controlled trial
Participants	129 patients with severe sepsis or septic shock over 18 years of age. Patients were excluded if they were pregnant, had a history of allergy to HES or gelatin, had severe acute or chronic renal dysfunction, or previous administration of HES or mannitol
Interventions	1) 6% HES (n = 65) 2) 3% Fluid-modified gelatin (n = 64)
Outcomes	Death (data obtained on contact with study author) Length of stay in ICU Acute renal failure

Schortgen 2001 *(Continued)*

Notes	Follow-up while in ICU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation was by sealed opaque envelopes serially numbered and used in sequence

Schramko 2009

Methods	Randomised controlled trial
Participants	45 patients undergoing elective primary cardiac surgery. Exclusion criteria: preoperative coagulation disorder; renal or hepatic failure; received warfarin, heparin, clopidogrel, or acetylsalicylic acid within 5 days before surgery
Interventions	1) 6% HES 200/0.5 (n = 15) 2) 6% HES 130/0.4 (n = 15) 3) 4% HA (n = 15)
Outcomes	Haemodynamic variables PRBCs transfused
Notes	Final follow-up first postoperative morning. Mortality data obtained from study author (relates to study period only, inhospital mortality not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate 'closed envelopes were prepared before the beginning of the study'

Schramko 2010

Methods	Randomised controlled trial
Participants	45 patients undergoing elective cardiac surgery. Exclusion criteria: known coagulation disorder; renal or hepatic failure; preoperative left ventricular ejection fraction < 40%; received warfarin, heparin, clopidogrel, or acetylsalicylic acid within previous 5 days
Interventions	1) 6% HES (n = 15) 2) 4% Gelatin (n = 15) 3) Ringer's acetate (n = 15)
Outcomes	Haemodynamic variables Units of RBC and FFP transfused

Schramko 2010 *(Continued)*

Notes	Follow-up 18 hours postoperatively. Mortality data obtained from study author (relates to study period only, inhospital mortality not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate 'closed envelopes were prepared before the beginning of the study by a person who did not take part in the treatment of the study subjects'

Shatney 1983

Methods	Controlled clinical trial. Patients were assigned to groups in an alternating fashion No loss to follow-up No mention of blinding
Participants	32 patients with multisystem trauma or haemorrhagic shock, or both. Patients with cardiac arrest on hospital admission or during the first 30 minutes after admission were excluded from the study
Interventions	1) PPF 5% solution (n = 16) 2) Hetastarch 6% (n = 16) Study patients continued to receive the assigned colloid solution for the first 8 days whenever colloid was thought necessary
Outcomes	Hepatic, pulmonary and renal function Clotting variables Volume of fluids infused Deaths
Notes	Follow-up 8 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Inadequate. Patients assigned by alternation

Standl 2008

Methods	Randomised controlled trial. Randomisation in blocks of 4 using a 1:1 ratio
Participants	82 children younger than 2 years of age undergoing non-cardiac surgery. Exclusion criteria: intracranial bleeding within 6 weeks prior to randomisation, ASA risk score > 3, pre-existing severe organ insufficiencies, coagulation abnormalities and Hb below critical age-appropriate levels
Interventions	1) HES 130/0.4 (n = 41) 2) 5% HA (n = 41)
Outcomes	Death Haemodynamic variables

Standl 2008 *(Continued)*

	Coagulation variables RBC transfused
Notes	Final follow-up first postoperative day

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate 'sealed randomisation envelopes that were opened by the investigator only after final enrolment of the patient'

Stockwell 1992

Methods	Randomised controlled trial. No information given on method of randomisation No loss to follow-up Blinding not mentioned
Participants	475 patients admitted to the ICU. Patients were excluded from the study if they were < 18 years or if admitted for cardiac monitoring or cardiac thrombolytic therapy
Interventions	1) 4.5% Albumin (n = 226) 2) Synthetic colloid polygeline (Haemaccel) (n = 249) for IV volume replacement
Outcomes	Death Length of stay in ICU Incidence of renal failure Pulmonary oedema
Notes	Follow-up until discharge from ICU

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Stoddart 1996

Methods	Randomised blinded trial Anaesthetist unaware of intervention No loss to follow-up
Participants	30 neonates undergoing major surgery. They were excluded if the body weight < 2 kg or > 5 kg; preoperative Hb < 14 g/dL; they had previously received blood or colloid; or they had suspected major cardiac, renal, metabolic, or chromosomal abnormalities. Neonates were withdrawn from the study if either blood or > 40 mL/kg of colloid was required either during or within the first 24 hour after surgery
Interventions	1) HA 4.5% (n = 15) 2) Haemaccel (n = 15)

Stoddart 1996 *(Continued)*

Outcomes	Haemodynamic variables Plasma albumin Hb
Notes	Follow-up 24 hours postoperatively. Information on allocation concealment was obtained on contact with the study author

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Tollofsrud 1995

Methods	Randomised controlled trial No loss to follow-up Blinding not mentioned
Participants	30 patients undergoing elective coronary artery bypass surgery. Patients with left ventricular ejection fraction < 40%, valvular heart disease, ventricular aneurysm, arrhythmia, diabetes mellitus, renal failure, or lung disease were excluded
Interventions	1) Polygeline (Haemaccel) (n = 10) 2) Dextran 70 (n = 10) 3) Albumin 40 (n = 10) A fourth group received RL (n = 10)
Outcomes	Death Haemodynamic variables Respiratory data Cost of fluid regimens
Notes	Follow-up 48 hours during and after surgery. Information on allocation concealment was obtained on contact with the study authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Sequentially numbered sealed opaque envelopes

Van der Linden 2004

Methods	Randomised controlled trial Blinding not clear
Participants	110 patients (average age 63 years) undergoing cardiac surgery under cardiopulmonary bypass (elective coronary artery or single valve surgery). Exclusion criteria: undergoing combined cardiac surgery or redo operations, history of allergic reactions to starches or gelatins, significant liver or renal dysfunction

Van der Linden 2004 *(Continued)*

Interventions	1) 6% HES (n = 55) 2) 3.5% Urea-lined gelatine (n = 55) If additional colloid required 4.5% HA given
Outcomes	Death Haemodynamic variables Blood transfused
Notes	Follow-up 18 hours after surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. Patients were randomly allocated by opening an envelope (not enough information provided to classify as adequate)

Van der Linden 2005

Methods	Randomised controlled trial Blinding unclear
Participants	132 patients with a preoperative left ventricular ejection fraction > 35% undergoing elective primary cardiac surgery
Interventions	1) 6% HES 130/0.4 (48.9 ± 17.2 mL/kg) (n = 64) 2) 3% GEL (48.9 ± 14.6 mL/kg) (n = 68)
Outcomes	Haemodynamic variables Blood loss Blood transfused
Notes	Follow-up until 5 postoperative days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Veneman 2004

Methods	Randomised controlled trial
Participants	61 critically ill hypoalbuminic patients (serum concentration < 20 g/L)
Interventions	1) Albumin (n = 15) 2) HES 10% 500 mL (n = 15) 3) HES 10% 1000 mL (n = 15) A fourth group received saline

Veneman 2004 *(Continued)*

Outcomes	Death Haemodynamic variables Adverse events (from study author)
Notes	Follow-up 72 hours postoperatively, mortality 30 days

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation by sealed envelopes kept outside of hospital

Verheij 2006

Methods	Randomised controlled trial
Participants	67 patients undergoing either vascular (n = 28) or cardiac surgery (n = 40) Exclusion criteria: age > 79 years and known anaphylactoid reactions to colloids
Interventions	1) 4% Gelatine (n = 16) 2) 6% HES (n = 18) 3) 5% HA (n = 18) A fourth group received normal saline
Outcomes	Death Haemodynamic variables
Notes	Follow-up not clear

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Hospital pharmacy assigned patients via sealed enveloped method

Vogt 1994

Methods	Randomised controlled trial. No information given on method of randomisation
Participants	40 patients undergoing major surgery. Exclusion criteria included anaemia and renal, liver, and coagulation disorders
Interventions	1) 5% HA (n = 20) 2) 6% HES (n = 20)
Outcomes	Haemodynamic variables Coagulation Haematological parameters Blood loss and blood intake
Notes	-

Vogt 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Vogt 1996

Methods	The patients were divided into 2 groups using random numbers Blinding not mentioned No loss to follow-up
Participants	41 patients undergoing total hip arthroplasty during the perioperative period. Exclusion criteria: weight < 60 kg, age < 18 years, ASA grade > 3, haematocrit < 34% or > 44%, history of coagulopathies or a Quick's prothrombin test of < 75%, PTT > 45 seconds, platelet count < 100,000/mm^3, impaired liver function and renal failure
Interventions	1) 6% HES (n = 20) 2) 5% HA (n = 21)
Outcomes	Haemodynamic and clotting variables
Notes	Follow-up 6 hours postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Vogt 1999

Methods	Randomised controlled trial. No information given on method of randomisation
Participants	50 patients undergoing radical prostatectomy or cystectomy with bladder replacement Exclusion criteria: weight < 60 kg; age < 21 years; ASA 1 or 2; Hb < 12 g/dL; history of clotting disorders, liver function disorders, advanced renal insufficiency, or hypoproteinaemia
Interventions	1) 5% HA 2) 6% HES 200/0.5
Outcomes	Haemodynamic variables Blood loss
Notes	Follow-up 3 days

Risk of bias

Bias	Authors' judgement	Support for judgement

Vogt 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Volta 2007

Methods	Randomised controlled study. List of random numbers generated by computer. Patients were managed postoperatively by anaesthetists who were masked to the aims of the study
Participants	36 patients undergoing major abdominal surgery for colon cancer. Exclusion criteria: aged < 18, cardiac insufficiency, kidney dysfunction, altered liver function, preoperative anaemia, preoperative coagulation abnormalities, and long-term use of corticosteroids or NSAIDs
Interventions	1) 3.4% Poligeline (n = 12) 2) HES 130/0.4 (n = 12) A third group received RL (n = 12)
Outcomes	Haemodynamic variables
Notes	Follow-up 72 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. Data on allocation not provided

von Sommoggy 1990

Methods	Randomised controlled trial. No information given on method of randomisation No loss to follow-up
Participants	24 patients undergoing infrarenal aortofemoral bifurcation grafting
Interventions	1) FFP and 5% HA (n = 13) 2) HES 200 10% and HES 450 6% (n = 11)
Outcomes	Haemodynamic variables Clotting variables Influence on organ function
Notes	Follow-up 6 hours postoperatively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Wahba 1996

Methods	Randomised controlled trial. Computerised system was used for randomisation Blinding not mentioned Loss to follow-up not mentioned
Participants	20 patients who had had coronary artery bypass grafting. Patients with abnormal left-ventricular function as judged from cine-angiography were excluded as were patients on anticoagulants < 10 days before the operation
Interventions	1) 5% Albumin (n = 10) 2) Haemaccel (n = 10)
Outcomes	Death (data on death were obtained on contact with the study author) Haemodynamic variables
Notes	Follow-up 2 weeks. Data on method of allocation concealment were obtained on contact with the study author

Risk of bias

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

Watkins 1990

Methods	Randomised controlled trial. No information given on method of randomisation
Participants	12 patients undergoing major surgery
Interventions	1) LMW polystarch 2) Polygelatine (Haemaccel) for postoperative volume replacement
Outcomes	Death Adverse reactions
Notes	Follow-up 24 hours after infusion

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Unclear. No information given on allocation

Woittiez 1997

Methods	Randomised controlled trial
Participants	60 patients who had developed hypoalbuminaemia (< 20 g/L) after major surgery

Woittiez 1997 *(Continued)*

	2 patients died after randomisation and before treatment started. These were excluded from the analysis
Interventions	1) Albumin 20% (300 mL/24 hours) (n = 15) 2) HES 10% (500 mL/24 hours) for 3 days (n = 27) Aim was to restore COP A third group received saline (n = 16)
Outcomes	Death (data on death obtained on contact with the study author) Changes in fluid balance, serum albumin, COP, and clinical signs of oedema were followed daily
Notes	Follow-up unspecified

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Adequate. Allocation by sequentially numbered sealed opaque envelopes

Yang 2011

Methods	Randomised controlled trial. Computer-generated random numbers
Participants	90 patients aged 18 to 75 years with hepatocellular carcinoma scheduled for hepatectomy - received fluids postoperatively. Exclusion criteria: renal insufficiency requiring dialysis, cardiac insufficiency, steroid therapy, pre-existing signs of bacteraemia, and known allergic reactions to starch preparations
Interventions	1) 20% HA (n = 30) 2) 6% HES (n = 30) 3) LR (n = 30)
Outcomes	Death Haemodynamic variables Liver function Inflammatory response parameters
Notes	Follow-up until hospital discharge

Risk of bias

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

AAA: abdominal aortic aneurysm; ALI: acute lung injury; aPPT: activated partial thromboplastin time; ASA: American Society of Anesthesiologists; COP: colloid osmotic pressure; CRF: chronic renal failure; CVP: central venous pressure; CVS: cardiovascular system; EVLW: extravascular lung water; FFP: fresh frozen plasma; HA: human albumin; Hb: haemoglobin; HES: hydroxyethyl starch; HMW: high molecular weight; ICU: intensive care unit; ITBVI: intrathoracic blood volume index; ITT: intention to treat; IV: intravenous; LMW: low molecular weight; LVEDP: left ventricular end diastolic pressure; MMW: medium molecular weight; MAP: mean arterial pressure; MFG: modified fluid gelatin; MI: myocardial infarction; NSAID: non-steroidal anti-inflammatory drug; NYHA: New York Heart Association; PAWP:

pulmonary artery wedge pressure; PAOP: pulmonary artery occlusion pressure; PCWP: pulmonary capillary wedge pressure; PPF: plasma protein fraction; PRBC: packed red blood cell; PT: prothrombin time; RBC: red blood cell; RL: Ringer's lactate; SBP: systolic blood pressure; WP: wedge pressure.

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

Study	Reason for exclusion
Boks 2007	Pump priming for patients undergoing cardiac surgery
Boldt 1993	Pre-bypass volume loading
Boldt 2000b	Compares 2 starches with each other
Boldt 2006	The paper was retracted by the journal as Institutional Review Board approval could not be verified
Boldt 2008	The paper was retracted by the journal as Institutional Review Board approval could not be verified
Brehme 1993	Haemodilution
Bremerich 2000	Compares 2 different starches (acetyl starch with hydroxyethyl starch)
Charlet 1991	Study compared 2 different gelatins with each other and not with other colloids
Christ 1997	Non-randomised trial
Emery 1992	Compares 20% and 4.5% albumin with each other and not with other colloids
Gan 1999	Compares Hextend (a plasma volume expander based upon 6% hetastarch) with 6% hetastarch in saline (HES)
Green 2010	Compares HES versus ringers
Haisch 2001a	The paper was retracted by the journal as Institutional Review Board approval could not be verified
Haisch 2001b	The paper was retracted by the journal as Institutional Review Board approval could not be verified
Hankeln 1990	Haemodilution
Harke 1976	Unable to find out if a randomised controlled trial. Methodology unclear
Hiippala 1996	Patients were expected to have minimal blood loss
Hopkins 1994	Insufficient information to include in review
Huet 2000	Compares 2 starches with each other
Huttner 2000	The paper was retracted by the journal as Institutional Review Board approval could not be verified
Jones 2004a	Haemodilution
Jovanovic 1997	Does not mention if study was randomised. Unable to contact author for further information
Korttila 1984	Healthy volunteers and cross-over trial
Kotzampassi 2008	Not clear how many participants were in each group

Study	Reason for exclusion
Langeron 2001	Compares 2 starches with each other
Palumbo 2006	Authors do not report the number of patients randomised to each group
Puri 1983	There is no mention of a method of randomisation. Just reports "Twenty-five patients studied in each group were well matched"
Rauch 2000	Compares 2 starches with each other
Rehm 2000	Haemodilution
Romero 1999	Does not mention randomisation
Strauss 1985	Healthy volunteers
Vanhoonacker 2009	Pump priming for cardiac surgery
Waxman 1989	Cross-over study
Yap 2007	Pump priming cardiac surgery

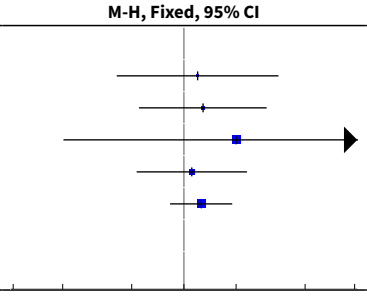
DATA AND ANALYSES

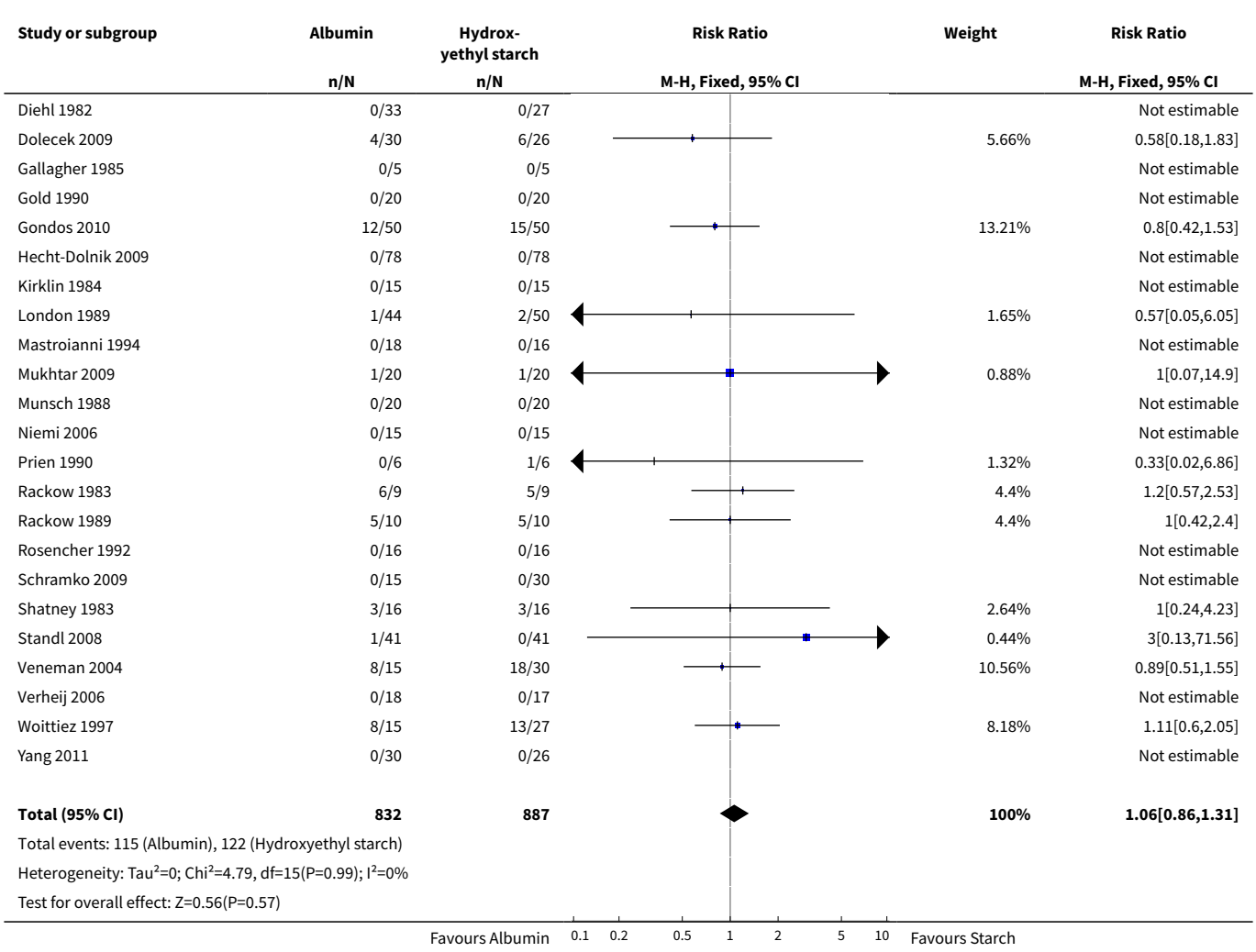
Comparison 1. Albumin or PPF versus HES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	31	1719	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.86, 1.31]
2 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 1.1. Comparison 1 Albumin or PPF versus HES, Outcome 1 Death.

Study or subgroup	Albumin n/N	Hydroxyethyl starch n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boldt 1993a	0/15	0/30			Not estimable
Boldt 1995	6/30	5/30		4.4%	1.2[0.41,3.51]
Boldt 1996a	9/30	7/30		6.16%	1.29[0.55,3]
Boldt 1996b	2/15	1/15		0.88%	2[0.2,19.78]
Boldt 1996c	10/28	9/28		7.92%	1.11[0.53,2.31]
Boldt 1998	39/150	31/150		27.29%	1.26[0.83,1.9]
Brock 1995	0/7	0/14			Not estimable
Brutocao 1996	0/18	0/20			Not estimable





Analysis 1.2. Comparison 1 Albumin or PPF versus HES, Outcome 2 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)

Study	Notes
Arellano 2005	HA group received median of 1 unit each; HES median of 3 units each
Boldt 1998	Total units of red blood cells transfused given for each group (Hetastarch 356, albumin 371). No means, medians, or measures of variation given
Brock 1995	The amount of blood derivatives ('blutderivate') was given in millilitres as a mean and standard deviation (SD). In the 10% starch group the mean was 379 (SD 483), in the 6% starch group the mean was 243 (SD 192) and in the 5% albumin group the mean was 171 (SD 236)
Brutocao 1996	Packed red cell transfusion is given in mL/kg. In the HES group the mean was 0.3, the SD 1.3, and the range of 0 to 6.4. In the albumin group the mean was 1.1, the SD 3.7, and the range 0 to 13.1
Claes 1992	Blood transfused was not recorded. Authors state "none of the patients lost an abnormally large quantity of blood or experienced a clinically perceptible coagulation disorder"

Blood/red cells transfused (skewed or inadequate data)

Study	Notes
Diehl 1982	18% (n = 5) of the albumin group and 15% (n = 5) of the HES group received banked blood during their stay. Blood transfused was recorded as mean number of units per person. In the albumin group this was 0.37 units per person and in the HES group this was 0.36 units per person
Falk 1988	Packed red blood cells transfused at 24 hours was given in millilitres. The albumin group received a mean of 375 with a standard error of the mean (SEM) of 244 and the HES group received a mean of 700 with an SEM 228
Gallagher 1985	Amount of blood products transfused postoperatively was given as a mean in millilitres with the SEM. For the albumin group the mean was 560 (SEM 149.2) and for the starch group the mean was 566 (SEM 72.6)
Gold 1990	Packed red blood cells is given in units. The albumin group received a mean of 2.05 and the HES group received a mean of 2.50
Hecht-Dolnik 2009	Data given as mean number of units (SD) RBC: HES 1.13 (2.52), HA 0.40 (0.89), P = 0.0002 Platelets: HES 0.35 (0.77), HA 0.13 (0.38), P = 0.0001 FFB: HES 0.56 (1.24), HA 0.15 (0.56), P value not significant
Hiippala 1995	Amount of red cell concentrates transfused was given as a mean and SD of millilitres per kilogram body weight (mL/kgBW). For albumin the mean was 20 (SD 14), for 4% HES the mean was 20 (SD 14) and for 6% HES the mean was 25 (SD 17)
Jones 2004	HA group received mean of 0.5 units (range 0 units to 1 unit), HEs group received mean of 1 unit (range of 0 units to 2 units)
Kirklin 1984	The amount of red cells given up to the first 24 hours postoperatively was recorded. In the HES group the mean was 430 with a standard error of 90, and in the albumin group the mean is 440 with a standard error of 76
London 1989	Total postoperative blood transfused is given in millilitres. In the albumin group the figures are given as 838 mL (630 mL) and the HES group 894 mL (600 mL). It does not report what the figures represent (they may be mean and SD). Intraoperatively the blood given in the albumin group was 400 mL (346 mL) and in the HES group 336 mL (400 mL)
Mastroianni 1994	The mean of packed red cells given was recorded in millilitres. For pentastarch the mean was 167 and for albumin it was 234. Another figure was given 163 for pentastarch and 148 for albumin but it was not clear what this represented
Mukhtar 2009	Reported as units of PRBCs, mean and range. Intraoperatively HA 4 (0 to 6), HES 4 (0 to 10), postoperatively HA 4 (0 to 8), HES 2 (0 to 8)
Munsch 1988	The amount of whole blood transfused was given as a median volume. For the albumin group it was 830 mL (range 260 mL to 1800 mL), and for the HES group it was 830 mL (range 50 mL to 1840 mL)
Niemi 2006	The mean and SD of number of RBC units transfused was given. HA mean 0.2 (SD 0.6), HES mean 0.3 (SD 0.6)
Prien 1990	The mean and SEM for the amount of packed red cells given was recorded. For the albumin group the mean was 1.2 (SEM 0.7). In the HES group the mean was 1.8 (SEM 0.7)
Rackow 1983	Total amount of blood transfused was given in millilitres at the end of the maintenance period. For the albumin group the mean was 363.9 (SEM 186) and for the starch group the mean was 757.1 (SEM 201)
Rackow 1989	No data on units transfused. The authors say "there was no evidence of clinical bleeding"
Shatney 1983	The amount of red blood cells transfused was given in a graphical form not figures

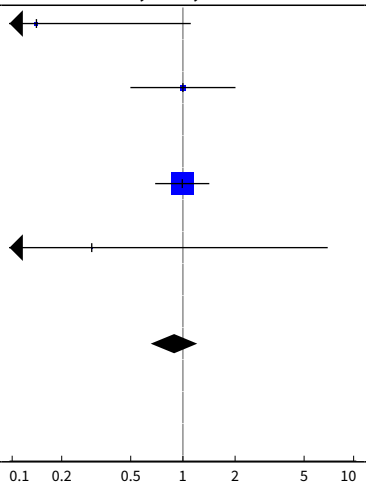
Blood/red cells transfused (skewed or inadequate data)	
Study	**Notes**
Standl 2008	Data given as mean number of units with SD RBC: HES 52.2 (139.2), 53.4 (155.9) FFP: HES 22.4 (117.9), HA 25.2 (90.7) No significant difference between groups
Vogt 1994	Amount of EK given was recorded as a mean and SD of the millilitres given. For the albumin group it was 1138 (SD 763.5), and for the HES group it was 944.4 (SD 466.2)
Vogt 1996	The mean and SD of packed red blood cells transfused was given for the end of surgery and at 6 hours. For the albumin group at the end of surgery the mean was 798 (SD 1147) and at 6 hours it was 1333 (SD 1399). For the HES group at the end of surgery the mean was 763 (SD 923) and at 6 hours the mean was 1538 (SD 1074)
Vogt 1999	Amount of packed red blood cells was given as mean and SD. In the HES group the mean was 1510 mL (SD 765 mL) and in the albumin group the mean was 1410 mL (SD 946 mL)
von Sommoggy 1990	The trialists report 'no increased bleeding in the HES group'

Comparison 2. Albumin or PPF versus gelatin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	9	824	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.21]
2 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 2.1. Comparison 2 Albumin or PPF versus gelatin, Outcome 1 Death.

Study or subgroup	Albumin or PPF n/N	Gelatin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Akech 2006	1/44	7/44		10.27%	0.14[0.02,1.11]
Boldt 1993a	0/15	0/15			Not estimable
Gondos 2010	12/50	12/50		17.61%	1[0.5,2.01]
Karanko 1987	0/15	0/12			Not estimable
Niemi 2006	0/15	0/15			Not estimable
Stockwell 1992	45/226	50/249		69.8%	0.99[0.69,1.42]
Tollofsrud 1995	0/10	0/10			Not estimable
Verheij 2006	0/18	1/16		2.32%	0.3[0.01,6.84]
Wahba 1996	0/10	0/10			Not estimable
Total (95% CI)	**403**	**421**		**100%**	**0.89[0.65,1.21]**
Total events: 58 (Albumin or PPF), 70 (Gelatin)					
Heterogeneity: Tau^2=0; Chi^2=3.97, df=3(P=0.26); I^2=24.46%					
Test for overall effect: Z=0.74(P=0.46)					



Analysis 2.2. Comparison 2 Albumin or PPF versus gelatin, Outcome 2 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)

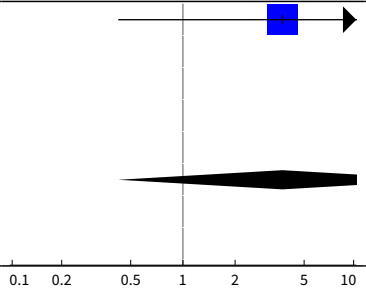
Study	Notes
Evans 2003	No data on amount of units transfused. Author reports that there was no significant difference in the median total blood loss between the groups (P = 0.5587)
Niemi 2006	The mean and standard deviation (SD) of RBC units transfused was given. HA mean 0.2 (SD 0.6), Gel mean 0.2 (SD 0.4)
Stockwell 1992	The volume of blood products given was recorded as a mean with the range also given. In the albumin group the mean was 1.45 L (range 0-29) and in the haemacell group the mean was 1.39 L (range 0 L to 66 L) (P = 0.65, Mann-Whitney U test)
Tollofsrud 1995	The amount of erthrocytes given was recorded as a mean and SD. In the albumin group the mean was 240 (SD 310), and in the polygeline group the mean was 490 (SD 548)

Comparison 3. Albumin or PPF versus dextran

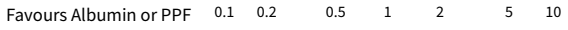
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4	360	Risk Ratio (M-H, Fixed, 95% CI)	3.75 [0.42, 33.09]
2 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 3.1. Comparison 3 Albumin or PPF versus dextran, Outcome 1 Death.

Study or subgroup	Albumin or PPF n/N	Dextran n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Hedstrand 1987	4/142	1/133		100%	3.75[0.42,33.09]
Karanko 1987	0/15	0/10			Not estimable
Lisander 1996	0/20	0/20			Not estimable
Tollofsrud 1995	0/10	0/10			Not estimable
Total (95% CI)	**187**	**173**		**100%**	**3.75[0.42,33.09]**
Total events: 4 (Albumin or PPF), 1 (Dextran)					
Heterogeneity: Not applicable					



Study or subgroup	Albumin or PPF n/N	Dextran n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.19(P=0.23)					



Analysis 3.2. Comparison 3 Albumin or PPF versus dextran, Outcome 2 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)

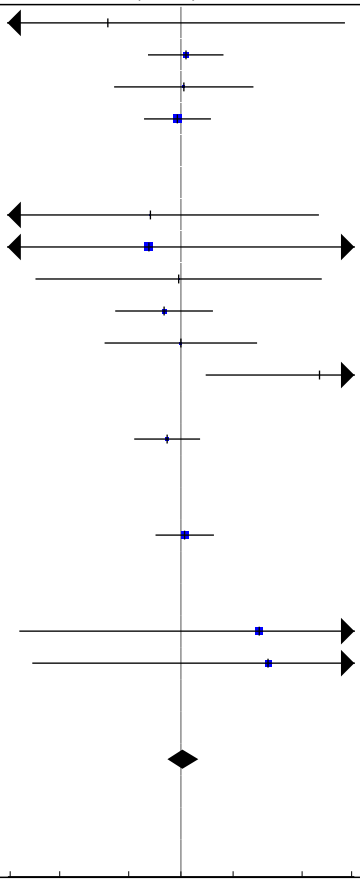
Study	Notes
Hedstrand 1987	The perioperative and postoperative amount of red blood cells transfused was reported as a mean and standard deviation (SD) of units given. For the plasma group the mean was 5.2 (SD 4.8) and for the dextran group the mean was 5.8 (SD 4.4)
Hiippala 1995	Amount of red cell concentrates transfused was given as a mean and SD of millilitre per kilo gram body weight (mL/kgBW). For albumin the mean was 20 (SD 14) and for dextran the mean was 19 (SD 12)
Jones 2004	Mean of 0.5 unit HA (range 0 to 1), mean of 1 for DEX (range 0 to 2)
Lisander 1996	Total red blood cells transfused is given. For the albumin group the mean was 2.3 (SD1.6), in the dextran group the mean was 3.8 (SD 2.4). Red cells autotransfused was also given as 312 (SD 184) in the albumin group and 383 (SD 259) in the dextran group
Tollofsrud 1995	Erythrocytes given was recorded as mean and SD. The mean for the albumin group was 240 (SD 310) and the mean for the dextran group was 390 (SD 417)

Comparison 4. Modified gelatin versus HES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	22	1612	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.84, 1.26]
2 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 4.1. Comparison 4 Modified gelatin versus HES, Outcome 1 Death.

Study or subgroup	Gelatin n/N	Hydroxyethyl starch n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Allison 1999	0/21	1/24		1.21%	0.38[0.02,8.83]
Asfar 2000	12/18	10/16		9.11%	1.07[0.65,1.76]
Beards 1994	6/15	5/13		4.61%	1.04[0.41,2.62]
Berard 1995	31/153	31/146		27.3%	0.95[0.61,1.49]
Beyer 1997	0/22	0/19			Not estimable
Boldt 1993a	0/15	0/30			Not estimable
Boldt 2000	1/50	3/100		1.72%	0.67[0.07,6.25]
Boldt 2001	0/25	1/50		0.87%	0.65[0.03,15.5]
Godet 2008	2/34	2/33		1.75%	0.97[0.15,6.49]
Gondos 2010	12/50	15/50		12.91%	0.8[0.42,1.53]
Inal 2010	5/15	5/15		4.3%	1[0.36,2.75]
Mahmood 2007	6/20	2/42		1.11%	6.3[1.39,28.49]
Mittermayr 2007	0/21	0/19			Not estimable
Molnar 2004	10/15	12/15		10.33%	0.83[0.54,1.29]
Niemi 2006	0/15	0/15			Not estimable
Ooi 2009	0/45	0/45			Not estimable
Schortgen 2001	29/64	28/65		23.91%	1.05[0.71,1.55]
Schramko 2010	0/15	0/15			Not estimable
Van der Linden 2004	0/55	0/55			Not estimable
Van der Linden 2005	1/68	0/64		0.44%	2.83[0.12,68.14]
Verheij 2006	1/16	0/17		0.42%	3.18[0.14,72.75]
Watkins 1990	0/6	0/6			Not estimable
Total (95% CI)	**758**	**854**		**100%**	**1.02[0.84,1.26]**
Total events: 116 (Gelatin), 115 (Hydroxyethyl starch)					
Heterogeneity: Tau^2=0; Chi^2=8.61, df=13(P=0.8); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					



Analysis 4.2. Comparison 4 Modified gelatin versus HES, Outcome 2 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)

Study	Notes
Allison 1999	The mean volume of packed red blood cells (PRBC) transfused was given for each day up to and including the 5th day. For the first postoperative day the hydroxyethyl starch (HES) group received a total of 3067 mL of PRBCs and the gelatine group received 2643 mL of PRBCs
Berard 1995	Blood transfused was given in units, 2.6 units for the gel group and 2.5 units for the HES group (presumably this figure is mean)

Blood/red cells transfused (skewed or inadequate data)

Study	Notes
Beyer 1997	Blood transfused is given in graphical form and not figures
Boldt 2000	The amount of PRBC transfused is given as the total number of units for each group By the first post operative day the number of units of PRBCs transfused was: HES 70: 38 units, HES 200: 40 units, Gelatin: 44 units
Boldt 2001	The amount of PRBC transfused is given as the total number of units for each group By the first post operative day the number of units of PRBCs transfused was: HES 200: 18 units, HES 130: 16 units, Gelatin 18 units
Carli 2000	The amount of PRBC transfused is given as the total number of units for each group 1 unit of blood was given in the gel group and 0 units of blood were given in the starch group
Mahmood 2007	Amount of red cells and FFP is given as median number of units (range) Red cells: HES 200/0.62 = 7.0 (4.5 to 10), HES 130/0.4 = 6.0 (4.0 to 8.0), gelatin = 7.0 (5.25 to 9.75). P = 0.360 (no statistical difference between groups) FFP: HES 200/0.62 = 4 (0 to 6), HES 130/0.4 = 2 (0 to 5), gelatine = 4 (0 to 7). P = 0.420 (no statistical difference between groups)
Mittermayr 2007	Total red cells units transfused Gelatin n = 13, HES n = 9 Number of patients transfused Gelatin n = 8/21, HES n = 3/19
Niemi 2006	The mean and SD of red blood cell (RBC) units transfused was given. Gel mean 0.2 (SD 0.4), HES 0.3 (0.6)
Ooi 2009	Data reported as number of patients who received at least 1 unit PRBCs: HES = 40, gelatin = 42. P = 0.46 FFP: HES = 17, gelatin = 24. P = 0.14 No statistical difference between groups
Schramko 2009	Data given as number of units of RBC and FFP transfused

Blood/red cells transfused (skewed or inadequate data)

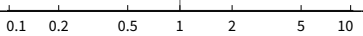
Study	Notes
	RBC: HES 200/0.5 = 11, HES 130/0.4 = 5, HA = 5 FFP: HES 200/0/5 = 1, HES 130/0.4 = 1, HA = 0 No significant difference between groups
Schramko 2010	Data given as number of units of RBC and FFP transfused HES group received 15 units of RBC and 2 units of FFP Gel group received 21 units of RBC and 2 units of FFP No significant difference between groups
Van der Linden 2004	HES group received total of 12 units of PRBC, GEL group received 3 units of PRBC
Van der Linden 2005	No of patients receiving allogenic blood in each group HES group n= 24, GEL n= 21 No of units of PRBC (median and range) HES 0 (range 0-6), Gel 0 (range 0-6)

Comparison 5. Modified gelatin versus dextran

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	3	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 5.1. Comparison 5 Modified gelatin versus dextran, Outcome 1 Death.

Study or subgroup	Gelatin n/N	Dextran n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Gombocz 2007	0/20	0/20			Not estimable
Karanko 1987	0/12	0/10			Not estimable
Tollofsrud 1995	0/10	0/10			Not estimable
Total (95% CI)	**42**	**40**			**Not estimable**
Total events: 0 (Gelatin), 0 (Dextran)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Favours Gelatin — Favours Dextran

Analysis 5.2. Comparison 5 Modified gelatin versus dextran, Outcome 2 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)	
Study	**Notes**
Gombocz 2007	Units of red blood cells transfused Dextran (group A): mean 1.8 (standard deviation (SD) 1.3) Oxypolygelatin (group B): mean 1.6 (SD 1.2) P = 0.548
Tollofsrud 1995	Erythrocytes given was recorded as mean and SD Polygeline: mean 490 (SD 548) Dextran: 390 (SD 417)

Comparison 6. HES versus dextran

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood/red cells transfused (skewed or inadequate data)			Other data	No numeric data

Analysis 6.1. Comparison 6 HES versus dextran, Outcome 1 Blood/red cells transfused (skewed or inadequate data).

Blood/red cells transfused (skewed or inadequate data)	
Study	**Notes**
Hiippala 1995	Amount of red cell concentrates transfused in millilitres/kilogram body weight (mL/kgBW) was given as a mean and standard deviation Dextran mean 19 (SD 12) 4% Starch mean 20 (SD 14) 6% Starch mean 25 (SD 17)

APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Specialised Register (searched: 1 December 2011)
1. (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*)
2. (fluid* or volume or plasma or rehydrat* or blood or oral) and (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)
3. 1 and 2

Cochrane Central Register of Controlled Trials 2011, issue 4 (*The Cochrane Library*)
#1 MeSH descriptor Colloids explode all trees in MeSH products

(Continued)

#2 MeSH descriptor Plasma explode all trees in MeSH products
#3 MeSH descriptor Albumins explode all trees in MeSH products
#4 (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*)
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Fluid Therapy explode all trees in MeSH products
#7 MeSH descriptor Plasma Volume explode all trees
#8 (fluid* or volume or plasma or rehydrat* or blood or oral) near1 (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)
#9 (#6 OR #7 OR #8)
#10 (#5 AND #9)
#11 (#10), from 2007 to 2011

MEDLINE (Ovid) (1948 to November Week 3 2011)

1. exp Albumins/
2. exp plasma/
3. exp colloids/
4. (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*).ti,ab.
5. 1 or 2 or 3 or 4
6. Exp Plasma volume/
7. Exp Fluid Therapy/
8. ((fluid* or volume or plasma or rehydrat* or blood or oral) adj1 (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)).ab,ti.
9. 6 or 7 or 8
10. 5 and 9

EMBASE (Ovid) (1974 to 2011 Week 47)

1. exp ALBUMIN/
2. exp HYDROCOLLOID/
3. exp PLASMA/
4. (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*).ti,ab.
5. 1 or 2 or 3 or 4
6. exp Fluid Therapy/
7. exp Plasma volume/
8. ((fluid* or volume or plasma or rehydrat* or blood or oral) adj1 (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)).ab,ti.
9. 6 or 7 or 8
10. 5 and 9
11. exp Randomized Controlled Trial/
12. exp controlled clinical trial/
13. randomi?ed.ab,ti.
14. placebo.ab.
15. *Clinical Trial/
16. randomly.ab.
17. trial.ti.
18. 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp animal/ not (exp human/ and exp animal/)
20. 18 not 19
21. 10 and 20
22. (2007* or 2008* or 2009* or 2010* or 2011*).em.
23. 21 and 22

ISI Web of Science: Science Citation Index Expanded (1970 to 1 December 2011),
ISI Web of Science: Conference Proceedings Citation Index-Science (1990 to 1 December 2011)

#1 Topic=((colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*)) AND Topic=((fluid* or volume or plasma or rehydrat* or blood or oral) NEAR/1 (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*))
#2 TS=((singl* OR doubl* OR trebl* OR tripl*) NEAR/1 (blind* OR mask*)) OR TS=((clinical OR control* OR placebo OR random*) NEAR/1 (trial* or group* or study or studies or placebo or controlled)) NOT TI=(Animal* or rat or rats or rodent* or mouse or mice or murine or dog or dogs or canine* or cat or cats or feline* or rabbit or rabbits or pig or pigs or porcine or swine or sheep or ovine* or guinea pig*)

(Continued)
#3 #1 and #2

CINAHL (EBSCO) (1982 to 2011)
S1. (fluid* or volume or plasma or rehydrat* or blood or oral) N3 (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)
S2. colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*
S3. S1 and S2 (limit to Publication Type: Randomized Controlled Trial)

PubMed [www.ncbi.nlm.nih.gov/sites/entrez/] (searched 1 December 2011: Limit-Humans, published in the last 90 days)
#1((randomized controlled trial[pt] OR controlled clinical trial[pt]) OR (randomized OR randomised OR randomly OR placebo[tiab]) OR (trial[ti]) OR ("Clinical Trials as Topic"[MeSH Major Topic])) NOT (("Animals"[Mesh]) NOT ("Humans"[Mesh] AND "Animals"[Mesh]))
#2 (fluid* or volume or plasma or rehydrat* or blood or oral) and (replac* or therapy or substitut* or restor* or resuscitat* or rehydrat*)
#3 (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*)
#4 (("Albumins"[Mesh]) OR "Colloids"[Mesh]) OR "Plasma"[Mesh]
#5 #3 or #4
#6 #1 and #2 and #5

NRR up to issue 1, 2007
#1 (colloid* or albumin* or albumen* or plasma* or starch* or dextran* or gelofus* or hemacc* or haemacc* or hydrocolloid*)
#2 ((plasma* or fluid* or volum*) and (therap* or restor* or resuscita* or substitut* or replac*))
#3 #1 and #2

ZETOC searched on 23 March, 2007
Colloid* fluid* resusc*

WHAT'S NEW

Date	Event	Description
16 October 2012	Amended	Minor copy edits made to analysis labels

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 2, 1999

Date	Event	Description
12 June 2012	New citation required but conclusions have not changed	Due to the retraction of four studies (Boldt 2006; Haisch 2001a; Haisch 2001b; Huttner 2000), the review has been amended. The retracted studies, and their associated data, are now excluded from the review. The conclusions of the review have not changed.
1 May 2012	New citation required but conclusions have not changed	The review has been updated to December 2011. Twenty additional studies have been included (Akech 2006; Dolecek 2009; Friedman 2008; Godet 2008; Gombocz 2007; Gondos 2010; Haas 2007; Hecht-Dolnik 2009; Inal 2010; Jin 2010; Mahmood 2007; Mittermayr 2007; Mukhtar 2009; Ooi 2009; Reine 2008; Schramko

Date	Event	Description
		2009; Schramko 2010; Standl 2008; Volta 2007; Yang 2011). The conclusions of the review have not changed.
30 April 2012	New search has been performed	The review has been updated to December 2011.
10 February 2011	New citation required but conclusions have not changed	The editorial group is aware that a clinical trial by Prof. 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 which 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 (Boldt 1986, Boldt 1993a, Boldt 1995, Boldt 1996a, Boldt 1996b, Boldt 1996c, Boldt 1998, Boldt 2000, Boldt 2001, Boldt 2006a, Haisch 2001c, Haisch 2001c, Huttner 2000a) on the conclusions of the review.
11 July 2008	Amended	Converted to new review format.
2 October 2007	New search has been performed	The search for the review was updated in March 2007 and thirteen new studies were added to the review.

CONTRIBUTIONS OF AUTHORS

FB screened citations for eligibility, obtained references, contacted authors, extracted data, entered data and wrote the review. DT screened citations for eligibility and extracted data. PA, VH, and SA contributed to earlier versions of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of Hertfordshire, UK.

External sources

- NHS Research and Development Programme, UK.

NOTES

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 which 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 (Boldt 1986; Boldt 1993a; Boldt 1995; Boldt 1996a; Boldt 1996b; Boldt 1996c; Boldt 1998; Boldt 2000; Boldt 2001; Boldt 2006a Haisch 2001c Haisch 2001c Huttner 2000a) on the conclusions of the review.

Emma Sydenham, Managing Editor, performed the sensitivity analysis in 2011. The authors agreed with the changes to the manuscript.

INDEX TERMS

Medical Subject Headings (MeSH)

Blood Proteins [therapeutic use]; Colloids [*therapeutic use]; Dextrans [therapeutic use]; Fluid Therapy [*methods] [mortality]; Hydroxyethyl Starch Derivatives [therapeutic use]; Plasma Substitutes [*therapeutic use]; Randomized Controlled Trials as Topic;

Rehydration Solutions [therapeutic use]; Resuscitation [*methods] [mortality]; Serum Albumin [therapeutic use]; Serum Albumin, Human; Serum Globulins [therapeutic use]

MeSH check words

Humans