Fluid resuscitation with colloid or crystalloid solutions in critically ill patients: a systematic review of randomised trials

Schierhout G, Roberts I

Authors' objectives
To determine the effect on mortality of resuscitation with colloid solutions compared with resuscitation with crystalloids.

Searching
The Cochrane Controlled Trials Register, MEDLINE, EMBASE and Index to Scientific and Technical Proceedings (via BIDS) were searched up until June 1997 (further search details available on request from authors). In addition 29 international journals were handsearched along with the proceedings of several international meetings on fluid therapy. The reference lists of trials and review articles were also checked and authors were contacted for information about other published and unpublished trials. There were no language restrictions.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and quasi-RCTs were included. Randomised crossover trials were excluded as were trials of pre-loading in preparation for elective surgery and trials in patients undergoing fluid loading during cardiopulmonary bypass. Authors were contacted for further information where the method of randomisation was not clearly stated. The length of follow-up of those trials included in the review varied from 1 day to 5 years, but most of the trials only followed participants to discharge (n=9 studies).

Specific interventions included in the review
Various colloid and crystalloid (hypertonic and isotonic) resuscitation fluids. Colloids included dextran in Ringer's solution, Haemacell, hydroxyethyl starch, albumin in Ringer's solutions (various compositions of solutions). Crystallids included Ringer's solution, NaCl and dextrose (various compositions of solutions). Interventions or combinations of interventions were compared with each other, including comparisons such as colloid in hypertonic crystalloid with isotonic crystalloid, isotonic crystalloid with hypertonic crystalloid. Trials with a 'double' intervention e.g. colloid in hypertonic crystalloid with isotonic crystalloid were considered as confounded and were analysed separately (see extra data and analysis at http://www.bmj.com/content/316/7136/961/related)

Participants included in the review
Critically ill patients (excluding neonates) requiring fluid resuscitation. Patients included those with trauma and burns, those undergoing surgery or those with other critical conditions such as complications of sepsis, adult respiratory distress syndrome and vascular leak syndrome.

Outcomes assessed in the review
All cause mortality at the end of the follow-up period.

How were decisions on the relevance of primary studies made?
Two reviewers independently determined the relevance of the studies and disagreements were resolved by discussion.

Assessment of study quality
The level of allocation concealment was assessed. The adequacy of allocation concealment was assessed using the criteria of Schulz (see Other Publications of Related Interest no.1). The trials were awarded either one, two or three points, three points suggesting that the allocation concealment was adequate. The authors do not state how many of the reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data from the studies and disagreements were resolved by discussion. Tables
reported in the review include the following information: bibliographic details, number of participants, intervention details, length of follow-up, type of injury, mortality rate and adequacy of allocation concealment. Authors were contacted for additional information where necessary.

**Methods of synthesis**

How were the studies combined?

Pooled relative risks (RRs) and 95% confidence intervals (CI) were calculated on an intention to treat basis using the Mantel-Haenszel method. Pooled RRs were presented for both all studies regardless of injury type and for the different types of injuries. The regression approach to assessing funnel plot asymmetry proposed by Egger et al (see Other Publications of Related Interest no.2), was used to assess publication bias.

How were differences between studies investigated?

A chi-squared test, with p equivalent to 0.05 or less indicating significant heterogeneity, was used. When no significant heterogeneity was detected a fixed-effect model was used to pool the data. In the event of significant heterogeneity if the heterogeneity was obviously related to the type of injury or allocation concealment the analyses were stratified according to these dimensions. Graphical displays for the summary effect measures of individual trials were also presented in view of the lack of power associated with statistical tests of heterogeneity.

**Results of the review**

Thirty-seven RCTs (n=1622 participants) were included in the review, of which 26 were unconfounded comparing colloids with crystalloids (n=1622 participants). Seven trials were in trauma patients (n=661 participants), 12 in surgery patients (n=366 participants), four in burns patients (n=416 participants), and three in other patients (n=179 participants).

The eleven confounded trials included ten trials comparing colloid in hypertonic crystalloid with isotonic crystalloid (n=1422 participants) and one trial comparing colloid in isotonic crystalloid with hypertonic crystalloid (n=38 participants). Only the results for the 26 unconfounded studies were presented in this article the remaining studies were described on the BMJ website (http://www.bmj.com/content/316/7136/961).

Only the results of the 26 unconfounded studies were presented (see http://www.bmj.com/content/316/7136/961 for further details of the remaining confounded trials).

**Risk of death:**

- Trauma patients (n=6 studies): RR=1.30 (95% CI: 0.95, 1.77), chi-square=1.68 (df=4).
- Surgery patients (n=7 studies): RR=0.55 (95% CI: 0.18, 1.65), chi-square=1.75 (df=5).
- Burns patients (n=4 studies): RR=1.21 (95% CI: 0.88, 1.66), chi-square=4.63 (df=3).
- Other patients (n=2 studies): RR=1.08 (95% CI: 0.73, 1.61), chi-square=1.48 (df=1).
- All patients (n=19 studies): RR=1.19 (95% CI: 0.98, 1.45), chi-square=11.67 (df=16).

Only trials with adequate concealment of allocation (n=4 studies): RR=1.29 (95% CI: 0.94, 1.77).

**Publication bias:**

The regression approach to funnel plot asymmetry yielded an intercept of 0.006 and P=0.308, indicating no statistical evidence for publication bias.

**Quality of the studies:**

Only four of the 26 unconfounded RCTs were classed as having adequate allocation concealment (i.e. a score of 3 points). Six RCTs only scored one point for allocation concealment and the remaining 16 trials scored two points.
Cost information
The authors state in their conclusions that colloids are considerably more expensive than crystalloids, but they do not present any cost data.

Authors' conclusions
Resuscitation with colloid solutions was associated with an absolute increase in the risk of mortality of 4% (95% confidence interval 0% to 8%), or four extra deaths for every 100 patients resuscitated. As colloids are not associated with improved survival and are considerably more expensive than crystalloids, it is hard to see how their continued use outside randomised controlled trials in subsets of patients of particular concern can be justified.

CRD commentary
This is well conducted and clearly presented review. A thorough search was made for both unpublished and published material, thereby reducing the risk of publication bias and no language restrictions were used. In addition, to confirm the low risk of publication bias the authors reported the findings of funnel plots (regression approach). The inclusion/exclusion criteria are clearly stated and the methods used to select studies, assess validity and extract data are reported, with the exception of the number of authors involved in assessing study validity. Only randomised or quasi-randomised trials were included in the review and the quality of the studies was rated in terms of the adequate concealment of treatment allocation. The issue of confounding comparisons is discussed and only data from unconfounded studies were presented in the paper. Details of the confounded studies were available on the Internet. Information regarding the other confounded studies was however available on the journal's web pages.

Considering the data presented the studies would appear to have been pooled appropriately and the authors have considered the issue of heterogeneity between the studies. The findings of the review would therefore appear to be reasonable.

Implications of the review for practice and research
Practice: The authors state that 'compared with crystalloids, use of colloids was associated with an increase in absolute risk of mortality of 4%'. Also 'there was no evidence for differences of effect among different types of injury necessitating fluid resuscitation'.

Research: The authors do not state any implications for research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.