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# Colloids versus crystalloids as priming solutions for cardio-pulmonary bypass : a meta-analysis of prospective, randomised clinical trials

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**Summary** : Using Cochrane methodology a review was performed of prospective randomized clinical trials comparing colloidal pump priming solutions for cardiopulmonary bypass. Dextrans were not considered. Database searches from 1966 through December 2002 delivered 265 articles. Seventeen studies finally met the eligibility criteria involving 997 patients. Summary odds ratio estimates from the 5 studies reporting mortality were 1.46 (n = 326 ; *95%-Confidence-Interval* : .55 to 3.85 ; p = .49) for crystalloids against colloids and .74 (n = 150 ; *95%-Confidence-Interval* : .17 to 3.36 ; p = .49) for albumin versus synthetic colloids. Most commonly used outcome measures further included postoperative blood loss, platelet-count, fluid-balance and, colloid osmotic pressures from which Standardized Mean Differences (SMD) and their 95%-Confidence-Interval (95%CI) were extracted. Colloids produced significantly higher oncotic pressures and less positive fluid-balances. Although across 9 studies postoperative bleeding between colloids and crystalloids did not differ (n = 663 ; SMD : -.03, 95%CI : -.18 to .12 ; p = .69), platelet counts significantly favoured crystalloids (n = 465 ; SMD :-.42 ; 95%CI : -.68 to -.16 ; p = .00). However, compared to albumin platelet counts were significantly disfavoured only by starches (n = 321 ; SMD : -.55 ; 95%CI : -.77 to -.32 ; p = .00). To conclude, using mere crystalloids produced more pronounced positive fluid balances and their avoidance as a single pump-prime component can be suggested. Since albumin is not necessarily associated with better outcomes and is more expensive, it is hard to continue its use. However, there is still insufficient evidence available to allow definitive conclusions.

**Key words** : Meta Analysis ; Albumin ; Colloids, hydroxy-ethyl-starch, gelatine ; Cardiopulmonary bypass, fluids, priming.

## Introduction

Recent meta-analyses demonstrated adverse effects on outcome of using colloids (8, 41, 51). By contrast, the results of an older meta-analysis by Velanovich concluded colloids were rather beneficial during elective surgery but not in trauma resuscitation (49). The latter is again in agreement with the more recent findings by Choi (9). Controversial conclusions result from ignoring underlying differences between subgroups, requiring separate analyses.

Therefore, although still a matter of debate (4, 6, 50), colloids might have advantages in well-defined sub-populations such as these exposed to cardio-pulmonary-bypass [CPB] (2, 12, 42, 44). Maintaining acceptable oncotic pressures during CPB should contribute to more optimal fluid balances and better clinical outcomes (20, 21, 38). On the other hand, some colloids known to have already negative effects *per se* on blood coagulation and platelet function may aggravate the CPB related effects on the haemostatic system (7, 10, 26, 52).

The actual meta-analysis tested mainly the following hypotheses :

(I) using colloids for the CPB pump-prime is more beneficial than crystalloids and,

(II) the choice of the pump-prime can modify postoperative blood-loss.

Only comparative trials of fluid loading during cardiopulmonary bypass were included, to avoid interferences with conditions in which fluids were given for other purposes.

## Methods

Following the Cochrane methodology (36) a review was performed of relevant comparative, prospective clinical trials available by December 2002 that included either albumin (**ALB**) or hydroxy-ethyl-starches (**HES**) or gelatines (**GEL**)

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*Table I*

Major end-points of the included prospective, randomized clinical trials

| Reference | Patients (n) | Major comparable end-points shared within the different trials |
|---|---|---|
| Boldt [3] | 46 | Postoperative Bloodloss, Platelet Counts and Function |
| Hallowell [11] | 62 | Mortality, Fluidbalance |
| Himpe [18] | 105 | Mortality, Postoperative Bloodloss, Platelet Counts, Colloid Osmotic Pressure, Acid-base status |
| Hoeft [19] | 20 | Colloid Osmotic Pressure, Extra Vascular Lung Water, |
| Jansen [20] | 20 | Postoperative Bloodloss, Fluid Balance, Colloid Osmotic Pressure, Clinical Score & Hospitalstay |
| Kuitunen [25] | 45 | Postoperative Bloodloss,Platelet Counts |
| London [28] | 90 | Mortality, Postoperative Bloodloss, Platelet Counts, Fluid Balance & Hospitalstay |
| Marelli [30] | 100 | Mortality, Postoperative Bloodloss |
| Öhqvist [31] | 14 | Fluid Balance, Colloid Osmotic Pressure |
| Palanzo I [32] | 79 | Postoperative Bloodloss, Platelet Counts, Colloid Osmotic Pressure |
| Palanzo II [33] | 84 | Postoperative Bloodloss, Platelet Counts |
| Sade [37] | 83 | Postoperative Bloodloss, Platelet Counts, Body Weight Gain (Fluidbalance), Colloid Osmotic Pressure |
| Saunders [39] | 20 | Postoperative Bloodloss, Platelet Counts, Body Weight Gain (Fluidbalance) |
| Scott [43] | 93 | Postoperative Bloodloss, Platelet Counts, Fluidbalance |
| Tabuchi [45] | 60 | Postoperative Bloodloss |
| Tigchelaar [46] [47] | 36 | Postoperative Bloodloss, Fluid Balance, Colloid Osmotic Pressure |
| Tollofsrud [48] | 40 | Mortality, Postoperative Bloodloss, Fluid Balance |
| Total : | 997 | |

as components of the CPB pump-prime. Dextrans were not considered. A search of bibliographic databases (MEDLINE & EMBASE) and other resources such as conference reports and abstracts was performed. Also examined were the references in colloid-related prior published meta-analyses (8, 9, 41, 49, 51, 52).

*End Points*

Mortality, if reported, was considered a major outcome. Other commonly retrieved end-points consisted of fluid balance, colloid osmotic pressure, blood-loss and, platelet-count after cardiopulmonary bypass. Based on statistical grounds, a pool of 150 individual patients sharing a given end-point across several studies was considered a minimum to allow valid meta-analysis (35).

*Statistical Analysis*

In the case of reported mortality the odds ratios were obtained. For continuous data such as blood loss and fluid balances, the Standardized Mean Difference (SMD) and its 95% confidence interval (95%CI) between the randomized groups was calculated. This standardization transforms study results to a common scale (standard deviation units) facilitating the pooling of data (23, 35). According to Wilkes, it is appropriate for comparisons across studies that report fluid balance data or postoperative bleeding in different units using different measurement methods or apply techniques associated with substantial differences in, for instance, recorded blood-loss (52). Heterogeneity between trials was taken into account (15). Forest-plots express Standardized Mean Differences (SMD) per study as boxes scaled according to weighting. Error bars indicate 95% confidence intervals. Summary estimates are shown at the bottom as diamonds that span the confidence interval. The specialized software package ***Comprehensive Meta-Analysis*** (Biostat, NJ, USA) was used for the necessary calculations and transformations.

## Results

From 265 references a set of 21 prospective, comparative clinical trials were selected. Due to duplicate publication one study was dropped from the analysis (47). Another publication on complement activation could not be factored in since none of the other selected studies shared this particular end-point (5). The studies respectively by Abbott (1) on intra-ocular pressure and by Lumb (29) on extra-vascular lung-water (EVLW) were excluded for similar reasons.

Seventeen eligible trials finally remained, including 997 patients prospectively studied (Table I). The enrolment of the study with the relevant steps of hypothesis testing is displayed in figure 1.

Table II summarizes the different prime compositions of the included trials. Priming fluid regimens vary widely. In most institutions, pump circuits are filled up with a quantity of crystalloids, to which one or more units of a colloid are added

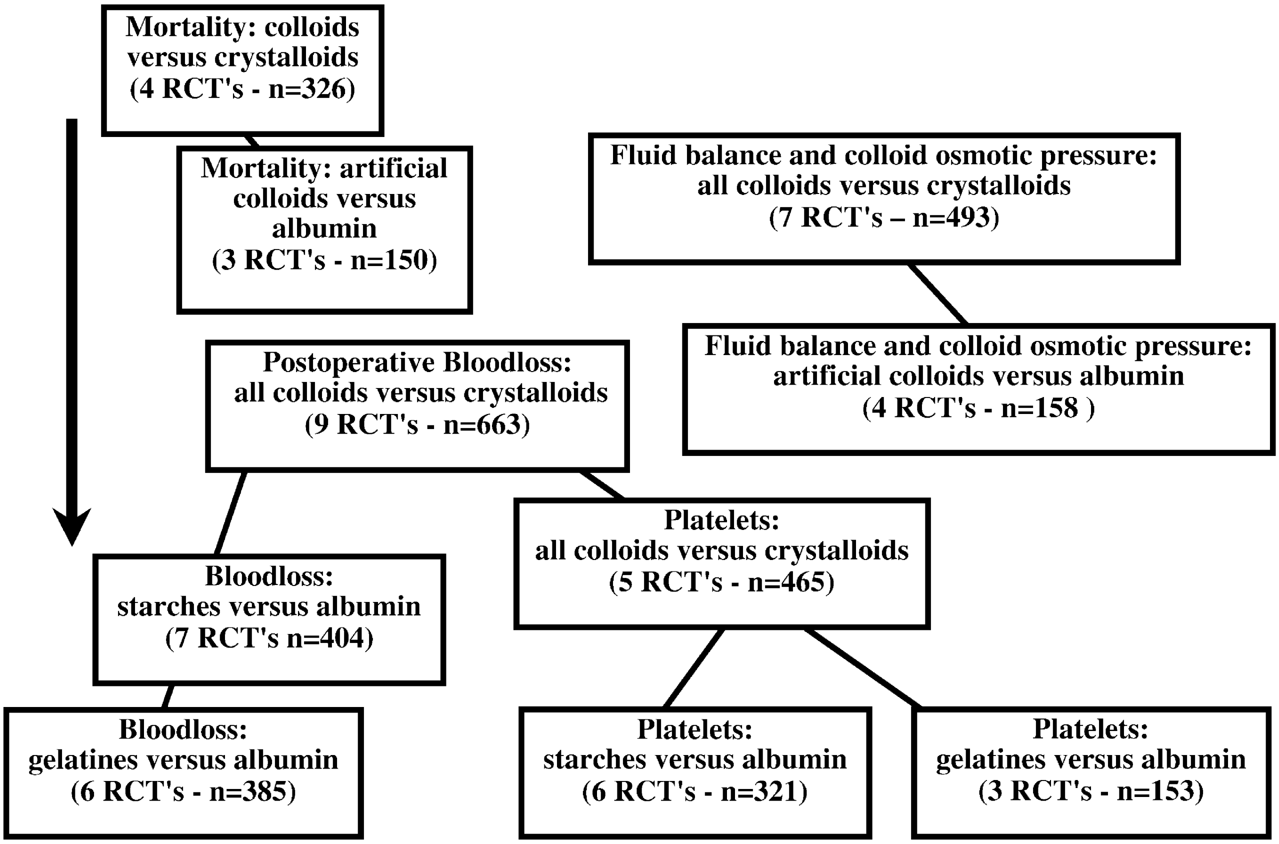


Fig. 1. — Flowchart representing the sequences, direction and, the different steps of the relevant hypotheses tested. The numbers of Randomized Controlled Trials (RCT) and patients (n) involved at each stage of the meta-analysis are noted between brackets.

arbitrarily. Depending on which colloid and what amount of it supplemented, the oncoticity of the final mixtures may vary consistently. In 3 studies the commercially available (iso-oncotic) synthetic colloidal solutions were used as such without mixing them with other fluids (18, 45, 46).

Data on mortality are available from 5 studies (11, 18, 28, 30, 48). As illustrated by the forest-plots in figure 2 no differences could be demonstrated between either crystalloids or colloids and, more specific, between albumin and all artificial colloids combined. Mortality was never related to adverse effects during or immediately after CPB. None of the included studies reported allergic reactions.

In all comparisons, all indicators of fluid-balance are favouring the colloidal prime regimens ($p < 0.05$), which was associated with significantly higher colloid osmotic pressures [COP] during CPB (see Fig. 3). No differences, however, could be demonstrated between albumin and artificial colloids both for the fluid-balance across 7 studies (n=260 ; SMD : -.19 ; 95%CI : -.63 to .23, p= .36) and the oncotic pressure across 5 studies (n=248 ; SMD : .015 ; 95%CI : -1.17 to 1.21 ; p= .98).

No overall differences were found in the 9 studies comparing postoperative bleeding between colloids and crystalloids used as a CPB prime (n = 663 ; SMD : -.03, 95%CI : -.18 to .12 ; p = .69). A separate comparison of starches and gelatines to the golden standard albumin revealed no differences in postoperative blood-loss in respectively seven and six pooled studies (starch *vs* albumin : n = 404 ; SMD : -.05 ; 95%CI : -.29 to .19 ; p = .68 and, gelatine *vs.* albumin : n = 385 ; SMD : -.03 ; 95%CI : -.23 to .17 ; p = .76).

Platelet counts by the end of CPB favoured significantly crystalloids when compared to colloids (n = 465 ; SMD : -.42 ; 95%CI : -.68 to -.16 ; p = .0016). As shown in figure 4, however, platelet counts only significantly favoured albumin when solely compared to starch (6 trials). By contrast, comparing platelet counts between gelatine and albumin primes, no differences could be demonstrated (3 trials).

End-points like hospital-stay, clinical scores and, acid-base status did not reach an acceptable minimum pool of subjects for a valid meta-analysis.

*Table II*

Characteristics and individual composition of the different prime study-groups from the included prospective, randomized clinical trials. Roman numbers refer to the different sub-groups compared per trial

| Reference | Albumin | Starch | Gelatine | Crystalloids |
|---|---|---|---|---|
| Boldt [3] | I : 250 mL<br>5% human albumin ;<br>1000 mL Ringer's ;<br>1000 mL<br>Dextrose 5% ;<br>II : 400 mL<br>20% human albumin ;<br>1850 mL Ringer's | III. 500 ml 10%<br>low molecular<br>weight starch 1750 mL Ringer's<br>200.000 ;<br>1750 mL Ringer's | IV. 500 mL 3.5%<br>polygeline ; | V. 2250 mL<br>Ringer's |
| Hallowel [11] | I. 200 mL<br>25% human albumin ;<br>2800 mL Ringer's lactate ;<br>10 ml Dextrose 50% | | | II. 3000 mL<br>Ringer's lactate ;<br>10 ml Dextrose 50% |
| Himpe [18] | I. 300 mL<br>20% human albumin ;<br>1900 mL Hartmann ; | | II. 2200 mL 3.5%<br>polygeline ;<br>III. 2200 mL 3%<br>succinylated<br>gelatine in a<br>balanced electrolyte<br>solution with lactate | |
| Hoeft [19] | I. 400 mL<br>20% human albumin ;<br>1000 mL Ringer's lactate ;<br>100 ml Bicarbonate ;<br>500 ml Dextrose 5% | | | II. 1400 mL<br>Ringer's lactate ;<br>100 ml Bicarbonate ;<br>500 ml Dextrose 5% |
| Jansen [20] | | | I. 1000 mL 4%<br>succinylated<br>gelatine in saline ;<br>500 mL Ringer's<br>lactate ;<br>50 mL 8.4%<br>sodium bicarbonate ;<br>100 mL 20%<br>mannitol | II. 1500 mL<br>Ringer's lactate ;<br>50 mL 8.4%<br>sodium bicarbonate ;<br>100 mL 20%<br>mannitol |
| Kuitunen [25] | | I. 20 mL/kg 6%<br>low molecular<br>weight starch<br>120.000 ;<br>Ringer's acetate<br>up to 2000 mL<br>II. 20 mL/kg 6%<br>high molecular<br>weight starch<br>400.000 ;<br>Ringer's acetate<br>up to 2000 mL | | III. 2000 mL<br>Ringer's acetate |
| London [28] | I. 300 mL 25%<br>human albumin ;<br>1700 mL<br>Ringer's lactate | II. 750 mL<br>10% pentastarch<br>in 0.9% saline ;<br>1250 mL<br>Ringer's lactate | | III. 2000 mL<br>Ringer's lactate |
| Marelli [30] | I. 200 mL 25%<br>human albumin ;<br>? mL<br>Ringer's lactate | | | II. ? mL<br>Ringer's lactate |
| Öhqvist [31] | I. 200 mL 20%<br>human albumin ;<br>1800 mL<br>Ringerdex | | | II. 2000 mL<br>Ringerdex |

*Table II* — Continued

| Reference | Albumin | Starch | Gelatine | Crystalloids |
|---|---|---|---|---|
| Palanzo I [32] | I. 300 mL 25%<br>Human albumin ;<br>1600 mL<br>Ringer's lactate ;<br>45 mEq bicarbonate | II. 1000 mL 6%<br>high molecular weight<br>(heta) starch ;<br>800 ml Ringer's lactate ;<br>100 mL 50% dextrose ;<br>45 mEq bicarbonate | | |
| Palanzo II [33] | I. 300 mL 25%<br>Human albumin ;<br>1500 mL<br>Ringer's lactate ;<br>100 mL<br>50% dextrose ;<br>45 mEq bicarbonate | II. 1000 mL 6%<br>high molecular weight<br>hetastarch ;<br>800 ml Ringer's lactate ;<br>100 mL<br>50% dextrose ;<br>45 mEq bicarbonate | | |
| Sade [37] | I. 800 mL/m²<br>hydroxyethylstarch ;<br>Ringer's lactate<br>up to 2500 mL | | | II. 2500 mL<br>Ringer's lactate |
| Saunders [39] | I. 200 mL 25%<br>human albumin ;<br>1800 mL<br>Plasmalyte A ;<br>50 g mannitol | II. 1000 mL 6%<br>high molecular weight<br>hydroxyethylstarch ;<br>1000 mL<br>Plasmalyt A ;<br>50 g mannitol | | |
| Scott [43] | I. 1000 mL 4.6%<br>human albumin ;<br>1000 mL<br>Plasmalyte | | | II. 2000 mL<br>Plasmalyte |
| Tabuchi [45] | I. 400 mL 20%<br>human albumin ;<br>1500 ml<br>Ringer's lactate<br>Ibis. Idem plus<br>Aprotinin | | II. 2000 mL<br>oxypolygelatine<br>IIbis. Idem plus<br>aprotinin | |
| Tigchelaar [46] [47] | human albumin ;<br>1600 ml<br>Ringer's lactate | I. 400 mL 20%<br>low molecular<br>weight starch<br>200.000 ;<br>1500 mL<br>Ringer's lactate | II. 500 mL 6%<br>succinylated<br>gelatine in<br>Ringer's lactate | III. 2000 mL 3% |
| Tollofsrud [48] | I. ? mL<br>4% human albumin<br>to keep CPB volume<br>above minimum ;<br>2000 mL<br>Ringer's acetate | | II. ? mL<br>3.5% polygeline<br>to keep CPB volume<br>above minimum ;<br>2000 mL<br>Ringer's acetate | III. ? mL<br>Ringer's acetate to<br>keep CPB volume<br>above minimum :<br>2000 mL<br>Ringer's acetate |

## Discussion

The majority of the included trials addressed non-mortality (intermediate) outcome measures reporting significant differences between priming fluids. Amongst the retrievable variables analysed, blood-loss is arguably one of the most common and clinically relevant outcomes after cardiac surgery (7, 10, 52).

Blood-loss after cardiac surgery can be the result of either incomplete surgical haemostasis or an acquired transient platelet dysfunction (3, 26). Albumin was long considered the fluid of choice to reduce these undesired effects on platelets (12, 34). In this meta-analysis however, significantly higher platelet counts were found with crystalloids compared to all colloids combined. This can in part be explained by a more pronounced haemo-dilution

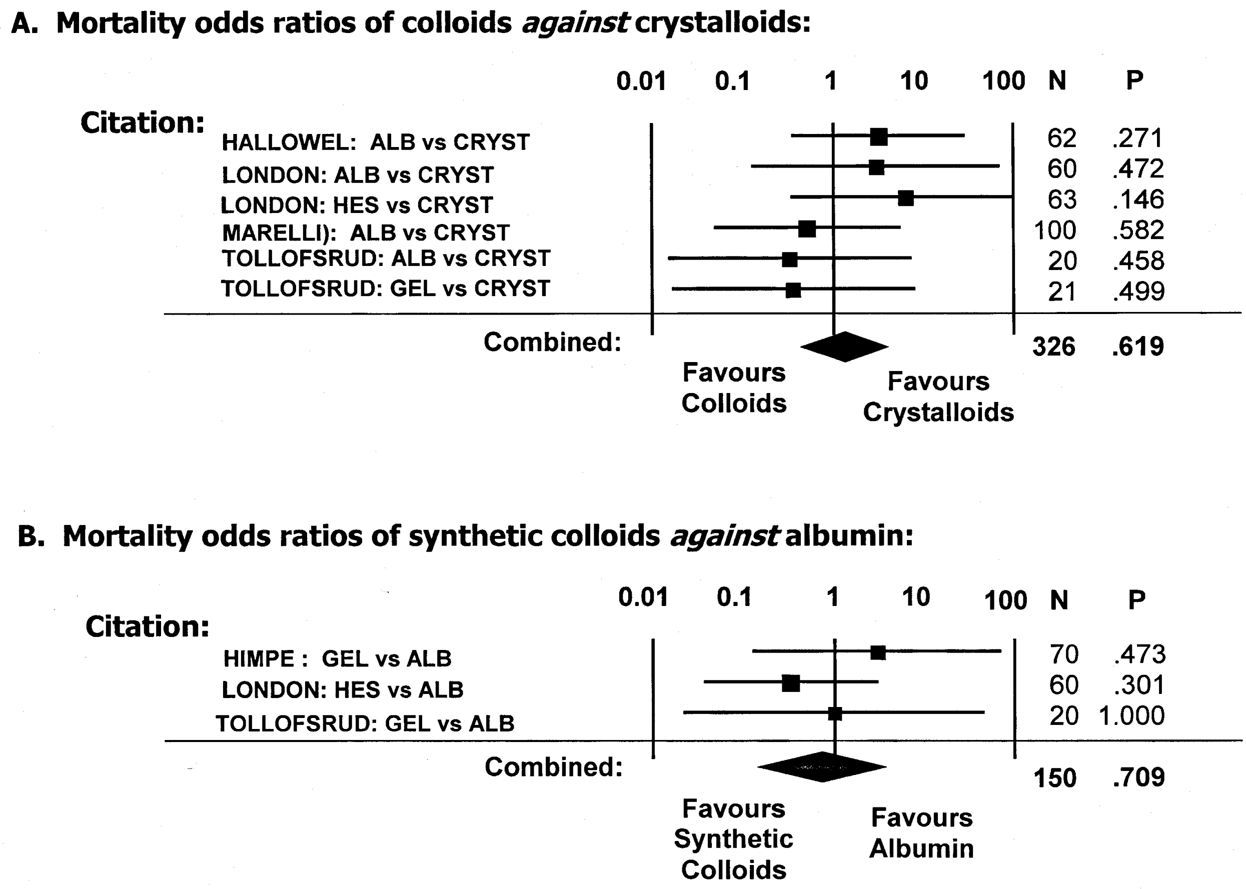


Fig. 2. — Odds ratios of mortality for individual trials shown as boxes scaled according to weighting. Error bars indicate 95% confidence intervals. Summary estimates are shown at the bottom as diamonds that span the confidence interval. Panel A illustrates the forest-plot of all colloids combined versus all crystalloids combined and panel B shows the forest-plot of all artificial colloids versus albumin. Summary diamonds all overlap the line of identity, which means that no differences in mortality are demonstrated. [Albumin : ALB ; hydroxyethylstarches : HES ; gelatines : GEL and crystalloids : CRYST].

with the use of colloids (24) but also by the starches disfavouring platelet counts more than other colloids. Platelet counts did not differ from albumin when using gelatines. In spite of these observed differences in platelet counts, the hypothesis that pump fluid management may modify the postoperative blood-loss itself was not verified by the present meta-analysis.

This is in contrast with the recent meta-analysis by Wilkes (52), the retrospective study by Canver (7) and, the earlier review by Cope (10) all demonstrating significantly increased risks of postoperative bleeding when starches are used during the peri-operative course of cardiac surgery. The present meta-analysis failed to support this conclusion.

Reviewing exclusively studies comparing pump-primes, it was based on a consistently smaller number of patients. Even if the characteristics were comparable, the power can therefore be questioned, which can explain some non-significant summary effect measures (23). Across the few studies reporting mortality, this meta-analysis in fact did not demonstrate differences in spite of the significantly higher oncotic pressures and more optimal fluid-balances found with colloids. Although a leaky micro-vasculature is known to be present to some degree during CPB (14), colloids seem to be sufficiently retained in the intravascular space. This is not in agreement with the reported poor performance of colloids in trauma patients, which is mostly attributed to a mechanism of uninhibited passage of colloids trough highly permeable capillaries worsening interstitial oedema (9, 49). Apparently, clinical effects or the extent of increased capillary permeability may vary between trauma patients and cardiac surgical cases.

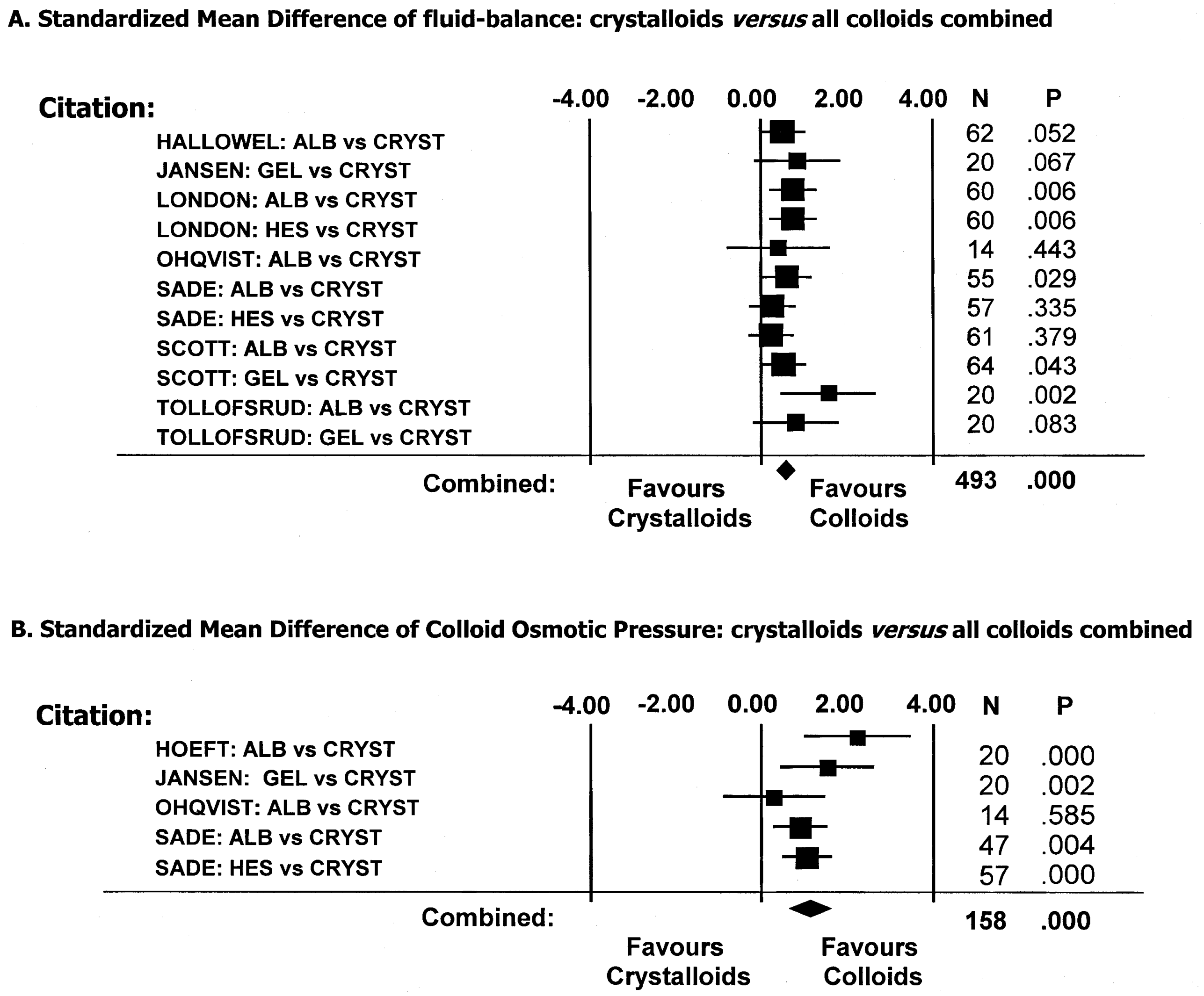


Fig. 3. — Forest-plots expressing standardized mean differences of crystalloids versus all colloids combined in fluid-balance (panel A) and colloid osmotic pressure (panel B). Individual trials are shown as boxes scaled according to weighting. Error bars indicate 95% confidence intervals. Summary estimates are shown at the bottom as diamonds that span the confidence interval, which do not include the line of identity (zero) : colloids are favouring more equilibrated fluid-balances and higher colloid osmotic pressures. [Albumin : ALB ; hydroxy-ethyl-starches : HES ; gelatines : GEL and crystalloids : CRYST].

As albumin in the CPB prime is not necessarily associated with improved survival and is more expensive, it is hard to continue its use. Starches have an increased risk for lower platelets, which was not the case with gelatines. The newest low-molecular starch 6% 130/0.4 (Voluven®) should be more promising in this regard but relevant and convincing data are still missing.

Incorporating artificial colloids in CPB fluid regimens may have beneficial implications on hospital stay and clinical scores (20, 28). Much can be expected from more suitable mixtures of balanced salt solutions and a selection of colloids to improve outcome in general (22, 40).

In future trials matters can be improved if time and effort are devoted to defining *a priori* non-surrogate outcomes of interest to be recorded in the same way. Using identical measures and subjects in studies, summary statistics may therefore become more relevant and conclusive. Trials of particular concern such as acid-base status (13, 16, 27), systemic inflammation (26), ischaemia-reperfusion (17), ICU and hospital stays (20) are justified.

This systematic review synthesised the available evidence extracted from published papers on CPB pump priming solutions. Considering the thousands of procedures performed using CPB, too

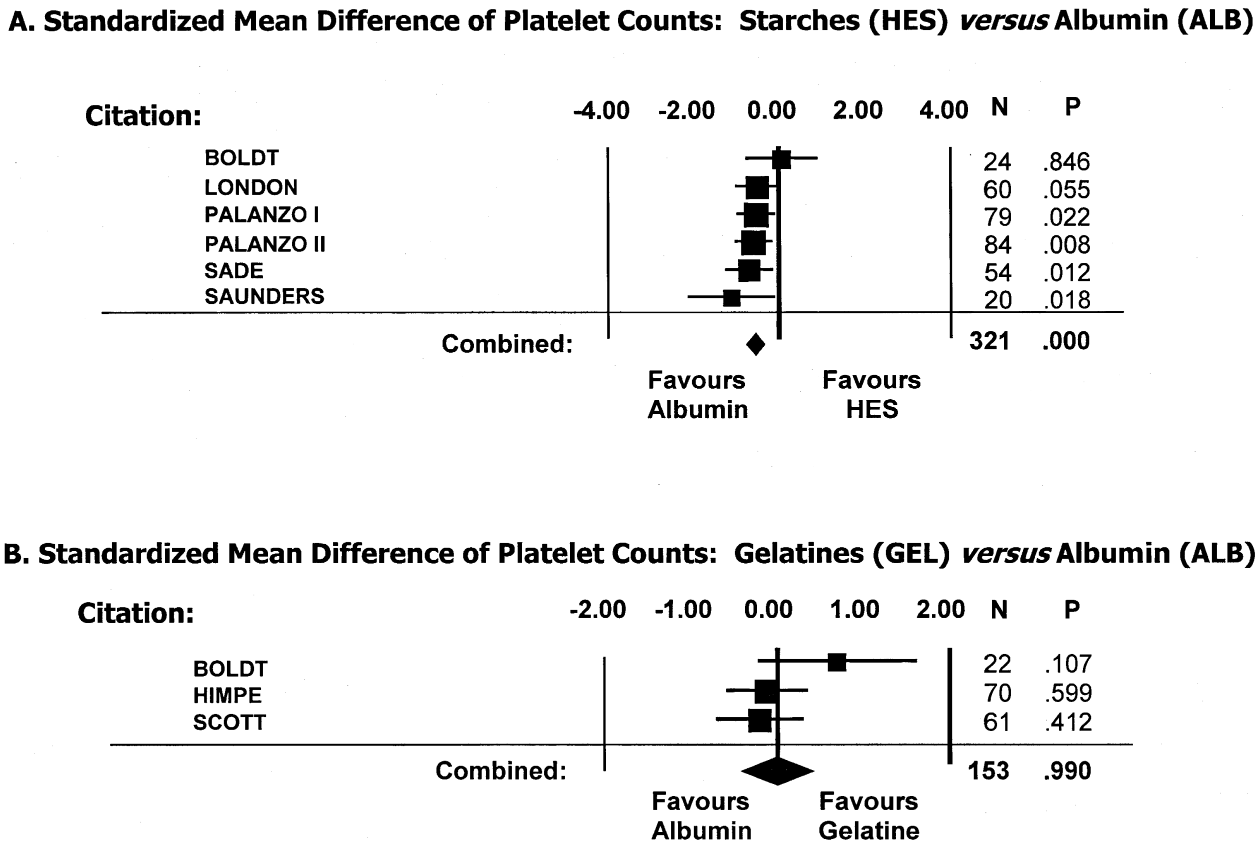


Fig. 4. — Forest-plots expressing standardized mean differences in platelet counts between starches and albumin (panel A) and, between gelatines and albumin (panel B). Individual trials are shown as boxes scaled according to weighting. Error bars indicate 95% confidence intervals. Summary estimates are shown at the bottom as a diamond that spans the confidence interval. The diamond does not include the line of identity (zero) in the case of starches versus albumin : starches are disfavouring platelet counts.

few prospective trials on prime solutions are still available for more definitive conclusions.

## References

1. Abbott M. A., McLaren A. D., Algie T., *Intra-ocular pressure during cardiopulmonary bypass : a comparison of crystalloid and colloid priming solutions*, ANAESTHESIA, **49**, 343-6, 1994.
2. Boks R. H., van Herwerden L. A., Takkenberg J. J., *et al.*, *Is the use of albumin in colloid prime solution of cardiopulmonary bypass circuit justified ?*, ANN. THORAC. SURG., **72**, 850-3, 2001.
3. Boldt J., Zickmann B., Ballesteros B. M., Stertmann F., Hempelmann G., *Influence of five different priming solutions on platelet function in patients undergoing cardiac surgery*, ANESTH. ANALG., **74**, 219-25, 1992.
4. Boldt J., *The good, the bad, and the ugly : should we completely banish human albumin from our intensive care units ?*, ANESTH. ANALG., **91**, 887-95, 2000.
5. Bonser R. S., Dave J. R., Davies E. T., *et al.*, *Reduction of complement activation during bypass by prime manipulation*, ANN. THORAC. SURG., **49**, 279-8, 1990.
6. Boykin M. P., Ecklund J. M., Riley J. B., McCall M. M., *Adding hetastarch to the adult cardiopulmonary bypass prime does not affect patient outcomes*, J. EXTRA-CORPOR. TECHNOL., **29**, 25-9, 1997.
7. Canver C. C., Nichols R. D., *Use of intraoperative hetastarch priming during coronary bypass*, CHEST, **118**, 1616-20, 2000.
8. Cochrane Injuries Group Albumin Reviewers, *Human albumin administration in critically ill patients : systematic review of randomised controlled trials*, BR. MED. J., **317**, 235-40, 1998.
9. Choi P. T., Yip G., Quinonez L. G., *et al.*, *Crystalloids vs. colloids in fluid resuscitation : a systematic review*, CRIT. CARE MED., **27**, 200-10, 1999.
10. Cope J. T., Banks D., Mauney M. C., *et al.*, *Intraoperative hetastarch infusion impairs hemostasis after cardiac operations*, ANN. THORAC. SURG. **63**, 78-83, 1997.
11. Hallowell P., Bland J. H., Dalton B. C., *et al.*, *The effect of hemodilution with albumin or Ringer's lactate on water balance and blood use in open-heart surgery*, ANN. THORAC. SURG., **25**, 22-9, 1978.
12. Haneda K., Sato S., Ishizawa E., Horiuchi T., *The importance of colloid osmotic pressure during open heart surgery in infants*, J. EXP. MED., **147**, 65-71, 1985.
13. Hayhoe M., Bellomo R., Liu G., McNicol L., Buxton B., *The aetiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime*, INTENSIVE CARE MED., **25**, 680-5, 1999.
14. Heltne J. K., Koller M. E., Lund T., *et al.*, *Studies on fluid extravasation related to induced hypothermia during cardiopulmonary bypass in piglets*, ACTA ANAESTHESIOL. SCAND., **45**, 720-8, 2001.
15. Higgins J. P., Thompson S. G., *Quantifying heterogeneity in a meta-analysis*, STAT. MED., 15, **21**, 1539-58, 2002.
16. Himpe D., Neels H., De Hert S., Van Cauwelaert P., *Adding lactate to the prime solution during hypothermic cardiopulmonary bypass : a quantitative acid-base analysis*, BR. J. ANAESTH., **90**, 440-5, 2003.

17. Himpe D. G., De Hert S. G., Vermeyen K. M., Adriaensen H. F., *Oxygen transport and myocardial function after the administration of albumin 5%, hydroxyethylstarch 6% and succinylated gelatine 4% to rabbits*, EUR. J. ANAESTHESIOLOGY, **19**, 860-7, 2002.
18. Himpe D., Van Cauwelaert P., Neels H., *et al.*, *Priming solutions for cardiopulmonary bypass : comparison of three colloids*, J. CARDIOTHORAC. VASC. ANESTH., **5**, 457-66, 1991.
19. Hoeft A., Korb H., Mehlhorn U., *et al.*, *Priming of cardiopulmonary bypass with human albumin or Ringer lactate : effect on colloid osmotic pressure and extravascular lung water*, BR. J. ANAESTH., **66**, 73-80, 1991.
20. Jansen P. G., te Velthuis H., Wildevuur W. R., *et al.*, *Cardiopulmonary bypass with modified fluid gelatin and heparin-coated circuits*, BR. J. ANAESTH., **76**, 13-9, 1996.
21. Jenkins I. R., Curtis A. P., *The combination of mannitol and albumin in the priming solution reduces positive intraoperative fluid balance during cardiopulmonary bypass*, PERFUSION, **10**, 301-5, 1995.
22. Kellum J. A., *Fluid resuscitation and hyperchloremic acidosis in experimental sepsis : improved short-term survival and acid-base balance with Hextend compared with saline*, CRIT. CARE MED., **30**, 300-5, 2002.
23. Kjærgaard L. L., Villumsen J., Gluud C., *Reported methodologic quality and discrepencies between large and small randomized trials in meta-analyses*, ANN. INTERN. MED., **135**, 982–9, 2001.
24. Kmiecik S. A., Stammers A. H., Petterson C. M., *et al.*, *The effect of volume replacement on serum protein concentration during cardiopulmonary bypass*, J. EXTRA-CORPOR. TECHNOL., **33**, 227-32, 2001.
25. Kuitunen A., Hynynen M., Salmenperä M., *et al.*, *Hydroxyethyl starch as a prime for cardiopulmonary bypass : effects of two different solutions on haemostasis*, ACTA ANAESTHESIOL. SCAND., **37**, 652-8, 1993.
26. Levy J. H., Tanaka K. A., *Inflammatory response to cardiopulmonary bypass*, ANN. THORAC. SURG., **75**, S715-20, 2003.
27. Liskaser F. J., Bellomo R., Hayhoe M., *et al.*, *Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis*, ANESTHESIOLOGY, **93**, 1170-3, 2000.
28. London M. J., Franks M., Verrier E. D., *et al.*, *The safety and efficacy of ten percent pentastarch as a cardiopulmonary bypass priming solution. A randomized clinical trial*, J. THORAC. CARDIOVASC. SURG., **104**, 284-96, 1992.
29. Lumb P. D., *A comparison between 25% albumin and 6% hydroxyethyl starch solutions on lung water accumulation during and immediately after cardiopulmonary bypass*, ANN. SURG., **206**, 210-3, 1987.
30. Marelli D., Paul A., Samson R., *et al.*, *Does the addition of albumin to the prime solution in cardiopulmonary bypass affect clinical outcome ? A prospective randomized study*, J. THORAC. CARDIOVASC. SURG., **98**, 751-6, 1989.
31. Ohqvist G., Settergren G., Bergström K., *et al.*, *Plasma colloid osmotic pressure during open-heart surgery using non-colloid or colloid priming solution in the extracorporeal circuit*, SCAND. J. THORAC. CARDIOVASC. SURG., **15**, 251-5, 1981.
32. Palanzo D. A., Parr G. V., Bull A. P., *et al.*, *Hetastarch as a prime for cardiopulmonary bypass*, ANN. THORAC. SURG., **34**,680-683, 1982.
33. Palanzo D. A., O' Neill M. J., Williams D. R., Parr G. V., *Hetastarch as a Clear Prime for Cardiopulmonary Bypass*, J. EXTRA-CORPOR. TECHNOL., **16**, 55-57, 1984.
34. Palanzo D. A., Zarro D. L., Montesano R. M., Manley N. J., *Albumin in the cardiopulmonary bypass prime : how little is enough ?*, PERFUSION, **14**, 167-72, 1999.
35. Parmar M. K., Torri V., Stewart L., *Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints*, STAT. MED., **17**, 2815-34, 1998.
36. Pedersen T., Møller A. M., Cracknell J., *The mission of the cochrane anesthesia review group : preparing and disseminating systematic reviews of the effect of health care in anesthesiology*, ANESTH. ANALG., **95**, 1012-8, 2002.
37. Sade R. M., Stroud M. R., Crawford F. A., *et al.*, *A prospective randomized study of hydroxyethyl starch, albumin, and lactated Ringer's solution as priming fluid for cardiopulmonary bypass*, J. THORAC. CARDIOVASC. SURG., **89**, 713-22, 1985.
38. Sanchez de Leon R., Paterson J. L., Sykes M. K., *Changes in colloid osmotic pressure with plasma albumin concentration associated with extracorporeal circulation*, BR. J. ANAESTH., **54**, 465-73, 1982.
39. Saunders C. R., Carlisle L., Bick R. L., *Hydroxyethyl starch versus albumin in cardiopulmonary bypass prime solutions*, ANN. THORAC. SURG., **36**, 532-9, 1983.
40. Scheingraber S., Rehm M., Sehmisch C., Finsterer U., *Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery*, ANESTHESIOLOGY, **90**, 1265-70, 1999.
41. Schierhout G., Roberts I., *Fluid resuscitation with colloid or crystalloid solutions in critically ill patients : a systematic review of randomised trials*, BR. MED. J., **316**, 961-64, 1998.
42. Schupbach P., Pappova E., Schilt W., *et al.*, *Perfusate oncotic pressure during cardiopulmonary bypass. Optimum level as determined by metabolic acidosis, tissue edema, and renal function*, VOX SANG., **35**, 332-44, 1978.
43. Scott D. A., Hore P. J., Cannata J., *et al.*, *A comparison of albumin, polygeline and crystalloid priming solutions for cardiopulmonary bypass in patients having coronary artery bypass graft surgery*, PERFUSION, **10**, 415-24, 1995.
44. Shin'oka T., Shum-Tim D., Laussen P. C., *et al.*, *Effects of oncotic pressure and hematocrit on outcome after hypothermic circulatory arrest*, ANN. THORAC. SURG., **65**, 155-64, 1998.
45. Tabuchi N., de Haan J., Gallandat Huet R. C., *et al.*, *Gelatin use impairs platelet adhesion during cardiac surgery*, THROMB. HAEMOST., **74**, 1447-51, 1995.
46. Tigchelaar I., Gallandat Huet R. C., Boonstra P. W., *et al.*, *Comparison of three plasma expanders used as priming fluids in cardiopulmonary bypass patients*, PERFUSION, **13**, 297-303, 1998.
47. Tigchelaar I., Gallandat Huet R. C., Korsten J., *et al.*, *Hemostatic effects of three colloid plasma substitutes for priming solution in cardiopulmonary bypass*, EUR. J. CARDIOTHORAC. SURG., **11**, 626-32, 1997.
48. Tølløfsrud S., Svennevig J. L., Breivik H., *et al.*, *Fluid balance and pulmonary functions during and after coronary artery bypass surgery : Ringer's acetate compared with dextran, polygeline, or albumin*, ACTA ANAESTHESIOL. SCAND., **39**, 671-7, 1995.
49. Velanovich V., *Crystalloid versus colloid fluid resuscitation : a meta-analysis of mortality*, SURGERY, **105**, 65-71, 1989.
50. Vincent J. L., Dubois M. J., Navickis R. J., *et al.*, *Hypoalbuminemia in acute illness : is there a rationale for intervention : a meta-analysis of cohort studies and controlled trials*, ANN. SURG., **237**, 319-34, 2003.
51. Wilkes M. M., Navickis R. J., *Patient survival after human albumin administration., A meta-analysis of randomized, controlled trials*, ANN. INTERN. MED., **135**, 149-64, 2001.
52. Wilkes M. M., Navickis R. J., Sibbald W. J., *Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery : a meta-analysis of postoperative bleeding*, ANN. THORAC. SURG., **72**, 527-34, 2001.