Effect of perioperative crystalloid or colloid fluid therapy on hemorrhage, coagulation competence, and outcome
A systematic review and stratified meta-analysis
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Abstract
Background: A meta-analysis concerning perioperative coagulation competence, hemorrhage, and outcome was conducted including the use of hydroxyethyl starches (HESs), dextran, or albumin versus administration of a crystalloid as control to assess the efficacy and safety of colloids and crystalloids for fluid administration during major elective surgery. Surgery was restricted to cardiovascular and noncardiovascular surgery, and HESs were stratified to HES 130/0.4 and HES 200/0.5.

Methods: We searched Cochrane Central Register of Controlled Trials, MEDLINE, ISI Web of Science, EMBASE, conference proceedings, reference lists, and databases of ongoing trials.

Results: Thirty one primary clinical randomized controlled trials included 2287 patients undergoing major surgery from January 2000 to August 2015. The perioperative changes in coagulation competence were measured by thromboelastography (TEG) maximum amplitude (MA) in 9 studies administering crystalloids versus HES and in 4 studies administering albumin versus HES. All studies but 1 disclosed increased reduction in TEG-MA following HES administration \( (P=0.0001 \text{ and } 0.0002) \). The total loss of blood was reported in 17 studies in which crystalloids were compared to HES and 12 studies reported increased blood loss after administration of HES \( (P < 0.003) \). When administering albumin versus HES, 6 studies reported reduced hemorrhage associated with albumin administration \( (P = 0.005) \). Reoperation was not significantly reduced by the use of crystalloids, but may be more frequent after HESs compared to albumin \( (P < 0.03) \). In this analysis, more patients admitted to administration of HESs were exposed to decrease coagulation competence, compared to perioperative crystalloids and albumin administration.

Conclusion: This stratified meta-analysis showed that increased blood loss was found in noncardiovascular surgery among patients receiving HES compared with crystalloids, followed by a marked reduction in TEG-MA, and infusion of 3rd-generation HES products did not influence the results significantly.

Abbreviations: HA = human albumin, ICU = intensive care unit, MD = mean difference, OR = odds ratio, RCT = randomized controlled trial, TEG = thromboelastography, TEG-MA = thromboelastography-maximum amplitude.

Keywords: coagulation, colloid, crystalloid, fluid therapy, hemorrhage, perioperative

1. Introduction

Colloids and crystalloids are used to maintain tissue perfusion and oxygenation for surgical, traumatic, and critical care patients. The use of colloid fluids during major surgery is controversial and neither the safety nor the efficacy of hydroxyethyl starch (HES) 130/0.4 are demonstrated in systematic reviews with meta-analysis.\textsuperscript{[1–16]}

During surgery the circulation is supported by a crystalloid and eventually by a colloid that stays within the circulation while as much as 30\% to 60\% of the crystalloid fluids may be “lost” to the interstitial space.\textsuperscript{[17]} The use of colloids to support the circulation during surgery is considered when hemorrhage is significant in order to delay the need for blood transfusion.\textsuperscript{[18]} On the other hand, it is accepted that the use of synthetic colloids affects coagulation competence, but whether – or to what extent – that translates into increased blood loss does not seem to be settled.

Monitoring perioperative coagulation relies on clinical estimates besides on classic plasma coagulation tests. However, plasma coagulation tests were designed to test for lack of coagulation factors and not for predicting risk of bleeding or for guiding hemostatic therapy. In contrast, viscoelastic evaluation of whole blood enables for rapid diagnosis of the cause of bleeding.
and may be displayed in real time within the operating theater. Thus, the use of perioperative coagulation monitoring by, for example, thromboelastography (TEG) for targeted treatment of coagulopathy is recommended by the European Society of Anaesthesiology (ESA).119

To address perioperative hemorrhage, coagulation competence, and patient outcome, a systematic review was undertaken including a meta-analysis for randomized controlled trials (RCTs) for the use of perioperative infusion of crystalloids versus colloids during major surgery. The meta-analysis for the evaluation of perioperative hemorrhage, coagulation competence, and outcome were conducted with the use of 3 colloids; HESs, dextran, and albumin with the administration of crystalloids solution as control.

2. Methods

2.1. Search strategy and selection criteria

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines were followed. We searched the Cochrane Central Register of Controlled Trials (2015, Issue 5), MEDLINE (2000 to August 2015), ISI Web of Science (2000 to August 2015), EMBASE (2000 to August 2015), and databases of ongoing trials. We also checked the reference lists of trials and review articles. Search terms included: Ringer, albumin, dextran, hydroxyethyl starch, HES, surgery, operative, bleeding, hemorrhage, coagulation, and random allocation (See Supplementary Table 1, http://links.lww.com/MD/B175).

RCTs comparing crystalloids with HES, dextran, and albumin, besides albumin with HES in adult patients undergoing major surgery were eligible. As the systematic review was based on published trial data approved by ethic committee were waived with no language restriction.

2.2. Data extraction and quality assessment

Two investigators (KCR and TP) independently determined trial eligibility and extracted data from the reports. The title and abstract of each article were screened to identify eligible RCTs. If the citation seems to contain a relevant RCT, the article was retrieved to undergo full evaluation. Differences in interpretation were resolved through discussion. Extracted data included the numbers of patients; colloids or crystalloids regimen, volume of the provided fluid, mean and SD for the blood loss (mL) from the start of surgery until discharge from the recovery room, thromboelastography-maximum amplitude (TEG-MA, lowest measured MA in the perioperative period), treated postoperative complications (surgical incidents needing treatment, e.g., bleeding and leaks requiring reoperation, cardiopulmonary events, including stay in intensive care unit [ICU], mortality, and duration of hospital stay. The quality of the RCTs were evaluated using the Jadad score (1–5) assessing randomization method, allocation concealment, and blinding.20

2.3. Statistical analysis

The between group standardized mean differences (MDs) for blood loss, coagulation competence, and outcome were analyzed with 95% confidence intervals (CIs). A heterogeneity test was applied for each meta-analysis by I^2 statistics. Thresholds for the interpretation of I^2 may be misleading, since the importance of inconsistency depends on several factors. A rough guide to interpretation is as follows – 0% to 40%; might not be important; 30% to 60%; may represent moderate heterogeneity; 50% to 90%; may represent substantial heterogeneity; and 75% to 100% considerable heterogeneity.

Publication bias was assessed by funnel plot using the risk of blood loss as the end-point. A funnel plot is a scatter plot and may be used to explore the presence of bias in meta-analysis.21 In the funnel plot, treatment effect is plotted on the horizontal axis and the standard error on the vertical axis. The vertical line represents the summary estimated derived using fixed-effect meta-analyses. Two diagonal lines represent 95% confidence limits (effect ± 1.96 SE) around the summary effect for each standard error on the vertical axis. These show the expected distribution of studies in the absence of heterogeneity or of selection bias. In the absence of heterogeneity, 95% of the studies should lie within the funnel defined by these diagonal lines.

Sensitivity analyses were conducted to compare cardiovascular and noncardiovascular surgery and to evaluate administering the more recently developed HES preparations with low molecular weight (130kDa) and low molar substitution (<0.5).

All P values were 2-sided and a P value < 0.05 was considered significant. All analyses were conducted by Review Manager 5.3 software package (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2015).

3. Results

The literature search yielded 393 hits after removal of duplicates, from among which 224 studies were excluded – leaving 169 trials retrieved for detailed evaluation (Fig. 1). However, 138 investigations failed to meet the inclusion criteria, resulting in finally including 32 RTCs.

The meta-analysis covered studies comparing HES-, dextran-, and albumin versus crystalloids besides HES versus albumin and HES 130/0.4 versus HES 200/0.5. In total 38 comparisons in the 32 RCTs evaluated HES versus crystalloids (20,22–41) dextran versus crystalloids (2),42,43 albumin versus crystalloids (2)39,44 or HES versus albumin (10),23,39,45–52 and HES 130/0.4 versus HES 200/0.5 (4).53

Together 2287 patients reported from 2000 to 2015 were included in the meta-analysis (Table 1).22–53 A few trials compared more than 2 IV fluids, and therefore the number of single comparisons (38) does not always equal the number of trials included (32).

The quality of the RCTs is evaluated by elements from Jadad scale because this scale is reliable, extern valid, and empirically correlated with bias. More than 50% of the trials were classified in the upper half (3–5) of the scale and 5 studies were classified with the highest score (5).33,38–41,52 The evaluation of the study quality is shown in Table 1. Thirty two percent of the trials declared not to be funded by a medical company, while 34% was supported by research grants from medical companies and 34% of the trials did not inform about funding at all.

3.1. Impact of crystalloids and colloids on hemorrhage

The volume of lost blood during administration of crystalloids was reported in 17 studies compared to HES22,24–30,32,34–43 in 2 studies compared to dextran42,43 and albumin19,44 besides in
9 studies comparing albumin to HES.\cite{39,45–52} Twelve studies reported increased blood loss after administration of HES compared to crystalloids (MD 21.8, 95%CI 7.6–36.1; \(P < 0.003\)).\cite{22,24,26–28,32,34,36–41} Restricting the analysis of hemorrhage during surgery to studies about cardiovascular surgery versus noncardiovascular surgery did change the results, as significant hemorrhage was found after noncardiovascular surgery when administered HES was compared to crystalloids (MD 26.4, 95%CI 10.8–42.0; \(P < 0.0009\), Fig. 2). During cardiovascular surgery no difference in hemorrhage was found between HES and crystalloid groups. Perioperative hemorrhage during noncardiovascular surgery increased by 20% with the use of HESs rather than crystalloids. Although hemorrhage occurred at the same level when comparing HES and crystalloids, After administration of dextran versus crystalloids (Fig. 3) no difference was found in hemorrhage. However, crystalloids versus albumin revealed 2 studies that reported reduced hemorrhage during crystalloid administration (MD 167.1, 95%CI 106.5–217.7; \(P = 0.003\)).\cite{45,47–50,52} Moderate heterogeneity among studies was found for crystalloids versus HES comparisons (39%), whereas substantial heterogeneity was found evaluating albumin versus HES (75%).

Together, more than 70% (12 of 17 RCTs) showed increased loss of blood during administration of HES and 5 studies found increased hemorrhage during administration of lactated Ringer solution. The quality of the studies, assessed by the Jadad scale, was higher in trials favoring crystalloids versus HES (3.2 [mean figure missing from original article].
in crystalloids studies vs 2.2 in HES studies); however, according to Funnel plot analysis, publication bias was not the point.

### 3.2. Impact of crystalloids and colloids on coagulation competence

The perioperative changes in coagulation competence were measured by TEG-MA in 9 studies administering crystalloids versus HES[22,28,29,31,36,38,40,41] (Fig. 2) and in 4 studies administering albumin versus HES (Fig. 5)[146-48,51] All these studies but one[41] disclosed increased reduction in TEG-MA following HES administration (Figs. 2 and 5) (P<0.0001 and 0.0002). Substantial heterogeneity among studies was found for the HES versus crystalloids comparison (69%). Subgroup analysis of studies concerning cardiovascular surgery versus noncardiovascular surgery did not change the results, as significant changes in TEG-MA was found after noncardiovascular surgery when administrated HES compared to crystalloids (MD 5.2, 95%CI −6.6 to −3.9; P<0.0009), and after cardiovascular surgery (MD −2.7, 95%CI −4.9 to −0.4; P<0.02, Fig. 2)

### 3.3. Postoperative cardiopulmonary complications and reoperation

No statistically significant difference was found using the outcome variable “re-operation” when analyzing crystalloids versus HES products[33,34,37-40] crystalloids versus dextran[42,43] or crystalloids versus albumin[39,44] (P=0.44, 0.49, and 0.75). Yet, when comparing albumin versus HES, a greater number of reoperation was found in the HES group (19/267, 7.1%) in all 4 studies compared to the albumin group (6/221, 2.7%)[39,43,47,51] (OR = 3.7, 95%CI 0.15-0.92; P=0.03) (Fig. 5). The heterogeneity might not be important in this comparison (P<0.00% and 32%). Regarding the outcome variables cardiopulmonary complications and mortality, only a few incidents were reported and they do not form the basis of a trend toward difference between crystalloids versus HES or the latter versus albumin.

### 3.4. Sensitivity analysis according to different type of hydroxyethyl starch (HES)

Restricting the meta-analysis to include studies administering low molecular HES preparations only[24-30,32,34-41] did not change the volume of hemorrhage (MD 21.2, 95%CI 6.9-33.6; P<0.004) nor the coagulation competence (MD −4.5, 95%CI −6.8 to −2.2; P<0.0001) when crystalloid was used as comparator. The incidence of reoperations remained equal in both groups (P=0.25).

In contrast, when restricting the meta-analysis to include studies administering low molecular HES products versus albumin[39,46,47,51,52] the results changed. The difference in volume of hemorrhage became without significant difference (MD 4.0, 95%CI 48.4-56.4; P=0.88); however, the coagulation
The competence was still reduced in the HES 130/0.4 groups (MD 3.8, 95%CI 1.1–6.5, \( P < 0.006 \)) and the incidence of reoperations was higher after administration of low molecular HES (10/94, 10.6%) compared to albumin (4/91, 4.4%), although the difference was insignificant (OR 0.41, 95%CI 0.13–1.30; \( P = 0.13 \)). Finally, perioperative hemorrhage did not change with the use of low molecular HES 130/0.4 rather than old HES products (Fig. 6).
4. Discussion

Perioperative hemorrhage depends not only on surgical technique but also on coagulation competence of blood. Thus, there is a relation between the perioperative blood loss and reduction in coagulation competence as expressed as the “maximal amplitude” (MA) by TEG both with the use of HES 130/0.4, older HES products and albumin,[38,39,44] and increased hemorrhage were seen in noncardiovascular surgery after HES compared to crystalloids. Furthermore, a reduction in TEG-MA during surgery by the use of HES 130/0.4 and old HES products was confirmed in the presented systemic meta-analysis.

Perioperative coagulation competence if of interest because administration of blood seems to be an independent predictor of complications including death.[54] Yet, a reduction in MA needs not translate into increased use of blood products during surgery. The presented stratified meta-analysis disclosed that perioperative hemorrhage tended to increase by 5.9% with the use of HES 130/0.4 and by 6.1% with the use of older HES products rather than crystalloids, while the use of HES 130/0.4 rather than albumin increased the loss of blood by 3.0%. Thus, there may be an increased need for reoperation following administration of HESs compared to administration of albumin or a crystalloid.

Most RCTs evaluated the quality of coagulation competence by TEG and concluded that clot firmness was reduced following administration of HES products compared to crystalloid solutions.[22,23,29,31,36–38,40,41] The TEG-MA varied between trials, resulting in high heterogeneity (69%). The coagulation competence was evaluated during almost equal number of cardiac, orthopedic, and abdominal surgery besides 1 neurological RCT in the prone position. The loss of blood in these trials varied from 0.2 to 1.0 L, the number of participants from 30 to 202 – except, Lee et al[29] and Yates et al[40] who evaluated more than 100 patients each. One RCT only did not disclose reduced firmness of the clot by administering HES 130/0.4.[41] During the investigation coagulation competence was evaluated in 34 patients on pump cardiac surgery with mean 0.80 and 0.78 L loss of blood in the 2 groups. In the HES group, the priming solution consisted of 20 mL/kg HES 130/0.42 with additional Ringer solution up to 2 L, and only Ringer acetate solution was given during the cardiopulmonary bypass.
resulting in maximum clot firmness on 57 and 55 mm in the HES and Ringer group, respectively. Conclusively, we could not directly demonstrate reasons in the design that explain the unique results on coagulation competence in that trial. The sensitivity analysis still reveals the coagulation competence to be more reduced in the HES 130/0.4 rather than in the crystalloids groups.

As regards trials comparing coagulation competence during administration of HES 130,0.4 and human albumin (HA) all the RTCs agreed upon favoring albumin to HES 130/0.4. The trials were much alike regarding their number of participants (15 in each group) and volume of lost blood (around 1 L).

![Figure 5](image1.png)

Figure 5. Impact of HESs and human albumin on hemorrhage (A), coagulation competence (lowest measured maximum amplitude, TEG-MA) (B), and outcome (reoperation) (C) in surgical patients. HES = hydroxyethyl starch, TEG-MA = thromboelastography maximum amplitude.

The meta-analysis of 12 RCTs showed increased bleeding following administration of HES products and 5 RCTs showed increased hemorrhage following infusion of...
5. Limitations and strengths

The search strategy included studies conducted between 2000 and 2015 for which reason trials conducted late in the 20 century evaluating high molecular HES products were not included. Furthermore, RCTs were excluded when misconduct was admitted. The strength of this meta-analysis includes a strict selection process of the included trials besides evaluation of their methodological quality by Jadad score, and more than half of the RCTs were scored in the top of this scale. It is not about designing a moral compass, but one third of the studies were supported by a medical company.

The trials included in the presented meta-analysis were often small and single-center studies, and also publication bias may exist, as described in other meta-analyses. However, using blood loss as an end-point in studies comparing crystalloids and HES, the funnel plot suggests that publications bias does not seem to be substantial in this meta-analysis. The dose of the allocated trial fluids was different among the RCTs, and the treatment regimens also seemed different resulting in a high level of heterogeneity, as seen in some of the meta-analysis. There are obviously flaws of the statistical meta-analysis, but the main purpose of the analysis is to borrow strength from multiple trials, which do not show statistically significant effect, and therefore is not a limitation of the analysis. Finally, it is not a limitation that the effects in some studies are less precise than in other studies, since precision is used to weight the trials in this meta-analysis.

Patients going through cardiac surgery on pump are distinct due to their postoperative inflammatory response that may confound the effect of fluid therapy choice. For this reason, results from those trials may not be generalized to nonpump and noncardiac RCTs during major surgery. Furthermore, perioperative outcomes favored a goal directed therapy rather than liberal fluid therapy without hemodynamic goals as described in the meta-analysis by Corcoran et al and is therefore not debated as well as the volume of blood transfusion was not an endpoint and therefore not noted here.

On the basis of the presented meta-analysis concerning fluid therapy for 2287 patients during elective surgery, there seems to be evidence for administering crystalloid as perioperative fluid therapy and – at severe hemorrhage – add HA in order to avoid transfusion of blood.

6. Conclusion

In this analysis, more patients admitted to HESs administration were exposed to decreased coagulation competence evaluated by TEG-MA, while perioperative hemorrhage tended to increase when HESs rather than crystalloids and albumin was administered. The stratified meta-analysis disclosed that increased blood loss was found during noncardiovascular surgery among patients receiving HES compared with crystalloids, followed by a marked reduction in TEG-MA, and infusion of 3rd-generation HES products HES 130/0.4 did not influence the results significantly.

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