Systematic Review and Meta-Analysis

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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 ($P = 0.0001$ 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.[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.[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.[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

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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).[19]

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 was 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. For effect size estimation for continuous parameters, standardized MD was used. For binary, dichotome end-points we used odds ratio (OR). Fixed-effects models were applied to derive estimates and 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 $\pm$ 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 (130 kDa) 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/.04 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).[33,39–41,52] 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 HES,[22,24–30,32,34–41] in 2 studies compared to dextran,[42,43] and albumin,[39,44] besides in

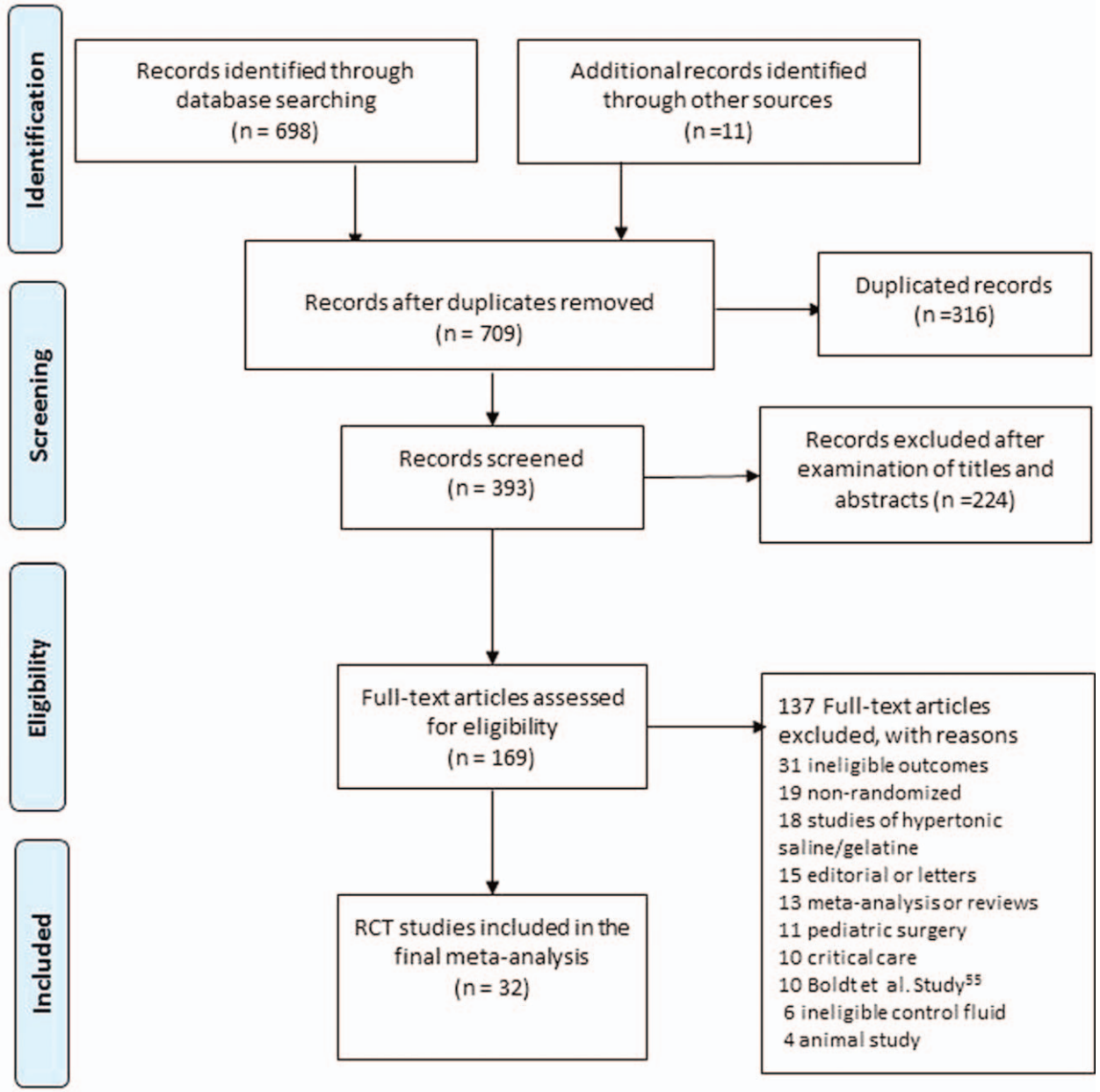

Figure 1. Flowchart of study search, screening, and selection.

9 studies comparing albumin to HES.[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; $P < 0.003$).[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 administrated 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 16.89–317.3; $P < 0.03$) (Fig. 4).[39,44] After albumin versus HES (Fig. 5), 6 studies reported reduced hemorrhage associated with albumin administration (MD, −64.1, 95%CI 106.5–21.7; $P = 0.003$).[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]

Table 1

Characteristics of trials included in the meta-analysis comparing: crystalloid versus hydroxyethyl starch (HES, n = 20), crystalloid versus dextran (n = 2), crystalloid versus albumin (n = 2), albumin versus HES (n = 10), and HES 130/0.4 versus HES 200/0.5 (n = 4).

Trials	Type of surgery	N	Fluid management strategy	Jadad score
Innerhofer et al 2002[22]	Knee surgery	40	Lactated Ringer vs HES 6% 200/0.5	2
Verheij et al 2006[23]	Cardiovascular surgery	51	NaCl vs HES 6% 130/0.4 and albumin 5%	3
Mittermayer et al 2007[24]	Orthopaedic spine surgery	40	Ringer lactate solution vs HES 6% 130/0.4	2
Tiryakioglu et al 2008[25]	Cardiac surgery	140	Ringer lactate vs HES 6% 130/0.4	1
Ando et al 2008[26]	Abdominal surgery	21	Acetated Ringer solution vs HES 70/0.5	1
Jin & Yu 2009[27]	Colon surgery	24	Lactated Ringer vs HES 6% 130/0.4	2
Schramko et al 2010[28]	Cardiac surgery	30	Ringer acetate vs HES 6% 130/0.4	3
Lee et al 2011[29]	Cardiac surgery	106	Crystalloid vs HES 6% 130/0.4	2
Alavi et al 2012[30]	Cardiac surgery	61	Ringer solution vs HES 6%	2
Topçu et al 2012[31]	Orthopaedic surgery	50	Ringer lactate vs HES 6% 130/0.4	4
Zhang et al 2012[32]	Gastrointestinal surgery	40	Lactated Ringer vs HES 130/0.4	4
Feldheiser et al 2013[33]	Cytoreductive surgery (ovarian cancer)	48	Balanced crystalloid vs balanced colloid HES (Volulyte)	5
Gurbuz et al 2013[34]	Cardiac surgery	200	Balanced crystalloid vs HES 6% 130/0.4	2
Lindroos et al 2013[35]	Craniotomy (sitting position)	28	Ringer acetate vs HES 6% 130/0.4	3
Hung et al 2014[36]	Major abdominal surgery	80	Lactated Ringer vs HES 130/0.4	3
Lindroos et al 2014[37]	Neurosurgery (prone position)	30	Ringer acetate vs HES 6% 130/0.4	3
Rasmussen et al 2014[38]	Cystectomy	33	Lactated Ringer vs HES 6% 130/0.4	4
Skhirtladze et al 2014[39]	Cardiac surgery	236	Ringer lactate vs HES 6% 130/0.4 vs albumin 5%	5
Yates et al 2014[40]	Colorectal surgery	202	Balanced crystalloid (Hartmann) vs HES 6% 130/0.4	5
Schramko et al 2015[41]	Cardiac surgery	34	Ringer acetate vs HES 6% 130/0.4	5
Bueno et al 2004[42]	Cardiac surgery	50	NaCl 7.5% vs dextran 70	2
Rasmussen et al 2015[43]	Cystectomy	37	Ringer lactate vs dextran 70	4
Rasmussen et al 2016[44]	Cystectomy	39	Ringer lactate vs albumin	4
Bennett-Guerrero et al 2001[45]	Cardiopulmonary surgery	147	Albumin 4% vs HES 450	2
Choi et al 2010[46]	Cardiopulmonary surgery	36	Albumin 5% vs HES 6% 130/0.4	4
Kuitunen et al 2004[47]	Cardiac surgery	45	Albumin 4% vs HES 130/0.7 vs HES 140 (Hespan)	1
Niemi et al 2006[48]	Cardiac surgery	30	Albumin 4% vs HES 6% 200/0.5	2
Niemi et al 2008[49]	Cardiac surgery	30	Albumin 4% vs HES 6% 200/0.5	2
Hecht-Dolnik et al 2009[50]	Cardiac surgery	156	Albumin vs HES 6% hetastarch	3
Schramko et al 2009[51]	Cardiac surgery	45	Albumin 4% vs HES 6% 130/0.4 vs HES 200/0.5	2
Van der Linden et al 2013[52]	Cardiac surgery	61	Albumin 5% vs HES 6% 130/0.4	5
Kasper et al 2003[53]	Cardiac surgery	117	HES 6% 130/0.4 vs HES 200/0.5	3

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. 5B).[46–48,51] 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,[23,34,37–40] 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%)[39,45,47,50] (OR = 0.37, 95%CI 0.15–0.92; $P = 0.03$) (Fig. 5). The heterogeneity might not be important in this comparison ($I^2 = 0\%$ 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 6.9–35.6; $P < 0.004$) 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

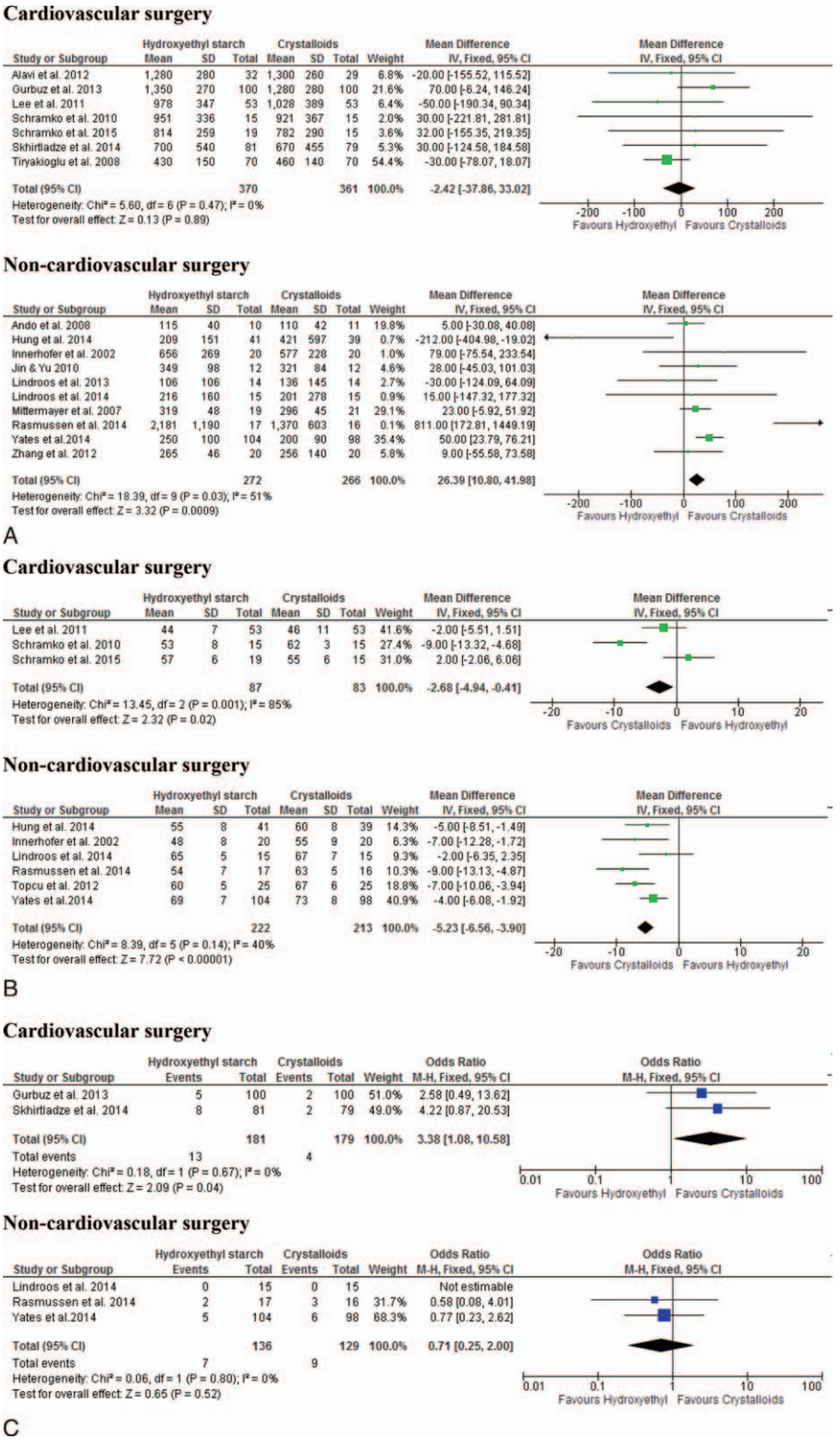

Figure 2. Impact of HES and crystalloids infusion on hemorrhage (A), coagulation competence (lowest measured, TEG-MA) (B), and outcome (reoperation) (C) within subgroups: cardiovascular and noncardiovascular surgical patients. HES = hydroxyethyl starch, TEG-MA = thromboelastography-maximum amplitude.

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).

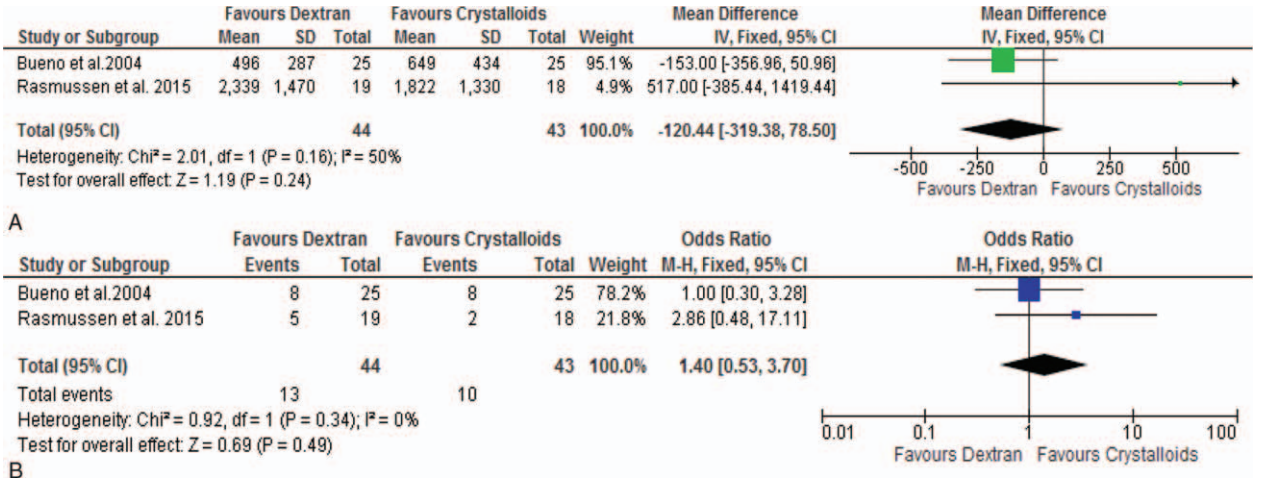

Figure 3. Impact of crystalloids and dextran on hemorrhage (A), and outcome (reoperation) (B) in surgical patients.

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 seem in noncardiovascular surgery after HES compared to crystalloids. Furthermore, a reduction in TEG-MA during surgery by the use 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.[22,28,29,31,36–38,40,41] 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

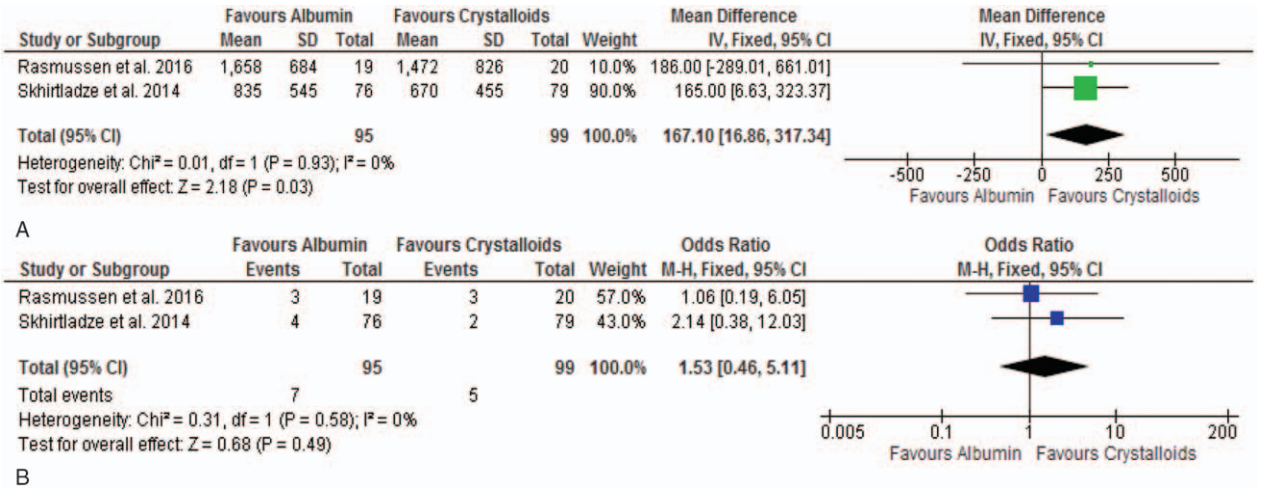

Figure 4. Impact of crystalloids and human albumin on hemorrhage (A), and outcome (reoperation) (B) in surgical patients.

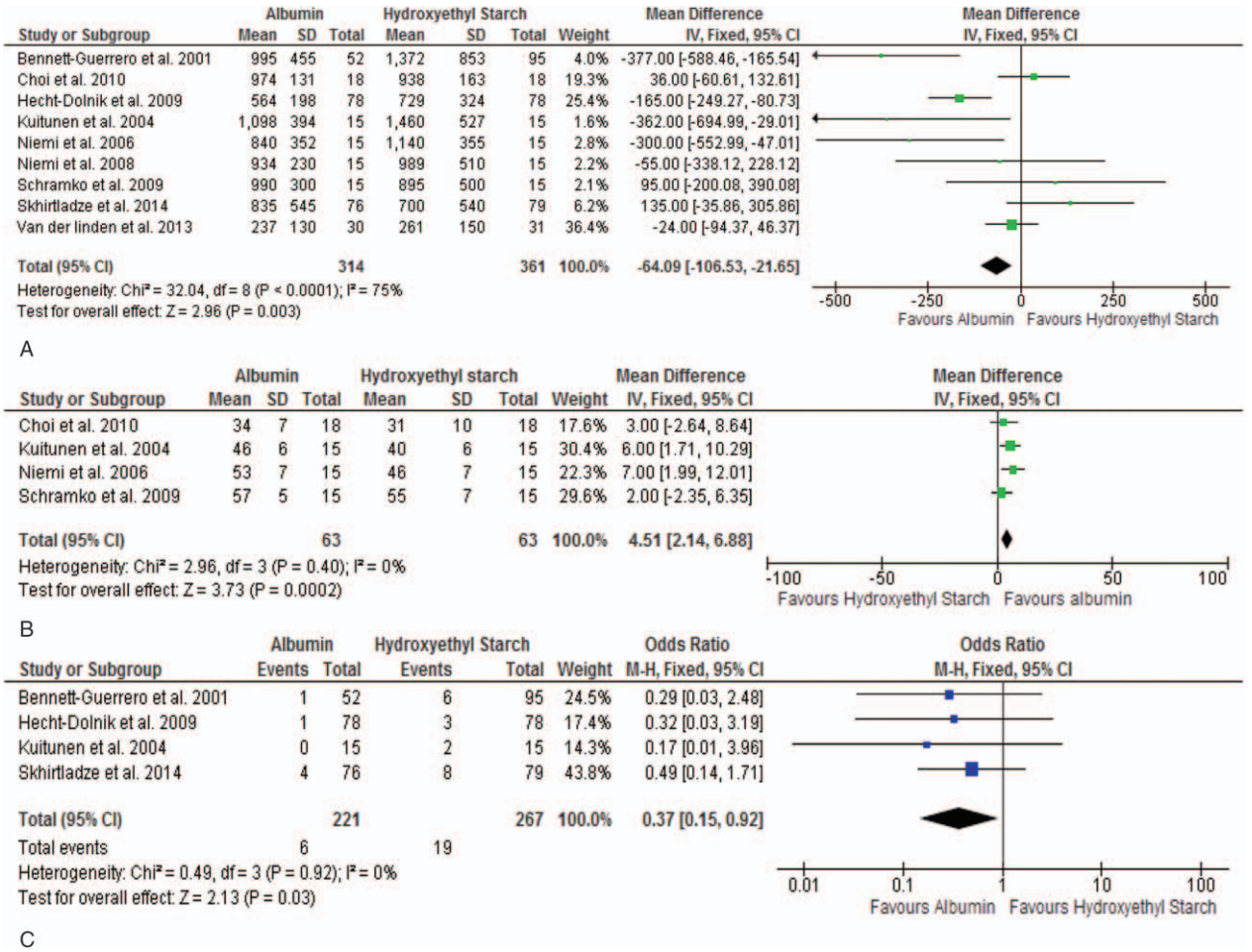

Figure 5. Impact of HESs and human albumin on hemorrhage (A), coagulation competence (lowest measured maximum amplitude, TEG-MA) (B), and outcome (reoperation) (C) in surgical patients. HES = hydroxyethyl starch, TEG-MA = thromboelastography-maximum amplitude.

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).[46–48,51] All studies were conducted during cardiac surgery, the one half added the trial fluid into the priming solution (500 or 1400 mL), and the other half administered the trial fluid when the patient arrived at the ICU after cardiopulmonary bypass. The sensitivity analysis did not change the positive association between albumin administration and lesser influence on coagulation competence compared to low molecular HES administration.

The meta-analysis of 12 RCTs showed increased bleeding following administration of HES products[22,24,26–28,32,34,36–41] and 5 RCTs showed increased hemorrhage following infusion of

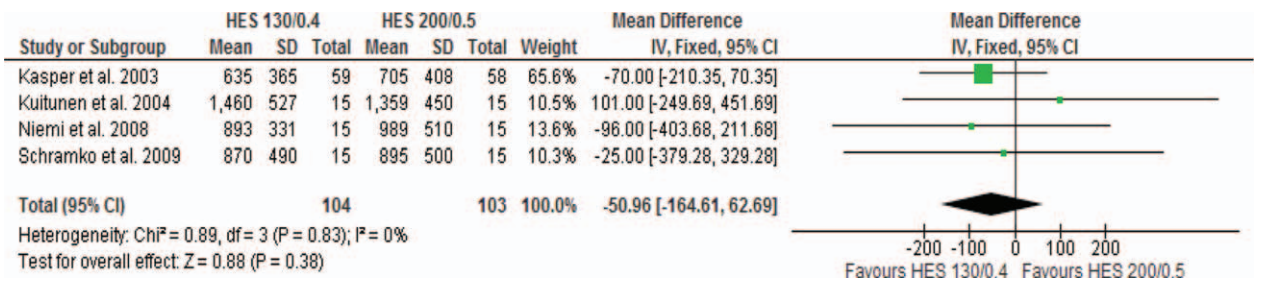

Figure 6. Impact of hydroxyethyl starches (HES) 130/0.4 (low molecular hydroxyethyl) and HES 200/0.5 on hemorrhage in surgical patients.

crystalloids.[25,29,30,35,36] In the 12 trials favoring administrating of crystalloids to HES, the heterogeneity was moderate; for instance the number of participants enrolled in each study varied from 21 to 240, and the blood loss from 0.1 to 2.2 L. In this group also, the investigations were conducted during different types of surgery; cardiovascular and noncardiovascular (abdominal, orthopedic, and neurologic) surgery. The subgroup analysis showed increased blood loss in noncardiovascular surgery among patients receiving HES compared with crystalloids, followed by a marked reduction in TEG-MA ($P < 0.00001$). On the contrary no difference in hemorrhage following HES or crystalloid was found during cardiovascular surgery. This results is, perhaps, not surprizing, because the HES solution in the cardiovascular studies was given only at the start of the anesthesia in the priming solution before bypass surgery,[25,29,34,41] or postoperatively in the ICU.[28,30] Furthermore, the administered volume of study solution (mL/kg) varied between the RCTs; however, when calculating the administered total infused fluid volume, the studies often used two thirds of the maximum allowed daily fluid volume – except for priming doses during cardiac surgery. One for another trial was conducted as off pump surgery and in contrast to most studies concerning hemorrhage, the patients were treated with clopidogrel and aspirin 5 days prior to surgery.[29] Restricting this meta-analysis to studies administering low molecular weight HES product only did not change the association between lesser bleeding and administration of crystalloids.

The main findings concerning RCTs evaluating hemorrhage with HA versus HES 130/0.4 were in favor of albumin administration.[45,47–50,52] All these trials were completed during cardiac surgery, either by adding the trial fluid to the priming solution or by administering the trial fluid immediately after surgery at the ICU. Restricting this meta-analysis to compare HES 130/0.4 and albumin infusion did not reveal significant difference in the volume of perioperative lost blood. This result is not surprizing, because the 4 excluded studies[45,48–50] resulted in a stratified analysis consisting of only 5 RCTs, and the statistical power to detect differences in those studies was therefore limited. At least theoretically, 3rd-generation HES preparations, tetrastarches, may seem to be safer due to their lower molecular weight, rapid turnover, and conceivable reduced impact on coagulation competence.

Two studies administered albumin versus crystalloids and both studies found increased blood loss following albumin infusion ($P = 0.03$).[39,44] Only 2 RCTs administered dextran versus crystalloids and no difference was found regarding blood loss in those 2 groups.[42,43]

For the outcome variable "reoperation", only few RCTs reported events describing postoperative bleeding or leaks, and the number of trials that inform about the frequency of reoperations were small. Five RTCs compared HES products with crystalloids, 2 compared dextran and other 2 HA to crystalloids, while 4 studies compared HA to HES preparations.[34,37–40] During the last mentioned 4 trials, reoperations seemed to occur more often after HES infusion compared to albumin, as 19 patients in the HES group needed reoperation compared to only 6 patients in the albumin group. This is according to the meta-analysis of Navickis et al,[14] who shows that the increase in blood loss is accompanied by more frequent reoperation for bleeding. The remaining 9 RCTs did not disclose differences in number of reoperations, among which the studies by Yates et al[40] and Bueno et al[42] were weighted high in the forest analysis – 48% and 78%, respectively. Five other studies declare no difference in their number of reoperations when administration of a colloid was compared to a crystalloid.

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.[55] 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 RTCs 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-analysis.[13] 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.[52] For this reason, results from those trials may not be generalized to nonpump and noncardiac RCTs during major surgery.[56] 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[57] 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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