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ORIGINAL ARTICLE

Comparison of hydroxyethyl starch colloids with crystalloids for surgical patients

A systematic review and meta-analysis

Mohamed Raiman, Colin G. Mitchell, Bruce M. Biccard and Reitze N. Rodseth

BACKGROUND Fluid therapy is one of the most ubiquitous medical therapeutic interventions. There is a debate over whether colloids or crystalloids are better for fluid resuscitation. Recent large trials and meta-analyses suggest no mortality benefit and possible harm with hydroxyethyl starch (HES) use. However, these trials were conducted in critically ill and septic patients and their applicability to perioperative patients has been challenged.

OBJECTIVE We aimed to evaluate the impact of HES use in scheduled and elective surgical patients.

DESIGN Systematic review and meta-analysis of randomised controlled trials (RCTs).

ELIGIBILITY CRITERIA Only RCTs comparing the use of the synthetic colloid HES with any crystalloid in adults undergoing noncardiac surgery (up to 24 h postop) were considered eligible. For each eligible trial, we extracted the outcomes of all-cause mortality within 90 days, length of hospital stay, major infectious complications, acute kidney injury (AKI) and renal replacement therapy (RRT).

RESULTS We identified 1555 citations, selected 90 for full-text evaluation, and identified 13 eligible RCTs. Trials were small ($n = 20$ to 202) with low event rates. There was a trend to increased mortality with HES within 90 days [13/373 vs. 3/368; risk ratio 2.97; 95% confidence interval (95% CI) 0.96 to 9.19; $I^2 = 0\%$], no difference in AKI and RRT (risk ratio 1.11; 95% CI 0.26 to 4.69; $I^2 = 34\%$), and no difference in major infectious complications (risk ratio 1.19; 95% CI 0.59 to 2.39; $I^2 = 0\%$). Patients resuscitated with HES had a shorter length of hospital stay (mean difference −1.52 days; 95% CI −2.87 to −0.18), although heterogeneity was high ($I^2 = 90\%$).

CONCLUSION This meta-analysis, based on small studies with low event rates, suggests that there are currently insufficient data to identify a difference in outcomes associated with crystalloids and HES in scheduled or elective noncardiac surgery.

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Introduction

Intravenous fluid therapy is one of the most ubiquitous medical therapeutic interventions. Crystalloids and colloids are the two major categories of resuscitative fluid therapy. There has been an ongoing debate in the literature as to which of the two is the safer and more effective resuscitative fluid. Colloids have been used as volume expanders for acute fluid resuscitation in trauma, perioperatively and in shocked ICU patients. This is because colloids are thought to have longer intravascular persistence and therefore a longer volume replacement effect, resulting in lower volume requirements and less extravascular oedema. However, colloids are costly, may cause anaphylaxis and have possible adverse renal and coagulation effects.

Recent large trials[1–4] and subsequent meta-analyses[5,6] have concluded that there is no significant mortality benefit from resuscitation with colloids. Rather, the use of hydroxyethyl starch (HES) in septic critically ill patients has been associated with acute kidney injury

From the Department of Anaesthesia, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban (MR), Department of Anaesthesia, Grey's Hospital, Pietermaritzburg (CGM), Perioperative Research Group, Department of Anaesthesia, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban (BMB), Perioperative Research Group, Department of Anaesthesia, Grey's Hospital, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Pietermaritzburg, South Africa, and Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, USA (RNR)

Correspondence to Mohamed Raiman, Department of Anaesthesia, Inkosi Albert Luthuli Central Hospital, Private Bag X03, Mayville, Durban 4058, South Africa
E-mail: drmraiman@gmail.com

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(AKI) and increased mortality. These trials have been criticised for using HES improperly, late patient enrolment, inadequate evidence of hypervolaemia and the need for volume resuscitation, and the lack of properly targeted endpoints for resuscitation.[7,8] Recently, another large study in critically ill patients, wherein patients were recruited early and were documented to be hypovolaemic, failed to demonstrate similar harm and alluded to possible benefit with colloids.[9] Although these trials have limitations, they have raised concern that HES use may be harmful.

It is unclear whether the findings from trials conducted in critically ill septic patients can be generalised to perioperative surgical patients. We aimed to evaluate the impact of HES compared with crystalloids in randomised controlled trials involving scheduled or elective adult noncardiac surgery on mortality, length of stay (LOS), renal dysfunction and severe infections, defined as sepsis, septic shock or pneumonia, up to 90 days post admission.

Materials and methods

Only published randomised controlled trials comparing the use (up to 24 h postop) of the synthetic colloid HES with any crystalloid in adults (≥18 years) undergoing scheduled or elective noncardiac surgery were considered eligible. Trials were included if data on any of the following outcomes were available either in the publication or from the author in correspondence: mortality (in-hospital, at 30 days or at 90 days), author-defined AKI, need for renal replacement therapy (RRT), hospital LOS or major infections (defined as sepsis, septic shock or pneumonia). Trials were included regardless of language, sample size or date of publication. This systematic review and meta-analysis has not been registered.

We searched the following electronic databases:

(1) EMBASE – from 1974 to 19 August 2013;
(2) OVID Health Star – from 1966 to July 2013;
(3) Ovid Medline In-process and other nonindexed citations and Ovid Medline – from 1946 to 20 August 2013;
(4) Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews;
(5) Web of Science.

We used the following expanded search terms: 'albumin OR colloid OR starch and fluid therapy OR plasma volume'. The search was limited to adults, randomised controlled trials or controlled clinical trials, and humans. The search was updated on 15 February 2015.

The search was conducted by one author (R.R.). The title and abstract of each citation was independently screened by two sets of two reviewers to identify potentially eligible trials. If either reviewer felt that the citation may contain a relevant trial, the article was retrieved to undergo full-text evaluation. Full texts of all citations identified as being potentially relevant were then independently evaluated by two reviewers (M.R., C.M.) to determine eligibility. Disagreements were resolved by consensus. Chance-corrected interobserver agreement for trial eligibility was tested using kappa statistics.

In addition, to obtain additional data studies we attempted to contact the authors of 39 trials by emailed correspondence. Depending on what data were missing from the publication, we asked the following questions related to our outcomes of interest: number of deaths in each group, infectious complications in each group and definition of infection, LOS for each group and AKI (and definition used) or need for RRT.

For each eligible trial, the data were extracted by two authors (M.R. and B.B.) and included author; year of publication; journal; surgical group studied; number of individuals; starch used; comparator fluid used; goal-directed [fluid] therapy (GDT); commercial support; all-cause mortality within 90 days, length of hospital stay, author-defined AKI, need for RRT and infection (where reported).

Trial quality was evaluated using the Jadad score. We also evaluated the following criteria: randomisation methodology; completeness of patient follow-up; method of patient follow-up; blinded outcome assessment; consistent end-point assessment; and the use of intention-to-treat analysis. Trials were assessed using the Cochrane Collaboration risk of bias tool. This tool assesses selection bias, allocation bias, performance bias, detection bias, attrition bias and other bias. All assessments of bias in individual studies were conducted by two investigators (M.R. and B.B.) and disagreements were resolved through consensus. Sensitivity analyses for all outcomes were also conducted by removing high-bias studies (Jadad score <3) from each outcome meta-analysis.

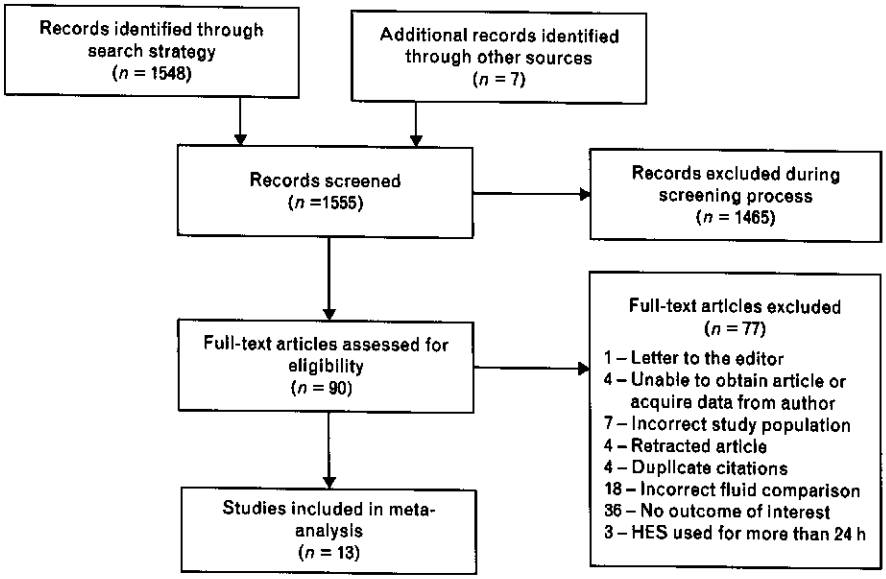
Statistical analysis

Meta-analysis was conducted using a random effects model in Review Manager Version 5.1. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Heterogeneity was assessed using I^2 and χ^2 analysis. Pooled dichotomous outcomes are reported as risk ratios and 95% confidence intervals (95% CIs). Continuous outcomes are reported as mean difference and 95% CI. As GDT may positively affect surgical outcomes,[10,11] all outcomes are reported in subgroups dependent on the presence or absence of GDT in the included trial.

We constructed a funnel plot to assess for the possibility of publication bias. In order to exclude selective reporting by the authors, we contacted the authors of all the included studies to determine whether they had

Fig. 1



Study selection process.

collected data on any of the outcomes of interest that were not reported in the original publication.

Results

We identified 1555 citations, from which 90 were selected for full-text evaluation (Fig. 1); 18 authors responded to our correspondence and provided additional data. We reviewed all 90 citations – together with the additional data provided – and from this identified 13 eligible randomised controlled trials that included 741 patients.[12–24] Interobserver agreement for trial eligibility was fair (kappa = 0.58).

Table 1 summarises the characteristics of the selected trials. All trials were single-centre randomised trials. Eight of the trials used tetrastarch 6% HES 130/0.4. Comparators were all balanced crystalloid solutions. Seven of the 13 trials[15,17–20,22–24] used GDT for volume resuscitation in the perioperative period.

All but four trials[14,16,19,23] had a Jadad score of three or more. A breakdown of the individual trial scores is provided in Appendix 1 (supplementary data content, http://links.lww.com/EJA/A76). The risk of bias graph and summary for the individual studies is reported in Appendices 2 and 3 (supplementary data content, http://links.lww.com/EJA/A76). The main risk of bias was related to inadequate blinding of personnel and patients, and blinding of outcome assessment. This was evident in more than 50% of the included studies.

The source of the outcomes (publication, author correspondence, not recorded) and the outcome definitions used are reported in Appendices 4 and 5, respectively (supplementary data content, http://links.lww.com/EJA/A76).

Thirteen trials ($n = 741$) reported mortality within 90 days of randomisation (Fig. 2). In the HES group, 3.5% of patients died (13 of 373) compared with 0.8% of patients (three of 368) in the crystalloid group. There were no deaths in nine of these trials. All the deaths occurred in trials that used GDT. There was a trend to higher mortality associated with HES administration, with a risk ratio of 2.97 (95% CI 0.96 to 9.19), with no heterogeneity for the outcome ($I^2 = 0\%$). None of the high-bias studies reported mortality.

Seven trials (518 patients in total) reported either AKI or need for RRT (Fig. 3). There was no difference in AKI and RRT (risk ratio 1.11; 95% CI 0.26 to 4.69; $I^2 = 34\%$) associated with HES in comparison with crystalloid. The differences in the definitions of renal dysfunction and length of follow-up may account for some of the heterogeneity in the meta-analysis. None of the high-bias studies reported renal dysfunction outcomes.

Eight trials including 456 patients contained data on hospital LOS (Appendix 6, supplementary data content, http://links.lww.com/EJA/A76). There was a significantly shorter length of hospital stay in the HES group (mean difference −1.52 days; 95% CI −2.87 to −0.18, $I^2 = 90\%$). After excluding the low-quality studies,[14,16] the mean difference still favoured HES but became nonsignificant (mean difference −0.90; 95% CI −2.28 to 0.47). Heterogeneity was high ($I^2 = 95\%$) and this persisted when low-quality studies were excluded ($I^2 = 86\%$). The trend to a shorter hospital stay was consistent between the GDT

Table 1 Characteristics of hydroxyethyl starch vs. crystalloid trials

Trial	Setting	Number of patients randomised	Starch	Comparator	Goal-directed therapy[a]	Jadad score
Butscher *et al.*[12]	Lumbar intervertebral disc surgery	20	Hydroxyethyl starch 6%	Ringer's solution	No	3
Mark *et al.*[13]	Elective open AAA surgery	30	Hetastarch	Ringer's lactate	No	3
Guo *et al.*[14]	Gynaecological oncology surgery	40	6% HES 200/0.5	Ringer's lactate	No	2
Senagore *et al.*[15]	Laparoscopic colectomy	42	Balanced 6% hetastarch	Ringer's lactate	Yes	4
Ando *et al.*[16]	Elective abdominal surgery	21	Low MW HES 70/0.5 (Hespander)	Ringer's acetate	No	1
Zhang *et al.*[17]	Elective abdominal surgery	60	6% HES 130/0.4	Ringer's lactate	Yes	4
Feldheiser *et al.*[18]	Gynaecological oncology surgery	50	Balanced 6% HES 130/0.4 (Volulyte)	Balanced crystalloid (Jonosteril)	Yes	5
Lindroos *et al.*[19]	Elective craniotomy	30	6% HES (130/0.4) (Voluven)	Ringer's acetate	Yes	3
Rasmussen *et al.*[20]	Elective cystectomy	33	6% HES (130/0.4)	Lactated Ringer's solution	Yes	4
Hung *et al.*[21]	Elective major abdominal surgery	84	6% HES (130/0.4)	Lactated Ringer's solution	No	3
Krebbel *et al.*[22]	Elective hip replacement surgery	20	6% HES (130/0.4)	Ringer's solution	Yes	5
Szturz *et al.*[23]	Elective major urological surgery	115	6% HES 130/0.4 (Voluven)	Ringer's solution	Yes	3
Yates *et al.*[24]	Elective colorectal surgery	202	6% HES (130/0.4) Volulyte	Balanced crystalloid (Hartmann's solution)	Yes	5

AAA, abdominal aortic aneurysm; HES, hydroxyethyl starch; LOS, length of stay; MW, molecular weight; RCT, randomised controlled trial; RRT, renal replacement therapy. [a]Goal-directed therapy defined as fluid resuscitation endpoint that includes a variable other than blood pressure or central venous pressure.

and non-GDT subgroups, with no statistical difference for effect.

Seven trials including 489 patients reported on major infections (Appendix 7, supplementary digital content, http://links.lww.com/EJA/A76). There was no difference in major infectious complications between the groups (risk ratio 1.19; 95% CI 0.59 to 2.39; $I^2 = 0\%$). There was no heterogeneity for this outcome. Removing the high-bias study that reported major infections[23] had little effect on the meta-analysis (risk ratio 1.33; 95% CI 0.62 to 2.85; $I^2 = 0\%$). There was no significant subgroup effect for GDT on major infections.

A funnel plot of trials used in the mortality analysis showed no evidence of publication bias. There was also no evidence of publication bias for renal dysfunction or major infections.

No additional analyses were conducted.

Discussion

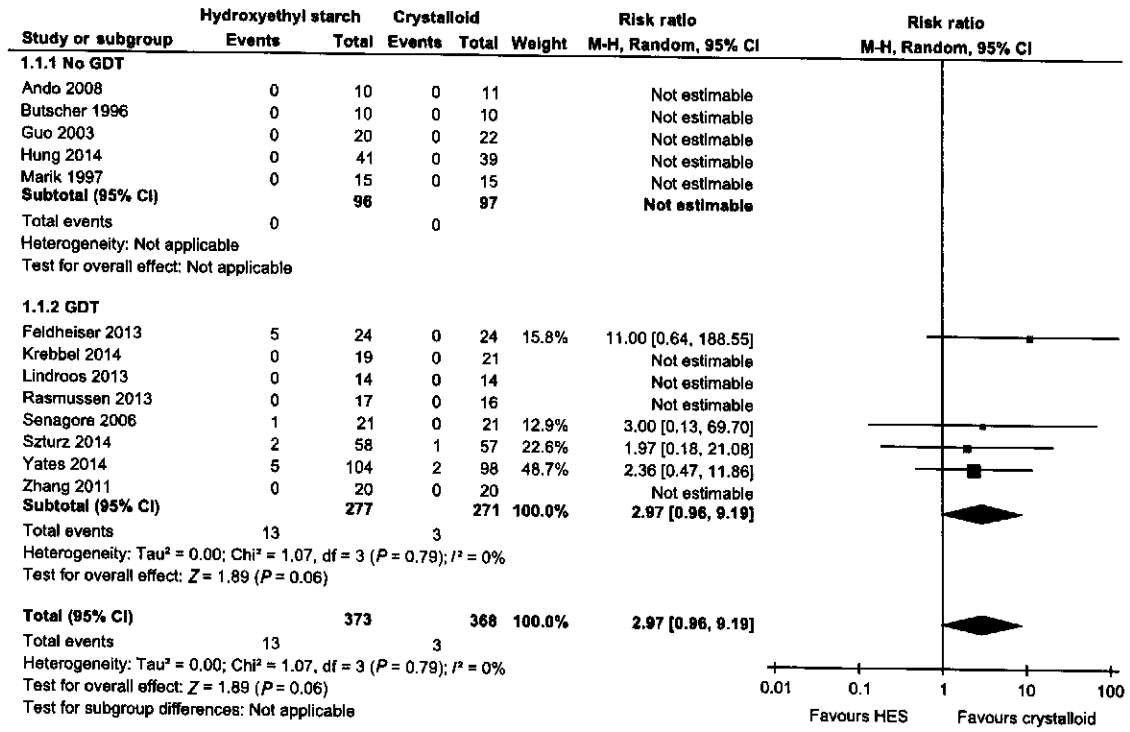
When crystalloids, as opposed to HES, are used for perioperative resuscitation for scheduled or elective surgery, we found no statistically significant difference in mortality with HES within 90 days, no difference in AKI and RRT and no difference in major infectious complications. Patients resuscitated with HES had a shorter length of hospital stay, although heterogeneity was high. Although there was a trend towards increased mortality with HES in the trial by Feldheiser *et al.*,[18] the five deaths in the HES group were all deemed to be unrelated to the study protocol prior to unblinding. These deaths were included in our review so as to follow intention-to-treat principles. If these deaths were independent of the fluid administered and they are removed from the meta-analysis, the risk ratio for mortality associated with HES is 2.33 (95% CI 0.68 to 7.96; $I^2 = 0\%$). Thus, the point estimate shows a trend towards increased mortality, but the sample size is underpowered for this outcome.

There was a shorter length of hospital stay in the HES group. Although LOS may act as a surrogate for a complicated postoperative course, it is also possible that the insignificantly higher early mortality in the HES group could partly account for this. However, the high heterogeneity ($I^2 = 90\%$) and the fact that the result becomes nonsignificant when the low-quality studies are excluded make this result less reliable.

No difference was found between the groups for AKI or RRT. Only one of the trials that reported this outcome[19] had a long-term follow up (3 to 6 months). All others followed patients until hospital discharge, making it possible that delayed adverse renal effects of HES use were not identified.

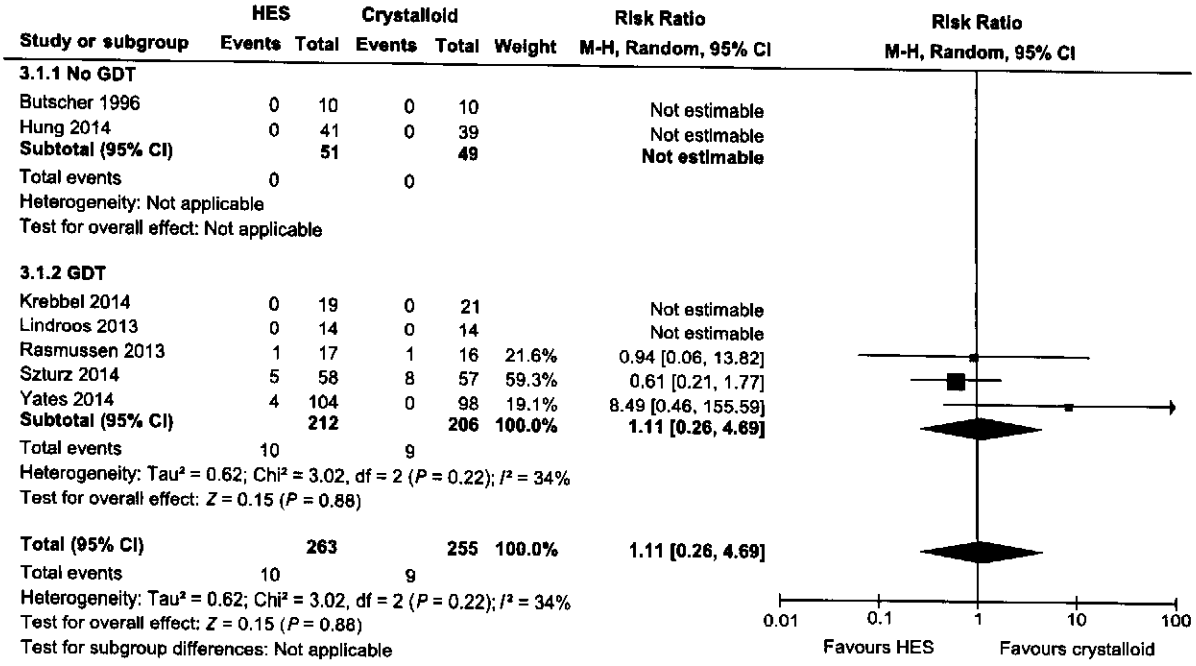
Other meta-analyses[25–28] have attempted to evaluate starch safety perioperatively. All evaluated renal safety

Fig. 2



Forest plot – mortality. CI, confidence interval; HES, hydroxyethyl starch.

Fig. 3



Forest plot – renal dysfunction. CI, confidence interval; HES, hydroxyethyl starch.

whilst two[27,28] also considered mortality. Gillies *et al.*[28] compared HES with any other fluid (including other colloids) in both cardiac and noncardiac surgery, with in-hospital mortality, AKI and RRT as outcomes. They found no difference in hospital mortality, AKI or RRT. Van der Linden *et al.*[27] found a statistically insignificant trend towards mortality benefit in the tetrastarch group when compared with other fluids (including other starches). The updated Cochrane review by Mutter *et al.*[25] in 2013 examined the effect of starches on renal function in all settings. In their surgical and trauma patients (nonsepsis) subgroup, the relative risk for RRT if HES was used was 1.25 (95% CI 0.96 to 1.61).

There are limitations to these reviews. First, all[25–28] compared HES or tetrastarches with any other fluid (i.e. crystalloids, gelatins, albumin and other starches), not crystalloids alone. These meta-analyses assume that the comparator fluids are equally well tolerated to surgical patient outcome. This assumption is incorrect because it is possible that other colloids such as gelatins[29] may also be associated with potential harm, although there are currently insufficient data to confirm this. It is possible that the inclusion of mixed fluid comparators (if some are potentially associated with harm) may have minimised the effect size of any potential harm associated with HES. It would be more appropriate to compare the HES group with a more homogenous fluid comparator group, for example crystalloids alone.

Second, all these meta-analyses[25–28] include cardiac surgery in their reviews. Cardiac surgical patients are a distinct set of patients and the marked inflammatory response seen after cardiopulmonary bypass may confound the effects of the fluid therapy choice. Results from this set of patients may therefore not be generalisable to the noncardiac surgical patient.

Finally, the choice of risk difference as the summary statistic used in the meta-analyses by Martin *et al.*[26] and Gillies *et al.*[28] is potentially misleading. Summary statistics that present the relative differences between groups (e.g. risk ratio) are more consistent than absolute differences (e.g. risk difference). Risk difference suggests that the absolute difference in outcomes per group is consistent, which is unlikely in a mixed cohort of cardiac and noncardiac surgical patients. Furthermore, our own unpublished data suggest that the use of risk difference as the summary statistic in a meta-analysis may hide a potentially significant difference in outcome between groups, which is evident when a relative difference summary statistic is used.

Strengths of our review include a rigorous selection process and evaluation of methodological quality of selected trials. We only included randomised trials of scheduled and elective noncardiac surgical patients wherein HES was compared with crystalloids. We did not include other colloids as a comparator, thus making this the only analysis currently in the literature, as far as we are aware, of HES vs. crystalloids in the perioperative setting.

Our study has several potential limitations. Trials included were limited to a few, small, single-centre studies with poor blinding of participants, physicians and outcome assessors, all of which increase bias. The small number of trials within each outcome means that the larger trials have a disproportionately high impact on our findings. Furthermore, the low numbers of total participants makes this meta-analysis underpowered for the outcomes of mortality, renal dysfunction and major infections. To power a study with an event rate of 5% and a 20% absolute increase in risk would require over 6500 patients per group. Finally, we considered all HES solutions, not just the tetrastarches that are more commonly used nowadays and purportedly associated with fewer adverse effects.

There is a paucity of studies that have evaluated either safety or benefit of the use of HES in the perioperative setting. This is partly due to the retraction of a number of perioperative HES studies due to research misconduct.[30] Although the volume expansion effects of HES are evident, it is unclear whether this translates into mortality benefit. Studies in the ICU setting[1–4] have suggested possible deleterious renal effects of HES. Whether a similar risk exists if HES is used in the perioperative setting remains unclear. A large, well conducted study evaluating the use of HES and crystalloids in the perioperative setting is long overdue. This meta-analysis highlights the importance of a robust study design in which blinding, in particular, is adequately addressed.

Conclusion

This meta-analysis based on 13 surgical studies showed that there are currently insufficient data to determine the effect of HES on mortality, renal dysfunction and major infections in noncardiac surgical patients.

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