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REVIEW ARTICLES

Incidence of postoperative death and acute kidney injury associated with i.v. 6% hydroxyethyl starch use: systematic review and meta-analysis

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Editor's key points:

- The use of hydroxyethyl starch (HES) solutions has been linked to an increase in in-hospital mortality by some clinical studies, but results have been conflicting.
- HES solutions have also been implicated in causing kidney injury.
- This systematic review and meta-analysis identified no consistent effect on mortality or renal function when reviewing 456 and incorporating 19 research papers.
- However, no positive effect was also found, and the authors conclude that they are unable to recommend the continued use of 6% HES solutions.

Background. Trials suggest that the use of i.v. hydroxyethyl starch (HES) solutions is associated with increased risk of death and acute kidney injury (AKI) in critically ill patients. It is uncertain whether similar adverse effects occur in surgical patients.

Methods. Systematic review and meta-analysis of trials in which patients were randomly allocated to 6% HES solutions or alternative i.v. fluids in patients undergoing surgery. Ovid Medline, Embase, Cinhal, and Cochrane Database of Systematic Reviews were searched for trials comparing 6% HES with clinically relevant non-starch comparator. The primary end-point was hospital mortality. Secondary endpoints were requirement for renal replacement therapy (RRT) and author-defined AKI. Pre-defined subgroups were cardiac and non-cardiac surgery.

Results. Four hundred and fifty-six papers were identified; of which 19 met the inclusion criteria. In total, 1567 patients were included in the analysis. Dichotomous outcomes were expressed as a difference of proportions [risk difference (RD)]. There was no difference in hospital mortality [RD 0.00, 95% confidence interval (CI) −0.02, 0.02], requirement for RRT (RD −0.01, 95% CI −0.04, 0.02), or AKI (RD 0.02, 95% CI −0.02 to 0.06) between compared arms overall or in predefined subgroups.

Conclusions. We did not identify any differences in the incidence of death or AKI in surgical patients receiving 6% HES. Included studies were small with low event rates and low risk of heterogeneity. Narrow CIs suggest that these findings are valid. Given the absence of demonstrable benefit, we are unable to recommend the use of 6% HES solution in surgical patients.

Keywords: hetastarch; meta-analysis; surgery

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Approximately 230 million patients undergo surgery each year with reported mortality rates between 1 and 4%.[1 2] There is great interest in the optimal approach to i.v. fluid therapy in the perioperative period, which may have important effects on patient outcomes.[3] The choice of i.v. fluid solution is a central aspect of fluid therapy, but the evidence base informing this decision is limited with wide international variations in practice.[4] Hydroxyethyl starch (HES) solutions, which are derived from maize or potato starch, are commonly used for i.v. fluid therapy. Modern starches are typically presented in a concentration of 6%, molecular weights (MWs) of 130–200 kDa, and a molecular substitution ratio of 0.4 or 0.42 (tetrastaches). Older starch solutions have higher substitution ratios [e.g. 0.5 (pentastarch) and 0.7 (hetastarch)]; some of these solutions are still commercially available.[5] The findings of two recent large randomized trials have suggested a small but important increase in the incidence of acute kidney injury (AKI) and mortality associated with the use of HES solutions in critically ill patients.[6 7] Potential mechanisms for starch-mediated kidney injury are unclear, but may be associated with more concentrated

solutions (e.g. HES 10) and also molecules with high MW and greater degree of substitution.[5 8 9] Concerns have also been raised regarding the effects of HES on the coagulation profile. It now seems likely that these solutions will be withdrawn from practice in the care of critically ill patients.[10 11]

However, the generalizability of these findings to other patient groups is uncertain and the use of HES for i.v. volume replacement continues in cardiac and non-cardiac surgical patients. There is a paucity of quality data regarding the safety of starch solutions in the surgical population. To compound matters, several studies investigating the use of HES in surgical patients which were conducted by Joachim Boldt have been retracted after allegations of scientific misconduct.[12] At least five meta-analyses on the safety of starch have been published in the last 3 yr.[13–17] The majority of these reviews have focused on the use of starch in critically ill, septic, or acutely unwell adults.[13–15] Three of these studies have considered the safety of starch in other groups. The extensive systematic review and meta-analysis conducted by Dart and colleagues included a non-sepsis subgroup largely (but not exclusively) composed of surgical trials.[13] Two further reviews and meta-analyses focus on the use of starch primarily in surgical patients,[15 16] but these are limited because they evaluate only the effects of tetrastach, in some cases in comparison with other starch solutions, and include a heterogeneous group of studies, including those undertaken in trauma, burns, paediatric, and transplant surgery. We undertook a systematic review and meta-analysis on the effect of all 6% HES solutions compared with non-starch solutions in clinical use on mortality and AKI exclusively in the adult surgical population.

Methods

Search strategy

Ovid Medline (1946–present), Embase, Cinhal, and Cochrane Database of Systematic Reviews were searched for suitable studies using the following search strategy: Starch.mp or starch/OR Hetastarch.mp or hetastarch/OR Voluven.mp OR Volulyte.mp OR Haes-steril.mp OR Hespan.mp OR Tetraspan.mp AND Surgery.mp or General Surgery/. Search results were limited to randomized controlled trials in adult subjects. Non-English language papers were included. The bibliographies of evaluable studies and other selected papers were hand searched. Experts were contacted to ascertain if they were aware of any other studies not identified by our search strategy. The literature search was conducted independently by two authors (M. Habicher and S.J.). Disparities in the literature search were resolved by consensus of all authors. Search strategy and analysis were carried out according to the 'Preferred Reporting Items for Systematic Review and Meta-analysis' (PRISMA) statement 2009.[18]

Study selection criteria

Search results were reviewed and evaluated independently by two authors (R.M.P. and M.S.). Randomized controlled trials (RCTs) in surgical patients were included where hospital mortality, requirement for postoperative renal replacement therapy (RRT), or author-defined postoperative AKI were reported. Trials comparing perioperative administration of 6% HES of any MW or substitution ratio with any non-starch fluid were included, with the exception of trials where comparator fluids were experimental haemoglobin-based fluids (MPOX4 and HBOC21) and hypertonic saline. Trials in subjects undergoing all types of surgery were considered with the exception of neurosurgery, transplantation, burns, or obstetric surgery. Studies where Joachim Boldt was a named author were also excluded. Studies were screened for methodological quality using the Jadad score, an established method of assessing methodological quality of studies to be included in meta-analysis.[19]Assessment was made of the appropriateness of randomization, blinding, and whether patient withdrawal information was provided. The maximum score attributable was 5. Only studies with a Jadad score of ≥ 3 were included. Disagreements on studies to be included in the final analysis were resolved by consensus within the whole group.

Data extraction

Data extracted for each eligible study included: author; year of publication; surgical group studied; number of subjects; starch used; comparator fluid used; primary and other study outcomes; commercial support; hospital mortality; incidence of postoperative RRT; and incidence of author-defined AKI (where reported).

Outcomes

Primary outcomes studied were hospital mortality and postoperative requirement for RRT. Secondary outcome was the incidence of author-defined postoperative AKI. If data on mortality were not reported, data on AKI or RRT were used; conversely, if data on mortality only were available, then this was used. It was decided *a priori* that a subgroup analysis would be performed on patients undergoing cardiac surgery.

Statistical analysis

Statistical analysis was carried out using Review Manager (RevMan, v5.2). RevMan is the software used for preparing and maintaining Cochrane Reviews and forms part of the Cochrane Information Management System. Between-study statistical heterogeneity was assessed by χ^2 and I^2 tests; values of the index of 25, 50, and 75% indicated the presence of low, moderate, and high between-trial heterogeneity, respectively. A *P*-value of 0.1 was considered to denote the statistical significance of heterogeneity. Estimation of potential publication bias used the funnel plot method for any of the outcomes, either primary or secondary. Dichotomous outcomes were expressed as a difference of proportions [risk difference (RD)]. For all analyses performed, if no significant heterogeneity was noted, fixed effect model (FEM) analysis using the Mantel–Haenszel method was used; otherwise, results of the random-effects model analysis using the DerSimonian–Laird method were presented.

Results

Study selection

The process for literature search and study selection is outlined in Figure 1. Four hundred and fifty-six non-duplicate citations were screened; of which, 34 studies underwent full scoring and data extraction. However, only 19 trials were suitable for inclusion in the meta-analysis, including a total of 1567 subjects.[9 20–37]

Characteristics of included studies

The characteristics of included studies are summarized in Table 1. Two trials were multicentre trials, the remainder were single-centre trials. In 10 studies, the subjects were undergoing cardiac surgery; two studies were of patients undergoing major vascular surgery and one was a mixture of cardiac and major vascular surgery. The study undertaken by Gondos and colleagues was in a mixed group of surgical patients including those undergoing cardiac surgery. Two trials used HES 450/0.7 and one HES 400/0.7; the remainder used molecular sizes of ≤200 kDa. Comparators included crystalloid solutions, gelatin solutions, and albumin. In seven studies, there was a commercial sponsor. Funnel plot of studies used in the hospital mortality analysis showed no evidence of publication bias (Supplementary material). Studies excluded after full scoring and data extraction were conducted are summarized in Table 2. In six of these studies, hospital mortality, incidence of RRT, or AKI was not reported.[38–43] The remainder were excluded, because the

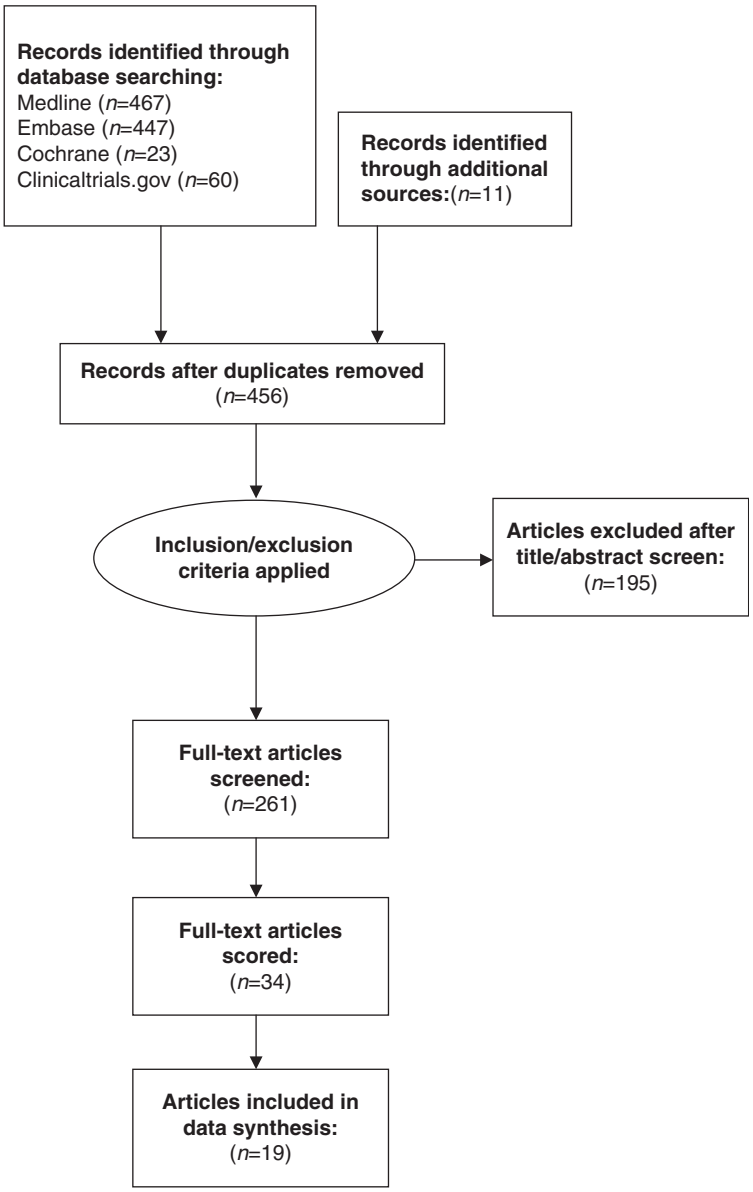

Fig 1 Preferred PRISMA flow diagram detailing search strategy and identification of studies used in data synthesis.

Table 1 Characteristics of included studies. RRT, renal replacement therapy; AKI, acute kidney injury; SCr, serum creatine; AKIN, Acute Kidney Injury Network

Study	Design	Type of surgery	*n*	Starch	Comparator	Jadad score	Reports mortality	Reports RRT	Reports AKI	Author-defined AKI	Commercial support
Alavi and colleagues[20]	RCT	Cardiac	92	6% HES 130/0.4	4% gelatin, RL	3	Yes	No	No	–	Not stated
Dehne and colleagues[21]	RCT	ENT	60	6% HES-200/0.5: 6% HES-200/0.62: 6% HES-450/0.7	RL	4	Yes	No	No	–	Fresenius
Diehl and colleagues[22]	RCT	Cardiac	60	6% HES-450/0.7	5% albumin	3	Yes	No	Yes	SCr >1.5 mg dl^{-1}	Not stated
Feldheiser and colleagues[23]	RCT	Gynaecological	50	6% HES 130/0.4	Balanced crystalloid	4	Yes	No	No	–	Fresenius-Kabi
Godet and colleagues[24]	Multicentre RCT	Vascular	65	6% HES 130/0.4	3% gelatin	4	Yes	Yes	Yes	Increase in SCr from baseline of >0.5 mg dl^{-1}	Fresenius-Kabi
Gondos and colleagues[25]	Multicentre RCT	Mixed	200	6% HES 130/0.4	RL, 4% gelatin, 5% albumin	3	Yes	No	No	–	Fresenius-Kabi
Guo and colleagues[26]	RCT	Gynaecological	42	6% HES-200/0.5	RL	3	Yes	Yes	No	–	Not stated
Hecht-Dolnik and colleagues[9]	RCT	Cardiac	156	6% hetastarch	5% albumin	4	Yes	No	No	–	None
Hung and colleagues[27]	RCT	Vascular	84	6% HES 130/0.4	RL	4	Yes	Yes	Yes	Not specified	Edwards
Kuitunen and colleagues[28]	RCT	Cardiac	45	6% HES 120/0.7: 6% HES 400/0.7	4% albumin	4	Yes	No	No	–	Not stated
Lee and colleagues[29]	RCT	Cardiac	106	6% HES 130/0.4	RL	3	No	Yes	Yes	AKIN criteria	None
Mahmood and colleagues[30]	RCT	Vascular	62	6% HES 200/0.6: 6% HES 130/0.4	4% gelatin	4	Yes	Yes	No	–	Fresenius-Kabi
Marik and colleagues[31]	RCT	Vascular	30	6% hetastarch	RL	4	Yes	No	No	–	Not stated
Munsch and colleagues[32]	RCT	Cardiac	40	6% HES-450/0.7	Plasma protein fraction	3	Yes	No	No	–	Not stated
Ooi and colleagues[33]	RCT	Cardiac	90	6% HES 130/0.4	4% gelatin	4	Yes	Yes	Yes	Not specified	Not stated
Sirvinskas and colleagues[34]	RCT	Cardiac	80	NaCl 0.72%/6% HES	RL	3	Yes	No	No	–	Not stated
Van der Linden and colleagues[35]	RCT	Cardiac		6% HES-200/0.5	3.5% gelatin	3	Yes	No	No	–	Not stated
van der Linden and colleagues[36]	RCT	Cardiac	132	6% HES 130/0.4 (Voluven)	3% gelatin	3	Yes	No	No	–	Not stated
Verheij and colleagues[37]	RCT	Cardiac or major vascular	67	6% HES 200/0.5	4% gelatin, NaCl 0.9%	4	Yes	No	No	–	Braun

Table 2 Articles scored but not included in data synthesis. HES, hydroxylethyl starch; AKI, acute kidney injury; RRT, renal replacement therapy; HBOC-21 and MP4-OX are artificial haemoglobin solutions

Paper	*n*	Reason excluded
Ando and colleagues[38]	21	Jadad score <3; incidence of hospital mortality, RRT, and AKI not reported
Belcher and colleagues[39]	73	Jadad score <3; incidence of hospital mortality, RRT, and AKI not reported
Challand and colleagues[50]	179	Control group received HES solution
Harten and colleagues[40]	29	Incidence of hospital mortality, RRT, and AKI not reported
Honkonen and colleagues[44]	49	Comparator hypertonic saline
Kasper and colleagues[45]	13	Comparator HBOC-21
Magder and colleagues[46]	237	Control group given HES solution
Mukhtar and colleagues[51]	40	Population studied liver transplant surgery
Olofsson and colleagues[47]	189	Comparator MP4-OX
Senagore and colleagues[41]	64	Incidence of hospital mortality, RRT, and AKI not reported
Shahbazi and colleagues[42]	70	Incidence of hospital mortality, RRT, and AKI not reported
Sirieix and colleagues.[48]	64	Control group given HES solution
Standl and colleagues[49]	12	Comparator HBOC-21
Tiryakioglu and colleagues[43]	140	Jadad score <3; incidence of hospital mortality, RRT, and AKI not reported
Van Der Linden and colleagues[54]	274	Comparator MP4-OX

comparator fluid was not valid,[38 44–50] or because the study population underwent transplant surgery.[51]

Primary outcomes

Hospital mortality

Hospital mortality was available in 18 of the 19 included RCTs, which include a total of 1461 patients. Of the 685 patients receiving HES, 19 (2.8%) died and of 776 patients receiving comparator fluid, 46 (5.9%) died. There were no deaths in 12 of the 18 included studies. There was no difference in mortality between compared arms [P=0.91, I^2=0%; FEM: RD=0.00, 95% confidence interval (CI) −0.02, 0.02]. Subgroup analysis of studies of 872 cardiac surgery patients from 10 studies also did not demonstrate any difference (P=1.0, I^2=0%; FEM: RD 0.00, 95% CI −0.02 to 0.01) (Fig. 2).

Secondary outcomes

Incidence of author-defined AKI

Data on postoperative incidence of author-defined AKI were available in 5 of the 19 trials included, which include a total of 401 patients. Of the 204 patients receiving HES, 11 (5.4%) developed author-defined AKI and in 197 patients receiving comparator fluid, 7 (3.6%) developed author-defined AKI. In two studies, no patient developed author-defined AKI. No difference in the incidence of author-defined AKI was observed between compared arms (P=0.34, I^2=0%; FEM: RD 0.02, 95% CI −0.02, 0.06). Two of these studies (n=196) were undertaken in cardiac surgery patients. No difference was observed in author-defined AKI between arms (P=0.56, I^2=0%; FEM: RD 0.01, 95% CI −0.02, 0.04) (Fig. 3).

Requirement for postoperative renal replacement therapy

Data on new requirement for postoperative RRT were available in 6 of the 19 included RCTs, which include a total of 445 patients. Of the 233 patients receiving HES, four developed a new requirement for postoperative RRT (1.7%) and of the 212 patients receiving comparator fluid, 4 (1.9%) developed new requirement for postoperative RRT. There were no instances of new requirement for postoperative RRT in two of these studies. No difference in the incidence of new requirement for postoperative RRT was observed between compared arms (P=0.62, I^2=0%; FEM: RD −0.01, 95% CI −0.04, 0.02) (Fig. 4).

Studies involving tetrastach only

Nine studies (n=856) compared tetrastach (substitution ratio of 0.4 or 0.42) with other non-starch fluids. Analysis of these studies did not detect any difference in either mortality (n=750, P=0.83, I^2=0%; FEM: RD 0.00, 95% CI −0.04 to 0.04) or new requirement for RRT (n=382, P=0.73, I^2=0%; FEM: RD −0.01, 95% CI −0.04 to 0.03) (Supplementary material).

Discussion

The principal finding of this systematic review and meta-analysis was that there was no difference in hospital mortality associated with the use of 6% HES solution in the treatment of patients undergoing surgery. Similarly, there were no differences in the secondary outcomes of AKI and the use of RRT. These findings were consistent in subgroup analyses of patients undergoing cardiac and non-cardiac surgery and in patients receiving tetrastarch only.

In total, 19 studies with <1600 participants were suitable for inclusion in the meta-analysis. Seven of the included studies were commercially sponsored, raising the possibility of publication bias (although we found no evidence of this). Despite widespread use for more than three decades, studies comparing perioperative use of HES with other i.v. fluids are small, largely single centre and vulnerable to bias. The most likely cause of HES-associated harm (and hence increased mortality) in the critically ill is causation or exacerbation of kidney injury. However,

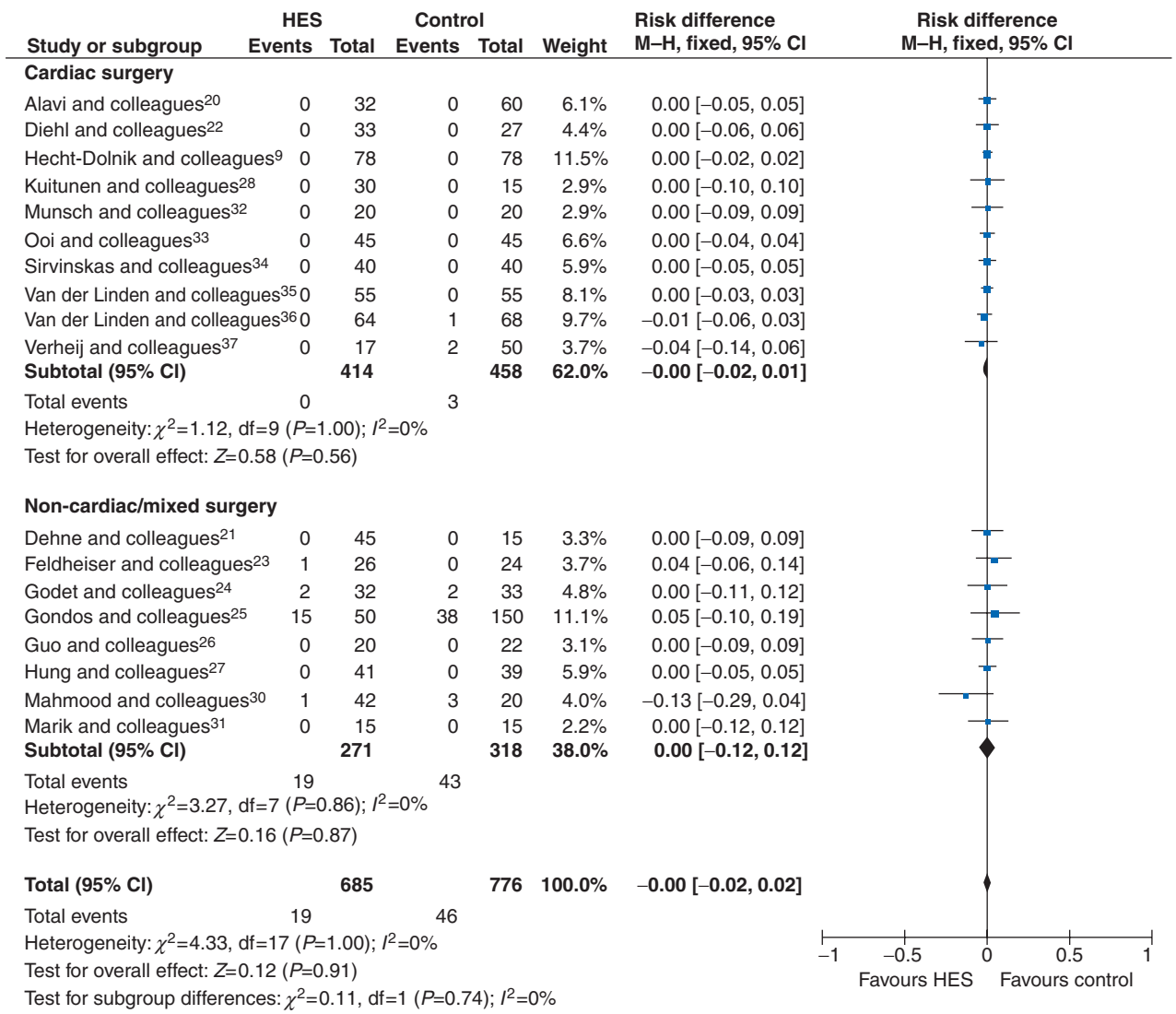

Fig 2 Forest plot of hospital mortality.

data describing kidney-associated harm are not well reported. Few studies consistently report the requirement for RRT or AKI using internationally defined criteria [e.g. Acute Kidney Injury Network (AKIN) and RIFLE Classification][52] and in those that did, patients may not have been systematically followed up for these outcomes. All studies reporting postoperative RRT describe either no difference or increased use of RRT in the HES group; however, this tendency towards increased use of RRT in the HES group was not statistically significant. The incidence of death, use of RRT and AKI is higher in the critically ill than in the surgical population and it is therefore possible that the low event rates for both death and AKI in included studies resulted in insufficient statistical power to detect a difference in these outcomes. It remains possible that HES solutions are associated with either undetected harm or benefit in the surgical population. We believe that our approach offers significant advantages over previously published work investigating the effects of starch solutions in surgical patients. The non-sepsis subgroup of the meta-analysis undertaken by Dart and colleagues included studies by Boldt, and those enrolling trauma paediatric and renal transplant patients. They also include four studies of 10% HES which is no longer in common use.[13] The study by Van der Linden and colleagues[17] also included studies of paediatric patients, trauma and burns. These heterogeneous groups were excluded from our analysis. The reviews conducted by Van der Linden and colleagues and Martin and colleagues only investigated tetrastach and compared it with other solutions, including alternative HES solutions. Moreover, Martin's study, which appears to be industry initiated, investigated only a single product (6% HES 130/0.4, Voluven, Fresenius, Germany). The authors of this study made no assessment of methodological quality of included studies, were supported by Fresenius-Kabi, manufacturers of the HES solution, Voluven, and utilized their 'study tracking system' for the literature search.[16] Several

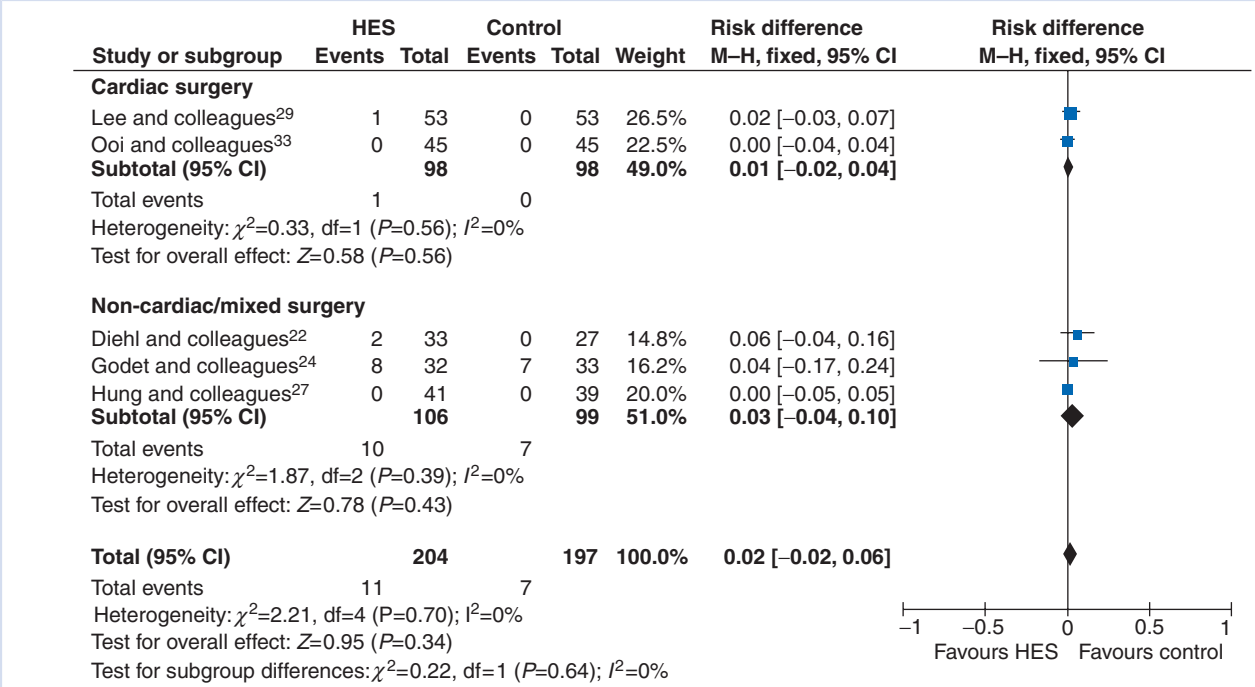

Fig 3 Forest plot of acute kidney injury.

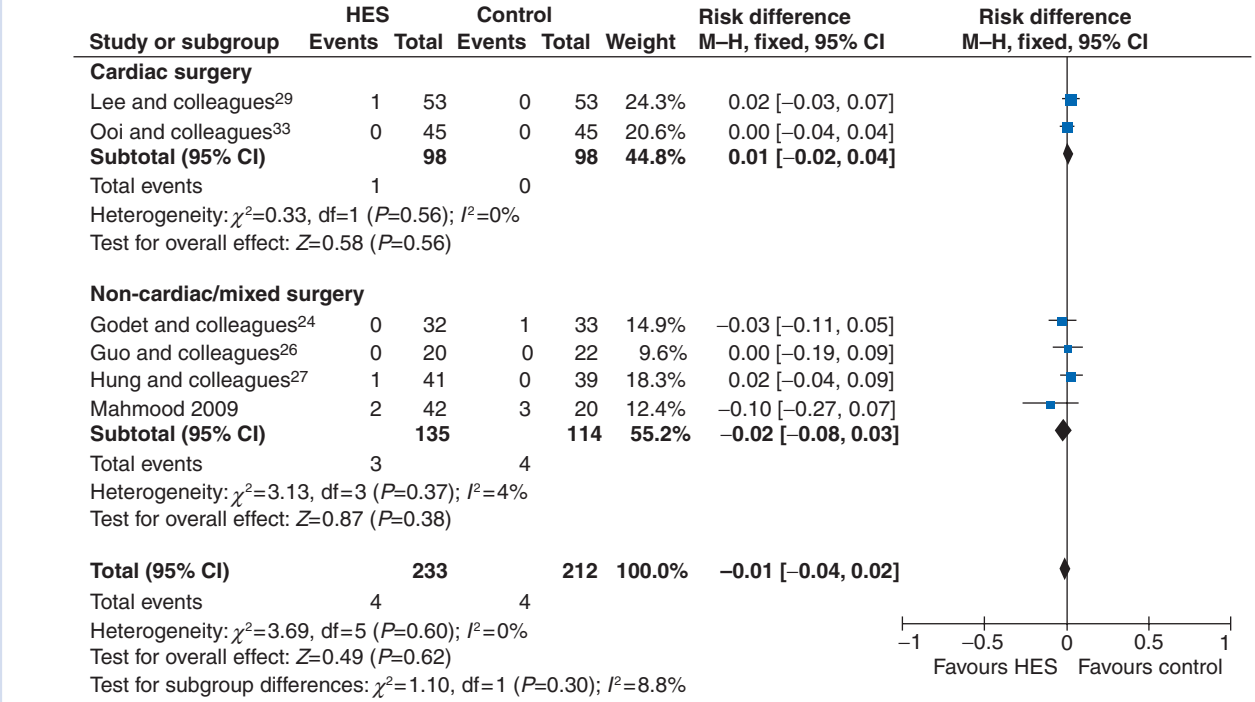

Fig 4 Forest plot of renal replacement therapy.

studies included in other meta-analyses were excluded in this analysis. This included the studies by Harten and colleagues[40] (excluded because outcomes and care in the control arm were unclear), Challand and colleagues (excluded because 6% HES may have been used in the control group),[50] and Tiryakioglu and colleagues (excluded because Jadad score was 2 and the incidence of outcomes of interest was not reported).[43]

Strengths of our review include a rigorous assessment of methodological quality of identified trials and selection of a homogeneous group of trials of direct relevance to perioperative medicine. The I^2 statistic confirms a low risk of between-study heterogeneity, and this combined with narrow confidence intervals suggests that our findings are valid. There are also potential limitations of this analysis. We included trials of 6% HES solutions of any MW or substitution, and did not restrict inclusion to one particular HES product. It has been suggested that HES solutions with higher MW and greater substitution may be associated with an increased incidence of AKI and use of these solutions has declined in recent years. Included trials were mostly small single-centre trials with a greater possibility of bias.

Synthetic colloidal solutions were introduced in the 1960s,[53] without large phase III trials. Despite little published evidence suggesting advantages over other i.v. fluids, and emerging evidence of harm in septic and critically ill patients, they remain a popular choice for perioperative fluid therapy.[40 50] Although our systematic review did not demonstrate any harm associated with the use of 6% HES solutions, these findings cannot be considered definitive. The Crystalloid versus Hydroxyethyl Starch Trial (CHEST) and Scandanavian Starch for Severe Sepsis/Septic Shock (6S) trials have provided robust evidence to the critical care community that resuscitation of the critically ill with 6% HES was associated with an increased incidence of AKI.[6 7] Many surgical patients receiving HES are considered at high risk of both AKI and death and may require periods of critical care after their surgery. The findings of this analysis suggest that although there should be equipoise to conduct such a trial in surgical patients, the low event rates of both death and new requirement for RRT in the surgical population indicate that a very large clinical trial would be required to confirm the safety of starch solutions in surgical patient population.

Conclusion

The principal finding of this study was that there was no difference in hospital mortality, requirement for RRT, or author-defined AKI associated with perioperative use of i.v. 6% HES solutions. Although most studies were small with low event rates, there was little between-study heterogeneity and narrow confidence intervals. A very large randomized trial of 6% HES solutions would be required to demonstrate either significant benefit or harm associated with the use of these solutions in surgical patients. Given the absence of demonstrable benefit, the clear risks in critically ill patients, and the additional cost over more widely used fluids, we are unable to recommend routine clinical use of 6% HES solution in surgical patients.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Authors' contributions

All authors contributed to protocol design, data acquisition, analysis, and preparation of the manuscript.

Declaration of interest

M.A.G. has received honoraria from LiDCO Ltd and Lilley & Co. M. Habicher, S.J., and M.S.: none declared. M.M. has received honoraria for speaking, or consultation, travel expenses, or both from Baxter, BBraun, Covidien, Fresenius-Kabi, Hospira, LiDCO. He is a National Clinical lead for the Department of Health Enhanced Recovery Partnership; Smiths Medical Professor of Anaesthesia and Critical Care UCL; Consultant to AQIX (start-up company with a novel crystalloid solution—pre-clinical); Director of Medical Defence Technologies LLC—('Gastrostim' patented); Co-Inventor of 'QUENCH' (pump) IP being exploited by UCL Business. M.M. has also received charitable donations and grants from Smiths Medical Endowment and Deltex Medical. M.M. is also co-author of the GIFTASUP guidelines on perioperative fluid management; a Board member of The Faculty of Intensive Care Medicine; Editor-in-Chief of *Perioperative Medicine*; on the Editorial Board of the *BJA* and *Critical Care*; a member of the Improving Surgical Outcomes Group; member of the NICE IV fluids guideline development group; and Co-Director Xtreme Everest. M. Hamilton has received lecturing fees, unrestricted educational grants, or both from Deltex Medical Ltd, Edwards Lifesciences and LiDCO Ltd. R.M.P. has received equipment loans from LiDCO Ltd, a research grant from Circassia Holdings Ltd and has performed consultancy work for Edwards Lifesciences, Covidien and Massimo, Inc. M.A.G. is a Chief Scientist Office (CSO) Scotland NHS Research Scheme Fellow. R.M.P. is a National Institute for Health Research (NIHR) Clinician Scientist.

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