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Review Article

CRITICAL CARE

Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials

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Abstract

Background: Hydroxyethyl starch (HES) 130 is a frequently used fluid to replace intravascular losses during surgery or trauma. In the past years, several trials performed in critically ill patients have raised questions regarding the safety of this product. Our aim in this meta-analysis was to evaluate the safety and efficacy of 6% HES during surgery and in trauma.

Methods: This systematic review and meta-analysis was registered at PROSPERO (CRD42018100379). We included 85 fully published articles from 1980 to June 2018 according to the protocol and three additional recent articles up to June 2020 in English, French, German, and Spanish reporting on prospective, randomised, and controlled clinical trials applying volume therapy with HES 130/0.4 or HES 130/0.42, including combinations with crystalloids, to patients undergoing surgery. Comparators were albumin, gelatin, and crystalloids only. A meta-analysis could not be performed for the two trauma studies as there was only one study that reported data on endpoints of interest.

Results: Surgical patients treated with HES had lower postoperative serum creatinine ($P<0.001$) and showed no differences in renal dysfunction, renal failure, or renal replacement therapy. Although there was practically no further difference in the colloids albumin or gelatin, the use of HES improved haemodynamic stability, reduced need for vasopressors ($P<0.001$), and decreased length of hospital stay ($P<0.001$) compared with the use of crystalloids alone.

Conclusions: HES was shown to be safe and efficacious in the perioperative setting. Results of the present meta-analysis suggest that when used with adequate indication, a combination of intravenous fluid therapy with crystalloids and volume replacement with HES as colloid has clinically beneficial effects over using crystalloids only.

Keywords: colloids; HES; hydroxyethyl starch; perioperative; renal failure; trauma; volume therapy

Editor's key points

- Colloids decrease the intravenous infusion volume requirement during surgical procedures. The benefit of this remains to be established.
- This review adds weight to the argument that modern hydroxyethyl starch, used in the correct context, is safe in terms of the risk of renal dysfunction. There is no evidence of increased blood loss when hydroxyethyl starch is used appropriately.
- Future studies should focus on benefit rather than safety.

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Appropriate fluid management plays a major role in anaesthetic practice.[1] Anaesthesiologists are aware that too much fluid may lead to tissue oedema, poor cardiac function, or impaired gut and pulmonary function.[2–4] Too little fluid may also be harmful, potentially leading to inadequate tissue perfusion, organ dysfunction, and impaired wound healing.[5] One major problem in fluid management is that there are widely varying recommendations on the volume, composition, and type of fluid in different circumstances.[1] Some physicians recommend the exclusive use of crystalloids for all patients in all situations for all types of fluid losses.[6] However, replacing losses from the intravascular compartment (e.g. blood losses) primarily with crystalloids, will inevitably lead to fluid overload.[7,8] The reason for this is the physiological distribution of crystalloids: as they are evenly distributed over the extracellular space, 20% of the infused amount remains in the intravascular target compartment whereas 80% is shifted into tissue.[9] A widely used alternative is the class of iso-oncotic colloids. In the perioperative situation, the most commonly used colloid is hydroxyethyl starch (HES). Although older generations of HES with large molecular sizes and large molar substitution showed potential side-effects on kidney function and coagulation,[10,11] this has not been shown consistently for the modern tetrastarch generation 6% HES 130/0.4–0.42.[12] There are many trials using HES in combination with crystalloids for perioperative goal-directed therapy showing clear advantages over a pure crystalloid treatment: shorter length of stay, less need for and shorter duration of invasive ventilation, better bowel function, fewer complications, and lower morbidity.[13–16] The German S3 guideline on intravascular volume therapy evaluated existing clinical data and concluded that HES 130 is safe and effective in surgery.[16]

In 2013, the Pharmacology Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) initially recommended the suspension of the marketing authorisations for HES solutions, after three trials,[17–19] which claimed to show negative effects of HES on mortality and kidney function in critically ill patients and more specifically patients with severe sepsis and septic shock. Although the results in the perioperative setting are convincing,[20] and despite some open questions concerning the validity and generalisability of the data,[21] the PRAC confirmed this recommendation of suspension in 2018 based on the observation that HES solutions are still used in at-risk patients. However, the Coordination group for Mutual recognition and Decentralised procedures – human (CMDh) concluded that HES solutions should remain on the market, provided that complementary measures to protect the patients were adopted. This advice, endorsed by the European Commission, was strongly supported by a large majority of the European anaesthesiologic societies.[22] Therefore, use of HES in the perioperative setting remained an acceptable treatment option. The effectiveness and safety of HES is likely to differ when used in surgery rather than in septic patients. Van der Linden and colleagues[23] performed a systematic literature research in 2013 without finding any adverse safety signal when tetrastarches were used intraoperatively or in the immediate postoperative period or both. Since then, several other studies have evaluated the safety of HES in different types of surgeries.[24,25] However, efficacy has not been systematically evaluated yet.

Our aim in conducting this meta-analysis was to evaluate both safety and efficacy of tetrastarches (i.e. HES 130/0.4 and 0.42) in comparison with crystalloids and non-HES colloids in surgery and trauma patients. Safety was assessed with respect to renal function and efficacy with respect to occurrence of oedema, the need for vasopressors, and hospital length of stay.

Methods

Search strategy

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and prospectively registered with PROSPERO as CRD42018100379 on July 17, 2018.[26] The eligibility criteria were prospective randomised, controlled clinical trials (blinded and non-blinded) from 1980 to June 2018 (all stages: print, electronic publication, ahead of print) in English, French, German, or Spanish language. Important trials were published during the initial evaluation period.[27–29] As requested by the journal reviewers, we extended the search to June 2020. Intervention had to include 6% HES with a molecular weight of 130 kDa and a molar substitution of 0.4 or 0.42 (including combinations of HES with crystalloids). Comparators were albumin, gelatin, crystalloids alone, and combinations of albumin or gelatin with crystalloids. Participation criteria were human; hospitalised patients with surgery, trauma, or both; receiving volume therapy. Exclusion criteria were septic patients, combination of HES with other colloids, and studies published by Boldt and colleagues[30] owing to scientific misconduct. The exact meta-analysis protocol describing the processes to identify eligible publications and methods of analysis is available for review and provided in Supplementary material 1.

Study selection criteria

Studies were identified by searching the electronic databases PubMed, Embase, and the Cochrane Library (Fig. 1). Tetrastarches obtained marketing authorisation in 1999. Therefore, the database search was restricted to publications from 1980 or newer. This period was assumed to cover all clinical studies during the development of tetrastarches. All data items were extracted by a qualified reviewer in a pre-designed database form. To guarantee the high quality of the selection process of data relevant for the meta-analyses, the data were controlled by a second reviewer for 100% of the publications. Disagreements were resolved by discussion between both reviewers. If no agreement could be reached, a third qualified reviewer was consulted. Study characteristics including detailed risk of bias and quality measurements are presented in Supplementary material 2.

Data extraction and endpoints

Data items extracted from the selected publications were for the following continuous endpoints: duration of renal replacement therapy (RRT), serum creatinine concentration, serum urea concentration, blood urea nitrogen (BUN) concentration, duration of vasopressor use, length of hospital stay. Exact details, calculations, and definitions of these endpoints can be found in Supplementary material 3. Binary endpoints were frequency of acute kidney injury (AKI) – defined by RIFLE, AKIN, or KDIGO, frequency of RRT, frequency of loss of kidney function, mortality, frequency of serious adverse events (SAE) and adverse events (AE), oedema, and need for vasopressors. Recorded details of study medication

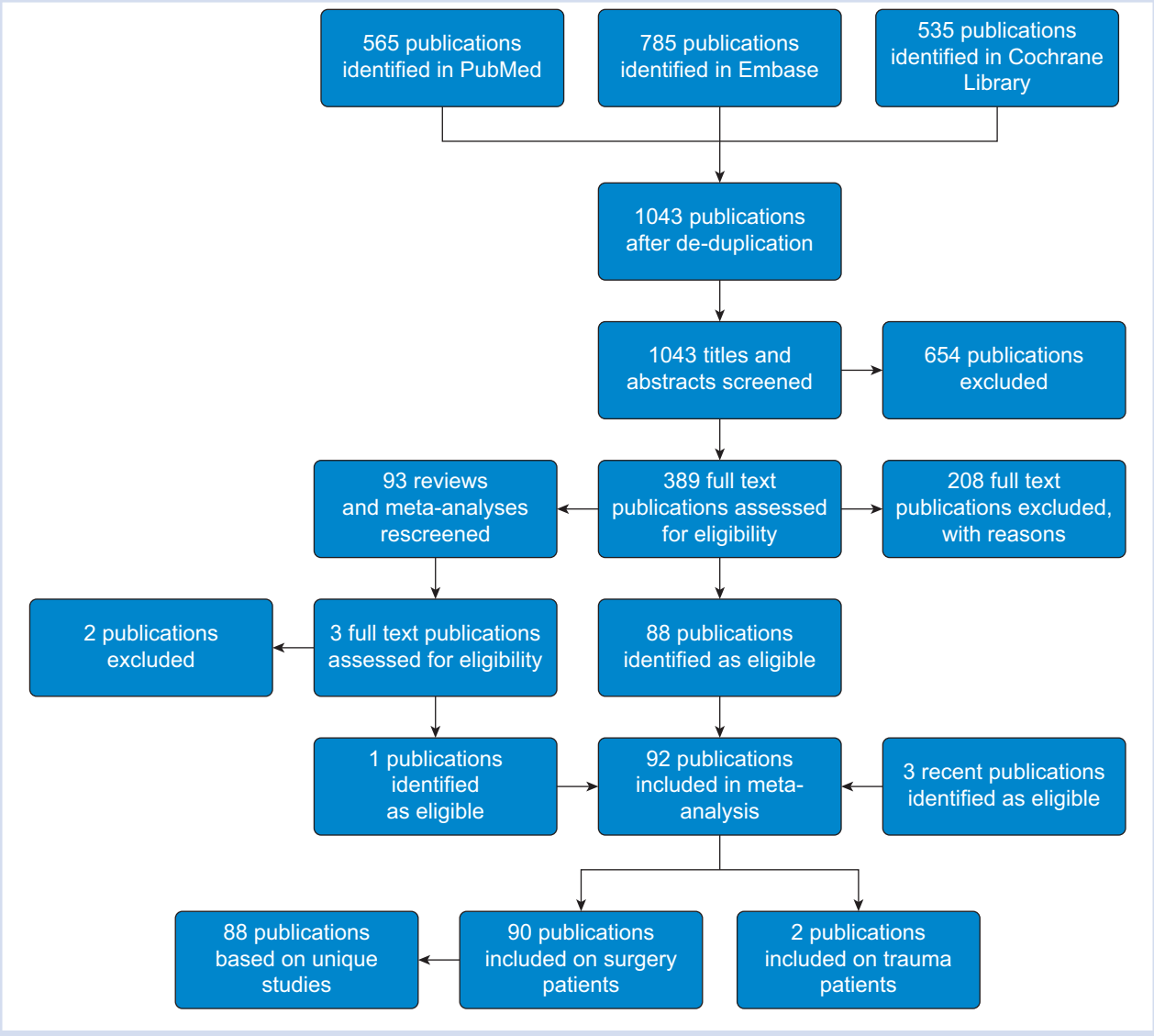

Fig 1. Study selection process.

were exact names and concentrations of HES/comparators used, time and dosage of administration, total fluid volume infused, duration of treatment, and whether a goal-directed therapy algorithm was used.

Statistical analysis

The statistical analyses described above were performed using the statistical analysis software (SAS) version 9.3. In the quality control step, the software package review manager (RevMan) 5.2 (The Nordic Cochrane Centre, Copenhagen, The Cochrane Collaboration, 2013) was used to check meta-analysis results as a second independent software. The point estimates and their associated 95% confidence intervals (CI) of differences were derived from fixed-effect meta-analysis models. Statistical methods were finalised and approved before analyses began, and further details on the statistical methods for meta-analyses are provided in Supplementary material 3.

Results

Of the 88 surgical studies included in the perioperative meta-analysis (Fig. 1),[14,27–29,31–113] about one-third of the studies were double-blinded RCTs, and about 20% of the studies were at least single-blinded. Only about 7% of the studies were reported to be performed open label. For the remaining 40% of the studies, no information on blinding was given in the publications. No meta-analysis was performed for trauma trials as two trials were eligible but only one study reported the endpoints of interest.

In these perioperative trials the increase in serum creatinine concentration was significantly lower for HES than all comparators (Fig. 2). In sub-group analysis, the increase in creatinine was comparable between tetrastarch and albumin. Gelatin showed significantly higher increases of serum creatinine than tetrastarch with a mean difference of 16 μmol L^{-1} ($P<0.001$). Importantly, serum creatinine increase in the

tetrastarch group was significantly lower compared with crystalloids (mean difference, −3.63; 95% CI, −4.72 to −2.53; P<0.001).

With respect to the frequency of AKI, events were similar after tetrastarch compared with all comparators (Fig. 3). The frequency of AKI events was more frequent in subgroup analysis comparing tetrastarch with crystalloid (common risk ratio, 1.31; 95% CI, 1.09–1.59; P=0.004), but less frequent when compared with non-HES colloid (common risk ratio, 0.77; 95% CI, 0.61–0.98; P=0.031).

Newly initiated RRT was an uncommon event after surgery. Only 14 of 3966 patients (0.35%) were reported to have received RRT in the tetrastarch group and 24 of 4317 patients (0.56%) in the combined comparator group (risk ratio, 0.64; 95% CI, 0.34–1.19; P=0.161; Fig. 4). Duration of RRT was only reported in one of these trials for one single patient receiving RRT for 2 days.

For the combined endpoint, loss of kidney function – defined according to AKI staging criteria as RIFLE Failure/Loss or End-stage, AKIN/KDIGO stage 3, RRT, or both, there were no differences between tetrastarch and any individual comparator, nor all comparators together. In general, the perioperative incidence was very low (tetrastarch, 0.9%; gelatin, 1.4%; albumin, 1.2%; crystalloids, 0.9%) (Fig. 5).

Mortality was comparably low in all treatment arms. For tetrastarch, mortality was 2.39% (50 of 2088 patients) and for the combined comparators 2.13% (49 of 2296 patients) with no differences between the individual comparators (P=0.58).

The use of vasopressors as a surrogate of haemodynamic instability was significantly more frequent in patients treated by crystalloid (63.4%) compared with those treated with tetrastarch (51.4%) (risk ratio, 0.80; 95% CI, 0.75 to 0.85; P<0.001; Fig. 6). A significant heterogeneity between trials was observed. There were no differences between tetrastarch and the individual colloid comparators (*vs* gelatin: P=0.72 and *vs* albumin: P=0.65), data not shown. None of the analysed trials reported on the duration of vasopressors.

The hospital length of stay was shorter for tetrastarch compared with crystalloids (−0.38 days; 95% CI, −0.61 to −0.16 days; P<0.001; Fig. 7). However, the mean difference was only 9 h. There were no differences between HES and non-HES colloids (0.07 days; 95% CI, −0.41 to 0.55 days; P=0.778), with a moderate heterogeneity between the trials.

There were not enough data available to enable a statistical analysis concerning the endpoints duration of RRT, serum urea concentration, BUN concentration, any related AE and SAE, oedema, and duration of vasopressor use.

Discussion

Our aim in conducting this meta-analysis was to evaluate the safety of tetrastarches (i.e. HES 130/0.4–0.42) in comparison

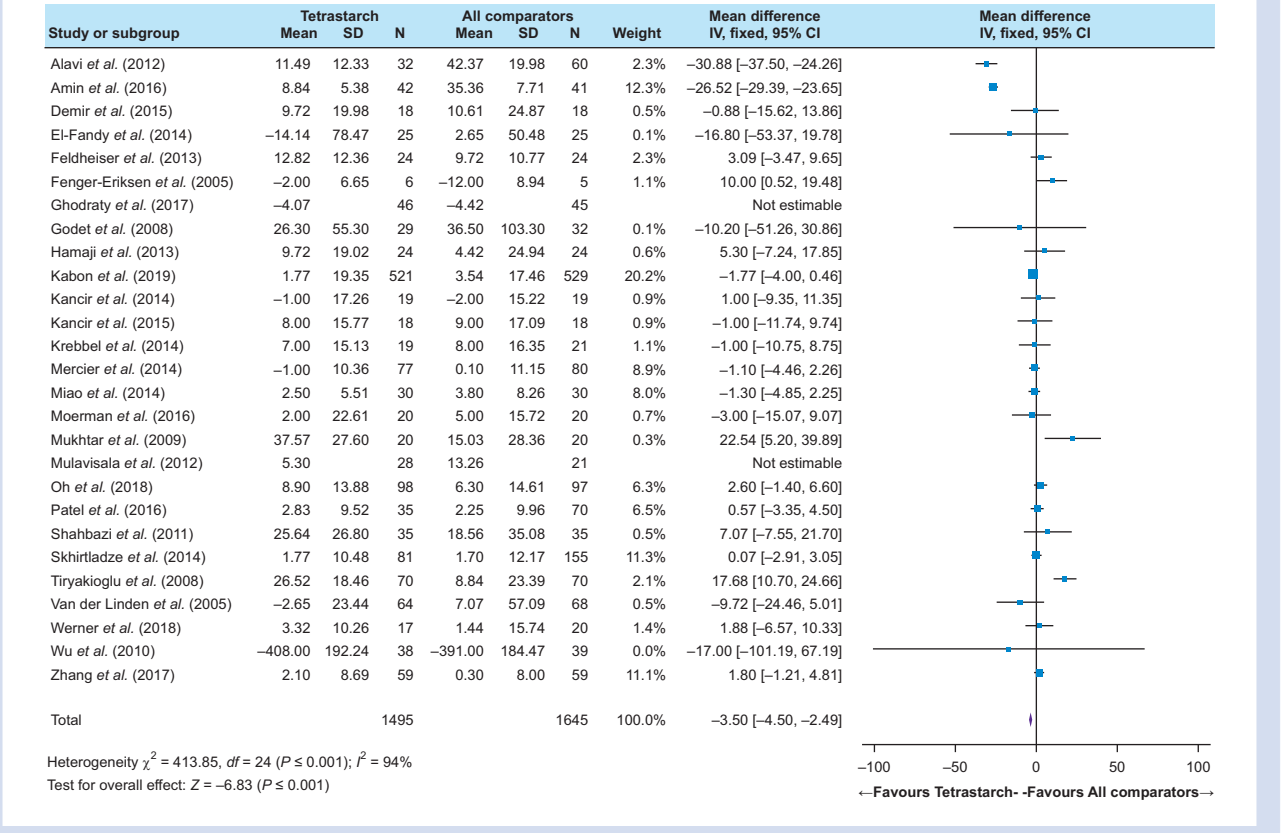

Fig 2. Increase in serum creatinine concentration (μmol L^{-1}): tetrastarch *vs* all comparators.

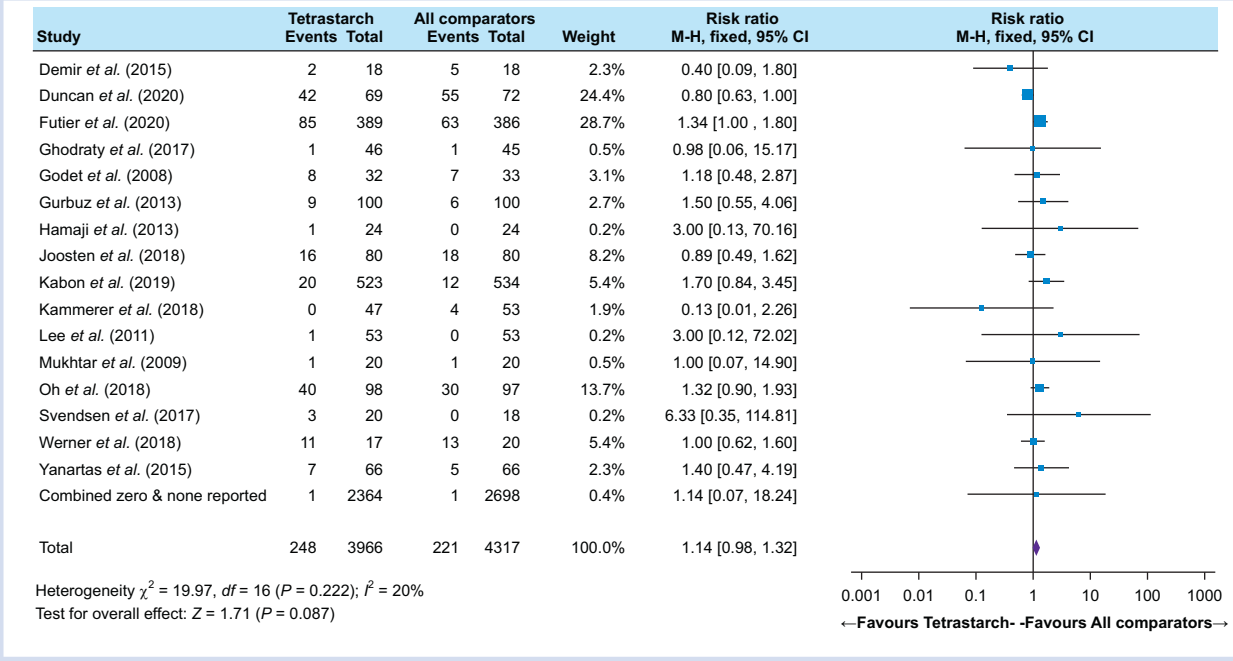

Fig 3. Frequency of acute kidney injury (AKI): tetrastarch *vs* all comparators. CI, confidence interval; SD, standard deviation.

with non-HES colloids and crystalloids in surgery and trauma patients concerning renal function, mortality, and AE. Furthermore, efficacy was evaluated with respect to need for vasopressors and length of hospital stay. Only one of the two eligible trauma trials fulfilling the criteria provided endpoints of interest.[114] Therefore, a meta-analysis for trauma was not possible. In the perioperative setting, 88 of the 90 eligible trials on surgical patients could be included in the final analysis. In line with most trials performing perioperative goal-directed therapy which favour the use of colloids, we found tetrastarches to be both safe and efficacious when used for volume replacement during surgery.

HES-containing medicinal products are colloidal solutions used for treatment of intravascular hypovolaemia.[115] During the past decades, the molecular weight and molar substitution of these solutions has been optimised, leading to an average molecular weight of about 130 kDa and a molar substitution of about 0.4.[116] Between the different generations of starches, there are clear clinical differences in terms of effects on coagulation or renal function with the modern generation presenting the best safety profile in surgical patients.[116] Especially in the field of perioperative goal-directed therapy, the use of colloids in general, and tetrastarches in particular, together with crystalloids has been shown to have clear

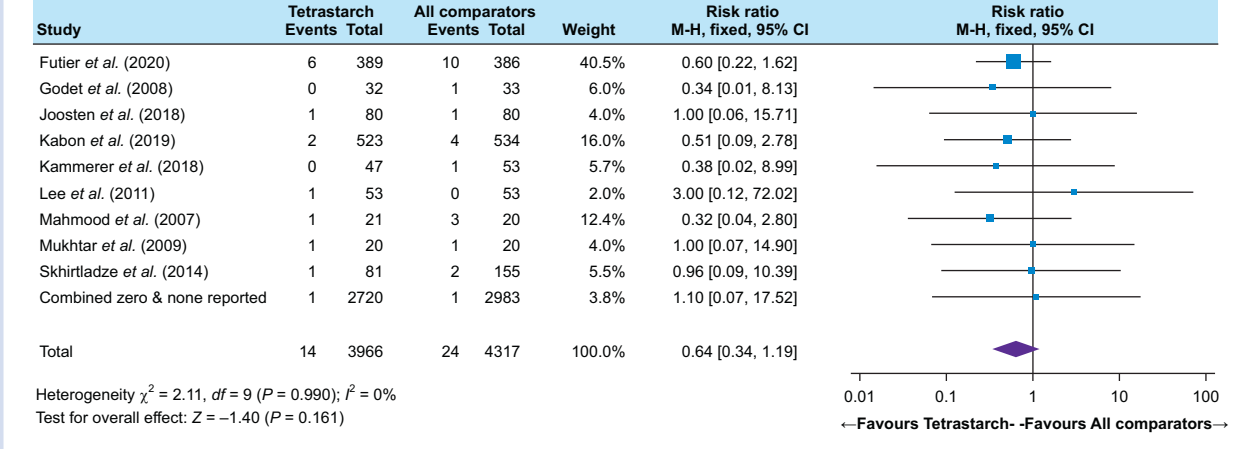

Fig 4. Frequency of renal replacement therapy (RRT): tetrastarch *vs* all comparators.

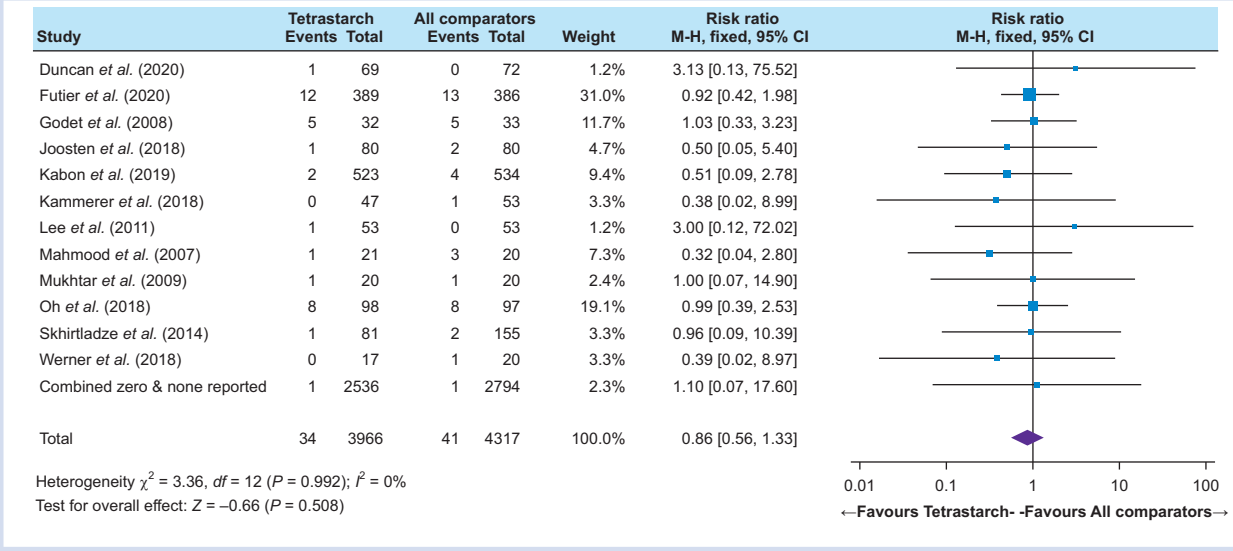

Fig 5. Frequency of loss of kidney function, use of RRT, or both: tetrastarch *vs* all comparators.

advantages over pure crystalloid therapy.[2,14] Nevertheless, the EMA issued restrictions on the marketing authorisations for all generations in recent years after three major trials in intensive care medicine.[22] Two of these trials in patients with septic shock, VISEP and 6S,[17,18] have been criticised for their study execution and interpretation of the data. The majority of patients were initially resuscitated using colloids (predominantly HES) even in the crystalloid group. Despite most patients being

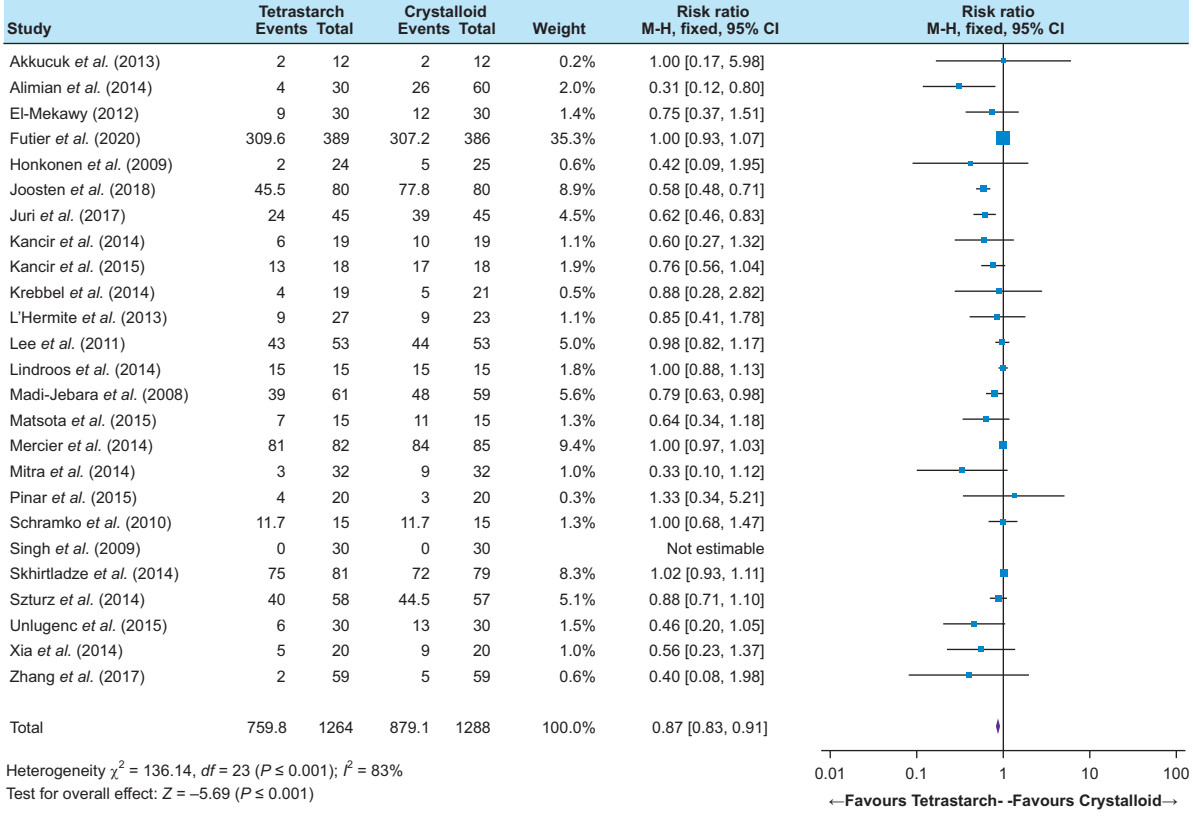

Fig 6. Frequency of vasopressor use: tetrastarch *vs* crystalloid.

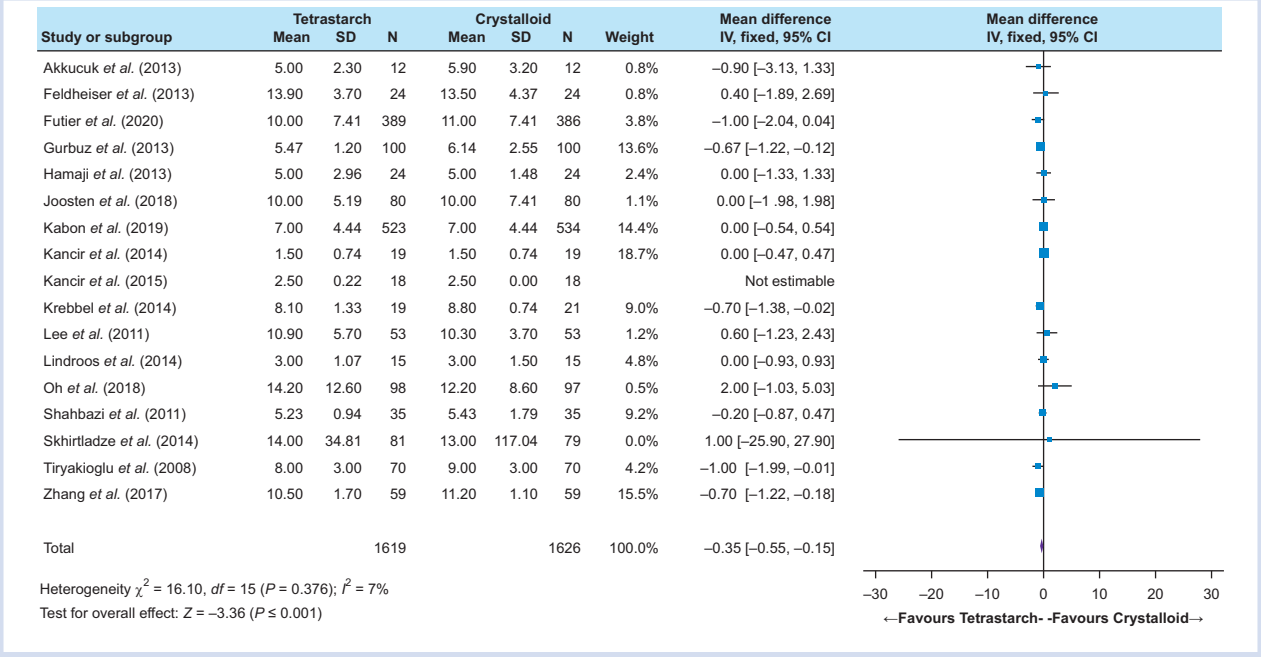

Fig 7. Length of hospital stay: tetrastarch *vs* crystalloid.

haemodynamically stabilised at study onset, the HES groups received large amounts of HES.[117,118] The third trial, Crystalloid *vs* Hydroxyethyl Starch Trial (CHEST),[19] actually showed a significantly lower rate of AKI in the tetrastarch group, but a borderline significant higher rate of RRT, for which no criteria were specified.[119] In order to understand the contradicting results and authors' conclusions in CHEST, 19 national anaesthesiology societies have asked to independently re-analyse the CHEST data, release the raw data, or both.[120] Unfortunately, this request has remained unanswered. Upon request from EMA, the European Society of Anaesthesiology and Intensive Care (ESAIC) is carrying out two large prospective double-blind randomised trials evaluating safety in surgical (PHOENICS) and trauma (TETHYS) patients, which are currently ongoing.[121,122]

The discussion concerning HES solutions and renal effects has been going on for a long time.[123] The first- and second-generation starches, with high *in vivo* molecular weights, had well-known negative effects, especially on coagulation.[124] Although registered doses of these old generation starches were considered as safe, most companies have withdrawn them voluntarily from the market years ago throughout Europe and replaced them with the modern tetrastarch. Several reviews and meta-analyses have previously addressed the effects of HES on renal function.[24,125,126] Unfortunately, most analyses did not take the different HES generations into account. For example, an analysis by Dart and colleagues[127] analysing kidney function pooled data for all HES preparations and concentrations, and thus different oncotic properties. It is, therefore, not surprising that this review highlights the negative effects of some very old starches such as HES 650. However, the authors inexplicably extend their results to all HES solutions.[127] In addition, the analysis was dominated by the above-mentioned VISEP trial, in which critically ill patients received a hyperoncotic 10% HES 200/0.5,[17] whereas the vast majority of studies with colloids used iso-oncotic preparations. Repetitive use of hyperoncotic solutions has been shown to induce renal dysfunction more than 30 years ago.[128] Another analysis, from the VISEP group, extensively reviewed the literature on HES 130/0.4.[129] However, with regard to renal outcome, the authors excluded several trials by using criteria that seem to be weakly defined. Most importantly, data from small trials were classified as 'random findings' and, therefore, excluded from the analysis. This seems questionable as the main merit of a meta-analysis or a literature review is its ability to gain evidence from pooling small studies that fulfill basic requirements in study design, especially given the obvious bias of the authors.[130] A further claim by these authors was that renal issues with HES may only become apparent after several weeks, a time span not regularly evaluated in perioperative trials at that time. This has changed with a recent double-blind RCT of fluid resuscitation in patients undergoing major abdominal surgery, that found no evidence for a difference in renal function at 1 year in patients receiving crystalloid and or tetrastarch.[15] However, patients in the HES group had a statistically significantly lower disability score after surgery and a significantly higher rate of disability-free survival.[15] Another recent study reported no change in 1 year renal function in patients undergoing cardiac surgery who had received balanced hydroxyethyl starch for fluid resuscitation, although there was no control group.[131] Kammerer and co-workers[53] reported comparable renal safety profiles of HES 130 and 5% albumin in more than 100 patients undergoing major urologic surgery. Despite including high-risk patients, about 40% of whom suffered from preoperative chronic renal disease, and including in-depth renal function parameters such as the ratio of serum cystatin C, estimated glomerular filtration rate (GFR), and neutrophil gelatinase-associated lipocalin, not one patient suffered renal failure (assessed as RIFLE F) at 90 days postoperatively. The safety and efficacy profile of

albumin and tetrastarch were very similar with no differences in AE, haemodynamic stability, transfusion rates, and infusions requirements.[53] Very recently the double-blind RCT 'FLASH' was published comparing 6% HES 130 *vs* saline in abdominal surgery patients at increased risk for postoperative kidney injury.[27] The tetrastarch group needed less fluid and significantly lower dosages of vasopressors, but there were no significant differences in a composite outcome of death, kidney injury, or major postoperative complications despite 24% of the patients suffering from preoperative kidney dysfunction (mean GFR, 54 ml min^{-1} 1.73 m^{-2}). The authors aimed to maximise stroke volume giving generous fluid volumes, which resulted in positive fluid balances of 3200 in the HES group and 3800 ml in the saline group.[27] One major advantage of colloids is to avoid such a fluid overload and its subsequent complications. This aspect and the fact that 11.7% in the saline group received a colloid during the trial might explain why there were no significant advantages in the HES group. Nevertheless, not including this trial in our analysis would have weakened our findings significantly, so we decided to conduct a sensitivity analysis to include recent major trials.[27–29] Another now included recent trial was from Kabon and coworkers[28] on 1057 patients undergoing open or laparoscopic abdominal surgery compared 6% HES 130 and Ringer's lactate solution. Similar to the FLASH trial, the HES group had significantly fewer cardiac complications and required less fluid, but otherwise no differences in outcome were shown. The authors found comparably low intraoperative blood losses (mean 250 ml), and no evidence of renal toxicity of HES compared with controls even 6 months after surgery. A mean of 1000 ml HES was infused into the patient intraoperatively, in addition to a preoperative 250 ml bolus.

In our analysis, frequency of AKI events was more frequent with tetrastarch compared with crystalloid although for the combined endpoint, loss of kidney function – defined according to AKI staging criteria as RIFLE Failure/Loss or End-stage, AKIN/KDIGO stage 3, RRT, or both, there were no differences between tetrastarch and any individual comparator, nor all comparators together. It is important to note that in several trials, tetrastarches were not used in accordance with the current summaries of product characteristics (SmPC).[16] Contraindications such as pre-existing kidney injury or sepsis need to be observed as meticulously and a correct indication including intraoperative blood loss.

In our analysis, although not demonstrating benefits in terms of major outcomes, HES not only proved to be safe but also efficacious when used in combination with crystalloids in the perioperative setting. Need for vasopressors and length of hospital stay were both reduced when using tetrastarches. The aspect of oedema was not included in our analysis because of the small amount of reported data in the trials available. However, even advocates of pure crystalloid infusion strategies recognise the higher volume effect of isooncotic colloids compared with crystalloids, together with the lower need for (additional) fluid and an improved (i.e. less positive) fluid balance after tetrastarch.[14,132] The present meta-analysis compares 6% HES 130/0.40–0.42 with various control solutions, including products that are considered safe concerning renal function such as balanced crystalloid solutions. There was substantial heterogeneity for some aspects, which should be kept in mind when interpreting the data. Given the range of different settings and comparators analysed for this meta-analysis, this is not surprising and is an aspect that has also previously been reported for many Cochrane meta-analyses. We are fully aware that our analysis focuses exclusively on elective surgical patients and does not allow the drawing of any conclusions concerning critically ill patients. A further limitation is, like in most meta-analysis, the sample size and power of the study. Also, not all variables used to assess renal function were available in all the analysed studies.

In summary, our meta-analysis shows that there is currently no evidence that 6% HES 130/0.4–0.42 causes renal dysfunction, increases in serum creatinine, renal failure, or RRT in patients undergoing surgical procedures. Large, randomised trials are necessary to further evaluate potential effects of tetrastarches on kidney function; however, based on currently available data, an indication- and protocol-based use of tetrastarches in surgery is both safe and efficacious.

Authors' contributions

Study concept/design: DC, PVdL, JRM, MFMJ
Data acquisition/analysis/interpretation: DC, PVdL, JRM, MFMJ
Writing of first draft: DC
Revision of manuscript for important intellectual content: DC, PVdL, JRM, MFMJ
Approval of final version: DC, PVdL, JRM, MFMJ
All authors agree to the submission to *BJA* and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Declarations of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.06.040.

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