Randomised trials of 6% tetrastarch (hydroxyethyl starch
130/0.4 or 0.42) for severe sepsis reporting mortality:
systematic review and meta-analysis

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Abstract

Purpose

To assess the impact of 6% tetrastarch (hydroxyethyl starch (HES) 130/0.4 and 130/0.42) in severe sepsis patients. The primary outcome measure was 90-day mortality.

Methods

A structured literature search to identify prospective randomized controlled trials (RCT) in adult patients with severe sepsis receiving 6% tetrastarch (potato or waxy maize origin), as part of fluid resuscitation in comparison to other non-HES fluids after randomisation, in the critical care setting was undertaken. A systematic review and meta-analysis was performed.

Results

Six RCTs were included (n = 3033): three from 2012 (n = 2913) had a low risk of bias. Median tetrastarch exposure was 37.4 ml/kg (range 30 to 43). Ninety-day mortality was associated with tetrastarch exposure (relative risk (RR) 1.13; 95% confidence interval (CI) 1.02 to 1.25; p = 0.02) compared to crystalloid. The number needed to harm (NNH) was 28.8 (95% CI 14.6 to 942.5). Publication bias and statistical heterogeneity ($I^2 = 0\%$) were not present. Tetrastarch exposure was also associated with renal replacement therapy (p = 0.01; NNH 15.7) and allogeneic transfusion support (p = 0.001; NNH 9.9). No difference between groups was observed for 28-day mortality, comparison with colloid as control, and for waxy maize derived tetrastarch, but power was lacking. Overall mortality was associated with tetrastarch exposure (RR 1.13; 95% CI 1.02 to 1.25; p = 0.02).

Conclusions

In our analysis, 6% tetrastarch as part of initial fluid resuscitation for severe sepsis was associated with harm, and as alternatives exist, in our view should be avoided.

Keywords

6% tetrastarch, 6% hydroxyethyl starch (HES) 130/0.4, severe sepsis, mortality, renal

Introduction

Hydroxyethyl starch (HES) solutions are in widespread use worldwide as a colloid to maintain or achieve volume expansion, and the resuscitation of critically ill patients with severe sepsis a major indication.[1, 2]

Specification of HES has evolved to 6% tetrastarch, launched in Germany in 1999, and licenced in the US in 2008. 6% tetrastarch products have an average molecular weight of 130 kDa (± 20 kDa), and somewhat overlapping molar substitution[3] (the number of hydroxyethyl groups per glucose molecule) of 0.38 to 0.45 (where the term tetrastarch is derived), often abbreviated as 6% HES 130/0.4 or 130/0.42. Starch preparations of waxy maize or potato origin are available in various crystalloid carrier solutions. They differ in terms of C2/C6 pattern of hydroxyethylation. It is currently unclear if these chemical differences are of clinical significance. Despite widespread clinical use, the safety and efficacy of HES are controversial.[4-7]

Large critical care randomised controlled trials (RCTs) in severe sepsis reporting harm from HES,[8, 9] concern over publication bias supporting HES,[5, 6] and retraction of studies, have raised safety and efficacy concerns.[4, 10-12] 6% tetrastarch products were studied in eleven retracted papers,[13] however, severe sepsis patients were not the main study population in these. A meta-analysis of 6% tetrastarch use in severe sepsis is lacking, and might address safety and efficacy.

Meta-analyses focusing on mortality associated with 6% tetrastarch,[5, 13] and other HES formulations,[14, 15] in various clinical groups and settings, have failed to

confirm adequate safety or efficacy. Most of the studies pooled were small, clinically and statistically heterogeneous, and were not designed to assess mortality. Their short follow-up (often hours to a few days) and low mortality rate means Type II error from low power is a major concern.[16] Variable length of follow-up may partly explain the high heterogeneity in overall mortality. Studies comparing 6% tetrastarch to older higher molecular weight HES solutions are unsatisfactory for the assessment of relative safety or efficacy[17-21] compared to non-HES solutions.

Patients with severe sepsis have a high mortality of 24 to 39% at 28 days, and 33 to 50% at 90 days.[22-24] Ninety-day mortality was the primary outcome in the 2012 6S[25] and CHEST[3] trials that compared 6% tetrastarch to crystalloid control fluid. 6S[25] (n = 798) reported harm at 90-days (p = 0.03),[25] and CHEST[3] no difference overall (n = 7000), or in the sepsis sub-group (n = 1937), at 28- and 90-days. CHEST mortality rate and power were lower than 6S, and the number of patients with severe sepsis or septic shock was not reported. However, persistent separation of Kaplan-Meier survival curves occurs between 5 and 15 days.[3, 25, 26]

To assess safety and efficacy, international consensus recommends 90-day mortality as the primary outcome measure in all sepsis studies.[27] Hence, we conducted a systematic review and meta-analysis to examine whether administration of 6% tetrastarch as compared to other non-HES fluids was associated with 90-day mortality in critically ill patients with severe sepsis. Other outcomes assessed were 28-day and overall mortality, requirement for renal replacement therapy, and allogeneic transfusion support.

Materials and Methods

Objectives

To use the PRISMA[28] statement methodology to conduct a systematic review and meta-analysis of randomized clinical trials to determine whether 6% tetrastarch consistently differs from control non-HES fluid regimens in its effects upon mortality. The primary outcome measure was 90-day mortality.[27] The secondary outcome measure was overall mortality at final follow-up.[27] Post hoc sub-groups were explored for these outcome measures: by type of control fluid (colloid or crystalloid), tetrastarch origin (potato or waxy maize) and C2/C6 hydroxyethylation ratio (6:1 or 9:1). Tertiary outcome measures were 28-day mortality, renal support (renal replacement therapy (RRT)), acute kidney injury according to creatinine-based RIFLE[29] categories, allogeneic transfusion support, and adverse events.

Identification of studies

A literature search of PubMed, PubMed Central, Web of Science (includes MEDLINE), OvidSP (includes EMBASE, Ovid MEDLINE), the Cochrane Library, clinicaltrials.gov, and controlled-trials.com was undertaken on the 1st of November 2012. The terms used were “sepsis” with all of the following: “hydroxyethylstarch”, “hydroxyethyl starch”, “hydroxy ethyl starch”, “hydroxy ethylstarch”, “starch”, “130/0.4”, “tetrastarch”, “Tetraspan”, “Voluven”, “HES”. No language or date restriction was applied. Reference lists of evaluable studies, systematic reviews, meta-analyses and reports were also hand searched for additional studies eligible for inclusion. Grey literature were also sought[30] through supplementary material published online, including international drug data sheets. For included studies, if

patients were in a pre-defined sub-group we made efforts to contact the corresponding author for clarification and additional data.

Screening of studies

Two reviewers independently screened the initially identified studies from the search. Full text articles of potentially eligible studies were independently assessed against the eligibility criteria. For each study, data extraction and appraisal of internal validity was undertaken independently. Disagreements between the two reviewers were resolved in meetings or referred to the third reviewer for resolution.

Eligibility criteria

All of the following criteria were met for inclusion of a study:

1. Prospective randomized clinical trial
2. Reporting on adult human subjects (18 years or older)
3. Critical/intensive care unit setting
4. Trial, or pre-defined subgroup, focused on patients diagnosed with severe sepsis[31] present at randomisation
5. Fluid therapy was administered for volume expansion after randomisation
6. At least one exposure group that received 130 kDa 6% tetrastarch (in any carrier or of any origin or of any molar substitution or hydroxyethylation) after randomisation
7. At least one control exposure group that received any non-HES fluid (crystalloid or colloid) after randomisation
8. Reporting of a mortality outcome at 90-days, and/or 28-days, and/or another follow-up time point.

9. At least one death in each of the 6% tetrastarch and control exposure groups (to facilitate meta-analysis).

Data extraction

Data from the longest complete follow-up was defined as overall mortality.[27] Data on the following study characteristics were collected: clinical setting, number of randomised patients, number of patients with severe sepsis, time of final follow-up, proportion of patients present at follow-up (data completeness), and primary end-point. When mortality was reported at different follow-up intervals, data from the longest complete follow-up was used along with 28- and 90-day values.[27] All cause death in the control group was used as a measure of baseline mortality for each study. Sufficient data were collected to calculate observed study power[32-34] for the end-point of mortality at final follow-up.

The overall sepsis management protocol used was recorded. Details of baseline patient characteristics by group were also collected: age, sex, marker of disease severity (Acute Physiology and Chronic Health Evaluation II (APACHE II))[35] or organ dysfunction (sequential organ failure assessment (SOFA)),[36] and an estimate of septic shock (and/or use of vasopressors or inotropes).[27, 31]

Data related to study fluid exposure were collected. This included days of trial fluid exposure, type of trial and control group fluid, prescribed fluid dose, and actual dose administered (total and daily trial fluid). Details of RRT support, RIFLE criteria[29] components, and allogeneic transfusion support by group were also collected.

Information on reported adverse effects, such as pruritus was also sought. Values

were calculated if not stated, and means or medians were accepted if reported. Infused doses of intervention and control fluids were extracted and normalized for a 70 kg person in ml/kg or ml/kg/day to allow comparison between studies.

For studies with greater than one control exposure group, a single non-HES containing comparator was selected, with preference given to crystalloid, then colloid. The remaining control groups were not included in the pooled analysis. Retracted studies were excluded.[10, 11, 13]

Quality assessment

Study quality and bias risk of individual studies and across studies was assessed with the Cochrane collaboration tool.[37] Studies at high risk of bias were included unless full evaluation was not possible for any reason, including lack of an English translated version of a publication. A funnel plot was used to determine publication bias.

Statistical analysis

The primary outcome summary measure was relative risk (RR) of 90-day mortality. The secondary outcome measure was RR of overall mortality. Post hoc sub-groups were 6% tetrastarch hydroxyethylation ratio/starch origin and type of control fluid for these two outcome measures. Tertiary outcome measures were RR of 28-day mortality, RR of RRT, RR of allogeneic transfusion, and RR of pruritus.

The RR of death for 6% tetrastarch compared to control fluid was calculated for each included study. Then pooled RR of studies and their 95% confidence intervals (CI) were calculated. Statistical heterogeneity was assessed using the Chi^2 test (Cochran

Q) and I^2 statistic.[38] I^2 values of 25%, 50%, and 75% were considered as low, moderate, and high.[39] A random effects model was used in the presence of statistical heterogeneity (Tau^2 was reported as another measure of statistical heterogeneity; >1 suggests heterogeneity). Clinical heterogeneity (judged by two reviewers) could not be excluded, so the more conservative random effects model[40] (Mantel-Haenszel method) was used.

Sensitivity analysis was performed by excluding studies with a high risk of bias, and also by using a fixed effects model. Sensitivity analyses with or without CHEST data was performed where appropriate because it was unclear if the reported pre-defined sepsis group represented only patients with severe sepsis. Studies in Forest plots were presented sorted by effect size. RevMan version 5.1.7 (Java 6), build 04/06/12 for Mac was used for analysis. Observed or post hoc power (at 95% CI without continuity correction) calculations were performed with OpenEpi version 2.3, May 2009.

Number needed to harm (NNH) or treat was calculated as the reciprocal of the absolute risk reduction with 95% CIs, if it was statistically significant, with an online calculator (clinicalevidence.bmj.com). Simple calculations, including means and medians were derived with Microsoft Excel for Mac version 14.2.4.

Results

Literature search and study selection

Figure 1 outlines a PRISMA[28] flow diagram illustrating the results of the literature search. Six RCTs[3, 25, 26, 41-43] published between July 2006 and October 2012 met the eligibility criteria and were included in this meta-analysis. They described adults suffering from severe sepsis in the critical care setting, and reported overall mortality in patients exposed to 6% tetrastarch and a non-HES control fluid after randomisation for volume resuscitation. Four reports[44-47] were excluded because of inadequate information or an English translation was not available for full appraisal. Their abstracts did not suggest that they reported our primary outcome measure of 90-day mortality. They were also not included by previous reviewers in their meta-analyses.[5, 13]

Study quality and bias

Assessment of within study bias (internal validity) is summarised in [Figure 1 \(online supplement\)](#). The three trials reporting 90-day mortality were of good quality and had low risk of bias. The 6S[25] and CHEST[3] trials were specifically designed to assess 90-day mortality (Table 1). The three[41-43] older smaller trials reporting mortality at other time points had risk of performance and detection bias, two had risk of selection bias[42, 43], one had risk of attrition bias,[41] while another had risk of reporting bias.[42] They were not designed to assess mortality, and the possibility of ascertainment bias could not be dismissed. Furthermore, information from other sources[14, 48] was required because of missing data.

The assessment of bias risk across studies (external validity) is shown in [Figure 2 \(online supplement\)](#). Overall risk of bias for the studies reporting our primary endpoint was low. The risk of selection bias was a major concern in studies not reporting 90-day mortality, where performance, attrition and other risks of bias were also evident. [Figure 3 \(online supplement\)](#) shows a funnel plot assessment that does not yield very clear evidence of publication bias relating to the six included studies. Trial design and clinical heterogeneity were evident mainly for studies not reporting 90-day mortality.

Description of studies and patients

The study characteristics extracted from the RCTs included are outlined in Table 1. Four[3, 25, 26, 43] of the six were multicentre, and randomised 3033 patients in critical/intensive care units across Europe, Australasia and South America. Five trials recruited patients with severe sepsis.[25, 26, 41-43] The largest trial[3] recruited sepsis patients in a pre-defined sub-group[49] but those with severe sepsis or septic shock were not reported separately. The median sepsis study sample size was 126 patients (range 24 to 1937). Completeness of overall mortality outcome data was 99.3% (n = 3013). The median baseline mortality assessed in the control group was 31.9% (range 13 to 54). The overall median observed study power for mortality was only 15.7% (range 6.4 to 56.5).

Baseline patient characteristics are outlined in [Table 1 \(online supplement\)](#). The mean age of patients exposed to 6% tetrastarch was 63.1 years (range 43 to 66) and 65 years in the control groups (range 47 to 67). Male patients represented a median 64% in the

6% tetrastarch groups (range 60 to 85) compared to 60% in the control groups (range 55 to 87). Only one[41] of the six studies reported a SOFA or APACHE II score in the 6% tetrastarch group that was greater than that in the control group; it was equal in two studies.[3, 25] A summary measure was not possible because of varied reporting. The proportion of patients with septic shock or those that required vasopressors or inotropes (these were interchangeably reported, often as a composite and variably defined) in four RCTs[25, 26, 41, 43] was 86.0% (range 46 to 100) in 6% tetrastarch groups and 87.5% in control groups, as shown in [Table 1 \(online supplement\)](#). CHEST trial[3] data for their sepsis group were not available.

6% tetrastarch exposure

Sepsis management protocols used in the RCTs and details of 6% tetrastarch product and crystalloid or albumin control fluid are outlined in [Table 2 \(online supplement\)](#). Patients were exposed to study fluids for a median of 3.5 days (range 1 to 5). Four studies[3, 25, 26, 41] reported pre-defined 6% tetrastarch dosing details. Five studies[3, 25, 26, 41, 43] reported a median total 6% tetrastarch volume infusion of 2615 ml (range 1379 to 3000). The median actual 6% tetrastarch dose exposure was 37.4 ml/kg (range 30 to 43) or 14 ml/kg/day (range 8 to 37).

Primary outcome: 90-day mortality

Three RCTs[3, 25, 50] reporting in 2012 (n = 2913) presented follow-up data to 90 days, the primary outcome measure to assess safety and efficacy. Figure 2 shows the excess mortality found in patients exposed to 6% tetrastarch (RR 1.13, 95% CI 1.02 to 1.25; p = 0.02). The NNH was 28.8 (95% CI 14.6 to 942.5). Statistical heterogeneity

was not present ($I^2 = 0\%$; Chi^2 0.81, $p = 0.67$; Tau^2 0.00). Sensitivity analysis performed by removing studies with risks of bias did not change this mortality difference (RR 1.13, 95% CI 1.02 to 1.25; $p = 0.02$), nor did the use of a fixed model (RR 1.12, 95% CI 1.01 to 1.25; $p = 0.03$). Exclusion of data from CHEST did not alter the finding of 6% tetrastarch-associated mortality (RR 1.18, 95% CI 1.03 to 1.35; $p = 0.02$), as shown in [Figure 4a \(online supplement\)](#). Post hoc sub-group analysis by control fluid type did not alter this association, as crystalloid was used for all three studies. Analysis by C2/6 hydroxyethylation ratio and starch origin is presented in [Figure 4b \(online supplement\)](#).

Secondary outcome: overall mortality

Overall mortality was increased in patients exposed to 6% tetrastarch (RR 1.13, 95% CI 1.02 to 1.25; $p = 0.02$). The NNH was therefore 29.2 (95% CI 14.9 to 896.7). Statistical heterogeneity was not present ($I^2 = 0\%$; Chi^2 3.49, $p = 0.62$; Tau^2 0.00). Sensitivity analysis performed by removing studies with risks of bias from the analysis did not significantly change the finding of 6% tetrastarch-associated mortality (RR 1.13, 95% CI 1.02 to 1.25; $p = 0.02$). Also, use of a fixed model (RR 1.12, 95% CI 1.01 to 1.24; $p = 0.03$) or exclusion of the CHEST data[3] yielded the same outcome (RR 1.17, 95% CI 1.02 to 1.34; $p = 0.02$). Figure 3 show the post hoc sub-group analyses of overall mortality by type of control fluid received, and [Figure 5 \(online supplement\)](#) by 6% tetrastarch origin/pattern of C2 to C6 hydroxyethylation, respectively.

Tertiary outcomes 1: 28-day mortality

In this group (n = 1049), a mortality difference between 6% tetrastarch and control was not detected in three trials,[25, 26, 41] as shown in Figure 4. Statistical heterogeneity was not present and sensitivity analysis performed by removing studies with risks of bias (RR 1.10, 95% CI 0.93 to 1.30; p = 0.28) or by using a fixed effects model (1.11, 95% CI 0.94 to 1.31; p = 0.21), did not alter the finding of possible harm or benefit. The CHEST trial[3] did not report 28-day mortality for their pre-defined sepsis group. For illustrative purposes, [Figure 6 \(online supplement\)](#) shows inclusion of CHEST[3] data (n = 6644) for enrolled patients in all subgroups, but this did not alter the outcome.

Tertiary outcomes 2a: renal replacement therapy (RRT) support

In two studies[25, 26] (n = 994), a median of 21.4% of patients in the 6% tetrastarch group (range 21.0 to 21.9) and 13.9% in the control group (range 11.5 to 16.3) received RRT ([Table 3, online supplement](#)). Figure 5 demonstrates that the requirement for RRT with 6% tetrastarch exposure was increased (RR 1.41, 95% CI 1.08 to 1.84; p = 0.01) compared to control fluid. The NNH was 15.7 (95% CI 8.9 to 64.4). Statistical heterogeneity was not present. Sensitivity analysis performed by removing studies with risks of bias did not alter this finding (RR 1.41, 95% CI 1.08 to 1.84; p = 0.01), nor did the use of a fixed model (RR 1.42, 95% CI 1.09 to 1.85; p = 0.01). The CHEST trial[3] reported this outcome as a composite of both sepsis and non-sepsis patients. For illustrative purposes, [Figure 7 \(online supplement\)](#) shows that including the CHEST[3] data (n = 6727) for enrolled patients in all subgroups did not alter the overall finding.

Tertiary outcomes 2b: acute kidney injury severity (RIFLE criteria)

Acute kidney injury severity defined by the RIFLE criteria for severe sepsis patients was reported in two studies[25, 26] using a creatinine-based score, which was thus used for analysis. [Table 4a \(online supplement\)](#) shows no difference was detected between groups in each RIFLE category, hence one cannot rule out the possibility of harm or benefit with 6% tetrastarch compared to control fluid, which was crystalloid. Sensitivity analysis by removing studies with a risk of bias or by using a fixed model did not alter this overall finding or for any of the RIFLE components. [Table 4b \(online supplement\)](#) shows for illustrative purposes the inclusion of creatinine-based RIFLE data from the CHEST trial[3], including both sepsis and non-sepsis patients. 6% tetrastarch exposure was associated with RIFLE –I and –F, but not RIFLE-R and the two clinical outcome components –L and -E. Sensitivity analysis performed by removing studies with a risk of bias or by using a fixed model did not alter these findings.

Tertiary outcomes 3: allogeneic transfusion

The median proportion of patients that received allogeneic transfusion in the 6% tetrastarch group in three studies [25, 43, 50] (n = 972) was 29% (range 22 to 65) compared to 21% (range 18 to 54) in the control group ([Table 3, online supplement](#)). Figure 6 demonstrates the increased RR of allogeneic transfusion in patients exposed to 6% tetrastarch (RR 1.21, 95% CI 1.08 to 1.36; p = 0.001) compared to control fluid, which were crystalloid. The NNH was 9.9 (95% CI 6.1 to 26.1). Statistical heterogeneity was not present. Sensitivity analysis performed by excluding the study with a risk of bias[43] did not alter the conclusion (RR 1.21, 95% CI 1.08 to 1.36; p = 0.001), nor did the use of a fixed effects model (RR 1.22, 95% CI 1.08 to 1.37; p =

0.0009). In three RCTs[25, 26, 42] this corresponded to a median transfusion volume of 1340 ml (range 214 to 1500) in the 6% tetrastarch group compared to 1055 ml (range 165 to 1400) in the control group ([Table 3, online supplement](#)). The CHEST trial did not report these outcomes in their sepsis subgroup.

Tertiary outcomes 4: pruritus

Pruritus was reported in two studies[3, 26] (CHEST reported this for all randomised patients) and was associated with 6% tetrastarch exposure (RR 1.81, 95% CI 1.37 to 2.38; $p = <0.00001$). Observed power was 99.0% and NNH was 56.1 (95% CI 38.6 to 102.9). Statistical heterogeneity was not present ($I^2 = 0\%$; $\text{Chi}^2 = 0.64$, $p = 0.42$; $\text{Tau}^2 = 0.00$). Sensitivity analysis with a fixed model did not alter this conclusion or any of the statistical values. Other reported adverse events were reported in included studies but these were not amenable to pooled summary.

Discussion

This meta-analysis has found that mortality in severe sepsis patients is associated with exposure to 6% tetrastarch products in the critical care setting (Figure 3; [Figure 5 online supplement](#)). This excess mortality was identified at 90-days (Figure 2) - the primary outcome measure.[27] The point estimates are concordant and the 95% CI is more precise than the 6S trial[25]. The results are generalizable to critical/intensive care patients but may not apply to perioperative or trauma patients, where 6% tetrastarch is used and has also been studied. In our analysis, 6% tetrastarch is neither safe or efficacious: overall or at 90-days, one patient died for every 29 patients treated with 6% tetrastarch products instead of control fluid.

This analysis was performed promptly when new data were published in 2012 adding significant individual study power (Table 1), and therefore updates previous meta-analyses of 6% tetrastarch for various indications, which were unable thus far to address long-term safety and efficacy concerns.[5, 13, 14] The addition of the 6S[25] and CHEST[3] trials add 90% of the weight in this analysis that focuses on sepsis to address the clear knowledge gap of existing data identified by the ESICM Task Force committee.[7]

The post hoc sub-group analysis of 6% tetrastarch origin was unsurprisingly not statistically significant for C2/C6 9-ratio waxy maize products, given the low power of 20.7% and the median baseline 90-day and overall mortality of 28.7% and 30%, respectively. However, generally concordant point estimates towards possible harm were found ([Figures 4b and 5, online supplement](#)). The 6S trial[25] was the only 6-

ratio potato-derived 6% tetrastarch study associated with harm and has already been published.[25] The 9-ratio product is 98% amylopectin, persists in the intravascular space for longer because of reduced susceptibility to plasma amylase degradation and has a lower viscosity compared to the 6-ratio product which is 75% amylopectin and 25% amylose, and more prone to form inclusion complexes with several endogenous lipophilic molecules.[51] For both, storage in the reticulo-endothelial system, and eventual conversion to water and CO₂ occurs. Furthermore, the mean degree of molar substitution is 0.42 for the potato and 0.4 for the waxy maize-derived products,[51] but when the latter was measured in CHEST it was 0.44 ([Table 2, online supplement](#)).[3] Thus, it is unclear if these chemical differences between 6% tetrastarches, particularly with different plasma amylase levels,[52] are clinically important. However, harm is associated with their exposure in severe sepsis (Figures 2 and 3), perhaps predicted by similar degrees of tissue uptake compared to older higher molecular weight HES preparations.[53]

Risk of bias in the large 2012 studies assessing 90-day mortality was low and study quality was good. Most patients were from this group (97.6% weight), control fluid was crystalloid ([Table 2, online supplement](#)), and the robust pooled results were unaffected by sensitivity analysis ([Figure 4a, online supplement](#)). The CHEST sepsis sub-group was not clearly described in the original report[3] and there were some missing data, but this did not affect the pooled mortality, RRT and allogeneic transfusion outcomes in our analysis. Pruritus was assessed in all CHEST patients, as this is not necessarily an adverse event specific to sepsis. A detailed sepsis analysis is awaited from the CHEST group (J Myburgh, personal communication) but patients with septic shock may have been underrepresented given the low baseline mortality

(Table 1). 6% tetrastarch-associated mortality was found in the pooled crystalloid sub-group (Figure 3). Ambiguity remains about relative safety in the underpowered albumin sub-group but the point estimates were also concordant with 6% tetrastarch-associated harm. There were risks of bias in the three smaller and older trials ([Figures 1 and 2, online supplement](#)). Their primary end-points were not focused on mortality, data were missing, and they had a very short or unclear follow-up (Table 1).

Statistical heterogeneity ranged from *not present* to *low* (Figures 2, 3, 4, 5, and 6; [Figures 4, 5, 6, 7, and Table 4, online supplement](#)). Greater degrees of statistical heterogeneity have hampered the results of previous meta-analyses.[5, 13, 14] Clinical heterogeneity of 6% tetrastarch dosing and frequency will remain within any meta-analysis ([Table 2, online supplement](#)). Therefore, the more conservative random effects model was used, which assumes that individual studies are estimating different treatment effects.

Pooled data published in 2012 demonstrates 6% tetrastarch exposure increases the requirement of RRT support (Figures 5). This was previously found for other HES formulations[8, 9, 12] and suspected for 6% tetrastarch.[54] The point estimates are concordant and the pooled CI is narrower than already reported in trials,[3, 25] improving precision. Sensitivity analysis did not alter this finding suggesting it is robust. A meta-analysis of predominantly older higher molecular weight HES formulations also found similar results.[55] The indication for initiating RRT might vary between centres and studies introducing potential risk of bias. However, this effect would be expected to be the same across the blinded RCT cohorts, reducing potential bias affecting one particular group. The total 6% tetrastarch dose exposures

were below 50 ml/kg, and 3000 ml or less ([Table 2, online supplement](#)), thus incorrect use was not a major factor.[54] Some of the renal toxicity has been attributed to 43% tissue uptake[53] and perhaps the effects of direct urinary ultrafiltration of less than 60 kDa molecules.[51] Overall, one patient with severe sepsis required RRT for every 16 patients treated with 6% tetrastarch instead of (crystalloid) control fluid.

Comparison of RIFLE criteria components between 6% tetrastarch and control fluid could not differentiate between safety and harm, partly because of low observed power ([Table 4a, online supplement](#)). With inclusion of septic and non-septic patients enrolled in to CHEST, the more severe RIFLE-I and –F acute kidney injury grades were associated with 6% tetrastarch exposure ([Table 4b, online supplement](#)). However, no firm conclusions can be drawn from this.

6% tetrastarch exposure was associated with allogeneic transfusion (Figure 6), and with a larger volume ([Table 3, online supplement](#)). The point estimates are concordant across all studies and the outcome withstands sensitivity analysis. This finding is consistent with non-significantly increased severe bleeding ($p = 0.09$) and significantly increased overall bleeding ($p = 0.003$) in the 6S study[25] but without major coagulation profile disturbance or blood loss in the smaller CRYSTMAS trial.[26] Anaemia from haemodilution,[56] reduced platelet function and clot strength, effects on von Willebrand factor, and on factor XIII might explain a normal coagulation screen in the presence of bleeding with HES exposure.[57-61] Moreover, effects on erythropoiesis from tissue uptake[53, 62, 63] in the bone marrow[64] of septic patients have not been adequately assessed, but lysosomal storage and toxicity might contribute. Hence this observation requires further investigation. A transfusion

protocol was not pre-defined thus risk of bias is possible. However, the blinding of fluids and all personnel would likely reduce the effect of variations across the RCT groups, reducing the risk of imbalance. Patient characteristics were similar between groups, including those with septic shock ([Table 1, online supplement](#)).

The open-label CRISTAL study (Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients: A Multinational Randomised Controlled Trial; ClinicalTrials.gov; NCT00318942) will report 28-day mortality as primary, and 90-day mortality as secondary endpoints. The results might be informative as a sufficiently powered large RCT is often recommended to confirm meta-analysis findings. The open-label Impact of Early Goal-directed Fluid Therapy in Septic Patients Undergoing Emergency Surgery trial (ClinicalTrials.gov; identifier: NCT01654003) will close in December 2013. It will report 28-day mortality in approximately 250 patients. The results of the single centre blinded BaSES RCT (n = 240) (ClinicalTrials.gov; identifier: NCT00273728), which completed in May 2011, are awaited.

The major strength of this study has been to improve power sufficiently to investigate the safety and efficacy of 6% tetrastarch products in a defined severe sepsis population using the recommended outcome measure of 90-day mortality.[27] A major limitation has been the inability to assess definitively some tertiary outcomes, partly due to inadequate power, and partly because of inconsistent or inadequate reporting of data. Studies at high risk of bias were included but their impact on the primary outcome was minimal, confirmed by subsequent sensitivity analysis with

these studies removed. We tested the impact of the available CHEST data but this did not affect our primary and secondary mortality outcomes.

Summary

Studies reporting 90-day mortality were of good quality. Overall and 90-day mortality was significantly higher in severe sepsis patients receiving 6% tetrastarch 130 kDa solutions as part of initial fluid resuscitation. On the basis of our meta-analysis of currently available data, in our view the use of 6% tetrastarch for volume resuscitation in severe sepsis cannot be recommended because of an association with harm, particularly as alternative fluids are available.

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Conflicts of interest

None

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Tables and figures

Figure 1. A PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses)[28] flow diagram detailing the search, identification, screening and inclusion of RCTs assessed in this systematic review and meta-analysis.

Figure 2. Forest plot assessing the RR of mortality at 90-days, the primary outcome measure for safety and efficacy. The observed overall power was 52.4%.

Figure 3. Forest plot assessing the RR of overall mortality, the secondary outcome measure, assessed at last follow-up. Observed power was 52.6%. Post hoc sub-groups of control group fluid type are shown. The observed power in the crystalloid control sub-group was 46.6% and median baseline mortality was 38.4% (range 23.7 to 53.8). In the colloid sub-group these were 18.6% and 21.7% respectively (Table 1).

Figure 4. Forest plot assessing the RR of mortality at 28-days, a tertiary outcome measure. The observed power was 24.1%.

Figure 5. Forest plot assessing the RR of RRT support, a tertiary outcome measure. The observed power was 73.4%.

Figure 6. Forest plot assessing the RR of allogeneic transfusion support, a tertiary outcome measure. The observed power was 88.4%.

Table 1. Characteristics of included critical care studies. The clinical setting, country and centres are presented with the diagnosis of recruited patients. The total numbers of patients randomised is presented, with baseline (control group) mortality and final follow-up. Data completeness for the outcome of mortality, along with observed power (at 95% CI) for the end-point of mortality at final follow-up, are presented. Each study end-point is also described.

RCT	Centre(s)	Country / countries	Clinical setting	Diagnosis	Patients	Baseline mortality (%)	Final follow-up (days)	Patient follow-up (%)	Observed power (%)	Primary endpoint
Dolecek et al. 2009[41]	1	Czech Republic	Critical care	Severe sepsis	56	13.3	28	100.0	15.4	Extravascular lung water
Dubin et al. 2010[43]	2	Argentina, Amsterdam	Critical care	Severe sepsis	24	53.8	1 [?]	100.0	25.1	Sublingual mucosa microcirculation imaging parameters
CRYSTMAS trial 2012[26]	24	France, Germany	Critical Care	Severe sepsis	196	33.7	90	99.0	15.9	Efficacy of initial hemodynamic stabilization
CHEST trial 2012[3]	32	Australia, New Zealand	Critical Care	Various (sepsis) ⁺	7000 (1937) [§]	23.7	90	99.2 [§]	13.7	All cause mortality at 90 days
Palumbo et al. 2006[42, 48]	1	Italy	Critical care	Severe sepsis	20	30.0	5 [?]	100.0	6.4	Unclear
6S trial 2012[25]	26	Denmark, Norway, Finland, Iceland	Critical Care	Severe sepsis	800	43.0	90	99.8	56.5	All cause mortality (or end-stage kidney failure (dialysis dependence) at 90 days

⁺Sepsis was a pre-defined subgroup; [§]sepsis; [?]uncertainty regarding time of mortality reporting.

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Randomised trials of 6% tetrastarch (hydroxyethyl starch
130/0.4 or 0.42) for severe sepsis reporting mortality:
systematic review and meta-analysis

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Tables and figures

Figure 1. Risk of bias summary displaying review authors' judgements about each risk of bias item for each included study, alphabetically listed.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
6S trial 2012							
CHEST trial 2012							
CRYSTMAS trial 2012							
Dolecek et al. 2009							
Dubin et al. 2010							
Palumbo et al. 2006							

Figure 2. Risk of bias summary displaying review authors' judgements about each risk of bias item across all the included studies.

Figure 3. Funnel plot assessment for publication bias, with 95% CI lines.

Figure 4a. Forrest plot assessing the RR of mortality at 90-days, the primary outcome measure for safety and efficacy, with exclusion of CHEST trial data for sensitivity analysis. The observed overall power was 63.5%.

Figure 4b. Forrest plot assessing the RR of mortality at 90-days, the primary outcome measure for safety and efficacy. The observed overall power was 52.4%. Sub-groups of 6% tetrastarch origin and C2/C6 hydroxyethylation ratio are shown. The observed power of the waxy-maize 6% tetrastarch sub-group was 20.7%, and median baseline mortality 28.7% (range 23.7 to 33.7). Table 1 outlines these parameters for the 6S study.

Figure 5. Forrest plot assessing the RR of overall mortality, the secondary outcome measure, assessed at last follow-up. Observed power was 52.6%. Post hoc sub-groups of 6% tetrastarch origin and C2/C6 hydroxyethylation ratio are shown. The observed power of the waxy-maize 6% tetrastarch sub-group was 20.7%, and median baseline mortality 30% (range 13.3 to 53.8). Table 1 outlines these parameters for the 6S study.

Figure 6. Forrest plot assessing the RR of mortality at 28-days, a tertiary outcome measure. CHEST trial data relates to all patients enrolled in to the sepsis and non-sepsis groups, thus is included for illustrative purposes. The observed power was 26.4%.

Figure 7. Forrest plot assessing the RR of RRT support, a tertiary outcome measure. CHEST trial data relates all patients enrolled in to sepsis and non-sepsis groups, thus is included for illustrative purposes. The observed power was 86.3%.

Table 1. Baseline patient characteristics. For each study the severe sepsis management protocol or principles are outlined along with age, sex, a marker of disease severity (APACHE II)[35] or organ dysfunction (SOFA),[36] and an indication of septic shock.

RCT	Management protocol	6% tetrastarch				Control fluid			
		Age	Male Sex (%)	SOFA or APACHE II	Shock or vasopressor (%)	Age	Male Sex (%)	SOFA or APACHE II	Shock or vasopressor (%)
Dolecek et al. 2009[41]	Surviving Sepsis guidelines[31]	43 [£] (23–67) ^{&}	84.6	8.8 [§] (3) [@]	65.4	47 [£] (19–81) ^{&}	86.7	8 [§] (2) [@]	60.0
Dubin et al. 2010[43]	EGDT principles	62 [§] (21) [@]	67	8.1 [§] (2.5) [@]	100.0	65 [§] (12) [@]	55	8.9 [§] (3.6) [@]	100.0
CRYSTMAS trial 2012[26]	EGDT principles	65.8 [§] (15.4) [@]	64	7.9 [§] (?) [@]	88.0	65.9 [§] (14.7) [@]	59	9.1 [§] (?) [@]	90.6
CHEST trial 2012[3]⁺	Clinician discretion	63.1 [§] (17) [@]	60.5	17 ^{£§} (12–23) [^]	45.6	62.9 [§] (16.9) [@]	60.3	17 ^{£§} (12–23) [^]	46.1
Palumbo et al. 2006[42]	Unclear	?	?	18.5 ^{§§} (3) [@]	?	?	?	19.7 ^{§§} (2.7) [@]	?
6S trial 2012[25]	Clinician discretion	66 [£] (56–75) [^]	60.0	7 [£] (5–9) [^]	84.4	67 [£] (56–76) [^]	61	7 [£] (5–9) [^]	84.3

[§]Mean; [£]median; [§]APACHE II score; [§]SOFA score; [@]standard deviation; [&]range; [^]interquartile range; EGDT (early goal-directed therapy);[65] ⁺severe sepsis data were not reported thus overall values are presented for all randomised patients; [?]not reported or unclear.

Table 2. Characteristics of both intervention and control group fluid exposures. The total days of study fluid exposure are outlined along with pre-defined doses for 6% tetrastarch and control fluid. The calculated actual fluid exposure volume and dose received are also presented.

RCT	6% tetrastarch						Control fluid				
	Days of exposure	HES 130 kDa (molar substitution)	Dose (ml/kg/day)	Total infused (ml)	Total dose received (ml/kg)	Dose received (ml/kg/day)	Control fluid	Dose (ml/kg/day)	Total infused (ml)	Total dose received (ml/kg)	Dose received (ml/kg/day)
Dolecek et al. 2009[41]	3	Voluven (0.4)	14.3	3000	42.9	14.3	20% albumin	2.9	600	9	2.9
Dubin et al. 2010[43]	1	Voluven (0.4)	Undefined [§]	2610 [§]	37.2	37.2	0.9% saline	Undefined [§]	6254 [§]	89.3	89.3
CRYST MAS trial 2012[26]	4	Voluven (0.4)	37.5 ^l	2615 [§]	37.4	9.4	0.9% saline	37.5 ^l	2788 [§]	39.8	10.0
CHEST trial 2012[3] ⁺	4	Voluven (0.4 or 0.44)*	50.0	2104 ^{§+}	30.1 ⁺	7.5 ⁺	0.9% saline	50	2464 ^{§+}	35.2 ⁺	8.8 ⁺
Palumbo et al. 2006[42]	5?	Voluven (0.4)	?	?	?	?	20% albumin	?	?	?	?
6S trial 2012[25]	3	Tetraspan (0.42)	33.0	3000 [£]	42.9	14.3	Ringer's acetate	33	3000 [£]	42.9	14.3

[§]Mean; [£]median; [§]dose according to clinical response; ^l50 on day 1, 25 on days 2 to 4.

⁺sepsis data were not reported thus overall values are presented for all randomised patients. [?]not reported or unclear. *Independent analysis of a random sample of CHEST study fluids reported a mean degree of molar substitution of 0.44.[3]

Tetrastarch fluid origin: Tetraspan is potato- and Voluven is waxy maize-derived.

Table 3. Characteristics of RRT and allogeneic transfusion support. The proportion of patients that required renal and transfusion support in the intervention and the control groups are outlined. The total volumes of allogeneic transfusion received during study fluid intervention are also presented.

	6% tetrastarch			Control fluid		
RCT	RRT (%)	Transfusion (%)	Transfusion (ml)	RRT (%)	Transfusion (%)	Transfusion (ml)
Dolecek et al. 2009[41]	?	?	?	?	?	?
Dubin et al. 2010[43]	?	22.2	?	?	18.2	?
CRYSTMAS trial 2012[26, 50]	21.0	29.0	214 ^{§§} (358) [@] (0–1394) ^{&}	11.4	20.8	165 ^{§§} (354) [@] (0–1661) ^{&}
CHEST trial 2012[3] ⁺	7.0	?	312 [§] (1000) [@]	5.8	?	240 [§] (760) [@]
Palumbo et al. 2006[42]	?	?	1500 ^{§§} (750) [@]	?	?	1400 ^{§§} (650) [@]
6S trial 2012[25]	21.9	64.6	1340 [£] (566–2700) [^]	16.3	53.7	1055 [£] (600–2755) [^]

[§]Mean; [£]median; [@]standard deviation; [&]range; [^]interquartile range; [§]packed red cells alone; [|]mean and standard deviation daily values multiplied by days of trial fluid intervention (Table 3); ⁺sepsis data were not reported thus overall values are presented for all randomised patients; [?]not reported or unclear.

Table 4a. Meta-analysis (random effects model) characteristics of acute kidney injury severity and clinical outcome as defined by the RIFLE criteria.[29] Assessment was based on creatinine alone. The observed power (at 95% CI) for each component was calculated.

RIFLE criteria	Effect size measure			Statistical heterogeneity			Power
	RR	95% CI	p	I ²	Chi ²	p	%
Risk	0.79	0.55 to 1.14	0.79	15	1.18	0.28	39.7
Injury	1.15	0.83 to 1.59	0.40	0	0.41	0.52	11.7
Failure	1.19	0.83 to 1.72	0.35	9	1.10	0.29	25.3
Loss	0.88	0.35 to 2.24	0.79	0	0.58	0.44	3.7
End stage kidney disease	1.01	0.06 to 16.10	0.99	NA	NA	NA	1.1

NA (not applicable) as there were no events in the CRYSTMAS[26] study.

Table 4b. Meta-analysis (random effects model) characteristics of acute kidney injury severity and clinical outcome as defined by the RIFLE criteria.[29] CHEST[3] trial data relates all patients enrolled in to sepsis and non-sepsis groups, thus is included for illustrative purposes. Assessment was based on creatinine alone. The observed power (at 95% CI) for each component was calculated.

RIFLE criteria	Effect size measure			Statistical heterogeneity			Power
	RR	95% CI	p	I ²	Chi ²	p	%
Risk	0.96	0.68 to 1.35	0.81	68	6.27	0.04	18.1
Injury	1.26	1.07 to 1.47	0.005	0	0.78	0.68	78.0
Failure	1.27	1.04 to 1.55	0.02	0	1.25	0.54	60.3
Loss	0.88	0.35 to 2.24	0.79	0	0.58	0.44	3.7
End stage kidney disease	1.01	0.06 to 16.10	0.99	NA	NA	NA	1.1

NA (not applicable) as there were no events in the CRYSTMAS[26] study.