BMJ

BMJ 2013;346:f839 doi: 10.1136/bmj.f839 (Published 15 February 2013)

RESEARCH

Hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis: systematic review with meta-analysis and trial sequential analysis

OPEN ACCESS

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Abstract

Objective To assess the effects of fluid therapy with hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin on mortality, kidney injury, bleeding, and serious adverse events in patients with sepsis.

Design Systematic review with meta-analyses and trial sequential analyses of randomised clinical trials.

Data sources Cochrane Library, Medline, Embase, Biosis Previews, Science Citation Index Expanded, CINAHL, Current Controlled Trials, Clinicaltrials.gov, and Centerwatch to September 2012; hand search of reference lists and other systematic reviews; contact with authors and relevant pharmaceutical companies.

Study selection Eligible trials were randomised clinical trials comparing hydroxyethyl starch 130/0.38-0.45 with either crystalloid or human albumin in patients with sepsis. Published and unpublished trials were included irrespective of language and predefined outcomes.

Data extraction Two reviewers independently assessed studies for inclusion and extracted data on methods, interventions, outcomes, and risk of bias. Risk ratios and mean differences with 95% confidence intervals were estimated with fixed and random effects models.

Results Nine trials that randomised 3456 patients with sepsis were included. Overall, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin did not affect the relative risk of death (1.04, 95% confidence interval 0.89 to 1.22, 3414 patients, eight trials), but in the predefined analysis of trials with low risk of bias the relative risk of death was 1.11 (1.00 to 1.23, trial sequential analysis (TSA) adjusted 95% confidence interval 0.95 to 1.29, 3016 patients, four trials). In the hydroxyethyl starch group, renal replacement therapy was used more (1.36, 1.08 to 1.72, TSA adjusted 1.03 to 1.80, 1311 patients, five trials), and the relative risk of acute kidney injury was 1.18 (0.99 to 1.40, TSA adjusted 0.90 to 1.54, 994 patients, four trials). More patients in the hydroxyethyl starch group were transfused with red blood cells (1.29, 1.13 to 1.48, TSA adjusted 1.10 to 1.51, 973 patients, three trials), and more patients had serious adverse events (1.30, 1.02 to 1.67, TSA adjusted 0.93 to 1.83, 1069 patients, four trials). The transfused volume of red blood cells did not differ between the groups (mean difference 65 mL, 95% confidence interval −20 to 149 mL, three trials).

Conclusion In conventional meta-analyses including recent trial data, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin increased the use of renal replacement therapy and transfusion with red blood cells, and resulted in more serious adverse events in patients with sepsis. It seems unlikely that hydroxyethyl starch 130/0.38-0.45 provides overall clinical benefit for patients with sepsis.

Introduction

Colloids are used more often for resuscitation in the intensive care unit than crystalloids. The choice of colloid varies noticeably between countries, but worldwide hydroxyethyl starch is most commonly used and thus more used than, for example, human albumin and gelatin.[1] The use of hydroxyethyl starch is controversial as the former higher molecular weight hydroxyethyl starch 200/0.5-0.6 caused acute kidney injury in two randomised clinical trials of patients with sepsis.[2 3] The newer starches with molecular weights of 130 kDa and substitution ratios ranging from 0.38 to 0.45 have been claimed to be safer, but the data to support this are insufficient.[4] Owing to the lack of data on hydroxyethyl starch 130/0.38-0.45, previous systematic reviews have been inconclusive about the

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Search strategy, details of included studies, and figures
Reasons for exclusion of trials

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benefits and harms of this colloid compared with other fluids.[4-8] The recent publication of three large trials comparing hydroxyethyl starch 130/0.38-0.45 with crystalloids in patients with sepsis calls for an updated systematic review to inform on the benefits and harms of this colloid in patients with sepsis, which is highly needed as fluid alternatives are available.[9-11]

We assessed the effects of hydroxyethyl starch 130/0.38-0.45 versus crystalloids or human albumin on all cause mortality, kidney injury, bleeding, and serious adverse events in patients with sepsis.

Methods

This systematic review is based on the methodology recommended by the Cochrane Collaboration.[12] The protocol was published in the PROSPERO register (www.crd.york.ac.uk/PROSPERO) before the literature search.

Eligibility criteria

Potentially eligible trials had to be prospective and randomised, include patients with sepsis, have one intervention group that received hydroxyethyl starch 130 with substitution ratios between 0.38 and 0.45 in any concentration and in any carrier solution, and have at least one other intervention group that received either crystalloid or human albumin.

We included trials irrespective of language, publication status, patient's age, indication for fluid therapy, and predefined outcomes. If the patients with sepsis constituted a subgroup of the trial population, we included the trial only if the randomisation was stratified for the presence of sepsis or if the population with sepsis was larger than 500 participants. We also included quasirandomised and observational studies with more than 500 patients receiving hydroxyethyl starch 130/0.38-0.45, but evaluated these for serious adverse events only. Exclusion criteria were studies in animals, patients without sepsis, hydroxyethyl starch products of other molecular weights or substitution ratios, crossover studies, and studies comparing hydroxyethyl starch with other synthetic colloid solutions.

Search strategy

We searched the Cochrane central register of controlled trials, Medline, Embase, Biosis Previews, Science Citation Index Expanded, and Cumulative Index to Nursing and Allied Health Literature. As hydroxyethyl starch 130/0.38-0.45 was introduced on the market in 1999 we limited the search to references from 1995 or later. We also hand searched the reference lists of included trials and other systematic reviews of fluid therapy for further trials.

Unpublished trials were sought through trial registries (www.controlled-trials.com, www.clinicaltrials.gov, and www.centerwatch.com), and we contacted relevant pharmaceutical companies for unpublished data. The electronic literature search was last updated 10 September 2012. See the supplementary file for details of the search, including the search string.

Study selection

Two authors (NH, LIH, BL, or MW) independently reviewed all titles and abstracts identified in the literature search and excluded trials that were obviously not relevant. The remaining trials were evaluated in full text. Disagreements were resolved with JW.

Data extraction

Two authors (NH, LIH) independently extracted information from each included trial by using a pre-made data extraction form. The extracted information included trial characteristics (single or multicentre and country), characteristics of the trial participants (age, sex, and disease severity), criteria for inclusion and exclusion, type of intervention (indication, dosing, duration, and comparator fluid), and outcomes.

The predefined primary outcomes of this review were overall mortality and number of patients still receiving renal replacement therapy at the maximum length of follow-up. The predefined secondary outcomes were the number of patients receiving renal replacement therapy at any time during the follow-up period, number of patients having acute kidney injury, number of patients receiving red blood cell transfusion, total volume of red blood cells transfused, number of patients having a bleeding episode, estimated blood loss, and number of patients having one or more serious adverse events. We contacted the corresponding authors for data on outcomes that were not reported in their publications.

Translators extracted data from all relevant non-English articles.

Risk of bias assessment

To determine the validity of the included trials, we assessed the risk of bias as advised by the Cochrane Collaboration,[12] including the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance, bias due to vested financial interest, and academic bias. If one or more domains were judged as being high or unclear, we classified the trial as having a high risk of bias. Since the need for fluids is difficult to assess objectively, the choice to give fluid instead of vasopressors or inotropes may depend on the expected potency of the fluid. Thus, unblinding may lead to systematic differences in interventions or cointerventions between the intervention groups, so we classified all unblinded trials as being at high risk of bias for all outcomes including mortality unless study fluids were given in fixed doses.

Statistical analysis

Review Manager 5.1.6 was used for statistical analyses, and we used the TSA program version 0.9 beta (www.ctu.dk/tsa) for trial sequential analyses. For each included trial we calculated the relative risks (95% confidence intervals) for dichotomous outcomes and risk difference (95% confidence intervals) for continuous outcomes, and we pooled these measures in meta-analyses.

Heterogeneity among trials was quantified with inconsistency factor (I^2) statistics. If the I^2 statistic was 0, we reported the results from a fixed effect model. If the I^2 statistic was greater than 0, we reported the results from both random effects and fixed effects models.

Sensitivity analyses included application of continuity correction in trials of zero events[13] and exclusion of the smallest trial, the largest trial, and trials financed by industry.

We did a predefined subgroup analysis with stratification of trials according to risk of bias. To further explore possible reasons for a high or moderate statistical heterogeneity we did an explorative post hoc subgroup analysis stratifying trials according to length of follow-up.

Some authors have suggested that conventional meta-analysis should not be trusted without further evaluation, as cumulative meta-analyses of trials are at risk of producing random errors

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because of sparse data and repetitive testing of accumulating data.[14 15] We therefore challenged the meta-analyses with the application of trial sequential analysis—a sensitivity analysis that widens the confidence intervals in case the data are too sparse to draw firm conclusions. Trial sequential analysis is similar to interim analysis in a single trial where the monitoring boundaries are used to decide whether the P value is sufficiently small to show the anticipated effect and whether the trial should be terminated early. In the same manner, trial sequential monitoring boundaries can be applied to meta-analyses.[14-17]

Trial sequential analysis depends on the quantification of the required information size (the meta-analysis sample size). We calculated a diversity, D^2, adjusted required information size since the heterogeneity adjustment with I^2 underestimate the required information size.[18] We did the trial sequential analysis with the intention to maintain an overall 5% risk of a type I error and a power of 80%. For the calculation of the required information size we anticipated an intervention effect of a 20% relative risk increase. For renal replacement therapy, bleedings, and serious adverse events we used an anticipated effect of 35%, since we expected a much lower event proportion for these outcomes. For mortality, we observed only an 11% relative risk increase in trials with low risk of bias and used this effect instead in the trial sequential analysis of mortality. We provide the 95% confidence intervals adjusted for sparse data and repetitive testing, which we describe as the trial sequential analysis adjusted 95% confidence intervals.

Results

Figure 1⇓ summarises the results of the search. The main reasons for exclusion of randomised trials were that the patients did not have sepsis and the trials evaluated a hydroxyethyl starch solution other than hydroxyethyl starch 130/0.38-0.45 (see supplementary table).[19-50] No language restrictions were applied; one paper was in Spanish, one in Japanese, four in Russian, and four in Chinese. Overall nine trials met the inclusion criteria.[9-11 51-56] One trial was still unpublished.[51] The authors of six trials were successfully contacted[9-11 51 53 54] and data were obtained for eight.[9-11 51 53-56] A Chinese researcher extracted data from two trials published in Chinese.[55 56] All other trials were published in English. No observational study was identified with more than 500 patients with sepsis receiving hydroxyethyl starch 130/0.38-0.45 to evaluate for adverse events.

Characteristics of trials

The four largest trials were blinded and had long term (>28 days) follow-up.[9-11 51] The remaining trials were either unblinded, had unclear methodology, or had shorter follow-up times (≤28 days). Table 1⇓ shows the characteristics of the included trials, and table 2⇓ the observation period for each outcome.

Participants

The included trials enrolled 3456 adults with sepsis on an intensive care unit. One trial included a broad spectrum of patients on the intensive care unit, but in this review only the subgroup of patients with sepsis were included.[10] All but two trials included patients with both sepsis and organ failure (severe sepsis).[10 51] The definitions of organ failure varied slightly between trials, but in most included various clinical signs of hypoperfusion as, for example, oliguria, hypotension, and increased lactate levels. Only one trial specifically stated that all patients had septic shock.[55]

Interventions

The type of hydroxyethyl starch studied was 6% Voluven (hydroxyethyl starch 130/0.4 (range 0.38-0.45) in saline, Fresenius Kabi, Bad Homburg, Germany) in six trials,[10 11 51-54] 6% Tetraspan (hydroxyethyl starch 130/0.42 (range 0.40-0.44) in Ringer's acetate, B Braun Melsungen, Melsungen, Germany) in one trial,[9] and 6% hydroxyethyl starch 130/0.4 without a statement of the brand name in two trials.[55 56] Two trials compared starch with human albumin 20%,[52 53] whereas the remaining trials used crystalloid as comparator. In one study two groups received hydroxyethyl starch 130/0.4 in isotonic saline or hypertonic saline.[56] These groups were pooled and compared with the third group receiving Ringer's lactate.

Trial fluid was used for resuscitation in eight trials[9-11 51 52 54-56] and given as fixed doses in one trial.[53] The duration of the intervention varied from 24 hours to the entire stay on the intensive care unit to a maximum of 90 days. Cumulative doses of hydroxyethyl starch ranged from 2.1 litres to 6.4 litres with no obvious relation between duration of intervention and total dose.

Bias risk assessment

The risk of bias could be fully judged in six trials.[9-11 51 53 54] Four of these were judged to be of low risk of bias in all domains,[9 10 51 53] the fifth was sponsored by industry and had potential academic bias,[11] and the sixth had a high risk of bias owing to lack of blinding.[54]

In the remaining three trials at least one domain was judged to be unclear, but all of these trials were judged to be of high risk of bias in other domains (table 3⇓, also see the supplementary file).

Clinical outcomes

All cause mortality

Mortality data were obtained from eight trials including 3414 patients.[9-11 51 53-56] The observation period in four of these trials (3156 patients) was longer than 28 days (table 2).[9-11 51] The meta-analysis of all eight trials showed no significant difference in mortality in patients treated with hydroxyethyl starch 130/0.38-0.45 compared with crystalloid or albumin (random effects: relative risk 1.04, 95% confidence interval 0.89 to 1.22; P=0.64; fixed effect: 1.08, 0.98 to 1.19; P=0.13; I^2=37%; fig 2⇓). The trial sequential analysis adjusted 95% confidence interval was 0.70 to 1.54 (see supplementary file). The predefined analysis of trials with low risk of bias showed a relative risk of 1.11 (1.00 to 1.23; P=0.05; I^2=0%), but the test for subgroup difference between trials with low versus high risk of bias was not significant (P=0.13, fig 2). Trial sequential analysis of trials with low risk of bias showed that 3016 of the required information size of 6237 patients was accrued. The cumulative z curve touched the conventional boundary for harm but did not cross the trial sequential monitoring boundary for harm (trial sequential analysis adjusted 95% confidence interval of trials with low risk of bias 0.95 to 1.29) (fig 3⇓). However, the z curve will need to pass through the futility area to reach the area of benefit, leaving little chance that hydroxyethyl starch will turn out to reduce the relative risk of death with 11% if further trials are conducted in patients with sepsis.

The post hoc subgroup analysis according to time of follow-up showed a significant increase in all cause mortality in trials with follow-up for more than 28 days (relative risk 1.11, 95% confidence interval 1.01 to 1.22; P=0.04; I^2=0%) versus a non-significant decrease in all cause mortality in trials with

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follow-up for 28 days or less (0.63, 0.35 to 1.15; P=0.13). The test for subgroup differences was not significant at the 5% level (P=0.07, see supplementary file). The trial sequential analysis adjusted 95% confidence intervals of trials with follow-up for more than 28 days was 0.95 to 1.29 (see supplementary file).

Renal replacement therapy at end of follow-up

Five trials had data on renal replacement therapy, with observation periods ranging from 24 hours to one year.[9 11 51 53 54] The Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial reported that two patients—one in each intervention group—were still being treated with renal replacement therapy at the end of follow-up.[9] In Basel Starch Evaluation in Sepsis (BaSES)[51] no patient required renal replacement therapy after one year, and in the trial by Guidet et al (CRYSTMAS)[11] one patient in the hydroxyethyl starch group was treated with renal replacement therapy for more than 28 days, but it was unclear whether this lasted until end of follow-up. These data did not undergo meta-analysis.

Renal replacement therapy at anytime during follow-up

The same five trials had data on the number of patients treated with renal replacement therapy at anytime during follow-up. One trial had zero events in three days.[53] The pooled analysis showed that patients receiving hydroxyethyl starch 130/0.38-0.45 had a significantly increased risk of receiving renal replacement therapy (relative risk 1.36, 95% confidence interval 1.08 to 1.72; P=0.009; I^2=0%; fig 4⇓). Application of an empirical continuity correction of 0.01 in the no event trial did not change the result. Trial sequential analysis showed that 1311 of the required information size of 1654 patients was accrued, but the cumulative z curve crossed the trial sequential monitoring boundary for harm providing firm evidence of increased use of renal replacement therapy in patients treated with hydroxyethyl starch compared with crystalloid or albumin (trial sequential analysis adjusted 95% confidence interval 1.03 to 1.80) (fig 5⇓).

Acute kidney injury

Acute kidney injury was defined as a twofold increase of serum creatinine levels during the observation period, as this was consistently reported in the four trials with data on kidney function.[9 11 53 54] The observation periods ranged from 24 hours to the entire stay on the intensive care unit. One trial had no events,[53] and the pooled analysis of the remaining three trials showed a non-significant increase in the risk of acute kidney injury in the hydroxyethyl starch group (relative risk 1.18, 95% confidence interval 0.99 to 1.40; P=0.07; I^2=0%) (see supplementary file). Application of an empirical continuity correction of 0.01 in the no event trial did not change the result. The trial sequential analysis adjusted 95% confidence interval was 0.90 to 1.54 (see supplementary file).

Transfusions with red blood cells, bleeding, and blood loss

Three trials provided data on transfusions, with observation periods ranging from 24 hours to the entire stay on the intensive care unit.[9 11 54] The risk of being transfused with red blood cells was significantly higher in the hydroxyethyl starch group (1.29, 95% confidence interval 1.13 to 1.48; P<0.001; I^2=0%) (see supplementary file). The trial sequential analysis adjusted 95% confidence interval was 1.10 to 1.51, providing firm evidence for an increased risk of transfusion with red blood cells if treated with hydroxyethyl starch 130/0.38-0.45 (see supplementary file).

The mean volume of red blood cells did not differ between the groups (mean difference 65 mL, 95% confidence interval −20 to 149 mL; P=0.13; I^2=0%) (see supplementary file).

The number of patients having at least one bleeding episode (relative risk 1.34, 95% confidence interval 0.81 to 2.21; P=0.26; I^2=38%) and blood loss (mean difference 26 mL, −89 to 140 mL; P=0.66; I^2=0%) were reported in two trials (see supplementary file).[9 11]

Serious adverse events

Four trials reported serious adverse events, two of which registered these during the entire stay on the intensive care unit.[9 11 53 54] In the 6S trial serious adverse events were restricted to severe bleeding and severe allergic reactions,[9] whereas CRYSTMAS used broad criteria.[11] The last two trials did not specify the definition of serious adverse events, and one of them had zero events in 24 hours follow-up.[54] According to the good clinical practice guidelines by the International Conference on Harmonisation, death should count as a serious adverse event in the analysis,[57] but we were unable to get the composite endpoint of either death or serious adverse events from more than one trial.[9]

The pooled analysis of the three trials showed a significantly increased risk of serious adverse events with hydroxyethyl starch 130/0.38-0.45 (relative risk 1.30, 95% confidence interval 1.02 to 1.67; P=0.03; I^2=0%) (see supplementary file). The application of a continuity correction to the zero event trial neither changed the estimate nor the confidence interval. The trial sequential analysis adjusted 95% confidence interval was 0.93 to 1.83 (see supplementary file).

Discussion

The main finding of this systematic review was that patients assigned to hydroxyethyl starch 130/0.38-0.45 had in conventional meta-analysis a statistically significant increased risk of getting renal replacement therapy, transfusion with red blood cells, and serious adverse events. The recent large, well designed trials showed consistent results with no statistical heterogeneity and the findings are likely to be confirmed when further data of the patients with sepsis in the Crystalloid versus Hydroxyethyl Starch (CHEST) trial[10] become available, since the hydroxyethyl starch group in this trial had more use of renal replacement therapy and transfusion with red blood cells and more serious adverse events.

The pooled analysis of mortality showed neither benefit nor harm, but trials with a low risk of bias suggested an excess mortality of 11%. In addition, our post hoc analysis of trials with follow-up for more than 28 days showed increased mortality. Thus the pooled analysis of mortality may be influenced by trials of poor quality and too short follow-up, making interpretation difficult.

The sensitivity analysis with trial sequential analysis widened the confidence intervals of the conventional meta-analyses when data were too sparse to draw firm conclusions. With this strict approach the increased risk of renal replacement therapy and transfusion with red blood cells remained statistically significant. For mortality in trials with low risk of bias and long term follow-up, trial sequential analysis indicated a lack of statistical significance for increased mortality, but also that it is unlikely that hydroxyethyl starch will result in a relative mortality

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reduction of 11% if further trials are conducted in patients with sepsis.

Our results are consistent with the fact that a high fraction of hydroxyethyl starch 130/0.38-0.45 is deposited in the tissues where it cannot be metabolised[58] and may act as a foreign body with long term toxic effects, which have been described in the kidney, liver, and bone marrow.[59-61] In addition, the use of renal replacement therapy has repeatedly been associated with death.[62 63] Our findings are in alignment with the results of two sepsis trials of hydroxyethyl starch 200/0.5-0.6 on renal impairment and late adverse effects.[2 3] Thus the adverse effects of hydroxyethyl starch may be a class effect independent of molecular weight and substitution ratio.

Some hypothesise that bad outcome in patients treated with hydroxyethyl starch is due to inappropriate dosing, including the lack of predefined triggers and goals for fluid resuscitation. No data currently support this belief, as there was no suggestion of an overall favourable outcome in any trial with adequate bias control and follow-up—not even in the trial designed by one of the manufacturers of hydroxyethyl starch.[11]

Strengths and limitations of the review

The compliance with the recommendations of the Cochrane Collaboration is a major strength of our systematic review. This included a prepublished protocol, an up to date extensive literature search with no language restrictions, independent screening of all references by two authors, inclusion of trials irrespective of publication and language status and reported outcomes, independent data extraction by two authors, bias risk assessment, and contact with the corresponding authors of the included trials for additional information. In addition, we reduced the risk of random error in the meta-analyses with the application of trial sequential analysis using predefined variables to increase the robustness of this analysis.

We excluded trials comparing hydroxyethyl starch with other synthetic colloids that may possess the same harmful effects and thereby mask any adverse effects of hydroxyethyl starch.[64] To get a clinical applicable result, we restricted the review to hydroxyethyl starch 130/0.38-0.45 as clinicians almost exclusively use these starches. Including all types of hydroxyethyl starch in the analysis would probably have resulted in a stronger group difference instead.

The post hoc subgroup analysis of mortality in trials according to length of follow-up might have resulted in spurious findings. In general, however, some adverse effects undoubtedly develop slowly, and if the observation period is too short, such events may not be captured. In the largest trials of hydroxyethyl starch in sepsis the relative risk of death increased from day 28 to day 90, indicating that the observation period for mortality should be longer than 28 days, and this was the rationale for our subgroup analysis.[2 9 10]

We chose to include trials with either crystalloid or albumin solutions as comparators as no adverse effects were seen with albumin versus saline in patients with severe sepsis in a large intensive care unit trial.[65] However, most of the included trials compared hydroxyethyl starch with a crystalloid, and this may prevent us from drawing firm conclusions on the effects of albumin. Neither can this review tell whether patients other than those with sepsis may experience adverse effects from hydroxyethyl starch, but the CHEST trial found increased serious adverse events and use of renal replacement therapy with hydroxyethyl starch in a broad population of intensive care unit patients, suggesting adverse effects beyond those seen in sepsis.

Additional limitations of this review are due to bias of the included trials, inadequate follow-up, and trials not reporting all the outcome measures. The definitions of serious adverse events were heterogeneous, so the group difference should be interpreted with caution. The RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal disease)[66] and AKIN (Acute Kidney Injury Network)[67] classifications may be better measures for acute kidney injury, but we used renal replacement therapy and doubling of creatinine levels instead as these more simple outcomes were more often reported.

Relation to other reviews and implication for future research

Several well conducted systematic reviews have been published on hydroxyethyl starch 130/0.38-0.45[4 8] and on hydroxyethyl starch and fluid therapy in general.[5-7] Owing to the previous lack of data on hydroxyethyl starch 130/0.38-0.45, these reviews have been inconclusive about the benefit and harm of hydroxyethyl starch 130/0.38-0.45 compared with other fluids. In comparison, this review contains data from new large trials and applies trial sequential analysis on the results.

Hydroxyethyl starch 130/0.38-0.45 is often used in the surgical setting and may continue despite the raised safety issues in patients with sepsis. If use does continue, then well powered surgical trials are urgently needed to ensure the safety of patients.

Conclusion

In conventional meta-analyses including recent trial data, hydroxyethyl starch 130/0.38-0.45 versus crystalloid or albumin in patients with sepsis was associated with an increased use of renal replacement therapy and transfusion with red blood cells and more serious adverse events. The pooled analysis of mortality showed no group difference, but this analysis may be influenced by trials of low quality. After trial sequential analysis adjustment for sparse data and multiple updating in cumulative meta-analysis it seems unlikely that hydroxyethyl starch provides overall clinical benefit for patients with sepsis.

We thank Sarah Klingenberg, search coordinator for the Cochrane Hepato-Biliary Group, for performing the literature search; Xia Yun for evaluating references in Chinese and extracting data from two Chinese articles included in the review; Dimitrenka Nikolova, Copenhagen Trial Unit, for evaluating four papers in Russian; Naoya Sakamoto for evaluating one paper in Japanese; and Arnaldo Dubin, Petr Svoboda, and Martin Westphal for providing data for this systematic review. The trial protocol was registered through PROSPERO (registration No CRD42011001762).

Contributors: NH developed the protocol, was responsible for the searches, selected trials, extracted data, assessed the risk of bias of trials, did the data analysis, and developed the final review. AP developed the protocol, analysed data, and developed the final review. LIH developed the protocol, selected trials, extracted data, assessed the risk of bias of trials, and developed the final review. MS extracted data, assessed the risk of bias of trials, and developed the final review. BL and MW developed the protocol, selected trials, and developed the final review. JW developed the initial idea for the review, developed the protocol, selected trials, advised on statistical methods, analysed data, and developed the final review. All authors read and approved the final manuscript. NH and JW are the guarantors.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: AP was principal

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What is already known on this topic

Hydroxyethyl starches (HES) with molecular weights of 130 kDa and substitution ratios ranging from 0.38 to 0.45 are the most commonly used colloids wordwide, but their safety and efficacy have not been established in patients with sepsis

Owing to lack of data, previous systematic reviews on HES 130/0.38-0.45 and on HES in general have been inconclusive about the benefits and harms of HES compared with other fluids

What this study adds

This systematic review includes the results of four recent randomised clinical trials of HES 130/0.38-0.45 comprising more than 3000 patients with sepsis

The pooled analysis of trials showed that treatment with HES increased the risk of having renal replacement therapy, red blood cell transfusion, and severe adverse reactions

It seems unlikely therefore that HES provides overall clinical benefit for patients with sepsis

investigator for the Scandinavian Starch for Severe Sepsis/Septic Shock (6S) trial and NH and JW were members of the steering committee. The 6S trial was funded by the Danish Research Council, the Rigshospitalet Research Council, and the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (the ACTA foundation). B Braun Melsungen delivered trial fluid to all sites free of charge. Neither the funders nor B Braun Melsungen had an influence on the protocol, trial conduct, data analyses, or reporting of the 6S trial. AP is head of research in his intensive care unit, which receives research funds from Fresenius Kabi and BioPorto. B Braun Melsungen has covered his travel expenses for presenting 6S data at the German Anaesthetic Congress 2012. MS was principal investigator for the Basel starch evaluation in sepsis (BaSES) trial. The BaSES trial was funded by the Department of Anaesthesia and Intensive Care of the University Hospital Basel. Fresenius Kabi delivered study fluids for free and paid for the packaging and blinding process. A signed contract between Fresenius Kabi and MS stated that MS was free to publish all data without influence from Fresenius Kabi. Fresenius Kabi covered travel expenses for MS's participation in meetings about fluid resuscitation.

Ethical approval: Not required.

Data sharing: No additional data available.

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Accepted: 30 January 2013

Cite this as: *BMJ* 2013;346:f839

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Tables

Table 1| **Characteristics of included studies**

Trial	No of patients	Centre status, setting	Blinding	No of intervention groups	Diagnostic group	Indication for intervention	HES solution	Comparator	Intervention period	Total dose of HES	Contact with authors successful
6S[9]	804	Multicentre, ICU	Yes	2	Severe sepsis	Resuscitation	6% Tetraspan*	Ringer's acetate	ICU stay. Maximum 90 days	Median 3000 (IQR 1507-5100)	Yes
BaSES[51]	241	Two ICUs in one hospital	Yes	2	Sepsis	Resuscitation	6% Voluven†	Isotonic saline	5 days	Median 3775 (IQR 2018-6347)	Yes
CHEST[10]	1937	Multicentre, ICU	Yes	2	Sepsis	Resuscitation	6% Voluven†	Isotonic saline	ICU stay. Maximum 90 days	Mean 2104 (SD 850‡)	Yes
CRYSTMAS[11]	196	Multicentre, ICU	Yes	2	Severe sepsis	Resuscitation	6% Voluven†	Isotonic saline	4 days	Mean 2615 (SD 1499)	Yes
Dolecek 2009[53]	56	Single, ICU	No	2	Severe sepsis	Fixed dose	6% Voluven†	Albumin 20%	3 days	4×250 mL/day in 3 days	Yes
Dubin 2010[54]	25	Multicentre, ICU	No	2	Sepsis and tissue hypoperfusion	Resuscitation	6% Voluven†	Isotonic saline	24 hours	Mean 2610 (SD 885)	Yes
Lv 2012[55]	42	Single, ICU	Unclear	2	Septic shock	Resuscitation	Unclear	Ringer's lactate	24 hours	Mean 2770 (SD 590)	No
Palumbo 2006[52]	20	Single, ICU	No	2	Severe sepsis	Maintenance of pulmonary capillary wedge pressure	6% Voluven†	Albumin 20%	Unclear	No information on doses	No
Zhu 2011[56]	135	Single, ICU	No	3	Severe sepsis	Resuscitation	6% HES 130/0.4 (unclear brand)	Ringer's lactate	24 hours	HES+hypertonic saline group: mean 5475 (SD 209), HES group: mean 6383 (SD 287)	No

HES=hydroxyethyl starch; ICU=intensive care unit; IQR=interquartile range; SD=standard deviation.

*6% hydroxyethyl starch 130/0.42 in Ringer's acetate (B Braun Melsungen, Melsungen, Germany).

†6% hydroxyethyl starch 130/0.4 in saline (Fresenius Kabi, Bad Homburg, Germany).

‡Only reported for first four days.

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Table 2| **Observation period for outcomes**

Trial	Mortality	Renal replacement therapy	Acute kidney injury	Red blood cell transfusion	Bleeding and blood loss	Serious adverse events
6S[9]	90 days	90 days	ICU	ICU	ICU	ICU
BaSES[51]	1 year	1 year	—	—	—	—
CHEST[10]	90 days	—	—	—	—	—
CRYSTMAS[11]	90 days	ICU	ICU	ICU	4/8 days	ICU
Dolecek 2009[53]	28 days	72 hours	72 hours	—	—	72 hours
Dubin 2010[54]	28 days	24 hours	24 hours	24 hours	—	24 hours
Lv 2012[55]	Unclear*	—	—	—	—	—
Palumbo 2006[52]	—	—	—	—	—	—
Zhu 2011[56]	24 hours	—	—	—	—	—

ICU=intensive care unit.

*Death in hospital or ICU, although not specifically stated.

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Table 3| **Risk of bias**

Trial	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Baseline imbalance	Vested financial interests	Academic bias
6S[9]	Low	Low	Low	Low	Low	Low	Low	Low
BaSES[51]	Low	Low	Low	Low	Low	Low	Low	Low
CHEST[10]	Low	Low	Low	Low	Low	Low	Low	Low
CRYSTMAS[11]	Low	Low	Low	Low	Low	Low	High	High
Dolecek 2009[53]	Low	Low	Low	Low	Low	Low	Low	Low
Dubin 2010[54]	Low	Low	High	Low	Low	Low	Low	Low
Lv 2012[55]	Low	High	Unclear	Unclear	Low	Low	Unclear	Unclear
Palumbo 2006[52]	Unclear	High	Unclear	Low	High	Low	Unclear	Low
Zhu 2011[56]	Unclear	High	High	Unclear	Low	Low	Low	Unclear

See supplementary file to support judgment.

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Figures

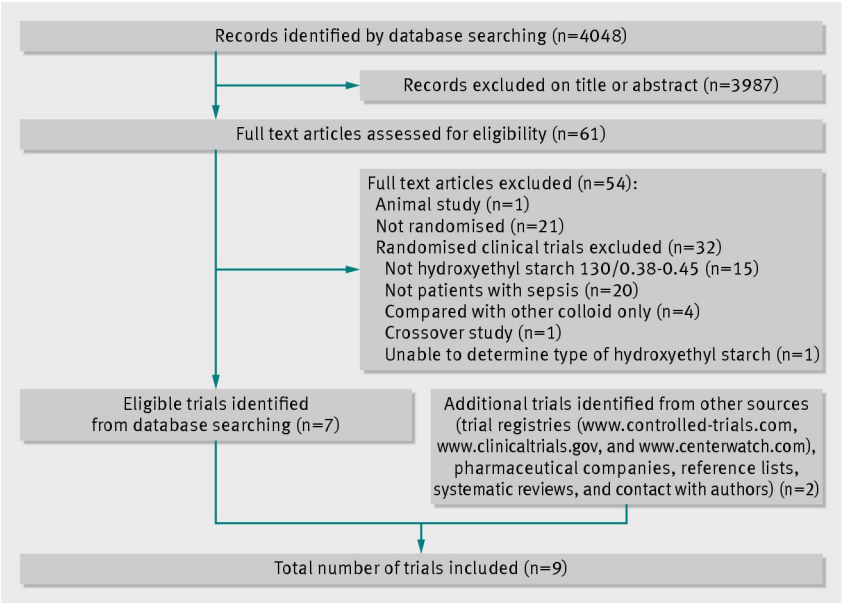

Fig 1 Flow of papers through review. Each of the 32 excluded randomised clinical trials may have more than one reason for exclusion

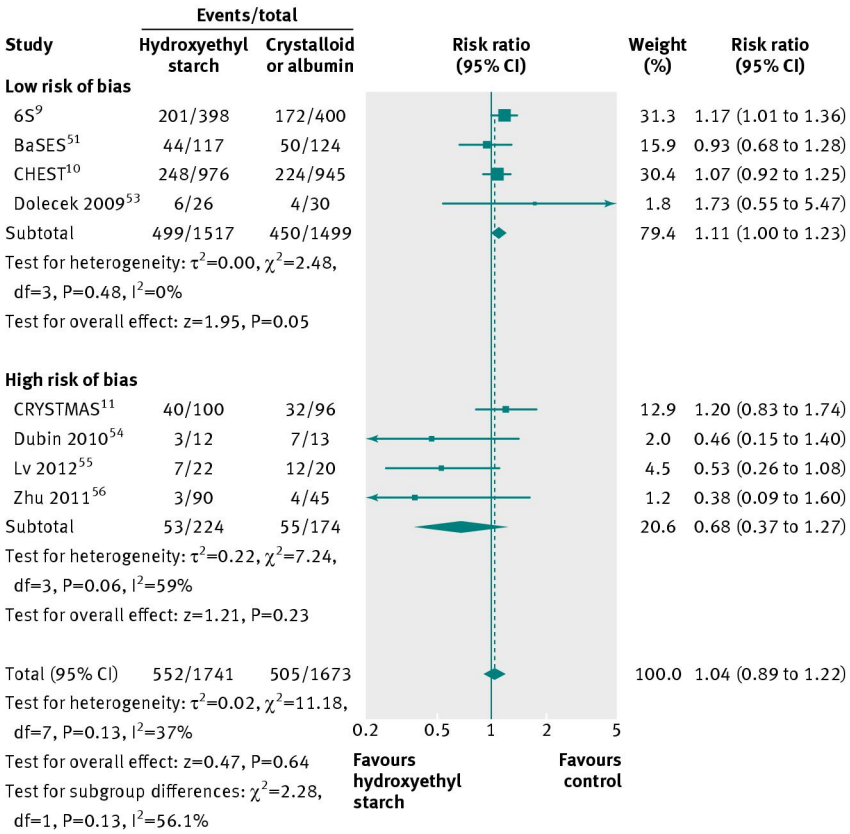

Fig 2 Forest plot of all cause mortality in relation to risk of bias in trials. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals

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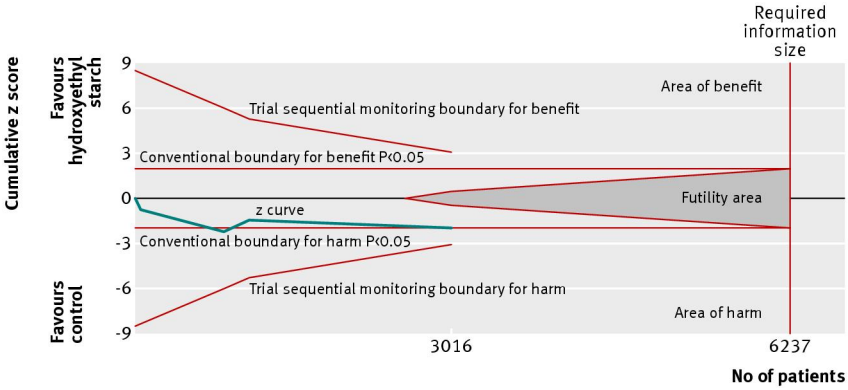

Fig 3 Trial sequential analysis of mortality in four trials with low risk of bias. A diversity adjusted information size of 6237 patients was calculated using α=0.05 (two sided), β=0.20 (power 80%), D^2=0%, an anticipated relative risk increase of 11%, and an event proportion of 30% in the control arm. The blue cumulative z curve was constructed using a random effects model

Study	Events/total: Hydroxyethyl starch	Events/total: Crystalloid or albumin	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
Low risk of bias					
6S[9]	87/398	65/400		64.4	1.35 (1.01 to 1.80)
BaSES[51]	28/117	23/124		22.2	1.29 (0.79 to 2.11)
CRYSTMAS[11]	21/100	11/96		11.2	1.83 (0.93 to 3.59)
Dolecek 2009[53]	0/26	0/30			Not estimable
Dubin 2010[54]	0/9	2/11		2.3	0.24 (0.01 to 4.44)
Total (95% CI)	136/650	101/661		100.0	1.36 (1.08 to 1.72)

Test for heterogeneity: χ^2=2.16, df=3, P=0.54, I^2=0%

Test for overall effect: z=2.61, P=0.009

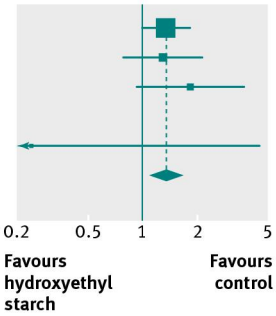

Fig 4 Forest plot of renal replacement therapy. Size of squares for risk ratio reflects weight of trial in pooled analyses. Horizontal bars represent 95% confidence intervals

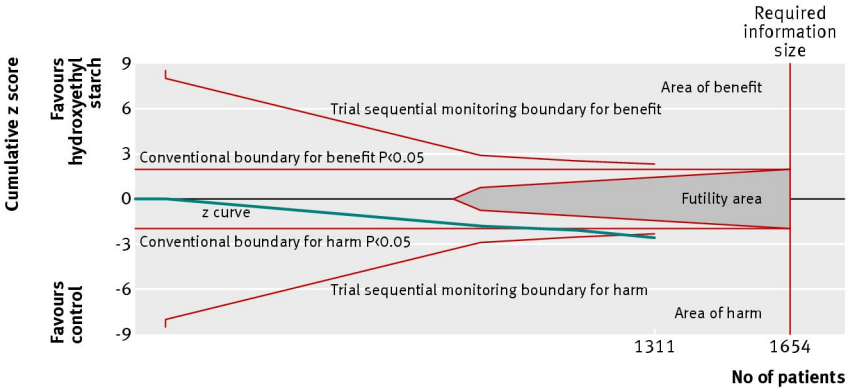

Fig 5 Trial sequential analysis of renal replacement therapy. A diversity adjusted information size of 1654 patients was calculated using α=0.05 (two sided), β=0.20 (power 80%), D^2=0%, an anticipated relative risk increase of 35% and an event proportion of 15% in the control arm. The blue cumulative z curve was constructed using a fixed effects model. Trials with no events were included in the analysis with an empirical continuity correction of 0.01

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