Hydroxyethyl starch 130 versus crystalloid and albumin for fluid resuscitation in septic patients: Effects on mortality, kidney function and hemostasis

Nicolai Haase, Louise Inkeri Hennings, Bo Lauridsen, Mik Wetterslev, Anders Perner, Jørn Wetterslev

Background
The mainstay treatment for intravascular volume depletion in critically ill patients is fluid resuscitation with either colloid or crystalloid solutions. Colloids are frequently used worldwide (Finfer 2010), but it is still debated whether these are superior to crystalloids. On one hand colloids are likely to result in faster circulatory stabilisation and potential decreased mortality, but on the other hand synthetic colloids in particular may result in adverse effects and thereby increased risk of death.

The hydroxyethyl starches (HES) are a group of synthetic colloids commonly used in practice which are produced with different molecular weights, degrees of hydroxyethylation (also called substitution ratio) and C2:C6 hydroxyethylation ratio. The pharmacinetic and -dynamic profiles of the HES molecules and thus the effect and side effect profile depend on all three parameters. So far, the use of HES in critically ill patients has not been proven to decrease mortality when compared to crystalloid solutions or other colloids (Perel 2007, Bunn 2008), but a potential benefit can still not be excluded. However, this potential beneficial effect of HES must be weighted against the risk of side effects, where kidney injury and coagulopathy are the main concerns.

Meta-analyses have shown increased risk of acute kidney failure in patients with severe sepsis who are resuscitated with high-molecular starches vs. other fluids (Wiedermann 2008; Dart 2010). However, these findings are based only on four randomised controlled trials of HES 200/0.5-0.6 (molecular weight in kDa / substitution ratio) with divergent results with respect to kidney failure (Boldt 1998, Schortgen 2001, Brunkhorst 2008, MacIntyre 2008) and with possible methodological weaknesses (Boldt 2001, Bracco 2008). Furthermore, two large cohort studies in intensive care patients showed divergent results with respect to the risk of adverse renal effects of starch treatment (Sakr 2007, Schortgen 2008).

HES is also associated with coagulopathy which might result in bleeding and increased rate of transfusion in critically ill patients. This effect appears to be more pronounced for solutions of higher molecular weight and molar substitution (Fenger-Eriksen 2005, Kozek-Langenecker 2008).

Due to the suspected adverse effects, the HES solutions with high molecular weight and high substitution ratio have been replaced by HES 130/0.4 which is believed to be the optimal HES-solution, and it is now the preferred colloid in Scandinavian ICUs (Perner 2008). It is possible that HES 130/0.4 has less impact on kidney function and hemostasis especially in septic patients or other critically ill patients, but this is still heavily debated (Reinhart 2010). To our knowledge there is no systematic review of septic patients assessing the effects and adverse effects of HES 130/0.4 compared to fluids that have none or minimal influence on the kidney function and hemostasis. Due to the widespread use of HES 130/0.4 such an analysis is needed.
In this review we would like to answer the following clinical question: What are the effects of hydroxyethyl starch 130/0.4 vs crystalloid or albumin on mortality, kidney function and bleeding in patients with sepsis?

**Objectives**
To assess the effects of hydroxyethyl starch 130/0.4 compared to any non-synthetic solution (crystalloid and albumin) for fluid resuscitation in septic patients.

**Methods**

**Criteria for considering studies for this review**

**Types of studies**
We will include randomized clinical trials of human subjects without consideration of publication status, blinding status or language. We will contact the investigators and the authors in order to retrieve relevant data.

We will include unpublished trials only if trial data and methodological descriptions can be provided either in written form or by direct contact with the authors.

We will include quasi randomised trials and large observational studies (n > 500) which report Serious Adverse Events as defined by the ICH-GCP guidelines (ICH Steering Commitee 1998). These studies will be evaluated for Serious Adverse Events, but not for benefits.

Crossover studies will be excluded due to the lack of a feasible and sufficient wash-out period in fluid management.

**Types of participants**
Patients with sepsis of all ages. If the septic patients constitute a subgroup of the randomised patients, the trial will be included only if its sample size is 500 or more. This is to ensure an equal distribution of known and unknown confounders between the two groups of septic patients.

In some publications, the authors may describe the patients as infected, but not specifically state that the patients were septic. However in such trials, if the authors of this review consider it very likely that all or most of the patients have sepsis (e.g. the infection leads to surgery or fluid resuscitation) the trial will be included as well.

Trials of animals or healthy human subjects will be excluded.

**Types of interventions**
HES 130/0.4 (molecular weight 130 kDa, molar substitution of 0.4 or 0.42) solution versus intravenous fluid therapy with crystalloid (i.e. saline or Ringer’s lactate/acetate/malate) or albumin. We will include studies with no regard to the indication for fluid therapy.

Trials comparing HES with blood products or synthetic solutions (dextrans, gelatin or HES solutions of another molecular weight) will be excluded.

**Types of outcome measures**
Primary outcomes
1.1 Overall mortality. We will use the maximal follow-up data from each trial.
1.2 Number of patients receiving renal replacement therapy at maximum length of follow-up.

Secondary outcomes
2.1 Number of patients receiving renal replacement therapy
2.2 Number of patients having author-defined acute kidney failure / injury
2.3 Number of patients receiving transfusion of red blood cells
2.4 Total volume of red blood cells transfused (ml or units)
2.5 Number of patients having a bleeding episode
2.6 Estimated blood loss
2.7 Number of patients having one or more serious adverse events

Search methods for identification of studies

Electronic searches
We will perform a systematic and sensitive search strategy to identify relevant randomized clinical trials with no language restrictions. The search will be conducted within six months of the date the draft is submitted for review.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (Ovid SP); EMBASE (Ovid SP); BIOSIS Previews (http://apps.isiknowledge.com.ep.fjernadgang.kb.dk); Science Citation Index Expanded (http://apps.isiknowledge.com.ep.fjernadgang.kb.dk) and Cumulative Index to Nursing & Allied Health Literature (CINAHL) (via EBSCO host).

Moreover, we will search for ongoing clinical trials and unpublished studies on the following Internet sites:

1. Current Controlled Trials;
2. ClinicalTrials.gov;
3. www.centerwatch.com;

The search will be limited to trials published in 1995 or later, since HES 130/0.4 was introduced in 1999. To our knowledge no other review of HES 130/0.4 has identified studies published before year 2000.

For specific information regarding our search strategies please see Appendices.

Searching other resources

We will handsearch the reference list of reviews, randomized and non-randomized studies, and editorials for additional studies. We will contact the main authors of studies and experts in this field to ask for any missed, unreported, or ongoing trials.

We will search the publication lists from the pharmaceutical companies which produce HES 130 (B Braun Medical, Baxter, Fresenius) for additional trials.

Data collection and analysis

Selection of studies
Two authors will independently screen the titles and abstracts identified by the literature search and exclude trials which are obviously not relevant. A detailed description of our search results will be provided.

The remaining trials will be evaluated in full text for eligibility, and the authors will provide detailed description of the included and excluded articles under the section "characteristics of studies".

**Data extraction and management**

Two persons will independently extract and collect the data on a standardized paper form. We will not be blinded to the author, institution, or the publication source of trials. We will approach all corresponding authors of the included trials for additional information on the review's outcomes measures and risks of bias components. For more specific information please see the section "Contributions of authors".

**Assessment of risk of bias in included studies**

The validity and design characteristics of each trial are evaluated. To draw conclusions about the overall risk of bias for an outcome it is necessary to evaluate the trials for major sources of bias also defined as *domains* (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance, bias due to vested financial interest and academic bias). The Cochrane Collaboration's recommended tool for assessing risk of bias is neither a scale nor a checklist but rather the *domain-based evaluation*. Any assessment of the overall risk of bias involves consideration of the relative importance of the different domains (Higgins 2008).

Even the most realistic assessment of the validity of a trial may involve subjectivity, since it is impossible to know the extent of bias (or even the true risk of bias) in a given trial. Some domains affect the risk of bias across outcomes in a trial; e.g., sequence generation and allocation sequence concealment, while others, such as blinding and incomplete outcome data, may have different risks of bias for different outcomes within a trial. Thus, the risk of bias is not the same for all outcomes in a trial. We will perform separate sensitivity analyses for each outcome (Higgins 2008).

We define the trials as having low risk of bias only if they adequately fulfil the criteria listed in the Cochrane Handbook by performing *summary assessments* of the risk of bias for each important outcome (across domains) within and across studies. We will apply a 'risk of bias graph' and a 'risk of bias summary' figure (Higgins 2008).

We will present results for all outcomes including adverse events in a summary of findings (SOF) table (Higgins 2008).

As there is no sufficiently well designed formal statistical method to combine the results of trials with high and low risk of bias, the major approach to incorporating risk of bias assessments in Cochrane reviews is to *restrict* meta-analyses to studies at low- (or lower) risk of bias (Higgins 2008). We will use the risk of bias (ROB) table described in the Cochrane Handbook section 8.5 (Higgins 2008) as a tool for assessing risk of bias in included studies. We will assess the risk of bias in the different domains as described below.

**Random sequence generation**
Low risk of bias: the method used generates random sequences, e.g., random number generation, toss of coin.
Unclear: no information on random sequence generation available.
High risk of bias: alternate medical record numbers or other non-random sequence generation.

**Allocation concealment**
Low risk of bias: allocation method prevents investigators or participants from knowing the next allocation, e.g., central allocation; sealed opaque envelopes; serially-numbered, sequentially-numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation.
High risk of bias: no information on allocation method available or the description did not allow a clear distinction.
Inadequate: allocation method allowed the investigators or participants to know the next allocation, e.g., alternate medical record numbers; reference to case record numbers or date of birth; an open allocation sequence, unsealed envelopes.

**Blinding**
Low risk of bias: we consider blinding as adequate if patients and personnel were kept unaware of intervention allocations after inclusion of participants into the study and the method of blinding involved placebo.
Unclear: blinding not described.
High risk of bias: not double blinded; categorized as an open-label study; or without use of placebo.

**Incomplete outcome data**
Low risk of bias: if the numbers and reasons for dropouts and withdrawals in the intervention groups were described or if it was specified that there were no dropouts or withdrawals.
Unclear: if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
High risk of bias: if the number or reasons for dropouts and withdrawals were not described.

**Selective outcome reporting**
Low risk of bias: if predefined or clinically relevant and reasonably expected outcomes are reported on.
Unclear: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.
High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.
Baseline imbalance
Low risk of bias: if there was no baseline imbalance in important characteristics.
Unclear: if the baseline characteristics were not reported.
High risk of bias: if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

Bias due to vested financial interest
Low risk of bias: the trial is not funded by an instrument, equipment or drug manufacturer.
Unclear: Conflicts of interest and founding sources are not stated.
High risk of bias: the trial is funded by a drug manufacturer.

Academic bias
Low risk of bias: The authors of the trial have not conducted previous trials addressing the same interventions.
Unclear: We will not be able to obtain any information on previous publications.
High risk of bias: The authors of the trial have conducted previous trials addressing the same interventions.

Measures of treatment effect
For dichotomous outcomes we will report relative risks (RR) with 95% confidence limits. For bleeding and renal replacement therapy at maximum length of follow-up, the Peto odds ratio (OR) will be calculated as well as the risk difference (RD) with 95% confidence limits and subsequently numbers needed to treat if possible. If a study reports mortality at more than one time point, we will use the mortality at the end of the study period only. Units or milliliters of blood transfused and estimated blood loss are continuous outcomes and the intervention effect will be reported as mean difference with 95% confidence limits.

Unit of analysis issues
Number of events in all binary meta-analyses. Units and milliliters of blood in the meta-analyses of blood transfused and estimated blood loss.

Dealing with missing data
We will contact all the first authors and contact persons of the trials with missing data in order to retrieve the relevant data. A modified Intention-to-treat (ITT) analysis will be performed including if possible all randomized patients.
ITT analysis is recommended in order to minimise bias in design, follow up and analysis of the efficacy of randomized clinical trials. It gives a pragmatic estimate of the benefit of a change in treatment policy rather than of potential benefit in patients who receive treatment exactly as planned (Hollis 1999). Full application of ITT is possible only when complete outcome data are available for all randomized participants. Despite the fact that about half of all published reports of randomized clinical trials state that ITT is used, handling of deviations from randomized allocation varies widely and many trials have
missing data on the primary outcome variable, and methods used to deal with this are generally inadequate, potentially leading to bias (Hollis 1999).

Performing an ITT analysis in a systematic review is not straightforward in practice since reviewers must decide how to handle missing outcome data in the contributing trials (Gamble 2005). No consensus exists about how missing data should be handled in ITT analyses, and different approaches may be appropriate in different situations (Higgins 2008; Hollis 1999).

In case of missing data, we will use a 'complete-case analysis' for our primary outcomes which simply excludes from the analysis all participants with the outcome missing. Additionally, we will conduct sensitivity analyses for our primary outcomes by applying sensitivity meta-analyses to the best and worst case scenarios. The best case scenario is: all patients lost to follow-up in the HES 130 group survived and all patients lost to follow-up in the other group died; all patients lost to follow-up in HES 130 group did not receive renal replacement therapy at maximum length of follow-up and all patients lost to follow-up in the other group did receive renal replacement therapy at maximum length of follow-up. The worst case scenario is: all patients lost to follow-up in the HES 130 group died and all patients lost to follow-up in the other group survived; all patients lost to follow-up in the HES 130 group received renal replacement therapy at maximum length of follow-up and all patients lost to follow-up in the other group did not receive renal replacement therapy at maximum length of follow-up.

Selective outcome reporting occurs when non-significant results are selectively withheld from publication (Chan 2004) and is defined as the selection on the basis of the results of a subset of the original variables recorded for inclusion in publication of trials. The most important types of selective outcome reporting are: selective omission of outcomes from reports; selective choice of data for an outcome; selective reporting of analyses using the same data; selective reporting of subsets of the data and selective under-reporting of data (Higgins 2008). Statistical methods to detect within-study selective reporting are still in their infant stage. We will explore for selective outcome reporting by comparing publications with their protocols if the latter are available.

Assessment of heterogeneity
The degree of heterogeneity observed in the results is quantified using diversity ($D^2$) (Wetterslev 2009) and inconsistency factor ($I^2$) statistics, which can be interpreted as the proportion of the total variation observed between the trials that is attributable to differences between trials rather than sampling error (chance) (Higgins 2002). $P \leq 0.10$ indicates significant heterogeneity, and $I^2$ with suggested thresholds for low (25% to 49%), moderate (50% to 74%), and high ($\geq$75%) values (Higgins 2003). If $I^2 = 0$, we will only report the results from the fixed-effect model. In the case of $I^2 > 0$ we will report the results from both the random-effects and the fixed-effect models. However, we believe that there is little value in using a fixed-effect model in cases of substantial heterogeneity which we suspect in this review due to inclusion of various patient types and outcome reporting. So we will emphasize the results from the random-effects model unless a few trials dominate the meta-analysis (eg. more than 50% of the cumulated fixed weight percentage). Additionally in case of $I^2 > 0$ (for the mortality and renal replacement therapy outcomes), we will seek to determine the cause of heterogeneity by performing meta-regression
analyses and relevant subgroup and sensitivity analyses. We aim to meta-analyse trial results only in case of low to moderate clinical heterogeneity.

**Assessment of reporting biases**

Publication bias occurs when the publication of research results depends on their nature and direction (Dickersin 1990). We examine this by providing funnel plots in order to detect either publication bias or a difference between smaller and larger studies ('small study effects') expressed by an asymmetry (Egger 1997). In case of asymmetry we will apply the "Arcsine-Thompson test" as proposed by Rücker (Rücker 2008).

Funding bias is defined as the biases in the design, outcome, and reporting of industry sponsored research in order to show that a drug shows a favourable outcome (Bekelman 2003). Relationships between industry, scientific investigators and academic institutions are widespread and often result in conflicts of interest (Bekelman 2003). We may conduct a sensitivity analysis in order to examine the role of funding bias if relevant (see 'Sensitivity analysis').

**Data synthesis**

We will use Review Manager software (RevMan 5.0) as statistical software. We will calculate the RR with 95% confidence intervals (CI) for dichotomous variables (binary outcomes). We will also calculate the risk difference (Keus 2009) but if the results are similar we will only report the RR. Additionally, we will calculate mean difference (MD, measure of absolute change) with 95% CI for continuous outcomes. We will use D² (Wetterslev 2009) and I² (Higgins 2002) to describe heterogeneity among the included trials. We will explore causes of substantial heterogeneity by meta-regression using Comprehensive Meta-Analysis (CMA version one) and Stata version nine. We will use the chi² test to provide an indication of heterogeneity between studies, with $P \leq 0.10$ considered significant.

Adverse effects may be rare but serious and hence important (Sutton 2002) when meta-analysis is applied for combining results from several trials with binary outcomes (i.e., event or no event). Most meta-analytic software packages do not include options for analysis including trials with 'zero event' in both arms (intervention versus control) when calculating RR. Exempting these trials from the calculation of RR and CI may lead to overestimation of a treatment effect as the control event proportion may be overestimated. Thus we will perform a sensitivity analysis by applying empirical continuity corrections to our zero event trials as proposed by Sweeting et al. (Keus 2009; Sweeting 2004) by applying an imaginary, small mortality in both arms.

Meta-analyses may result in type I errors due to sparse data and repeated significance testing when meta-analyses are updated with new trials (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). Systematic errors from trials with high-risk of bias, outcome reporting bias, publication bias, early stopping for benefit, and small trial bias may result in spurious P-values.

In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, group sequential monitoring boundaries (Lan 1983) are applied to decide whether a trial could be terminated early because of a sufficiently small P value, that is the cumulative Z-curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses as well, called trial sequential monitoring boundaries. In 'trial sequential
analysis' (TSA) the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to decide whether additional trials are needed (Wetterslev 2008). So far several meta-analysis and reviews have been published including an increasing number of trial results as new trials have been published (Perel 2007; Bunn 2008; Dart 2010). It therefore seems appropriate to adjust new meta-analysis for multiple testing on accumulating data to control the over-all type 1 error risk in cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008). The idea in TSA is that if the cumulative Z-curve crosses the boundary, a sufficient level of evidence is reached and no further trials may be needed. However, there is insufficient evidence to reach a conclusion if the Z-curve does not cross the boundary or does not surpass the required information size. To construct the trial sequential monitoring boundaries (TSMB) the required information size is needed and will be calculated as the least number of participants needed in a well-powered single trial (Brok 2008; Pogue 1998; Wetterslev 2008). We will adjust the required information size for heterogeneity with the diversity adjustment factor (Wetterslev 2009). We will apply TSA since it prevents an increase of the risk of type I error (< 5%) due to potential multiple updating and testing on accumulating data whenever new trial results are included in a cumulative meta-analysis (Pogue 1997; Pogue 1998) and provides us with important information in order to estimate the level of evidence of the experimental intervention (Pogue 1997; Pogue 1998; Thorlund 2009). Additionally, TSA provides important information regarding the need for additional trials and the required sample size herein (Wetterslev 2008; Wetterslev 2009). We will apply trial sequential monitoring boundaries according to an information size suggested by the trials with low-risk of bias (Wetterslev 2008; Wetterslev 2009) and an a priori 20% relative risk reduction (RRR) of SSI. As the frequency of patients with bleeding episodes and renal replacement therapy seems low in the trials conducted so far and hence the ability to detect small intervention effects low we will also perform a TSA with an information size estimated based on an a priori 35% RRR of mortality (Wetterslev 2008; Wetterslev 2009).

**Subgroup analysis and investigation of heterogeneity**

We plan to do the following subgroup analyses:

1. Comparing estimates of the pooled intervention effect in trials with low risk of bias to estimates from trials with high risk of bias (i.e., trials having at least one unclear or high-risk of bias component).
2. Comparing estimates of the pooled intervention effect in trials of septic patients to estimates from trials of infected patients that the authors of this review believe are very likely to be septic (see Types of participants).
3. Comparing estimates of the pooled intervention effect in trials comparing HES 130 vs. albumin to estimates from trials comparing HES 130 vs. a crystalloid.
4. Comparing estimates of the pooled intervention effect in trials of adult patients (>18 years old) to estimates from trials of children (<18 years old).
5. Comparing estimates of the pooled intervention effect in trials of surgical patients to estimates from trials of medical patients.
We will compare intervention effects in subgroups with test of interaction (Altman 2003). We consider P values < 0.05 indicative of significant interaction between HES 130's effect on mortality and subgroup category. (Higgins 2008, Chapters 9.6.1 and 9.7). Causes of moderate to high heterogeneity will be explored using meta-regression including the following covariates if possible: mean age of trial population at baseline, fraction of male patients, mean baseline SAPS II and SOFA-scores and fraction of surgical vs medical patients.

**Sensitivity analysis**

1. Assess the benefits and harms of HES 130 by conducting a continuity correction of trials with zero events.
2. Assess the benefits and harms of HES 130 when excluding data from the smallest or the largest trial.
3. Assess the benefits and harms of HES 130 when excluding data from trials only published as abstract.
4. Assess the benefits and harms of HES 130 when excluding data from trials with commercial funding.
5. Assess the benefits and harms of HES 130 when excluding trials published by Professor Joachim Boldt and his group.
6. Assess the benefits and harms of HES 130 when excluding trials that do not specifically state that the patients had sepsis.

We will calculate RR with 95% CI and apply a complete case analysis if possible for the sensitivity and subgroup analyses based on the primary outcomes of mortality and renal replacement therapy at maximum length of follow-up.

**Declarations of interest**

Anders Perner is sponsor-investigator of Scandinavian Starch for Severe Sepsis / Septic Shock (6S) Trial. Nicolai Haase and Jørn Wetterslev are members of the Steering Committee. B Braun Medical AG (Melsungen, Germany) delivers fluids for the trial, but were not able to influence the trial design, trial conduct and publication.

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**Altman 2003**

**Bekelman 2003**

**Boldt 1998**

**Boldt 2001**

Bracco 2008

Brok 2008

Brok 2009

Brunkhorst 2008

Bunn 2008

Chan 2004

Dart 2010

Dickersin 1990

Egger 1997

Fenger-Eriksen 2005

Finfer 2010

Gamble 2005

Higgins 2002

Higgins 2003

Higgins 2008

Hollis 1999

ICH Steering Commitee 1998

Keus 2009

Kozek-Langenecker 2008

Lan 1983

McIntyre 2008

Perel 2007

**Perner 2008**

**Pogue 1997**

**Pogue 1998**

**Reinhart 2010**

**RevMan 5.0**

**Rücker 2008**

**Sakr 2007**

**Schortgen 2001**

**Schortgen 2008**

**Sutton 2002**

**Sweeting 2004**

**Thorlund 2009**
**Wetterslev 2008**

**Wetterslev 2009**

**Wiedermann 2008**

**Appendices**

1 Data Extraction Form

**Hydroxyethyl Starch 130 versus crystalloid and albumin in infected patients: Effects on mortality, kidney function and hemostasis**

**Study Selection, Quality Assessment & Data Extraction Form**

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
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**Study eligibility**

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<th>RCT OR observational study &gt;500 patients</th>
<th>Relevant participants <em>Infected patients</em></th>
<th>Relevant interventions <em>HES 130/0.4 vs crystalloid or albumin</em></th>
<th>Relevant outcomes</th>
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<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No / Unclear</td>
<td>Yes / No* / Unclear</td>
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</table>

This issue relates to selective reporting when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in ‘Studies awaiting assessment’ until clarified. If no clarification is received after three attempts, study should then be excluded.

Do not proceed if any of the above answers are ‘No’. If study to be included in ‘Excluded studies’ section of the review, record below the information to be inserted into ‘Table of
excluded studies'.

Freehand space for comments on study design and treatment:

References to trial
Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one Study ID in RevMan.

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<tr>
<th>Code each paper</th>
<th>Author(s)</th>
<th>Journal/Conference Proceedings etc</th>
<th>Year</th>
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<tr>
<td>A</td>
<td>The paper listed above</td>
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Participants and Trial Characteristics

Single center ( ) Multicenter ( )

Country/contries: ____________________________________________

Population

Pediatric ( ) Adult ( )

Type of admission (%)
Medical _______ Surgical _______

Age:
HES-group: Mean: Median: IQR/range:
Other measures: Mean: Median: IQR/range:
Other group: Mean: Median: IQR/range:
Other measures: Mean: Median: IQR/range:
Total number of patients enrolled in the trial: ______________

Inclusion criteria clearly defined? Yes / No

Diagnosis
Sepsis ( )  Severe Sepsis ( )  Septic Shock ( )  Other infection: ____________________________

Other inclusion criteria:

Exclusion Criteria clearly defined? Yes / No

List exclusion criteria:

Baseline-score:
HES-group: Mean / median:  SD/IQR/range:
Other measures:
Other group: Mean / median:  SD/IQR/range:
Other measures:

Baseline-score II:
HES-group: Mean / median:  SD/IQR/range:
Other measures:
Other group: Mean / median:  SD/IQR/range:
Other measures:

Intervention

HES-product studied
Brand name: __________________
Degree of substitution / hydroxyethylation: __________________
C2:C6-ratio: __________________

Comparison fluid
Saline ( )  Ringer’s acetate ( )  Ringer’s lactate ( )
Albumin 5% ( )  Albumin 10% ( )  Albumin 20% ( )
Third group
Type of fluid:

Defined maximum dose of trial fluid: _________ / Max. dose not defined.

Volume of fluid given (mean, min, max, SD etc.)
HES 130-group: __________
Comparison group: __________
Ratio: ________________________

Other colloids given during study period
Human albumin ( )
Other: _______________________
Comments:

Where did the treatment take place?
Emergency department ( )
Operating room ( )
Elsewhere ( )
Intensive Care Unit ( )
High-dependency unit e.g. post-OP ( )
Duration of treatment: ______________________________

Follow-up and reporting

HES 130 group
Number of patients in this group: __________
How many patients received the intended intervention (per-protocol population)?
________________
How many patients were analysed? ___________________

Comparison group
Number of patients in this group: __________
How many patients received the intended intervention (per-protocol population)?
________________
How many patients were analysed? ___________________

Length of follow-up (median or range) reported in this paper
________________________ hours / days / weeks / years    Not stated ( )

Time points reported in the trial:
______________________________
Time points that we use in RevMan:

Methodological quality

| Random sequence generation | Low risk of bias: the method used generates random sequences, e.g., random number generation, toss of coin. | Low risk |
| High risk of bias: alternate medical record numbers or other non-random sequence generation. | High risk |
| Unclear: no information on random sequence generation available | Unclear |

| Concealment of allocation | Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding |
| Low risk of bias: allocation method prevents investigators or participants from knowing the next allocation, e.g., central allocation; sealed opaque envelopes; serially-numbered, sequentially-numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation. | Low risk |
| High risk of bias: no information on allocation method available or the description did not allow a clear distinction. | High risk |
| Inadequate: allocation method allowed the investigators or participants to know the next allocation, e.g., alternate medical record numbers; reference to case record numbers or date of birth; an open allocation sequence, unsealed envelopes. | Inadequate |

| Blinding | Low risk of bias: we consider blinding as adequate if patients and personnel were kept unaware of intervention allocations after inclusion of participants into the study and the method of blinding involved placebo | Low risk |
| High risk of bias: not double blinded; categorized as an open-label study; or without use of placebo. | High risk |
| Unclear: blinding not described. | Unclear |

| Incomplete outcome data | Low risk of bias, if the numbers and reasons for dropouts and withdrawals in the intervention groups were described or if it was specified that there were no dropouts or withdrawals | Low risk |
| High risk of bias, if the number or reasons for dropouts and withdrawals were not described | High risk |
| Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated | Unclear |

### Selective outcome reporting

| Low risk of bias, if predefined or clinically relevant and reasonably expected outcomes are reported on | Low risk |
| High risk of bias, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded | High risk |
| Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not | Unclear |

### Baseline imbalance

| Low risk of bias, if there was no baseline imbalance in important characteristics | Low risk |
| High risk of bias, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation | High risk |
| Unclear, if the baseline characteristics were not reported | Unclear |

### Bias due to vested financial interest

| Low risk of bias: the trial is not funded by an instrument, equipment or drug manufacturer. | Low risk |
| High risk of bias: the trial is funded by a drug manufacturer. | High risk |
| Unclear: Conflicts of interest and founding sources are not stated. | Unclear |

### Academic bias

| Low risk of bias: The authors of the trial have not conducted previous trials addressing the same interventions. | Low risk |
| High risk of bias: The authors of the trial have conducted previous trials addressing the same interventions. | High risk |
| Unclear: We will not be able to obtain any information on previous publications. | Unclear |

### Modified intention-to-treat

A intention-to-treat analysis is one in which all the participants in a trial being randomized are analysed according to the intervention to which they were allocated, whether they received it or not. A modified intention-to-treat analysis, however, is one in which the patients that did not fullfil the inclusion or had one or more exclusion criteria fulfilled and did not receive intervention is excluded from the analysis.
Analysed as modified ‘intention-to-treat’

<table>
<thead>
<tr>
<th>Available for the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes / No</td>
</tr>
</tbody>
</table>

Were withdrawals described?  Yes  No  not clear

Discuss if appropriate

Data Extraction

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Available for the trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 Overall mortality</td>
<td>Yes / No</td>
</tr>
<tr>
<td>1.2 Number of patients receiving renal replacement therapy at maximum length of follow-up</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.1 Number of patients receiving renal replacement therapy at any time during the trial</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.2 Number of patients having author-defined kidney failure / injury</td>
<td>Yes / No</td>
</tr>
<tr>
<td>How did the authors define kidney failure?</td>
<td></td>
</tr>
<tr>
<td>2.3 Number of patients receiving transfusion with red blood cells</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.4 Total volume of red blood cells transfused (ml or units)</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.5 Number of patients having a bleeding episode</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.6 Estimated blood loss</td>
<td>Yes / No</td>
</tr>
<tr>
<td>2.7 Number of patients having one or more serious adverse events. We have defined serious adverse events according to the International Conference on Harmonisation (ICH) Guidelines (ICH 1997) as &quot;any event that leads to death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability, and any important medical event, which may jeopardise the patient or requires intervention to prevent it&quot;. All other adverse events are considered non-serious.</td>
<td>Yes / No</td>
</tr>
</tbody>
</table>

For Continuous data

<table>
<thead>
<tr>
<th>Code of paper Eg. A, B etc</th>
<th>Outcomes</th>
<th>Unit of measurement (circle appropriate)</th>
<th>HES group</th>
<th>Other group</th>
<th>Details if outcome only described in text</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.4 Total volume of red blood cells transfused</td>
<td>Units / ml</td>
<td>n Mean (SD)</td>
<td>n Mean (SD)</td>
<td></td>
</tr>
</tbody>
</table>
2.6 Estimated Blood Loss ml

For Dichotomous data

<table>
<thead>
<tr>
<th>Code of paper</th>
<th>Outcomes</th>
<th>HES group E/N</th>
<th>Other group E/N</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E = number of events</td>
<td>E=number of events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = number of participants</td>
<td>n = number of participants</td>
</tr>
<tr>
<td>1.1 Overall mortality.</td>
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<td></td>
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<tr>
<td>1.2 Number of patients receiving renal replacement therapy at maximum length of follow-up.</td>
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</tbody>
</table>

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general, if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

Freehand space for writing actions such as contact with study authors and changes
References to other trials

<table>
<thead>
<tr>
<th>First author</th>
<th>Journal / Conference</th>
<th>Year of publication</th>
</tr>
</thead>
<tbody>
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<td></td>
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</tr>
</tbody>
</table>

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details

2 Search Strategy

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4, 2010) in The Cochrane Library

#1 MeSH descriptor Hetastarch explode all trees

#2 ((hydroxyet*yl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)

#3 (#1 OR #2)

MEDLINE (Ovid SP)(1950 to January 2011)

1. ((hydroxyet*yl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

2. exp Hetastarch/

3. 1 or 2

4. limit 3 to humans

EMBASE (Ovid SP)(1980 to January 2011)
1. exp HETASTARCH/
2. ((hydroxyethyl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]
3. 1 or 2
4. limit 3 to human

Science Citation Index Expanded
(http://apps.isiknowledge.com.ep.fjernadgang.kb.dk)(1900 to January 2011)
# 1 TS=((hydroxyethyl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)

# 3: #2 OR #1
# 2: TI=((hydroxyethyl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra) AND Taxa Notes=(Humans)
# 1: TS=((hydroxyethyl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra) AND Taxa Notes=(Humans)

CINAHL (EBSCO host)(1981 to January 2011)
S3 S1 or S2
S2 TX ((hydroxyethyl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)
S1 MM hydroxyethyl starch