Fluid resuscitation with 6% hydroxyethyl starch (130/0.4) in acutely ill patients: an updated systematic review and meta-analysis


CRD summary
The authors concluded that the published trials were of poor quality and there was not enough data to reliably estimate the benefits and risks of 6% hydroxyethyl starch 130/0.4, for fluid resuscitation in acutely ill adults. It appears that the authors' conclusions are justified and likely to be reliable.

Authors' objectives
To compare the patient-centred outcomes for acutely ill adults receiving 6% hydroxyethyl starch (hetastarch) 130/0.4 versus other colloid or crystalloid solutions, for fluid resuscitation.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and mRCT were searched, without language restrictions, to December, 2010. Search terms were reported in an appendix. Reference lists of published reviews were handsearched for additional studies; contact was made with experts to locate unpublished studies.

Study selection
Eligible studies were randomised controlled trials (RCTs) of resuscitation fluids for patients over 18 years old, who were acutely ill or undergoing major surgery. Trials had to be conducted in hospital or pre-hospital clinical settings, with at least one intervention group receiving 6% hetastarch 130/0.4 in any carrier solution, and the control group receiving another colloid or any type of crystalloid solution. Eligible outcomes included mortality, the need for renal replacement therapy, urine output, red blood cell transfusion, and estimated or measured blood loss.

Most included trials recruited patients who had undergone various types of major surgery. A few studies recruited patients in intensive care who had septic shock, hypovolaemia, severe sepsis or traumatic brain injury. The mean daily cumulative exposure of intervention patients to hetastarch ranged from less than one to over three litres, where reported. Almost half of the trials reported that comparators were other hetastarch formulations; a quarter had at least one crystalloid control group.

Two reviewers independently selected trials for inclusion.

Assessment of study quality
The risk of bias was assessed for randomisation, allocation concealment, blinding, intention-to-treat analysis, and loss of follow-up. The overall risk of bias was assessed as low, intermediate, or high. Further details were reported in the paper.

Two reviewers independently assessed trial quality; disagreements were resolved by consensus or referral to a third reviewer.

Data extraction
The number of deaths in treatment and control groups was extracted to calculate risk ratios, with 95% confidence intervals. Two reviewers independently extracted the data; disagreements were resolved by consensus or referral to a third reviewer.

Methods of synthesis
Risk ratios and 95% confidence intervals were pooled using a random-effects model. Statistical heterogeneity was assessed using $I^2$. Trials with no deaths were excluded from the meta-analysis; for those with no deaths in one of the groups, a value of 0.5 was added to each cell of the 2x2 table. Where trials had multiple control groups, preference was given to a crystalloid control, then another class of colloid, and lastly another hetastarch formulation.
The pre-specified subgroup analyses were the setting (intensive care unit versus other) and the control (crystalloid, non-hetastarch colloid, or other hetastarch solution). A sensitivity analysis including 11 retracted trials was performed.

**Results of the review**
Twenty-five RCTs were included in the review, with 1,608 patients. Eight trials had an intermediate risk of bias for all domains except blinding, and the other 17 trials had a high overall risk of bias.

Sixteen trials, with 1,184 patients, reported mortality. A non-significant difference in mortality was found for 6% hetastarch 130/0.4 groups, compared with control groups (RR 0.95, 95% CI 0.64 to 1.42; I²=0). This difference in risk remained non-significant when the 11 retracted trials were included (RR 0.92, 95% CI 0.63 to 1.34; I²=0).

The subgroup data could not be meta-analysed as there was too much variety in comparators and too few trials in intensive care units.

Four (16%) of the 25 trials reported renal replacement therapy events, with more events with gelatin or albumin than with hetastarch, in two trials, and equal events in the other two. Twenty studies (80%) reported red blood cell transfusions, and 18 (72%) reported bleeding, with a lot of variation in reporting (details not given).

**Authors’ conclusions**
The published trials were of poor quality and there was not enough data to reliably estimate the benefits and risks of 6% hydroxyethyl starch 130/0.4, compared with other fluid resuscitation.

**CRD commentary**
The review question was clear and supported by replicable inclusion criteria. Relevant databases were accessed and attempts were made to locate grey literature to avoid publication bias. No language restrictions were imposed, minimising the risk of language bias. Efforts were made to reduce reviewer error and bias in study selection, data extraction and quality assessment. The criteria for quality assessment seem to have been appropriate, but most trials had a high overall risk of bias. The trial characteristics were presented and the methods of synthesis seem to have been appropriate. The authors acknowledged that most data were not suitable for meta-analysis.

Given the poor quality of the included trials and scarcity of data, it appears that the authors’ conclusions are justified and reliable.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that the retraction of a number of trials highlighted the need for high-quality RCTs to determine the safety and efficacy of 6% hetastarch 130/0.4 particularly for critically ill patients. Given its widespread use, high-quality trials, with large numbers of events, were required urgently.

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