Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis

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CRD summary
After excluding seven trials by an investigator whose research was retracted due to scientific misconduct, this review concluded that, in critically ill patients who required acute volume resuscitation, hydroxyethyl starch was associated with significantly increased mortality and risk of acute kidney injury. The review was generally well conducted and the authors' conclusions are likely to be reliable.

Authors' objectives
To compare the efficacy and safety of hydroxyethyl starch, with that of other intravenous fluids, for acute fluid resuscitation in critically ill patients.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Global Health, HealthSTAR, Scopus, Web of Science, and ICTRP were searched for articles from their inception to October 2012. The search strategy was reported in an appendix. It seems that there were no language restrictions. The reference lists of reviews and included studies, and the conference proceedings, from seven organisations, for the preceding five years, were searched.

Study selection
Randomised controlled trials (RCTs) of critically ill adults (18 years or older), who required acute volume resuscitation and were treated in an emergency or intensive care setting, were eligible. Trials had to compare a hydroxyethyl starch solution with either a crystalloid solution, albumin, dextran, or gelatin. The incidences of death and renal injury were the primary outcomes.

Populations varied, but in most of the included trials the patients had sepsis, or had suffered a trauma. The mean patient age ranged from 28 to 79 years, and 61% of patients were men. The doses of hydroxyethyl starch varied across trials. Most trials had crystalloid or albumin as the comparator. Trials were published between 1982 and 2012.

Two reviewers independently selected trials for inclusion, with disagreements resolved by a third reviewer.

Assessment of study quality
Trial quality was assessed, using the Cochrane risk of bias tool, for the risk of bias in randomisation, allocation concealment, blinding of patients and personnel, blinding of outcome assessors, completeness of outcome data, selective outcome reporting, and other sources. The strength of the evidence was classified using the GRADE system.

The authors did not state how many reviewers assessed quality.

Data extraction
Data were extracted to calculate mean differences, standardised mean differences, risk ratios, absolute risks, or Peto odds ratios, with 95% confidence intervals. Two reviewers independently extracted these data, with disagreements resolved by a third reviewer.

Methods of synthesis
Meta-analyses were performed to calculate the pooled Peto odds ratios using a fixed-effect model; a random-effects model was used for the other effect estimates. Heterogeneity was assessed with $I^2$, with 95% uncertainty intervals.

A number of sensitivity, subgroup, and meta-regression analyses were undertaken, for all analyses where $I^2$ was over 50%. These included excluding trials by an author whose trials had been retracted. Publication bias was assessed in funnel plots, the Begg rank test, and the Egger regression test.
Results of the review
Thirty-eight RCTs (11,005 participants) were included. Sample sizes ranged from 12 to 7,000 participants. Most trials had an unclear or high risk of bias; three had a low risk of bias. The bias assessment results for individual trials were not reported.

Mortality: The risk ratio associated with hydroxyethyl starch was 1.06 (95% CI 1.00 to 1.13; 35 RCTs; I²=0) and the absolute risk was 1.20% (95% CI -0.26 to 2.66) in favour of the comparator; the strength of the evidence was low. Seven trials by one author who had had their research retracted, were removed – there was a statistically significant increase in mortality with hydroxyethyl starch (RR 1.09, 95% CI 1.02 to 1.17; 28 RCTs; I²=0; AR 1.51%, 95% CI 0.02 to 3.00); the strength of the evidence was moderate. These seven trials were a cause of heterogeneity and were removed from all subsequent analyses.

Other outcomes: Hydroxyethyl starch was significantly associated with an increased risk of receiving renal replacement therapy (RR 1.32, 95% CI 1.15 to 1.50; nine RCTs; I²=0; AR 3.12%, 95% CI 0.47 to 5.78), a higher incidence of red blood cell transfusion (RR 1.42, 95% CI 1.15 to 1.75; five RCTs; I²=0), and a reduction in urine output (SMD -0.15, 95% CI -0.19 to -0.10; 10 RCTs; I²=0). No significant differences were found between groups for intensive care length of stay (five RCTs), overall length of stay (six RCTs), and mean ventilation days (three RCTs).

Subgroup, sensitivity and meta-regression analyses showed no major differences from the overall results. There was no evidence of publication bias.

Authors’ conclusions
In critically ill patients who required acute volume resuscitation, hydroxyethyl starch, compared with other solutions, did not decrease mortality, and after excluding seven trials by an investigator whose research was retracted due to scientific misconduct, it was associated with significantly increased mortality and risk of acute kidney injury.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. Thorough attempts were made, using a variety of sources, to identify all relevant trials in any language. Duplicate processes were used to reduce the risks of reviewer error and bias in trial selection and data extraction, but the authors did not report such methods for the assessment of risk of bias. The risk of bias assessment results were not presented for individual trials, but they were used in interpreting the pooled results. Adequate trial details were provided. Appropriate methods were used to pool the data and to assess and investigate heterogeneity.

The review was generally well conducted and the authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that the use of hydroxyethyl starch for acute volume resuscitation was not recommended due to serious safety concerns. They noted that in light of the retracted studies, guidelines were being revised.

Research: The authors noted that two trials of hydroxyethyl starch were being conducted.

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