Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: a meta-analysis

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CRD summary
This review evaluated the safety of haemoglobin-based blood substitutes (HbBS) in surgical, trauma and stroke patients. The authors concluded that HbBS are associated with statistically significant increases in risk of mortality and myocardial infarction. Overall, this was a well-conducted review and the conclusions reliably reflect the evidence presented.

Authors' objectives
To evaluate the safety of haemoglobin-based blood substitutes (HbBS).

Searching
PubMed, EMBASE and the Cochrane Library were searched from 1980 to 25 March 2008 to identify relevant studies published in English; the search terms were reported. Additional data (including unpublished material) were sought from the U.S. Food and Drug Administration, from product manufacturers, and in press releases obtained via the Internet.

Study selection
Randomised controlled trials involving surgical, stroke and trauma patients receiving HbBS, and evaluating the effect on death or myocardial infarction (MI), were eligible for inclusion. Studies of healthy volunteers, or those aged under 19 years, were excluded. The majority of included patients were from trauma or other surgical specialities. The median study duration (where data were available) was 4 years (range: 1 to 6). Five different products with a range of doses were included in the review: PolyHeme, HemeAssist, Hemolink, Hemopure and Hemospan. The names of the manufacturers were reported. The $P_{50}$ values (partial pressure of oxygen required for 50% haemoglobin saturation) ranged from 10 mmHg of oxygen (highest affinity) to 38 mmHg (lowest affinity). The proportion of haemoglobin tetramer ranged from less than 1 to 100%. Control groups received various interventions including saline, red blood cells and plasma expanders.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Two independent reviewers extracted data on blinding. A third reviewer was consulted in the event of discrepancies.

Data extraction
Data were extracted in order to calculate the relative risk (RR). Amongst the descriptive data, the reviewers also collected information on control group therapy and trial enrolment dates. Summary counts of total event rates (without adjustment for length of follow-up) were collected for calculation of the number-needed-to-harm (NNH).

Two independent reviewers performed the data extraction. Intention-to-treat data were used, where possible. A third reviewer was consulted in the event of discrepancies.

Methods of synthesis
Pooled estimates of the RRs for mortality and MI, with 95% confidence intervals (CIs), were calculated using the Cochran-Mantel-Haenszel test in a fixed-effect model (R package metabin, http://www.r-project.org; accessed 05/09/08), and weighted by the inverse variance. Between-study heterogeneity in outcome measures was assessed using the Breslow-Day test and associated $I^2$ statistic. Cumulative meta-analyses (fixed-effect) for these outcomes were also performed for each year that studies were completed, published, or made public. Subgroup analyses for mortality and MI were carried out in terms of clinical indication and product, tetramer content, $P_{50}$ and publication status. Differences
between the subgroups were tested using a decomposed Breslow-Day test. Missing data were treated separately in a non-survival analysis.

**Results of the review**
Sixteen trials (n=3,711) were included in the review.

Four trials were double-blind (n=691), seven were single-blind (n=628), four were open-label or unblinded (n=934) and the blinding status of one was not reported (n=1,458). The overall test for heterogeneity was not significant for mortality or MI.

HbBS were associated with statistically significant increases in risk of death (164 deaths in the HbBS group compared with 123 in the control groups; RR 1.30, 95% CI: 1.05, 1.61) and risk of MI (59 MIs in the HbBS group and 16 in the control groups; RR 2.71, 95% CI: 1.67, 4.40). The NNH was 62 for treatment-related death and 50 for treatment-related MI. The subgroup analysis suggested that the increased risk was unrelated to a particular HbBS, clinical indication, or when missing data were dealt with as separate analyses. Cumulative meta-analyses suggested increases in RRs for both mortality and MI until the year 2000.

**Authors' conclusions**
HbBS demonstrate statistically significant increases in mortality and MI risks. These risks appear to be consistently higher, regardless of patient population or product type.

**CRD commentary**
This review was based on a clear research question and was supported by well-defined inclusion criteria. Relevant data sources were searched and attempts were made to retrieve unpublished material. However, the restriction to English language articles means that language bias is a possibility. There was limited assessment of the validity of included studies. However, the restriction to inclusion of randomised controlled trials and the incidence of blinding adds strength to the findings. Adequate study details were provided, and the method of synthesis was appropriate given the absence of heterogeneity. The review process was conducted largely with transparency, although it is not clear how the studies were selected for inclusion. The lead author disclosed previous financial interests connected with the manufacturers of the products under evaluation. Overall, this was a well-conducted review and the conclusions reliably reflect the evidence presented.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that the known toxicities of HbBS should be tested as pre-clinical trials in animal models prior to being authorised for clinical trials. This review also highlighted the urgency of prompt reporting of clinical trial data.

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