Treatment of anaemia in patients with heart disease. A systematic review

Kansagara D, Dyer E, Englander H, Freeman M, Kagen D

CRD summary
This review evaluated the benefits and harms of treatments for anaemia in adults with heart disease. The authors concluded that there was no consistent evidence that anaemia correction improves outcomes in patients with heart disease but there were some exceptions. This was a well-conducted review. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

Authors’ objectives
To evaluate the benefits and harms of treatments for anaemia in adults with heart disease.

Searching
EMBASE was searched to November 2010. MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Database of Systematic Reviews were searched to August 2012. Search terms and a detailed search strategy were reported. Additional articles were retrieved from systematic reviews, reference lists of relevant studies, other reviews and editorials, and by contacting experts. Ongoing and recently completed studies were sought from ClinicalTrials.gov up to April 2013. Papers written in English were included.

Study selection
Eligible studies were trials of blood transfusions, iron or erythropoiesis-stimulating agents (ESAs) that reported separately on adults with anaemia (haemoglobin levels <13g/dL in men and <12g/dL in women), symptomatic congestive heart failure (with or without decreased systolic function) or coronary heart disease (acute coronary syndrome, postacute coronary syndrome, history of myocardial infarction or angina). Comparators of interest were placebo or studies of more versus less intensive interventions (different transfusion thresholds or haemoglobin targets). Outcomes of interest included mortality, hospitalisation, exercise tolerance, cardiovascular events, quality of life and adverse effects of treatments.

In addition to trials, observational studies of red blood cell transfusion were included. The included studies were conducted in non-operative and perioperative settings. Patients were characterised by various conditions or procedures, including critical illness, acute coronary syndrome, myocardial infarction (MI), decompensated heart failure, with or without known heart disease, percutaneous coronary intervention or vascular surgery, and sustained hip fracture.

Two reviewers independently selected the studies. Disagreements were resolved by consensus.

Assessment of study quality
The authors used the Cochrane Collaboration tool to assess trials as being at low, high or unclear risk of bias. The overall quality of the evidence (low, moderate or high) was assessed for each outcome using criteria from the GRADE working group. Observational studies were assessed using adapted checklists and no overall summary assessment was calculated.

Two reviewers independently assessed study quality. Disagreements were resolved by discussion.

Data extraction
Data were extracted to enable the calculation of odds ratios, relative risks or mean differences), together with 95% confidence intervals).

It appeared that more than one reviewer extracted data. Authors were contacted for further information, where necessary.

Methods of synthesis
Where possible, results were statistically pooled in random-effects meta-analyses, and 95% confidence intervals were reported. Results were stratified by patient setting (non-operative or pre-operative). Where meta-analysis was not
possible, a narrative synthesis was reported. Sensitivity analyses were conducted according to the definition of short-term mortality and for all outcomes excluding studies with high or unclear risk of bias. Subgroup analyses were conducted according to medical condition of the patient. Statistical heterogeneity was assessed with the Cochrane Q test and the I² statistic.

**Results of the review**

Fifty-two studies were included in the review.

**Blood transfusions:** There were six trials (1,757 participants) with low-strength evidence and 26 observational studies (988,277 participants).

Overall, trials of liberal transfusion protocols did not significantly reduce 30-day mortality rates compared with less aggressive protocols (six trials; I²=16.8%). More aggressive transfusion protocols were associated with lower risk for cardiovascular events but the difference was not statistically significant (five trials; I²=0%).

In the non-operative setting, low-strength evidence from three trials and 23 observational studies suggested that more aggressive transfusion did not decrease mortality rates for patients who were critically ill with heart disease or those with acute coronary syndrome.

In the perioperative setting, low-strength evidence from three trials in hip fracture and vascular surgery patients with heart disease suggested no short-term difference in mortality between liberal and conservative transfusion strategies. Fewer cardiovascular events occurred with more aggressive use of transfusions in the perioperative setting. Trial evidence suggested that the risk of in-hospital myocardial infarction was significantly lower in a subgroup of patients with cardiovascular disease who received an aggressive transfusion (RR 0.50, 95% CI 0.27 to 0.91; 1,297 patients).

Full results from non-operative and perioperative settings were reported in the paper. Reporting of adverse transfusion reactions was sparse.

**Iron:** There were three trials (534 participants) with moderate-strength evidence.

Overall, intravenous iron improved exercise tolerance (improvements in Patient Global Assessment OR 2.51, 95% CI 1.75 to 3.61 and New York Heart Association functional class OR 2.40, 95% CI 1.55 to 3.71) and quality of life and there were significantly fewer cardiovascular events in patients with heart failure (27.6%) than the control group (50.2%). Mortality rates were similar between groups. Results were driven by one large trial (459 participants). Serious adverse events were infrequent and not significantly different between study groups.

**ESAs:** There were 17 trials (3,503 participants) with moderate- to high-strength evidence.

In studies with low risk of bias, ESAs did not result in any beneficial effect on mortality rates, cardiovascular events or hospitalisations. Moderate strength evidence showed that ESAs did not consistently improve quality of life.

A statistically significant association was found between ESAs and an increased risk of venous thromboembolism (RR 1.36, 95% CI 1.17 to 1.58; four trials; I²=0%). A significantly higher function score (New York Heart Association) was found in patients with congestive heart failure treated with ESAs (WMD -0.77, 95% CI -1.21 to -0.32; nine trials; I²=96%).

Further results were reported in the paper.

**Authors' conclusions**

There was no consistent evidence that anaemia correction improved outcomes in patients with heart disease but there were some exceptions. Higher transfusion thresholds did not consistently improve mortality rates. Intravenous iron may help to alleviate symptoms in patients with heart failure and iron deficiency. Erythropoiesis-stimulating agents did not seem to benefit patients with mild to moderate anaemia and heart disease and may be associated with serious harms.

**CRD commentary**

The review question was clear. Inclusion criteria were sufficiently detailed to enable replication. The search strategy

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was wide-reaching and consideration was given to on-going studies. Language restrictions may mean that some relevant studies were overlooked. The review process was conducted with adequate attempts to minimise error and bias. Appropriate quality assessment tools were applied and the results were summarised clearly. Study details were reported extensively and the chosen methods of synthesis seemed appropriate.

This was a well-conducted review. The authors' conclusions reflect the evidence presented and are likely to be reliable.

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

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

**Research:** The authors stated that larger trials were needed to evaluate the impact of higher blood transfusion thresholds in patients with heart disease on mortality rates. Further studies should investigate the role of intravenous iron in patients with heart failure and iron deficiency. It would also be helpful to clarify the role of ESAs in patients with preserved systolic function or those with coronary heart disease only.

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