Erythropoietin to minimize perioperative blood transfusion: a systematic review of randomized trials
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Authors' objectives
To determine the efficacy and side-effects of erythropoietin, given with or without autologous predonation, to patients undergoing orthopaedic or cardiac surgery.

Searching
MEDLINE was searched from 1985 to January 1997 to identify all articles with erythropoietin as a textword. EMBASE was also searched. Janssen -Ortho Inc Canada was asked to identify all relevant articles or reports. Full publications, abstracts or letters to the editor were included. No language restrictions were applied. Reference lists of retrieved studies were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that evaluated the efficacy of erythropoietin for minimizing perioperative blood loss were included if they reported the primary outcome. Articles described as randomised but in which the clinician could have been aware of the treatment allocation were excluded as were duplicate studies, and studies where randomisation was done postoperatively.

Specific interventions included in the review
Erythropoietin was given pre-operatively either intravenously or subcutaneously. Total dose ranged from 300 to 6400U/kg intravenously and from 400 to 4500 U/kg subcutaneously. The first dose of erythropoietin was given between 35 and 5 days pre-operatively. Erythropoietin was given alone or to augment autologous blood donation. Co-interventions included iron given orally or intravenously.

Participants included in the review
Patients were undergoing either elective cardiac or elective orthopaedic surgery. Children were excluded.

Outcomes assessed in the review
The primary outcome was the proportion of patients receiving at least one unit of allogeneic packed red blood cells. A secondary outcome was the mean number of units transfused.

How were decisions on the relevance of primary studies made?
Titles and abstracts were examined.

Assessment of study quality
Validity was assessed using the Jadad scale which evaluates the following: process of randomisation; double blinding; and description of withdrawals. Scores from the Jadad scale range from 0 (worst score) to 5 (best score). Validity was assessed by two reviewers independently with disagreements being resolved by consensus.

Data extraction
Data were independently extracted onto study data forms by two reviewers with disagreements being resolved by consensus. Where necessary, authors were contacted for clarification.

Methods of synthesis
How were the studies combined?
Analysis was done separately for cardiac and orthopaedic surgery. A random-effects model was used to estimate the pooled odds ratio (OR) and 95% confidence interval (CI).

How were differences between studies investigated?
Heterogeneity was tested statistically. No details were given. The influence of the following factors on the results was assessed: dose of erythropoietin (high defined as > 1800 units/kg vs low defined as < 1800 units/kg); route of delivery of erythropoietin (subcutaneous vs intravenous); type of control (placebo vs other); Jadad score (score < 3 vs rest); and erythropoietin alone.

Results of the review
Fourteen RCTs of orthopaedic surgery were included (825 patients).

Seven RCTs of cardiac surgery were included (224 patients).

Differences between studies included the timing of the first dose of erythropoietin, total dose, and frequency of administration. Orthopaedic surgery (11 RCTs): no significant heterogeneity among studies.

Erythropoietin was associated with a statistically significant decrease in the proportion of patients transfused with allogeneic blood: OR = 0.42 (95% CI: 0.28, 0.62; P < 0.0001).

Dose of erythropoietin: no effect. High dose OR = 0.41 (95% CI: 0.26, 0.65; P = 0.0002) vs low dose OR = 0.48 (95% CI: 0.24, 0.96; P = 0.04). Route of delivery of erythropoietin: no effect. Subcutaneous OR = 0.32 (95% CI: 0.18, 0.57; P = 0.0001) vs intravenous OR = 0.52 (95% CI: 0.31, 0.89; P = 0.016). Cardiac surgery (5 RCTs): Erythropoietin was associated with a statistically significant decrease in the proportion of patients transfused with allogeneic blood: OR = 0.25 (95% CI: 0.08, 0.82; P = 0.02).

Cardiac and orthopaedic surgery:

Type of control treatment: no effect. Placebo controlled OR = 0.45 (95% CI: 0.14, 1.44; P = 0.18) vs open-label OR = 0.04 (95% CI: 0.01, 0.29; P = 0.001).

Jadad score: score < 3 had similar odds ratios to studies with higher scores. Mean units transfused in orthopaedic surgery (7 RCTs): erythropoietin group required on average 0.14 units less than control group (95% CI: -0.31, 0.04; P = 0.34).

Erythropoietin alone: no statistically significant heterogeneity. Orthopaedic surgery (3 RCTs, 684 patients): OR 0.36 (95% CI: 0.24, 0.56; P = 0.0001). Cardiac surgery (2 RCTs): OR 0.25 (95% CI: 0.06, 1.04; P < 0.06). There were insufficient studies to evaluate the effect of the method of administration, total dose of erythropoietin, or the methodological quality of the report upon the efficacy of erythropoietin.

Frequency of postoperative deep venous thrombosis (1 orthopaedic study): erythropoietin group 12.3% vs 6.4% in placebo.

Aggregated frequency of myocardial infarction, angina, deep venous thrombosis, superficial phlebitis or peripheral vascular thrombosis (1 orthopaedic study, no method of surveillance described): erythropoietin group 4% vs placebo 9%.

Deaths within 2 months of surgery (1 cardiac study): erythropoietin group 7 deaths out of 126 (5.5%) patients vs 0 deaths out of 56 placebo patients. Vascular or thrombotic events (fatal and non-fatal): erythropoietin 23% vs placebo 29%. Another study of cardiac patients reported 4 deaths out of 38 in each group (10.5%).

Authors’ conclusions
Erythropoietin, when given alone or to augment autologous donation, decreased exposure to perioperative autologous transfusion in orthopaedic and cardiac surgery. Further studies are required to definitively establish the safety of
erythropoietin alone, to determine the optimal dose of perioperative erythropoietin, and to compare its efficacy and cost-effectiveness with other methods of minimising perioperative transfusion.

CRD commentary
The aims and inclusion criteria were stated. No language restrictions were applied to included studies. Methods used to extract data and assess validity were described. Heterogeneity was assessed statistically and the influence of various factors on the results was evaluated. The discussion included consideration of the following: lack of knowledge of the lowest effective dosing regime for erythropoietin; lack of screening in trials for thrombotic complications; risks of allogeneic blood; other factors that may have influenced results such as skill and commitment of the operative team to reducing blood loss; and unanswered question such as the most efficacious method of using erythropoietin and indications for its use. Some information on the frequency of adverse reactions was reported.

No details were given of the methods used to estimate the pooled odds ratio or test heterogeneity.

The authors conclusions were supported by the evidence presented.

Implications of the review for practice and research
Practice: The authors consider that it would be prudent to study erythropoietin in more peri-operative patients before using it widely in clinical practice.

Research: The authors consider that large randomised trials, preferable in a variety of settings, are needed to compare the effectiveness, safety, and cost-effectiveness of the various methods of minimising exposure to allogeneic blood transfusion.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.