BJA

British Journal of Anaesthesia, 115 (4): 511–19 (2015)

doi: 10.1093/bja/aev317
Review Article

Liberal transfusion strategy improves survival in perioperative but not in critically ill patients. A meta-analysis of randomised trials

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Abstract

Background: Guidelines support the use of a restrictive strategy in blood transfusion management in a variety of clinical settings. However, recent randomized controlled trials (RCTs) performed in the perioperative setting suggest a beneficial effect on survival of a liberal strategy. We aimed to assess the effect of liberal and restrictive blood transfusion strategies on mortality in perioperative and critically ill adult patients through a meta-analysis of RCTs.

Methods: We searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, Transfusion Evidence Library, and Google Scholar up to 27 March 2015, for RCTs performed in perioperative or critically ill adult patients, receiving a restrictive or liberal transfusion strategy, and reporting all-cause mortality. We used a fixed or random-effects model to calculate the odds ratio (OR) and 95% confidence interval (CI) for pooled data. We assessed heterogeneity using Cochrane's Q and I^2 tests. The primary outcome was all-cause mortality within 90-day follow-up.

Results: Patients in the perioperative period receiving a liberal transfusion strategy had lower all-cause mortality when compared with patients allocated to receive a restrictive transfusion strategy (OR 0.81; 95% CI 0.66–1.00; P=0.05; I^2=25%; Number needed to treat=97) with 7552 patients randomized in 17 trials. There was no difference in mortality among critically ill patients receiving a liberal transfusion strategy when compared with the restrictive transfusion strategy (OR 1.10; 95% CI 0.99–1.23; P=0.07; I^2=34%) with 3469 patients randomized in 10 trials.

Conclusion: According to randomized published evidence, perioperative adult patients have an improved survival when receiving a liberal blood transfusion strategy.

Key words: anesthesia; blood transfusion; critical illness; mortality; perioperative care

Accepted: July 9, 2015

Editor's key points

- In this meta-analysis the authors examined the association between blood transfusion strategy (liberal *vs* conservative) and mortality in perioperative and in critically ill patients receiving critical care.
- They found an extensive evidence base, and the data indicated that a liberal transfusion strategy was associated with improved survival in perioperative (but not critically ill) patients.

Blood transfusion is one of the most frequently used treatments in critically ill and surgical patients.[1 2] Approximately, 85 million red blood cell (RBC) units are transfused worldwide annually.[3] However, observational studies suggest that patients who received RBC transfusion are at increased risk of mortality, infection, and organ dysfunction.[4 5] Moreover, data from recent meta-analyses of randomized controlled trials (RCTs) show that a restrictive transfusion approach is as safe as[6–8] or even superior[9] to a liberal transfusion approach. Nevertheless, contemporary knowledge should be considered cautiously as the vast majority of published reviews combine results of studies conducted in different clinical contexts: adults, children, surgical, and critically ill patients.

Recently published RCTs in cardiac surgery,[10] oncology,[11] and hip fracture surgery[12] raised the possibility that mortality is lower using a liberal transfusion strategy when compared with a restrictive strategy. Therefore, we performed a meta-analysis of RCTs to investigate the influence of liberal and restrictive blood transfusion strategies on mortality in perioperative and critically ill adult patients.

Methods

Search strategy

We searched PubMed/Medline, Embase, Cochrane Central Register of Controlled Trials, Transfusion Evidence Library, and Google Scholar for relevant studies up to 27 March 2015, with keyword search terms including 'blood transfusion', 'red blood cell', 'RBC', 'transfusion', 'trigger', 'threshold', 'strategy', 'liberal', and 'restrictive'. The full PubMed search strategy is available in the supplement (Supplementary Digital Content 1). We also searched reference lists of selected articles, conference proceedings, and personal files for relevant citations. We screened ClinicalTrials.gov to ensure identification of relevant ongoing studies. We used no language restrictions.

This systematic review included studies with the following eligibility criteria: (1) population: patients aged more than 18 yr who were in the perioperative period or had critical illness; (2) intervention: allogeneic blood transfusion with the use of liberal (higher transfusion threshold) in one group and restrictive (lower transfusion threshold) protocol in the other group. Thresholds for transfusion were: haemoglobin or haematocrit concentrations, transfusion practice or predefined protocol; (3) outcome: all-cause mortality; (4) study design: randomized controlled trial. We excluded conferences proceedings if the abstracts were not published as full articles in the following 3 yr.

Data extraction and quality assessment

This study was performed at the Department of Anaesthesia and Intensive Care, IRCCS San Raffaele Scientific Institute, Milan, Italy. Two researchers screened the citations identified by the search strategies. Full text review was done to establish eligibility when screening reviewers believed that a citation potentially met inclusion criteria. Disagreements regarding inclusion were reconciled via consensus.

Two reviewers independently extracted data from the list of included studies. Details of the study design, clinical settings, patient characteristics, transfusion triggers, and mortality were collected. The methodological quality of individual studies (including description of randomization, allocation concealment, blinded assessor, and intention-to-treat data analysis) was assessed. We rated the risk of bias by applying a rating of 'Yes', 'No' or 'Unclear' to denote whether adequate measures were taken to protect against each potential source of bias in each study. The overall risk of bias was expressed as low, moderate, or high.

Data analysis

The primary outcome was 90-day all-cause mortality. If 90-day mortality was not reported we chose the closest mortality data available and reported the follow-up in Table 1. All analyses were done with Review Manager (RevMan, Version 5.3., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). We employed the Mantel-Haenszel method with fixed-effect model when the heterogeneity was less than 50%, according to Higgins's I^2 test and the P value for Cochrane's Q test had a critical level of significance more than 10%. We used odds ratios (ORs) to pool outcome with a two-sided significance level of 5%. Individual trial and summary results are reported with 95% confidence intervals (CIs). Data from each trial were considered as per the intention-to-treat principle. We also calculated the number needed to treat (NNT). To compare different groups (perioperative and critically ill) with each other, we performed tests for subgroup differences based on random-effects models. To assess for publication bias, we visually examined a funnel plot comparing effect measure for the primary outcome of mortality with study precision for evidence of asymmetry and applied both the Egger's and Begg's regression tests using the metabias command in STATA (StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). We performed sensitivity analyses by sequentially removing each study result from the pooled effect estimate. We also repeated analysis including only trials with low risk of bias, with multi-centre design, or trials enrolling more than 100 patients.

Results

Characteristics of included studies

The initial search strategy identified 10 045 citations (Fig. 1). Major exclusions (Supplementary references 1–28) are listed in the Supplementary material together with the reasons of exclusion (Supplementary Digital Content 1). Twenty-seven trials met the inclusion criteria (Table 1) for a total of 11 021 patients: 17 studies enrolled patients in perioperative settings[10–12 15–18 21–23 27–31 33 34] while 10 trials enrolled patients in critically ill settings.[13 14 19 20 24–26 32 35 36] Within the perioperative setting nine trials were in orthopaedic,[12 17 18 21 22 28–30 34] five in cardiac,[10 15 23 27 33] one in vascular,[16] one in oncology surgery,[11] and one trial in obstetrics.[31] Fourteen trials were multicentre[10 17–20 22 24–26 29 31 32 34 36] with 18 trials including more than 100[10–13 15 18 19 21–23 25 26 30–32 34–36] and two trials more than 1000 patients.[10 18] Leucocyte reduced blood was administered in 11