

Transfusion Evidence Synopsis

Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery (TRICS III trial)

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Abstract

CLINICAL QUESTION: Is transfusing red cell components using a restrictive transfusion threshold (Hb < 75g/L) as safe as a liberal transfusion threshold (Hb < 95g/L in intensive care and < 85g/L outside intensive care) during and after cardiac surgery for adults at moderate to high risk of death?

EVIDENCE FROM TRIAL: In adults undergoing cardiac surgery who were at moderate-to-high risk for death, using a restrictive red-cell transfusion threshold was as safe as a liberal red cell transfusion threshold (composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis at 6 months after surgery).

Introduction

Red cell transfusions are commonly given to adults undergoing cardiac surgery (Mazer, *et al* 2018, Mazer, *et al* 2017). However, there has been uncertainty on the appropriate red cell transfusion threshold from previous randomised-controlled trials (RCTs) (Carson, *et al* 2016, Murphy, *et al* 2015), with concerns raised about harm (increased risk of acute kidney injury, and increase risk of death at 90 days) associated with using a restrictive red cell transfusion threshold (Murphy, *et al* 2015). This large RCT has assessed different red-cell transfusion thresholds in adults undergoing cardiac surgery who are at moderate to high risk of death. This Transfusion Evidence Synopsis summarizes the paper describing outcomes at 6 months for this RCT in the NEJM (Mazer, *et al* 2018). This is the first RCT to assess longer-term outcomes, prior to this analysis the longest follow-up was 90 days (Murphy, *et al* 2015).

INSERT EVIDENCE BOX ABOUT HERE

Summary of the Results of the Study

The study achieved a well-defined contrast in treatment between the study arms; many more adults in the high-threshold group (%) received a red-cell transfusion (Table 1).

The main finding was that using a restrictive red-cell transfusion threshold in adults undergoing cardiac surgery was as safe as a liberal red-cell transfusion threshold after 6 months follow-up (Table 1).

There was no evidence of a difference in any of the outcomes that made-up the primary composite outcome (death from any cause, myocardial infarction, stroke, or new-onset renal failure requiring dialysis) (Table 1).

In this study's 28 day primary outcome results there was a significant interaction between patient's age and the composite outcome. A restrictive transfusion threshold was associated with a lower risk of the composite outcome in those aged 75 years or older (Mazer, *et al* 2017). At 6 months this effect was still seen (Mazer, *et al* 2018).

INSERT TABLE 1 ABOUT HERE

Limitations of the Trial

The restrictive transfusion threshold was only required for 28 days post-surgery or until hospital discharge. The authors did not assess the differences in haemoglobin levels or red-cell transfusions after this point, however red-cell transfusions and anaemia were much more likely in the initial hospital admission than in subsequent admissions.

It was an open-label trial, and was therefore at risk of bias for subjective outcomes, however this would not affect objective outcomes such as death due to any cause. Also, the authors tested the robustness of the results by performing multiple sensitivity analyses and found consistent results.

Outcome data were obtained from a variety of sources, including telephone contact, hospital records, and database registries, and there was some missing data but this did not appear to differ between study arms.

The authors were unable to determine underlying causes of death.

Evidence in context

This is the largest RCT of red-cell transfusion thresholds in adults at moderate or high risk of death requiring cardiac surgery. This RCT has followed-up participants for longer than any other trial (6 months). It showed a benefit of a restrictive red cell transfusion policy in those aged 75 years or older, this contradicts practice when a more liberal transfusion policy is used in older adults (Brown, *et al* 2014).

Implications for research

Data from this large RCT demonstrate no evidence of harm at 6 months post-surgery (Mazer, *et al* 2018).

Implications for practice

This trial supports new international consensus recommendations to use a restrictive red-cell transfusion threshold (< 75g/L) (Mueller, *et al* 2019). It clearly indicates that restrictive red-cell transfusion thresholds are as safe as liberal red-cell transfusion thresholds in adults in cardiac surgery, even if they are at high risk of death (EuroScore I > 6).

Conflicts of Interest

None to declare.

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Table 1 Outcomes from the TRICS III trial

Outcomes	Restrictive Red cell Tx (75g/L)	Liberal Red cell Tx (95g/L ITU, 85g/L non-ICU)	Relative effect Odds ratio (OR) or Hazards ratio (HR) (95% CI)
Primary composite outcome at 6 months	402/2317 (17.4%)	402/2347 (17.1%)	OR 1.02 (95% CI 0.87 to 1.18)
Death from any cause at 6 months	141/2291 (6.2%)	149/2318 (6.4%)	OR 0.95 (95% CI 0.75 to 1.21)
Myocardial infarction at 6 months	162/2226 (7.3%)	164/2237 (7.3%)	OR 0.99 (95% CI 0.79 to 1.24)
Stroke at 6 months	88/2199 (4.0%)	74/2222 (3.3%)	OR 1.21 (95% CI 0.88 to 1.66)
New onset renal failure requiring dialysis at 6 months	87/2222 (3.9%)	94/2237 (4.2%)	OR 0.93 (95% CI 0.69 to 1.25)
Hospital readmission or emergency department visit	786/2216 (35.5%)	746/2223 (33.6%)	OR 1.09 (95% CI 0.96 to 1.23)
At least one red cell transfusion up to 28 days	1271/2430 52.3%	1765/2430 72.6%	OR 0.41 (95% CI 0.37 to 0.47)

Evidence Box

Study design: Open-label, non-inferiority randomised controlled trial

Study years: January 2014 to March 2017

Countries: Australia, Brazil, Canada, China, Columbia, Denmark, Egypt, Germany, Greece, India, Israel, Malaysia, New Zealand, Romania, Singapore, South Africa, Spain, Switzerland, United States

Setting: Cardiac surgery

No. of patients: 5243 randomised (5092 analysed for primary outcome, 4860 per-protocol analysis)

Mean age (SD): 72 ± 10 years

Female: 1721/4860 (35.4%)

Type of surgery: CABG only (26.1%); %, CABG with another procedure (27.7%), and other, non-CABG procedure (46.2%).

Mean EuroSCORE I (SD): 7.8±1.9

Inclusion criteria: Adults (≥ 18 years) who were scheduled to undergo cardiac surgery with cardiopulmonary bypass and who had a preoperative additive EuroSCORE I ≥ 6 (risk in-hospital death ≥ 4%).

Exclusion criteria: unable to receive or declined blood products, were involved in a preoperative autologous donation program, were undergoing heart transplantation, were having surgery solely for the insertion of a ventricular assist device, or were pregnant or breastfeeding.

Comparison: red-cell transfusion when Hb < 75 g/L intraoperatively or postoperatively versus red-cell transfusion when Hb < 95g/L intraoperatively or postoperatively in the intensive care unit (ICU) or if Hb < 85 g/L when in a non-ICU ward.

Primary outcome: composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis

Secondary outcomes: death, myocardial infarction, stroke, or new-onset renal failure with dialysis, blood-product (including red-cell) transfusion, lengths of stay in the ICU and in the hospital, duration of mechanical ventilation, prolonged state of low cardiac output, infection, bowel infarction, acute kidney injury, seizure, delirium, and encephalopathy.