A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2)

Barnaby C Reeves,[1]* Katie Pike,[1] Chris A Rogers,[1] Rachel CM Brierley,[1] Elizabeth A Stokes,[2] Sarah Wordsworth,[2] Rachel L Nash,[1] Alice Miles,[1] Andrew D Mumford,[3] Alan Cohen,[4] Gianni D Angelini[5] and Gavin J Murphy[6] on behalf of the TITRe2 investigators†

[1]Clinical Trials and Evaluation Unit, School of Clinical Sciences, University of Bristol, Bristol, UK
[2]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK
[4]Division of Specialised Services, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[5]Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol, UK
[6]Department of Cardiovascular Sciences and National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular Medicine, University of Leicester, Leicester, UK

*Corresponding author
†Transfusion Indication Threshold Reduction (TITRe2) investigators are listed in *Appendix 1*

Declared competing interests of authors: Rachel CM Brierley, Alan Cohen, Alice Miles, Andrew D Mumford, Gavin J Murphy (up to 31 August 2012), Rachel L Nash, Katie Pike, Sarah Wordsworth, Elizabeth A Stokes and Barnaby C Reeves had varying percentages of their salaries paid for by the grant awarded for the trial. Some or all of the time contributed by Gianni D Angelini, Gavin J Murphy (from 1 September 2012) and Chris A Rogers was paid for by the British Heart Foundation. Barnaby C Reeves is a member of the National Institute for Health Research Health Technology Assessment Commissioning Board, Systematic Reviews Programme Advisory Board and the Efficient Studies Design Board.

Published August 2016
DOI: 10.3310/hta20600

Scientific summary

The TITRe2 trial

Health Technology Assessment 2016; Vol. 20: No. 60
DOI: 10.3310/hta20600

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Perioperative anaemia is common after cardiac surgery and is associated with an increased risk of morbidity and mortality. Transfusion of allogeneic red blood cells is the preferred treatment for acute anaemia but an 'acceptable' level of anaemia, and the risks and benefits of red blood cell transfusion, are unclear. Defining what constitutes a safe and effective red blood cell transfusion strategy is important; observational analyses suggest that reversing anaemia by transfusing red blood cells may worsen outcome, yet > 50% of cardiac surgery patients are transfused. Randomised controlled trials (RCTs) have sought to answer the question by comparing restrictive (lower haemoglobin) with liberal (higher haemoglobin) transfusion thresholds. However, RCTs in cardiac surgery populations have had insufficient power and RCTs in non-cardiac surgery populations, although generally supportive of restrictive practice, have recruited very low proportions of patients with unstable cardiac disease. Transfusion guidelines increasingly recommend restrictive transfusion but uncertainty about the safety of this strategy for cardiac surgery patients persists and is reflected in large variations in transfusion practice.

Objective

The Transfusion Indication Threshold Reduction (TITRe2) RCT tested the hypothesis that a restrictive threshold for red blood cell transfusion reduces post-operative morbidity and health-care costs compared with a liberal threshold.

Methods

Study design

A multicentre parallel-group RCT with an economic evaluation.

Settings and participants

Seventeen specialist cardiac surgery centres in UK NHS hospitals took part. Patients aged > 16 years undergoing non-emergency cardiac surgery were eligible if the haemoglobin fell < 9 g/dl post-operatively. Exclusion criteria were: patients unwilling to have transfusion owing to beliefs; platelets, red blood cell or clotting disorders; ongoing or recurrent sepsis; critical limb ischaemia; inability to give full informed consent; and participation in another interventional research study. Participants gave written informed consent before surgery and were only randomised after admission to intensive care units (ICUs) after surgery, if the haemoglobin fell < 9 g/dl. Participants were followed up by post or telephone 3 months after randomisation.

Interventions

Participants were randomised to a restrictive (transfuse if haemoglobin falls < 7.5 g/dl) or liberal threshold (transfuse if haemoglobin falls < 9 g/dl), which was applied during hospitalisation after surgery. One red blood cell unit was transfused, the haemoglobin rechecked and a second unit transfused only if the haemoglobin remained below the relevant threshold. Physicians could transfuse, or refuse to transfuse, in contravention of the allocated threshold but had to document the reason and the haemoglobin level.

Randomisation and blinding

Randomisation was achieved with a secure internet-based system that generated the allocation using cohort minimisation to balance allocations by centre and operation type, and concealed allocation until a participant's details were recorded. Physicians and nurses were not blinded to the allocation. We tried to blind participants and tested whether or not this was successful by asking if they knew their allocation.

Outcomes

The primary outcome was a composite of a serious infectious (sepsis or wound infection) or ischaemic event [permanent stroke, myocardial infarction, gut infarction or acute kidney injury (AKI)] in the 3 months after randomisation.

Secondary outcomes were: red blood cells and other blood products transfused; infectious events; ischaemic events; quality of life [European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L)]; duration of ICU and high-dependency unit (HDU) stay; duration of hospital stay; significant pulmonary morbidity; all-cause mortality; resource use, costs and cost-effectiveness.

Protocol adherence

Non-adherence was defined as (1) failing to transfuse red blood cells within 24 hours of breaching the allocated threshold or (2) transfusing red blood cells when the haemoglobin level was above the allocated threshold. Non-adherence was considered severe when it changed the classification of a participant as transfused or not.

Sample size

The primary outcome frequency was estimated to be 17% and 11% in the liberal and restrictive groups, respectively. A sample size of 1468 was required to detect this difference with 90% power and 5% significance (two-sided test). The target sample size was inflated to 2000 to allow for uncertainty about non-adherence, as higher than expected non-adherence would reduce power.

Statistical methods

All analyses were performed on an intention-to-treat basis and directed by a pre-specified analysis plan. All outcomes were compared using mixed-effects methods, adjusting for operation type and centre. Binary outcomes were analysed by logistic regression, time-to-event outcomes using Cox proportional hazards models and EQ-5D-3L scores using mixed-effects mixed-distribution models.

Primary outcome frequencies in pre-specified subgroups were compared by estimating allocation by subgroup interactions. Sensitivity analyses were performed for the primary outcome and for mortality. Pre-specified observational analyses adjusting for potential confounding by conventional regression and instrumental variable (IV) methods (using allocation as the instrument) investigated relationships between number of red blood cells units transfused, minimum haemoglobin and red blood cell storage time with morbidity and mortality.

A 5% significance level (two-sided) was applied for main treatment effects and subgroup analyses, and a 10% level for interactions between allocated group and time in longitudinal models. Likelihood ratio tests were used. We did not adjust for multiple testing or a planned interim analysis.

Economic evaluation

A within-trial cost–utility analysis assessed the incremental cost and cost-effectiveness of a restrictive compared with liberal transfusion threshold from the perspective of the UK NHS and Personal Social Services. The primary outcome was quality-adjusted life-years (QALYs) estimated using the EQ-5D-3L. Resource use was collected for all participants from surgery to 3 months postoperatively. The restrictive haemoglobin threshold was considered as cost-effective if the incremental cost-effectiveness ratio fell below £20,000.

Results

Trial cohort

Between July 2009 and February 2013, 11,483 patients were screened; 3565 consented to take part and 2007 were randomised. Four participants asked for their data to be excluded, giving an analysis population of 2003 participants (1000 and 1003 in the restrictive and liberal groups, respectively). Treatment of 47 participants (28 and 19 in the restrictive and liberal groups, respectively) was discontinued. Twenty-five participants (1.2%) could not be followed up.

Participant characteristics

Baseline characteristics were similar in the two randomised groups. Median age was 70.3 years [interquartile range (IQR) 63.5–76.4 years] and 68.5% were men. Median European System for Cardiac Operative Risk Evaluation was 5 (IQR 3–7). Most participants had undergone coronary artery bypass grafting (CABG) (40.7%) or valve (30.5%) surgery. One-quarter of participants had a red blood cell transfusion before randomisation (25.7%).

Success of blinding

At discharge, 15.1% of participants thought they knew their allocation, of whom 115 (75.6%) were correct. At 3 months, more participants thought they knew their allocation (27.5%) but fewer (56.6%) were correct.

Haemoglobin levels and transfusions

After randomisation, the mean nadir haemoglobin level was lower in the restrictive than the liberal group by approximately 1 g/dl; 53.4% and 92.2% of participants in the restrictive and liberal groups, respectively, were transfused after randomisation [risk ratio (RR) 0.58, 95% confidence interval (CI) 0.54 to 0.62; $p < 0.0001$]. The median numbers of red blood cell units transfused were 1 unit (IQR 0–2 units) and 2 units (IQR 1–3 units) in the restrictive and liberal groups, respectively. Use of other blood products was similar across groups.

Non-adherence

One or more instance of non-adherence was documented in 30.0% and 45.2% of participants in the restrictive and liberal groups, respectively. Severe non-adherence was reported for 9.7% and 6.2% in the restrictive and liberal groups, respectively.

Primary outcome

The primary outcome occurred in 35.1% and 33.0% of participants in the restrictive and liberal groups, respectively [odds ratio (OR) 1.11, 95% CI 0.91 to 1.34; $p = 0.30$]. Sensitivity analyses tested the robustness of this result. When participants transfused before randomisation were excluded, the OR increased (OR 1.23, 95% CI 0.97 to 1.54; $p = 0.084$). Including additional AKI events, identified from routinely collected creatinine data, as primary outcome events increased the treatment effect (OR 1.20, 95% CI 1.00 to 1.44; $p = 0.045$). Two sensitivity analyses, excluding primary outcome events in the first 24 hours after randomisation and excluding AKI events not supported by a creatinine rise, did not change the result. Restricting the primary outcome to serious events decreased the treatment effect (OR 0.99, 95% CI 0.77 to 1.27; $p = 0.94$). A further sensitivity analysis showed little heterogeneity between sites ($p = 0.65$) and no indication that the OR tended to the null with increasing severe non-adherence. There were no subgroup effects.

Secondary outcomes

There were more deaths in the restrictive than the liberal group [4.2% vs. 2.6%, respectively; hazard ratio (HR) 1.64, 95% CI 1.00 to 2.67; $p = 0.045$]; two sensitivity analyses, excluding participants transfused before randomisation and deaths within 24 hours of randomisation, shifted the HR away from the null. Percentages of participants with significant pulmonary morbidity, duration of ICU/HDU and hospital stay and EQ-5D-3L scores were similar across groups. Serious post-operative complications (excluding primary outcome events) occurred in 35.7% (664 events) and 34.2% (648 events) of participants in the restrictive and liberal groups.

Meta-analysis

A meta-analysis of mortality for TITRe2 and five earlier RCTs suggest an increased risk of death in the restrictive group, of borderline statistical significance (RR 1.41, 95% CI 0.98 to 2.04).

Economic evaluation

Mean QALYs to 3 months were 0.18 in both groups (restrictive minus liberal difference = 0.0004, 95% CI –0.0037 to 0.0045). The total costs from surgery up to 3 months were £17,945 and £18,127 in the restrictive and liberal groups, respectively (mean difference –£182, 95% CI –£1108 to £744); the cost difference was largely attributable to the difference in the costs of red blood cells. Several outliers substantially influenced the average cost of participants in the liberal group, altering the direction of the differences between groups when they were excluded.

In the base-case cost-effectiveness analysis, the point estimate suggested that the restrictive group was more effective and less costly than the liberal group (i.e. dominant) and, therefore, cost-effective. However, there was great uncertainty around these results partly owing to the negligible differences in QALYs gained. Bootstrap replicates of the cost and QALY differences covered all four quadrants of the cost-effectiveness plane, which shows that there is not a movement in one direction rather than another. There was a 43% probability that the restrictive group dominated the liberal group but also a 20% probability of the reverse scenario. There was a 65% chance that the restrictive group was cost-effective at a £20,000/QALY ceiling ratio. One subgroup effect was significant; participants in the restrictive group with chronic pulmonary disease or asthma gained a reduced number of QALYs compared with other participants ($p = 0.003$).

Observational analyses

A dose–response relationship between the number of red blood cell units transfused and occurrence of the primary outcome or death was apparent in a conventional multivariable regression model (OR 1.19, 95% CI 1.06 to 1.35). However, an IV analysis contradicted this result (OR 0.89, 95% CI 0.75 to 1.06). A multivariable regression model suggested that increasing haemoglobin level reduced the risk of primary outcome or death, particularly for non-CABG patients (estimate for valve patients; OR 0.62, 95% CI 0.48 to 0.79). An IV analysis estimated a reduced effect for all surgery types (OR 0.83, 95% CI 0.64 to 1.08). The third analysis investigating the effect of red blood cell storage time was infeasible.

Discussion

Main findings: study results

The frequency of the primary outcome did not differ between the restrictive and liberal groups. Subgroup analyses showed no differences, contrary to beliefs that 'at risk' groups should be transfused at different haemoglobin thresholds. More participants died in the restrictive group than the liberal group (4.2% vs. 2.6%, respectively). There were no differences in other secondary outcomes, including cost, between the two groups. In the economic evaluation, differences in cost and effect between the two groups were small. The cost-effectiveness result was very uncertain, although the restrictive threshold appeared to be dominant (more effective and less costly).

Strengths and limitations

There was better than expected power with TITRe2 because the outcome frequency was higher than expected. In addition, unlike previous trials, the trial only randomised participants who breached the liberal threshold, preventing any dilution of the treatment effect by including similar numbers of untransfused participants in both groups. TITRe2 was pragmatic and, therefore, should directly inform red blood cell transfusion practice in cardiac surgery patients with haemoglobin levels < 9 g/dl in similar settings. Transfusion thresholds were successfully implemented and there were few missing outcome data.

The main limitation was our inability to blind health-care staff. However, the use of objective end points or adjudication by blinded personnel protected against detection bias. The nature of protocol non-adherence differed by group but only affected the overall transfusion rate in a small percentage of participants. A second limitation was the unexpected way in which sepsis and AKI, less severe events, dominated the primary composite outcome. A third limitation was that prospective data collection failed to identify AKI events that were apparent from routinely collected serial creatinine data. The effects of the final two limitations were investigated in sensitivity analyses.

Lessons for the future

The results of the trial lead us to reject the hypothesis that restrictive transfusion is superior to more liberal transfusion in cardiac surgery. Our main analysis indicates no difference between the two strategies, although, given the increased cost of more liberal transfusion, these results are still supportive of restrictive practice. However, the results of our primary analysis notwithstanding, the secondary analyses create new uncertainty about recommending restrictive transfusion after cardiac surgery. Importantly, the risk of death was higher in the restrictive group and this finding strengthened in sensitivity analyses, although the trial does not provide a clear explanation for this finding. Causes of death and severe adverse events that preceded death did not suggest a mechanism. In addition to the mortality finding, a benefit from more liberal transfusion was also suggested by sensitivity analyses of the primary outcome, excluding participants who had received transfusion prior to randomisation and including AKI events based on serial creatinine data. These findings do not lead us to recommend using a liberal threshold after cardiac surgery; however, we believe that, collectively, they should lead to a new hypothesis that more liberal transfusion may be beneficial.

This hypothesis is clinically plausible. Unlike previous trials, all participants in TITRe2 had symptomatic cardiovascular disease, the principal indication for cardiac surgery, and a significant proportion will have developed oxygen supply dependency in the immediate post-operative period. As cardiac surgery patients are often at the limits of their cardiovascular reserve, they may constitute a high-risk group in whom more liberal transfusion is beneficial.

Conclusion

A restrictive threshold is not superior to a liberal threshold after cardiac surgery.

Implications for health care

Our primary finding supports use of either transfusion threshold evaluated in the trial. In practice, it is likely to lead to wider application of a restrictive strategy because this will reduce the consumption and cost of allogeneic red blood cells.

Recommendations for research

Our findings show that transfusion is safe but uncertainty remains as to the correct haemoglobin threshold or indication for transfusion at which the benefits outweigh the risks. We suggest that a more liberal transfusion threshold of approximately 9 g/dl may benefit cardiac surgery patients and that this hypothesis should be tested in a pragmatic trial. Identifying when the benefits of transfusion outweigh the risks is not straightforward because red blood cell transfusion is inevitably associated with haemoglobin level and the nadir haemoglobin level does not necessarily precede transfusion.

Trial registration

This trial is registered as ISRCTN70923932.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/402/94. The contractual start date was in December 2008. The draft report began editorial review in September 2014 and was accepted for publication in January 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).