The impact of REstrictive versUs Liberal Transfusion strategy on cardiac Injury in patients undergoing surgery for fractured Neck Of Femur: a feasibility randomised controlled trial (RESULT-NOF).

Gillies MA[1,2], Ghaffar S[1,2], Moppett IK[3], Docherty AB[1,2], Clarke S[2], Rea N[2], Stephen J[4], Keerie C[4], Ray DC[1], White TO[5], McLullich AMJ[6], Mills NL[7], Rowley MR[8], Murthy K[9], Pearse RM[10], Stanworth SJ[11,12,13], Walsh TS[1,2].

1. Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, EH16 4SA
2. Edinburgh Critical Care Research Group, University of Edinburgh, 47 Little France Crescent, Edinburgh, EH16 4TJ
3. Anaesthesia and Critical Care Section, Division of Clinical Neuroscience, Queen's Medical Centre, University of Nottingham, NG7 2UH
4. Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, 9 Little France Road, EH16 4UX.
5. Department of Trauma and Orthopaedics, Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, EH16 4SA
6. Geriatric Medicine, University of Edinburgh, Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, EH16 4SA
7. BHF Centre for Cardiovascular Sciences, University of Edinburgh, Little France Crescent, EH16 4SU
8. Scottish National Blood Transfusion Service, Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, EH16 4SA
9. Department of Emergency Medicine, Royal Infirmary Edinburgh, Little France Crescent, Edinburgh, EH16 4SA
10. William Harvey Research Institute, Queen Mary University of London, E1 2AD
11. Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
12. Radcliffe Department of Medicine, University of Oxford, Oxford BRC Haematology Theme, Oxford, UK
13. Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

Word Counts:

Abstract: 246 Manuscript: 3575 Tables and Figures: 5

Keywords: Anaemia, myocardial injury, hip fracture, feasibility, randomised controlled trial

Correspondence to Dr Michael Gillies, Michael.Gillies@ed.ac.uk

ABSTRACT

Abstract

Background: Optimum transfusion strategy in patients with fractured neck of femur (NOF) is uncertain, particularly if there is coexisting cardiovascular disease.

Methods: Prospective randomised feasibility trial of two transfusion strategies in a single hospital. We randomised patients undergoing surgery for NOF to a restrictive (haemoglobin 70-90 $g.L^{-1}$) or liberal (Haemoglobin 90-110 $g.L^{-1}$) transfusion strategy for duration of hospitalisation. Feasibility outcomes included: enrolment rate, protocol compliance, difference in haemoglobin and blood exposure. The primary clinical outcome was myocardial injury using troponin. Secondary outcomes included major adverse cardiac events, postoperative complications, duration of hospitalisation, mortality, quality of life.

Results: 200/907 (22% of eligible patients) were enrolled. 62 (31%) decreased haemoglobin to 90 $g.L^{-1}$ or less and were exposed to the intervention. Overall protocol compliance was 81% in the liberal group and 64% in the restrictive group. Haemoglobin concentrations were similar preoperatively and at postoperative day (POD) 1 but lower in the restrictive group at POD 2 (mean difference (MD) 7.0 $g.L^{-1}$ [95% CI 1.6, 12.4]). Lowest haemoglobin within 30 days/before discharge was lower in the restrictive group (MD 5.3 $g.L^{-1}$ [95% CI 1.7, 9.0]). 58% of patients in the restrictive group received no transfusion compared with 4% in the liberal group (difference in proportion 54.5% [95% CI 36.8%, 72.2%]). The proportion with the primary clinical outcome was 14/26 (54%, liberal) vs 24/34 (71%, restrictive), difference in proportion -16.7% [95% CI -41.3%, 7.8%] p=0.182.

Conclusion: A study of two transfusion strategies with a clinically relevant cardiac outcome is feasible.

Trial Registration: Clinical trials NCT03407573

INTRODUCTION

Epidemiological studies suggest that patient co-morbidities, including anaemia, are associated with increased rates of complications and death following surgery.[1–3] Anaemia either may reflect the severity of chronic disease or be the result of blood loss from injury or surgery, and may not have a causative relationship with poor outcomes. Patients commonly receive red cell transfusions to increase haemoglobin concentration with the belief that this may increase oxygen delivery to the tissues, particularly to the myocardium and improve clinical outcomes. Blood transfusion is associated with risks including fluid overload, immunosuppression and consequent risks of infectious complications and cancer recurrence.[4–8] Donated blood is also a finite and costly resource.

Evidence generally supports restrictive transfusion strategies (i.e. a transfusion trigger of 70 $g.L^{-1}$) in stable hospitalized adult patients,[9] but the optimum transfusion threshold for surgical patients remains uncertain, particularly if there is coexisting cardiovascular disease (CVD).[10] The need for more evidence is highlighted in recommendations from the National Institute of Clinical Excellence (NICE) and the Association of Anaesthetists. Both these guidelines recommend a restrictive transfusion practice, using 70 $g.L^{-1}$ as the default threshold, but recommend caution and highlight that higher thresholds might be considered for patients with CVD. NICE recommended further research in this area was a priority.[11]

People undergoing surgery for fractured neck of femur (NOF) are often frail and elderly with multiple comorbidities,[12] including perioperative anaemia from fracture or surgery-induced bleeding.[3,13,14] There is a high prevalence of pre-existing cardiovascular disease (CVD) in this population[15,16] and red cell transfusions are typically prescribed to prevent cardiac complications, improve mobilisation and reduce length of hospitalisation.[17–20] Concerns exist that current practice guidelines may be inadequate in this setting. Findings of a recent Cochrane review of transfusion strategy in patients with hip fracture did not find evidence to support a liberal transfusion strategy but conceded that the overall quality of the evidence was low.[21] The largest study of transfusion strategy in this population used higher liberal and restrictive targets which were less relevant to current practice.[22] A recent UK survey suggested wide variation in perioperative transfusion practice among anaesthetists, surgeons and perioperative physicians[23] and a need for further studies to identify the optimum transfusion threshold in the perioperative period, particularly if there is coexisting CVD. The latest generation of cardiac troponin assays can detect myocardial necrosis with a high degree of precision and when measured following surgery the presence of necrosis correlates strongly with adverse outcomes.[24] Isolated postoperative elevations in troponin without symptoms or other clinical signs have similar associations with mortality as myocardial infarction (MI) which fulfils universal diagnostic criteria.

We conducted a prospective feasibility study of two red cell transfusion strategies in people admitted to hospital following a fractured NOF. The study aims were twofold:

1. To investigate the feasibility, in terms of recruitment, protocol compliance and red cell transfusion, of conducting a randomised trial of liberal versus restrictive transfusion in patients with fractured NOF.
2. To investigate the effect of transfusion strategy on the clinical outcomes of myocardial injury, other postoperative complications, mortality, duration of hospitalisation, quality of life.

METHODS

Trial design and oversight

RESULT-NOF was a feasibility study of an open randomised trial of two transfusion strategies in people undergoing surgery for fractured NOF, conducted in a single NHS hospital in the United Kingdom. The study protocol was approved by a Scotland A Research Ethics Committee (Reference:17/SS/0053) and registered with ClinicalTrials.gov (NCT03407573). Written consent was obtained from all study participants or if they lacked capacity, their nearest relative or welfare attorney, in accordance with Scots Law. NHS Lothian and the University of Edinburgh acted as co-sponsors of the study (www.accord.scot). An independent data and safety committee met three times during the course of the study to review study outcomes.

Participants

People aged 50 years or older, within 48 hours of admission to the Royal Infirmary of Edinburgh (RIE) with a fractured NOF, and who had not yet undergone surgery met inclusion criteria for enrolment to this study. Those who were receiving palliative care, who had received a blood transfusion prior to recruitment in same hospital admission or who declined to give consent were excluded. Potential participants were identified directly from the orthopaedic wards, via daily screening of theatre lists, or transfers from the RIE Emergency Department (ED).

Randomisation

Participants were randomised 1:1 to either a restrictive or liberal transfusion strategy for the duration of their hospital stay or 30 days, whichever was sooner. A secure electronic internet-based randomisation system was used with a dynamically allocated block list (block sizes 4 and 6). The patient's clinical team and the hospital blood transfusion laboratory were informed of the patient's study status by the study team, having been concealed until that point, and that they were to be transfused according to the study protocol.

Study Procedure

Patients were enrolled preoperatively. A restrictive strategy was defined as a haemoglobin transfusion trigger of 70 $g.L^{-1}$ or less and a target haemoglobin range of 70-90 $g.L^{-1}$. This was the

target haemoglobin range recommended by UK guidelines. A liberal strategy was defined as a haemoglobin transfusion trigger of 90 $g.L^{-1}$ or less and a target haemoglobin range of 90-110 $g.L^{-1}$. It was recommended that participants requiring transfusion should be transfused one unit of red blood cells and the haemoglobin rechecked until within the target range (Electronic Supplementary Material, ESM). Physicians were able to transfuse participants in emergency or life-threatening situations e.g. major haemorrhage. In these situations, the protocol was temporarily suspended until the situation was resolved and recorded as a protocol deviation.

At enrolment we collected baseline demographic data: age, sex, ethnicity, cardiovascular risk factors, pre-admission cardiac medications, Charlson Comorbidity Index, and ASA Physiological Status (ASA) classification. Cardiac risk factors were defined prospectively as a pre-existing diagnosis of the following: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, age over 65 years, diabetes, hypertension or other cardiac disease.
Baseline haemoglobin measurement, plasma cardiac troponin I (cTnI) concentrations ($ARCHITECT_{STAT}$, Abbott Laboratories, Abbott Park, Illinois, USA) and a 12-lead electrocardiogram (ECG) were also performed.

Type of surgery, anaesthesia, surgical duration, and postoperative destination were recorded upon completion of surgery. Haemoglobin concentration measurement was made immediately after surgery in the recovery room using the HemoCue® Haemoglobin 201_+ system (*HemoCue AB, Angelholm, Sweden)*. Further laboratory haemoglobin sampling was taken on postoperative days (POD) one and two then thereafter at the discretion of the clinical team. A further ECG was performed on POD 3. Blood samples were drawn by venepuncture into a vacuum tube and subsequently analysed in the central NHS laboratory.

The study cohort of interest was those participants whose haemoglobin fell below a threshold haemoglobin of 90 $g.L^{-1}$ or less during their hospital admission as only these participants were exposed to the study intervention. From the time that an enrolled patient's haemoglobin dropped to 90 $g.L^{-1}$ or less, we measured troponin and haemoglobin on the first, second and fifth day thereafter. Blood sampling and full outcome data were only collected in these participants, however basic demographic and outcome data were collected for all participants enrolled. Serum troponin measurements taken solely for the purpose of this research study were suppressed from clinical staff. A cardiology and an anaesthesia specialist trainee, interpreted all ECGs after recruitment was completed. Dynamic ischaemic ECG changes were considered either as new or progressive ECG changes consistent with ischaemia between admission to the third postoperative day.

Number and volume of blood transfusion, complications, and death within 30 days following surgery or before acute hospital discharge (whichever was sooner) were recorded. Participants were also

contacted at 60 days following surgery to assess vital status and quality of life using the EuroQoL EQ-5D tool.

All data were entered directly onto a secure, trial specific database using REDCap: Research Electronic Data Capture (*Vanderbilt University, USA*). This is a secure, fully-audited password protected platform, hosted on University of Edinburgh servers. All identifiable data were removed before extraction for analysis.

Blinding

The clinical and research teams were not blinded to the intervention but were blinded to the primary outcome. The study statistician analysed data blinded from group allocation. The adjudicators who assessed ECGs and other data used to assess cardiovascular outcomes were also blinded.

Outcomes

Feasibility Outcomes

The feasibility outcomes were proportion of eligible patients recruited; protocol compliance; haemoglobin concentration distribution within 3 and 30 days of surgery (including nadir haemoglobin); red blood cell use within 5 days of anaemia, and within 30 days of surgery or hospital discharge). Three protocol deviations were prospectively defined as transfusion of red blood cells above the predefined transfusion trigger, transfusion without checking haemoglobin level and planned surgery postponed or not performed. All feasibility outcomes were measured between groups.

Clinical Outcomes

The primary outcome was postoperative myocardial injury defined as any serum cTnI concentration above the upper reference limit (URL) during the study period, measured using the ARCHITECT$_{STAT}$ high-sensitive troponin I assay (Abbott Laboratories, Abbott Park, IL, USA). The assay has a limit of detection of 1.2 ng.L^{-1} and an interassay coefficient of variation of <10% at 4.7 ng.L^{-1}. The mean (SD) concentration for a healthy reference population is 1.6 (3.1) ng.L^{-1}, and the 99th percentile upper reference limit (URL) for the whole population is 16 ng.L^{-1} and 34 ng.L^{-1} for women and men respectively.[25,26]

Secondary outcomes were mortality at 30 and 60 days, acute kidney injury (KDIGO definition), delirium, myocardial infarction (universal definition), major adverse cardiac events (MACE) and postoperative complications. Definitions for postoperative complications are supplied in the ESM. Other measured outcomes included: peak troponin concentration, area under a troponin-time curve, nadir haemoglobin within 30 days (or hospital discharge), hospital length of stay, discharge destination, hospital readmission and EQ-5D at 60 days.

Statistical Analysis

While no formal power calculation was made, it was estimated that 600 patients would be eligible for recruitment annually based on admission statistics to the RIE. Assuming a 50% refusal rate, a realistic target of 200 participants over a one year period was established.

The statistical analysis was performed based on a pre-specified analysis plan. Continuous data were presented as mean (95% confidence interval [CI]), or median (interquartile range [IQR]) if non-normally distributed. Binary data were presented as frequency (%). Feasibility outcomes were reported as a difference between groups with corresponding 95% CIs. Primary and secondary clinical outcomes were compared using a chi-squared or Fisher's exact test as appropriate and presented as a difference in proportions with corresponding 95% CIs. All analyses were based on a modified intention to treat (ITT) principle: we included all participants randomised into the RESULT-NOF study who become anaemic (haemoglobin 90 g.L-1 or less) during their treatment (and thus were exposed to the study intervention) and for whom outcome data was available. To assess the impact of missing follow-up cTnI measurements on the primary outcome, a sensitivity analysis was performed where those who did not have the primary outcome but had at least one follow-up cTnI measurement missing were classified as having myocardial injury. Finally, an exploratory analysis was undertaken where the universal definitions applied to diagnose Type 2 myocardial infarction (MI) or myocardial injury, including a rise and fall in troponin were applied.[27] All analyses were performed using SAS version 9.4.

RESULTS

The study enrolment period ran from 1st November 2017 until the 31st January 2019 when the 200th participant was recruited. Final patient follow-up was completed on the 31st April 2019.

Participants

A flowchart summarising patient recruitment is outlined in Figure 1. 1,041 patients were screened, 907 were eligible for recruitment and 200 (22%) participants were enrolled in the study. Of 200 participants, Sixty-two (31%) dropped their haemoglobin to 90 $g.L^{-1}$or less and were therefore exposed to the study intervention: 26 allocated to liberal and 36 to restrictive groups. All participants went on to have surgery, reflecting current practice. Baseline patient characteristics are reported in Table 1. There was a higher prevalence of cardiovascular risk factors in participants who became anaemic compared to those who did not.

Outcomes

Feasibility Outcomes

Feasibility outcomes are reported in Table 2. From 907 patients eligible for recruitment, 200 (22%) were recruited. Overall protocol compliance was 81% in the liberal group and 64% in the restrictive group. There was greater compliance to transfusion of red blood cells within the predefined trigger in the liberal compared to the restrictive group (Difference 25.6% [95% CI 7.1%, 44.1%]). Of the 18 participants transfused off-protocol, five were transfused in response to excessive bleeding in theatre and one was transfused in error after blood was prescribed for the wrong patient. There was minimal differences in haemoglobin concentration between liberal and restrictive groups preoperatively and at POD 1 with a larger difference at POD 2 (mean difference 7.0 $g.L^{-1}$ [95% CI 1.6, 12.4], Table 2. Figure 2. Supplementary Figure 2.). Lowest haemoglobin was lower in the restrictive group within 3 days of surgery (mean difference 3.1 $g.L^{-1}$ [95% CI -1.8, 8.0]) and within 30 days of surgery/hospital discharge (mean difference 5.3 $g.L^{-1}$ [95% CI 1.7, 9.0]). There was a difference in blood use between groups; 58% of participants in the restrictive group received no transfusion within 30 days of surgery/hospital discharge compared with only 4% in the liberal group (difference in proportions 54.5% [95% CI 36.8%, 72.2%]).

Primary Outcome

Patient outcomes are summarised in Table 3. There was no statistically significant difference in the proportion of participants with the primary outcome, (54% in the liberal group vs 71% in the restrictive group, mean difference -16.7% [95% CI -41.3%, 7.8%] p=0.182) or in the sensitivity analysis accounting for missing data. In the exploratory analysis using the universal definition of MI, the overall incidence of cardiac injury was smaller but with a similar pattern observed between groups (31% liberal vs 53% restrictive, mean difference -22.2% [95% CI -46.6%, 2.2%] p=0.086) (Table 3).

In those compliant with the protocol, 12/21 (57%) had the primary outcome in the restrictive arm and 12/21 (57%) in the liberal arm. Difference in proportions was 0.0% (-29.9% to 29.9%). We undertook a non-prespecified, post-hoc, per-protocol analysis which did not demonstrate any difference in the primary outcome (p-value=1.0).

Secondary Outcomes

The rate of ECG abnormalities was high: 57% in the liberal group vs. 59% the restrictive group, however only one myocardial infarction was diagnosed clinically in participants exposed to the intervention in the restrictive group. Rates of clinically diagnosed MACE were lower in the liberal (8%) compared to the restrictive (19%) group (difference in proportion -11.8% [95% CI -28.2%, 4.7%] p=0.282) but did not reach significance. There were no differences in other secondary clinical outcomes or mortality between groups (Table 3).

Safety Data

The rate of serious adverse events (SAE) was high in this group of patients with 15% (30/200) of patients suffering at least one or more SAE. Only one was possibly related to the study procedures, an episode of transfusion related circulatory overload (TACO) in the restrictive group.

DISCUSSION

This study found that recruitment to a randomised trial of two transfusion strategies in a population of patients with a high prevalence of cardiovascular and other comorbidities was feasible. Separation of groups by both haemoglobin concentration and blood usage was also demonstrated. Protocol compliance suggested that due to clinical reasons and clinician beliefs, there was a difference in the rate of protocol deviations between liberal and restrictive groups, with a higher non-compliance rate in the restrictive arm. Use of a primary outcome based on detection of myocardial infarction or injury using high sensitivity troponin assay, measured after patients became anaemic, was also feasible. Although this study was not powered to detect a difference in clinical outcomes between groups, findings suggested a signal for an increased rate of myocardial injury associated with restrictive transfusion strategies, although it should be noted that the rate of pre-existing ischaemic heart disease was not evenly distributed between the groups (Table 1).

Concerns regarding the potential effect of severe anaemia on cardiac injury remain. A large study of two transfusion strategies in 2000 patients with fractured NOF published in 2011 did not show a difference in a composite primary outcome of death or inability to walk unassisted across a room at 60 days.[22] This study reported the rate of acute coronary syndrome as a secondary outcome and observed no difference between groups. However, more recent systematic reviews of transfusion strategy in surgical patients have suggested that restrictive strategies are associated with increased rates of MI or MACE, particularly if there is pre-existing cardiac disease [28,29] and in patients undergoing surgery for fractured NOF.[30] One possible explanation is that the restrictive and liberal strategy used in earlier studies does not reflect current practice, which would consider a restrictive strategy to maintain haemoglobin between 70 and 90 $g.L^{-1}$ and a liberal strategy at between 90 and 110 $g.L^{-1}$. A clinician survey undertaken in the UK by our group suggests continued uncertainty in managing anaemia in this group, particularly in the setting of cardiac disease.[23] Our findings are consistent with other recent trial data, including a small trial in vascular surgery and in transfusion-dependent patients with myelodysplasia which identified improvements in quality of life domains for participants in the liberal compared to restrictive arm.[31]

Other findings of our study were a high rate of co-existing cardiovascular disease in this group, especially in those who were severely anaemic. This may account for protocol deviations among participants randomised to a restrictive strategy and may have represented clinical concern among clinicians, particularly as patient's haemoglobin levels fell close to the restrictive trigger of 70 $g.L^{-1}$. Our study also suggested a high rate of postoperative cardiac complications in this group, particularly when modern high sensitivity troponin assays are used routinely.

Strengths of this study are that it was a large feasibility trial that recruited within the planned timeframe, with low rates of missing data or participants lost to follow up. Participants in the liberal transfusion group had significantly higher exposure to blood and there was a mean difference in

haemoglobin following POD 2, despite some issues with protocol compliance. High rates of cardiac complications and mortality suggest these would be patient centred outcomes which could be studied in a future trial.

There were several weaknesses in the design which could be addressed in a refined protocol for a larger study. Firstly, 58% of eligible participants could not be recruited as they had already undergone surgery before the study team was able to approach them. This probably reflects quality improvement initiatives to expedite surgery and minimise the delay in operating on this group. It is possible that the more severely injured patients, and hence those with the greatest blood loss were excluded from the study for this reason, explaining the lower than anticipated rate of anaemia observed in this study. In this group there are high rates of cognitive impairment (both acute and pre-existing) necessitating the need for proxy consent and introducing a further delay. Strategies to identify and recruit patients at an earlier stage in their inpatient admission could address these issues. The optimal transfusion threshold in older patients may also be different and a future study should include a prespecified subgroup of older patients.

Although groups were balanced at the point of randomisation, only those who became anaemic (i.e. haemoglobin falling to 90 $g.L^{-1}$or less) were exposed to the study intervention and were part of the intention-to-treat analysis population which resulted in some imbalance in patient characteristics in the restrictive and liberal groups. This study design has been used in previous studies of transfusion strategy and we believe the imbalance between groups would have resolved with a larger sample size. A retrospective analysis of study data suggested that restricting recruitment to patients who were already anaemic (e.g. haemoglobin of 110 $g.L^{-1}$ or less) would not have enriched the recruitment of patients whose haemoglobin later fell to 90 $g.L^{-1}$or less.

Finally, protocol compliance is an area which would need be improved in a larger study. The overall compliance of 70% observed in this study is would need to be improved in a larger study. In studies of transfusion practice some protocol deviations are inevitable as the protocol must be suspended in episodes of major haemorrhage. As many of these deviations occurred in the perioperative period restricting the study intervention to the postoperative period, could improve this. Clinician focus groups may also be useful to identify how the protocol could be adapted to improve adherence over an often protracted hospital stay with multiple clinical teams involved.

Hip fracture is the most common serious injury in older people. Our study confirms that elderly patients having surgery for hip fracture have a high rate of pre-existing cardiac disease and postoperative cardiac events, including troponin release. There is a high rate of anaemia and blood transfusion in this population and the optimum transfusion threshold is not known. A larger study of liberal versus restrictive transfusion practice with a clinically relevant cardiac outcome in this population is warranted and is feasible in a National Health Service hospital setting. The future design of such a trial could be informed by the findings of this study. Based on our experience, we

would suggest that patients who drop their haemoglobin to 90 $g.L^{-1}$ or less postoperatively are the ideal study population. There is a significant incidence of mental incapacity in people with hip fracture which make recruitment and consent challenging. We suggest that a suitable primary outcome for such a study could be death or major adverse cardiac events within 30 days of surgery, to address the existing clinical controversy around cardiovascular complications. However, it is also important to measure the impact of transfusion practice on quality of life at hospital discharge and beyond.

ACKNOWLEGEMENTS

NLM is supported by the Butler Senior Clinical Research Fellowship (FS/16/14/32023) from the British Heart Foundation. MAG is a Chief Scientists Office Scotland NHS Research Scheme Clinician.

DECLARATION OF INTERESTS

NLM has received consultancy, research grants and speaker fees from manufacturers of cardiac troponin testing including Abbott Diagnostics, Roche, and Singulex. All other authors declare they have no conflicts of interest.

FUNDING

This study was supported by a British Journal of Anaesthesia/Royal College of Anaesthetists Grant (ID WKR0-2016-0018)

CONTRIBUTIONS

All authors contributed to the development of the study protocol and obtaining the research permissions. EC, SG, ABD, HD, AL, AMJM, TOW, DCR, MAG oversaw patient recruitment and research interventions. JS undertook all data management and statistical analyses with CK in a statistical advisory role. All authors contributed to the manuscript. MAG takes responsibility for the integrity of the manuscript.

REFERENCES

1. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. *Br J Surg* 2015;102:1314–24.
2. Davenport DL, Bowe EA, Henderson WG, Khuri SF, Mentzer RM, Mentzer Jr RM. National Surgical Quality Improvement Program (NSQIP) risk factors can be used to validate American Society of Anesthesiologists Physical Status Classification (ASA PS) levels. *Ann Surg.* 2006; 243: 634–6.
3. Potter LJ, Doleman B, Moppett IK. A systematic review of pre-operative anaemia and blood transfusion in patients with fractured hips. Anaesthesia. 2015;70(4):483–500.
4. Bihl F, Castelli D, Marincola F, Dodd RY, Brander C. Transfusion-transmitted infections. J *Transl Med.* 2007;5:25.
5. Li G, Rachmale S, Kojicic M, Shajehan K, et al. Incidence and transfusion risk factors for transfusion-associated circulatory overload among medical intensive care unit patients. *Transfusion.* 2011;51: 338–43.
6. Bolton-Maggs P. SHOT conference report 2016: serious hazards of transfusion–human factors continue to cause most transfusion-related incidents. T*ransfus Med*. 2016;26:401–5.
7. Hellings S, Blajchman MA. Transfusion-related immunosuppression. A*naesth Intensive Care Med.* 2009;10:231–4.
8. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn D. Transfusion practice. *Transfusion.* 2010;50:753–65.
9. Holst LB, Petersen MW, Haase N, Perner A, Wetterslev J. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ* 2015; 350: h1354
10. Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. BMJ 2016; 352: i1351.
11. Klein AA, Arnold P, Bingham RM et al. AAGBI guidelines: the use of blood components and their alternatives 2016. *Anaesthesia* 2016; 71: 829-42.
12. Lisk R, Yeong K. Reducing mortality from hip fractures : a systematic quality improvement programme. *BMJ Qual Improv Reports*. 2014; 3: w2103
13. Foss N, Kristensen M, Kehlet H. Anaemia impedes functional mobility after hip. *Age Ageing.* 2008; 37:173–8.
14. Foss NB, Kehlet H. Trauma Hidden blood loss after surgery for hip fracture. *J Bone Jt Surg.* 2006; 88:1053–9.
15. Hietala P, Strandberg M, Kiviniemi T, Strandberg N, Airaksinen KEJ. Usefulness of troponin T to predict short-term and long-term mortality in patients after hip fracture. *Am J Cardiol* 2014;

114:193–7.

16. Chew E, Ghaffar S, Docherty AB, et al. Myocardial injury and anaemia in patients undergoing surgery for fractured neck of femur: An observational study. *Eur J Anaesthesiol* 2019 36: 884–6.
17. Vochteloo AJH, Boudewijn L, Van DerBurg B et al. Outcome in hip fracture patients related to anemia at admission and allogeneic blood transfusion : an analysis of 1262 surgically treated patients. *BMC Musculoskelet Disord.* 2011;12: 262.
18. Bhaskar D, Parker MJ. Haematological indices as surrogate markers of factors affecting mortality after hip fracture. *Injury.* 2011;42:178–82.
19. Hagino T, Ochiai A, Sato E, Maekawa S, Wako M, Haro H. The relationship between anemia at admission and outcome in patients older than 60 years with hip fracture. *J Orthopaed Traumatol.* 2009 10:119–22.
20. Halm EA, Wang JJ, Boockvar K et al. The Effect of Perioperative Anemia on Clinical and Functional Outcomes in Patients With Hip Fracture. *J Orthop Trauma.* 2006;18: 369–74.
21. Brunskill SSJ, Millette SSL, Shokoohi, et al. Red blood cell transfusion for people undergoing hip fracture surgery. Cochrane Database Syst Rev. 2015 4: CD009699.
22. Carson JL, Terrin ML, Noveck H et al. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011 365: 2453–62.
23. Ghaffar, S; Ray, D; Walsh T et al. Survey of peri-operative transfusion practice among clinicians in the UK. *Anaesthesia.* 2017; 52: s80.
24. Devereaux PJ, Chan MT, Alonso-Coello P, Wet al. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA.* 2012 307:2295–304.
25. Shah ASV, Griffiths M, Lee KK, M et al. High sensitivity cardiac troponin and the under-diagnosis of myocardial infarction in women: prospective cohort study. *BMJ* 2015; 350: g7873.
26. Shah ASV, Anand A, Sandoval Y et al. High-sensitivity cardiac troponin i at presentation in patients with suspected acute coronary syndrome: A cohort study. Lancet. 2015; 386: 2481–8.
27. Thygesen K, Mair J, Giannitsis E et al. How to use high-sensitivity cardiac troponins in acute cardiac care. *Eur Heart J* 2012 33: 2252–7.
28. Myles PS. Liberal Transfusion Strategy in the Perioperative and Acute Care Settings. *Anesthesiology*. 2016; 125:46–61.
29. Docherty AB, Walsh TS. Anemia and blood transfusion in the critically ill patient with cardiovascular disease. *Crit Care* 2017 21:1–8.
30. Zhu C, Yin J, Wang B, Xue Q, et al. Restrictive versus liberal strategy for red blood-cell transfusion in hip fracture patients. *Medicine*. 2019 98:e16795.

31. Stanworth SJ. Red cell transfusion in outpatients with myelodysplastic syndromes: a feasibility and exploratory randomized trial. *Brit J Haematol.* 2020 doi: 10.1111/bjh.16347.