Association of Postoperative Anaemia with Patient-centred Outcomes

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STUDY AIMS and HYPOTHESIS

Primary aim - To investigate the relationship between postoperative anaemia and patient-centred outcomes after major abdominal surgery.

Secondary aim – To determine whether a more liberal perioperative IV fluid strategy increases the risk of postoperative anaemia (haemodilution).

Hypothesis: Adults with anaemia in the immediate postoperative period following major abdominal surgery have a poorer quality of recovery and higher risk of complications, leading to poor disability-free survival when compared with patients without postoperative anaemia.

BACKGROUND

More than 310 million people undergo major surgery each year around the worldwide,[1] for which intravenous (IV) fluid therapy is routine. Although restricting IV fluids to achieve zero balance has been recommended,[2-4] the RELIEF trial could not identify any outcome benefits using this approach in patients undergoing major abdominal surgery.[5] In fact, a moderately liberal IV fluid regimen led to better quality of recovery and reduced the risk of acute kidney injury [5]. Nevertheless, excess intravascular fluid volume may induce a dilutional anaemia.[6-8] This, therefore, opens up the possibility that a diagnosis of perioperative anaemia based only on haemoglobin (Hb) concentration may be misleading – that is, when actual red cell mass is within the normal range.[6,9] Traditional perioperative IV fluid regimens in abdominal surgery can lead to patients receiving 3 to 7 litres of fluid on the day of surgery and more than 3 litres per day for the following 3 to 4 days, leading to a 3- to 6-kg weight gain.[10,11] This complicates the diagnosis of anaemia and evaluation of its relationship with patient outcomes.

Both preoperative anaemia and red cell transfusion are independent risk factors in major surgery.[12-14] IV iron therapy is effective in treating anaemia in medical (heart failure, kidney disease), post-partum, and *preoperative* settings (orthopaedic surgery, colon cancer resection, hysterectomy, hip/knee joint replacement.[15-19] Patient blood management (PBM) describes a patient-specific, multidisciplinary, multimodal team approach to optimising, conserving and managing the patient's own blood.[20] PBM aims to reduce the need for blood transfusion in an effort to improve patient outcomes.[21,22] Australian PBM guidelines for the surgical patient are available,[23] but there is no specific PBM guidance on the treatment of *postoperative* anaemia.[24]

The consequences of *postoperative* anaemia remain unclear.[22,24,25] Data from the POISE-2 trial found that postoperative anaemia was associated with an increased risk of myocardial infarction after surgery.[26] Postoperative anaemia is more likely if there is pre-existing anaemia, but also increased perioperative blood loss, frequent blood sampling, excess IV fluids (leading to haemodilution), sepsis, and inadequate nutritional intake after surgery.[24] A nadir in Hb concentration is most often observed within the first 3–4 days after surgery.[24] Postoperative anaemia is believed to have deleterious effects on patient outcomes, including prolonged hospital stay, increased postoperative complications, and perhaps poor survival,[22] but there is very little data to support this belief.[25]

A recent consensus statement suggested that all patients recovering from major surgery (defined as blood loss > 500 ml or lasting > 2 h) and either had preoperative anaemia or moderate-to-severe blood loss during surgery must be screened for anaemia after surgery.[24] Furthermore, this consensus group recommended that patients recovering from uncomplicated major surgery should have their Hb concentration measured for at least 3 days after surgery to detect anaemia.[24] As outlined above, this is problematic if there is fluid retention.

The role of IV iron for the treatment of postoperative anemia is unclear, with the most recent systematic review concluding that neither oral nor IV iron had a significant effect on patient quality of life or functional outcomes following surgery.[25] A diagnosis of iron deficiency is very difficult in the postoperative period because the acute phase inflammatory response results in spuriously elevated ferritin levels,[27] and several

studies have demonstrated oral iron therapy is ineffective in this setting.[24] However, efficacy as defined by a Hb response has been seen with IV iron.[25,28] More recently, secondary findings in the PREVENTT study showed association between the use of IV iron and correction of postoperative anaemia (Hb response) and reduced hospital readmission for complications.

We therefore propose a study to investigate the incidence, extent, and outcomes of patients with anaemia after major surgery, including an assessment of the amount of IV fluids administered in the immediate perioperative period. ≥

STUDY DESIGN

A retrospective cohort study comparing patients with and without postoperative anaemia, using prospective data collected in a large, pragmatic, multicentre, randomized trial in which patients were randomly assigned to either a restrictive (zero balance) or liberal IV fluid regimen, stratified by site and planned HDU/ICU admission.[5]

Anaemia will be defined according to the World Health Organisation definition (males Hb <130 g/L, and females Hb <120 g/L). A secondary analysis of those with more marked anaemia (Hb <100 g/L) will be done.

Inclusion criteria:

1. Adults (≥18 years) undergoing elective major surgery and providing informed consent
2. All types of open or lap-assisted abdominal or pelvic surgery with an expected duration of at least 2 hours, and an expected hospital stay of at least 3 days
3. At increased risk of postoperative complications, as defined by any of the following criteria:
   - **a)** age ≥70 years
   - **b)** known or documented history of coronary artery disease
   - **c)** known or documented history of heart failure
   - **d)** diabetes currently treated with an oral hypoglycaemic agent and/or insulin
   - **e)** preoperative serum creatinine >200 μmol/L (>2.8 mg/dl)
   - **f)** morbid obesity (BMI ≥35 kg/m^2)
   - **g)** preoperative serum albumin <30 g/L
   - **h)** anaerobic threshold (if done) <12 mL/kg/min
   - **i)** or two or more of the following risk factors:
     - ASA 3 or 4
     - chronic respiratory disease
     - obesity (BMI 30-35 kg/m^2)
     - aortic or peripheral vascular disease
     - preoperative Hb <100 g/L
     - preoperative serum creatinine 150-199 μmol/L (>1.7 mg/dl)
     - anaerobic threshold (if done) 12-14 mL/kg/min

Exclusion criteria:

1. Urgent or time-critical surgery
2. ASA physical status 5 – such patients are not expected to survive with or without surgery, and their underlying illness is expected to have an overwhelming effect on outcome (irrespective of fluid therapy)
3. Chronic renal failure requiring dialysis
4. Pulmonary or cardiac surgery – different pathophysiology, and thoracic surgery typically have strict fluid restrictions
5. Liver resection – most units have strict fluid/CVP limits in place and won't allow randomisation
6. Minor or intermediate surgery, such as laparoscopic cholecystectomy, transurethral resection of the prostate, inguinal hernia repair, splenectomy, closure of colostomy – each of these are typically "minor" surgery with minimal IV fluid requirements, generally low rates of complications and mostly very good survival.

Study Procedures
Ethics Committee approval was obtained at all study centres before commencement of the trial, and all patients provided informed consent. All relevant factors were recorded on a trial case report form (CRF).

ERAS perioperative care principles were emphasised. All patients received prophylactic antibiotics according to established guidelines. Medications were mostly continued perioperatively unless or at the clinicians discretion, but we recommended withholding ACE-inhibitors and ARBs on the day of surgery. We recorded preoperative use of bowel preparation, fasting times, ERAS data, medications, and biochemistry and haematology results on the CRF. Choice of anaesthetic agents and perioperative analgesia were left to the discretion of the anaesthetist; such data were recorded.

The acceptable limits of low BP, and a definition of 'hypotension', vary widely.[29] We used a general guideline of systolic BP <90 mmHg for more than 5 mins, but also asked the attending anaesthetist to modify their acceptable lower limit of sBP at the commencement of surgery, and, according to randomly-assigned group, treat hypotension with additional IV fluid or vasopressor therapy. Such modifications to the acceptable lower sBP were recorded.

Patients were followed daily and outcomes were recorded until hospital discharge. We recommended that antihypertensive medications should be withheld until sBP was consistently at or above preoperative levels. Serum electrolytes, Hb/haematocrit, and a 12-lead ECG were ordered preoperatively and on Day 1 after surgery. CRP was measured on postoperative Day 3 and whenever sepsis was suspected. Additional laboratory tests were ordered if clinically indicated. On Day 3 all patients completed the 15-item quality of recovery score (QoR-15).[30]

On Day 30 all patients were contacted by phone to ascertain if they have experienced any outcomes, and if detected, further testing was arranged. The QoR-15 was repeated on Day 30 along with World Health Organization Disability Assessment Schedule 2.0 (WHODAS), and the WHODAS was repeated at 3-, 6- and 12-month follow-up to ascertain survival status and new-onset disability.[31]

Outcomes
There is a need for patient-centered outcome assessments in the study of perioperative anaemia.[32 25]

Primary Endpoint
Persistent disability or death by 90 days, where persistent disability was defined as a WHODAS 2.0 score of at least 24 points (on the 48-point scale) at both 30 days and 90 days post-operatively,[31] reflecting a disability level of at least 25% and being the threshold point between "disabled" and "not disabled" as per WHO guidelines.[33] Disability was assessed by the participant, but if unable then we used the proxy's report.

Secondary Endpoints
Secondary endpoints include an *a priori* composite of 30-day mortality or major septic complications (sepsis, surgical site infection, anastomotic leak, and pneumonia), plus each individually, blood transfusion, acute kidney injury, ICU and hospital stay, unplanned admission to ICU, and quality of recovery (QoR-15).[30] We used the following definitions:

1. Death: all-cause mortality at 90 days, then up to 12 months after surgery
2. A composite (pooled) and individual septic complications: sepsis, surgical site infection, anastomotic leak, and pneumonia
3. Sepsis: using Centers for Disease Control and Prevention (CDC) with National Healthcare Safety Network (NHSN) criteria[34]
4. Surgical site infection: using CDC criteria[34]

5. Pneumonia: The presence of new and/or progressive pulmonary infiltrates on chest radiograph plus two or more of the following:
    i. Fever ≥ 38.5°C or postoperative hypothermia <36°C
    ii. Leucocytosis ≥ 12,000 WBC/mm^3 or leucopenia < 4,000 WBC/mm^3
    iii. Purulent sputum and/or
    iv. New onset or worsening cough or dyspnoea.
6. Anastomotic leak: A defect of the intestinal wall at the anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- an extra luminal compartments.
7. Acute kidney injury: according to The Kidney Disease: Improving Global Outcomes (KDIGO) group criteria, but not urine output – for Stage 2 or worse AKI defined as at least 2-fold increase in creatinine, or estimated GFR decrease >50% [35]. We also plan to report renal replacement therapy up to 90 days after surgery
8. Unplanned admission to ICU within 30 days of surgery
9. Total ICU stay: additive, including initial ICU admission and readmission times up to Day 30
10. Hospital stay: additive, from the start (date, time) of surgery until actual hospital discharge , plus readmission(s) up to Day 30
11. Quality of recovery: QoR-15 score[30] on Days 3 and 30
12. Hospital re-admission at 3, 6 and 12 months.

Fluid Therapy and Blood Transfusion: General Guidelines

Excessive fluid resuscitation can cause haemodilution[7] and dilutional coagulopathy, and this may increase the need for red cell and other blood transfusion.[8] All patients had the same red cell transfusion threshold of 70 g/L, but this could be modified after assessment of cardiovascular risk[36,37] or concern for active bleeding.

Randomised group assignment

RELIEF was a large, randomized, parallel-group, controlled trial [5]. After stratification by centre and planned ICU/HDU admission (or not), patients were randomly assigned from a computer-generated list (1:1) to either a Restrictive or Liberal fluid Group. In brief, Liberal protocol group received a bolus of Hartmann's balanced salt crystalloid 10 ml/kg at the commencement of surgery followed by 8 ml/kg/h administered until the end of surgery, and then maintenance infusion continued at 1.5 ml/kg/h for at least 24 hours. Patients assigned to the Restrictive protocol group received approximately half of this IV fluid volume.[5]

Patients were blinded to Group allocation. Anaesthetists, surgeons, and intensivists had variable knowledge of Group identity. Research staff conducting all follow-ups were blinded to Group allocation.

Web-based data entry

Following completion of the paper-based CRF, data were entered by research staff to the database through a web-based data entry system. We audited the timeliness of data entry and reports were generated by the data quality committee regularly. We maximised data quality and protocol standardization by arranging start-up meetings at local scientific meetings or live streamed web based sessions, and provided regular feedback to each centre via phone and the trial web-site, along with a monthly newsletter. A complete procedures manual was produced. All study personnel had 24-h access to the study coordinating centre to resolve any questions that arose.

Adverse Event reporting was mandated.

Bias Control

RELIEF was a large trial, randomised trial. This retrospective cohort study is using all data collected during the RELIEF trial, as outlined above. All outcome data were collected by research staff blinded to Group allocation. All outcomes were clearly defined in the protocol, and most required source documentation and confirmation by blinded assessors in the endpoint adjudication committee.

STATISTICAL ANALYSIS

All statistical analysis will be done by Catherine Martin (biostatistician). Our initial sample size calculation was based primarily on our own data and other published studies.[38,39] This resulted in a final sample size of 3,000 that provided 80% power for the trial.[5] We plan to analyse the intention-to-treat population of the RELIEF trial.[5]

Descriptive statistics will be used to compare the baseline characteristics of patients with and without post-operative anaemia on Day 3, hereafter titled 'anaemia groups'. The binary primary outcome, persistent disability or death to 90 days, will be compared between anaemia groups using log-binomial regression to estimate risk ratios and 95% confidence intervals directly, adjusting for RELIEF randomised group, age, sex, ASA physical status, Charlson score, preoperative aspirin, haemoglobin, type of surgery, planned HDU/ICU (either), and duration of surgery. Further possible confounders will be determined prior to commencement of the statistical analysis. Should the log-binomial model fail to converge, modified Poisson regression with robust standard errors will be used. Other binary endpoints will be analysed similarly. Duration of stay outcomes will be summarised using medians and interquartiles ranges, and compared across anaemia groups using accelerated failure time models with adjustment for the same factors. QoR-15 scores will be summarised using medians and interquartiles ranges, and compared across anaemia groups using median regression.

To assess the secondary aim, the risk of postoperative anaemia at Day 3 will be compared between RELIEF randomised arms using proportions and analysis using (unadjusted) log binomial regression.

Baseline and pre-Day 3 characteristics of patients missing the Day 3 anaemia assessment will be compared with those who have the measurement present. If there is evidence of missing Day 3 anaemia being dependent on these characteristics then multiple imputation of Day 3 anaemia will be performed using chained equations, including baseline and post-baseline variables, including the relevant outcome variables in the imputation models.

Exploratory subgroup analyses will be done for persistent disability or death to 90 days, acute kidney injury, Day 3 QoR-15, and hospital stay according to (i) RELIEF randomised group, (ii) the presence of preoperative anaemia, and (iii) receipt of a red cell transfusion. These will be reported as a web-supplement.

Secondary analyses of those with and without more marked anaemia (Hb <100 g/L) will be done for the primary outcome (persistent disability or death to 90 days), plus Day 3 QoR-15 score and hospital re-admissions.

A more detailed statistical analysis plan will be prepared prior to commencement of data analysis.

AUTHORSHIP PLAN

RELIEF-Anaemia Study Authorship

Target Journal: JAMA Surgery or British Journal of Anaesthesia

Planned Authorship: *Myles PS, Richards T, Klein A, Wood E, Wallace S, Shulman M, Martin C, Bellomo R, Corcoran T, Peyton P, Story D, Leslie K, Forbes A, and the RELIEF Trial Investigators*

The trial will be described as a collaboration of the Australian and New Zealand College of Anaesthetists (ANZCA) Trials Group and the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group.

The planned writing committee will consist of Paul Myles, Toby Richards, Erica Wood, and Andrew Forbes.

All site investigators listed in the appendix of the final publication(s) can be considered an author and so can list the publication(s) on their CVs.

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