Association of Postoperative Anaemia with Patient Outcome in the RELIEF Trial

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Statistical Analysis Plan

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BACKGROUND

Both preoperative anaemia and red cell transfusion are independent risk factors in major surgery. Patient blood management (PBM) aims to reduce the need for blood transfusion in an effort to improve patient outcomes. Australian PBM guidelines for the surgical patient are available, but there is no specific PBM guidance on the treatment of *postoperative* anaemia.

The consequences of *postoperative* anaemia remain unclear. 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. A nadir in Hb concentration is most often observed within the first 3–4 days after surgery. Postoperative anaemia is believed to have deleterious effects on patient outcomes, including prolonged hospital stay, increased postoperative complications, and perhaps poor survival, but there is very little data to support this belief.

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 AIMS AND HYPOTHESES

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) at Day 3.

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.

STUDY DESIGN

A cohort study comparing patients with and without postoperative anaemia, using prospective data collected in a large, pragmatic, multicentre, randomized trial, the RELIEF 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] The intention-to-treat population of the RELIEF trial will be utilised, namely all participants who were enrolled, randomised and underwent induction of general anaesthesia for eligible surgery.

Inclusion and exclusion criteria are as for the RELIEF trial.[5]

GROUP AND ENDPOINT DEFINITIONS

ANAEMIA GROUP DEFINITION

Postoperative anaemia will be defined according to the World Health Organisation definition (males Hb <130 g/L, and female Hb <120 g/L), as measured on postoperative Day 3, using the "Lowest Haemoglobin concentration". Patients with missing Day 3 haemoglobin data will have these values imputed rather than these patients being excluded (details below).

A secondary group definition will be studied defined as patients with severe anaemia (Hb <100 g/L) at day 3 postoperatively.

LIBERAL PERIOPERATIVE IV FLUID GROUP DEFINITION

Liberal and restrictive perioperative IV fluid groups are defined as the corresponding randomised arms of the RELIEF trial. 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]

ENDPOINT DEFINITIONS

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, acute kidney injury, ICU and hospital stay, unplanned admission to ICU, hospital readmission 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. [Detailed clinical definitions are provided in the Protocol]
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 will also 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

PROCESS DATA CALCULATIONS

Red cell transfusions will be reported as dichotomous data (yes/no, where yes is any red cell volume ≥1 ml) data, and calculated for the intraoperative period plus recovery room (combined), and postoperative Days 1, 2 and 3.

IV fluids (total volume) will be tabulated according to reporting in the RELIEF trial, for intraoperative plus recovery room (combined), and Days 1, 2 and 3.

Daily weight and CRP (if done) on Day 3 will be reported as mean (SD).

STATISTICAL ANALYSES

All statistical analysis will be performed with the intention-to-treat population of the RELIEF trial.[5]

Descriptive statistics will be used to compare the baseline and pre-Day 3 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 (baseline), type of surgery, planned HDU/ICU (either), and duration of surgery. Should the log-binomial model fail to converge, modified Poisson regression with robust standard errors will be used. Methods for addressing missing Day 3 anaemia are provided below.

Other binary endpoints (#1-8, 12) will be analysed similarly. Duration of stay outcomes (#9,10) will be summarised using medians and interquartiles ranges, and compared across anaemia groups using parametric accelerated failure time models with adjustment for the same factors. QoR-15 scores (#11) will be summarised using medians and interquartiles ranges, and compared across anaemia groups using median regression with robust standard errors.

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 log binomial regression adjusted for planned ICU/HDU admission.

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 predictive of either Day 3 anaemia being missing or of Day 3 anaemia itself (defined by correlation >= 0.30 for either), 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 undertaken for the primary outcome (persistent disability or death to 90 days), plus Day 3 QoR-15 score and hospital re-admissions at 3 months.

REFERENCE

1. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med 2011;39:2665-71