The RELIEF Trial

REstrictive versus LIbERal Fluid Therapy in Major Abdominal Surgery

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On behalf of the Australian and New Zealand College of Anaesthetists Clinical Trials Network (ANZCA CTN), and the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG)

ClinicalTrials.gov Identifier: NCT01424150

SAP August 29, 2017

Study title: Restrictive versus liberal fluid therapy in major abdominal surgery

Protocol Number: Anaesthesia Research 046

Sponsor: Alfred Health, Melbourne

Funding source: The Australian National Health and Medical Research Council (APP1043755)

RELIEF Statistical Analysis Plan

August 29, 2017

We will apply the intention to treat principle, analysing all participants who are enrolled, randomised and undergo induction of general anaesthesia for eligible surgery. Patients are followed for the duration of the trial, unless they withdraw consent, for which we will use their data up until the time of withdrawal of consent.

ENDPOINT DEFINITIONS

Primary endpoint

The primary end point of the trial is disability-free survival at 1 year after surgery. Disability is defined as a persistent (at least 6 months) impairment in health status, as measured by the 12-item WHODAS score, of at least 24 points when using response scores of 1–5 for each item, reflecting a disability level of at least 25% and being the threshold point between 'disabled' and 'not disabled' as per WHO guidelines. If a single item is missing at an assessment, the mean value of the remaining items will be assigned to the missing item. If more than one item is missing the score will not be calculated for that assessment.

With WHODAS assessments being made at (baseline and) 30 days, 3 months, 6 months and 12 months, post-operative disability that persists for at least 6 months is able to be observed to be commencing at the 30 day assessment, the 3 month assessment, or the 6 month assessment. For example, persistent disability commencing at 3 months requires the initial observation of disability (WHODAS >=24) at 3 months which is sustained at each of the 6 and 12 month assessments. Missing WHODAS assessments in patients known to be alive will not be imputed in the primary analysis. Persistent disability observed to commence at the 30 day assessment will be assumed to be related to surgery and will be assigned an onset date of 0.10 days post-surgery. Onset of disability at 3 or 6 months postoperatively will typically be after an incident/illness in the postoperative follow-up period, and for these events the self-reported date of such onset will be utilised. If no such event is documented, then the current time point (interview date) will be used.

The time to the primary endpoint is defined as the time of the onset of persistent (>= 6-month) disability or death, whichever occurs first. Time at risk will commence at start of surgery to accommodate the potential for intraoperative mortality. Patients not experiencing the primary endpoint event will be censored at their date of last contact.

Two supplementary approaches will be utilised to assess sensitivity to handling of missing WHODAS assessments for subjects known to be alive at those assessment times: (a) they will be given a disabled score (WHODAS of 24), and (b) they will be imputed using information from baseline and post-baseline variables (see statistical analysis methods).

Alternative 'new onset disability' definition of the primary endpoint

An additional sensitivity analysis will done for an alternative definition of persistent disability, considered as 'new onset' persistent disability, defined as an increase from baseline of >=4 points in WHODAS scores that persists for at least 6 months. The definition of time to the first of new-onset persistent disability or death will use the same principles as for the primary endpoint.

Secondary endpoints

1. Death/survival: all-cause mortality at 90 days, and survival up to 12 months after surgery.

2. A composite (pooled) and individual incidence of 30-day mortality and major septic complications, where the latter is defined as the composite of sepsis, surgical site infection, anastomotic leak and pneumonia at 30 days post-surgery. [Detailed clinical definitions are provided in the Protocol]
3. Acute Kidney Injury (AKI): according to the Kidney Disease: Improving Global Outcomes group criteria, but not urine output—for Stage 2 or worse AKI defined as at least twofold increase in creatinine, or estimated glomerular filtration rate decrease >50%.

Since a restrictive intravenous fluid regimen may artificially elevate serum creatinine due to a smaller dilutional effect from less intravenous fluids, we will calculate adjusted creatinine following the approach of Liu (2011, Reference 1 below), where

adjusted creatinine = serum creatinine × (1 + cumulative fluid balance/total body water),

and assuming that total body water is 60% of body weight, expressed in mL. Serum creatinine is measured on days 1 and 3 and the maximum value in the patient's hospital stay. We will apply adjustments to creatinine levels at days 1 and 3 only. Fluid intake will be accumulated using IV fluids administered intraoperatively, in recovery, and on days 1 to 3 postoperatively, plus the volume of any blood transfusions administered. Fluid outputs from the time of surgery to Day 1 post-surgery will be accumulated using the recorded urine outputs, blood losses and volumes in surgical drains. Missing fluid output components will be imputed to prevent adjustment factors being missing when creatinine levels are present. Fluid outputs on days 2 and 3 are not recorded, so these will be estimated under the assumption of a net fluid balance of zero on each of days 2 and 3; this will form the principal analysis. Sensitivity to this assumption will be assessed using two alternatives: (a) assuming a zero cumulative fluid balance at day 3, and (b) assuming the ratio of intake to outputs up to day 1 persists on days 2 and 3. These two assumptions enclose that of the principal analysis.

We will also report the use of renal replacement therapy up to 90 days after surgery; and delta-creatinine, defined as the difference between the maximum (fluid-adjusted) postoperative serum creatinine level and the preoperative serum creatinine level.

4. *Pulmonary oedema: documented evidence of respiratory distress or impaired oxygenation and radiological evidence of pulmonary oedema.*
5. *Duration of mechanical ventilation: Defined as additive over all episodes up to 90 days after surgery. This will be reported as (a) the proportion of patients requiring ventilation; and (b) the duration of ventilation in patients receiving ventilation.*
6. *Inflammation: plasma C reactive protein concentration on day 3 after surgery.*
7. *Tissue perfusion marker: peak serum lactate concentration within 24 hours of surgery.*
8. *Any blood transfusion: including red cell, fresh frozen plasma or platelet transfusion, from the initiation of surgery; and quantity of transfusion in patients receiving each product.*
9. *Unplanned admission to HDU/ICU within 30 days of surgery.*
10. *Total HDU/ICU stay in patients admitted to HDU/ICU, including initial admission and readmission duration up to day 30*
11. *Total hospital stay, including any readmission up to day 30.*
12. *Quality of recovery: QoR-15 score on days 1, 3 and 30.*
13. *The rates of serious adverse events, and severity of adverse events (mild, moderate, severe), classified by organ system.*

STATISTICAL ANALYSES

Primary endpoint: disability-free survival

Disability free survival will be displayed with Kaplan-Meier plots, and described with event-free proportions in each treatment arm obtained from these plots at days 1, 30, 90, 180 and 365 days post-surgery. Comparison of overall time to events between treatment arms will be made using the log rank test and the Cox proportional hazards model to provide a hazard ratio and 95% CI. Assessment of proportionality of hazards will be based on tests using Schoenfeld residuals. The principal analysis will not impute missing WHODAS measurements for patients known to be alive at those assessment times. The first sensitivity analysis will impute all missing WHODAS assessments for subjects known to be alive at those assessment times by giving them a disabled score (WHODAS of 24). A second sensitivity analysis will impute the missing WHODAS assessments using multiple imputation, with the imputation model employing baseline and post-baseline information predictive of missingness or WHODAS scores, separately in each treatment arm, with results combined across imputations using Rubin's rules.

Alternative 'new onset' definition of the primary endpoint

Analysis of disability-free survival based on the `new onset' persistent disability definition will follow the same approach as for the primary endpoint.

Time to death

Analysis of time to death will follow the same approach as for the primary endpoint.

Other outcomes

Secondary outcomes measured on a binary scale (1, 2, 3, 4, 8, 9) will be summarised using proportions in each treatment arm and analysed using binomial regression with a logarithmic link to estimate Risk Ratios with 95% CIs and p-values, or exact logistic regression to approximate Risk ratios if the number of events in either arm is fewer than 10. Should there be convergence difficulties with log-binomial regression, a log-Poisson model will be employed with robust standard errors.
Duration and length of stay outcomes (5, 10, 11) will be summarised using medians and interquartile ranges, and compared across treatment arms using the Wilcoxon– Breslow–Gehan test, with length of stay in hospital and in intensive care censored at 30 days, and with in-hospital deaths assigned the highest length of stay.
Outcomes measured on a continuous or semi-continuous scale (6, 7, 8, 12) will be summarised by means and standard deviations if reasonably symmetrically distributed and compared between treatment arms using linear regression with robust standard errors. Skewed outcomes will be summarised by medians and interquartile ranges; right skewed outcomes will be log-transformed prior to analysis using linear regression, and left skewed outcomes will be analysed using median regression with robust standard errors.

Additional sensitivity analyses

Sensitivity analyses for all outcomes will use regression models with additional adjustment for the stratification variables of site and planned HDU/ICU destination status, plus any variables exhibiting substantial imbalance across treatment arms at baseline.
Sensitivity to missing outcome data will be performed using multiple imputation if the proportion of missing data for the particular outcome is >5%. These analyses will use multiple imputation, employing imputation models with baseline and auxiliary post-baseline variables, and results combined across imputations using Rubin's rule.

Subgroup analyses

Planned subgroup analyses will assess heterogeneity of treatment effects of the primary endpoint across patient sex, age groups (approximate quartiles), country, bowel surgery (yes/no) and intraoperative use of any goal-directed techniques (yes/no). The latter include invasive or non-invasive cardiac output, stroke volume or pulse pressure variation and oesophageal Doppler, but exclude central venous pressure monitoring.
Additional prespecified subgroups will be tested for heterogeneity of effect, and their results considered exploratory: BMI categories (defined as underweight <18.5, normal 18.5-25, overweight 25-30, obese 30-35, super obese >35), ASA physical status (1/2, 3, 4), pre-operative planned HDU/ICU destination status, duration of surgery (approximate quartiles), and pre-operative planned use of a goal directed device (excluding CVP monitoring).
Additional analyses of the above subgroups will be performed for the endpoints of new-onset disability, composite of 30 day mortality and septic complications, and acute kidney injury.
For these analyses, we will undertake tests for interaction by adding treatment-by-covariate terms to the regression models specified for the main analyses of each outcome.

SAMPLE SIZE RE-ESTIMATION

The original sample size calculation was as follows: Assuming a 12 month disability-free survival probability of 65%, 2650 patients were required to detect a hazard ratio of 0.80 with 90% power using the Freedman method for the sample size for a log rank test. Correspondingly, 850 events were expected to be observed. The sample size was inflated to a total of 2800 patients to account for withdrawals and loss to follow-up.

A sample size reassessment of the assumed primary endpoint event rate was performed after 2578 patients had been randomised. At that time there were 300 primary endpoint events with a 12 month event rate of approximately 15%. Increasing the target sample size to 3000 patients under this same event rate was expected to yield approximately 380 events and afford 80% power to detect a hazard ratio of 0.75.

REFERENCES

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