Colloid infusion for Optimal outcomes In Non-cardiac surgery(COIN): a randomized controlled trial.

Statistical Analysis Plan

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Protocol Version History

Date (dd-mm-yyyy)	Version	Reason for the update
07-01-2023	1.1	Updated Version Number; Updated Subgroups: The prespecified subgroup was divided according to their age (≧ 65 years vs < 65 years), gender, BMI, ASA grade (I, II, III), surgery type (open, endoscopic, endoscopic to open), and surgical site (Head & neck surgery, abdominal surgery, superficial surgery, and other surgery).
25-03-2023	2.1	• Updated Version Number; • Re-estimated Sample Size to 2020; • Updated Exclusion Criteria: 1. known allergy to hydroxyethyl starch and/or multiple electrolyte injection; 2. Morbid obesity (BMI > 37.5 kg/m^2 or > 32.5 kg/m^2 with metabolic diseases); 3. severe electrolyte disorder (Na^+ > 160 mmol/L and/or <120 mmol/L); • Updated Anaesthesia Induction: The anesthesia induction was conducted by the

		attending anesthesiologists , which follows the institutional routine of each sites. Updated Details of Treatment; --Colloid fluid group: 5 ml/kg of hydroxyethyl starch 130 / 0.4 electrolyte injection solution (from Fresenius Kabi) was given before anesthesia induction, and the infusion was administered by the infusion pump for 15min. --Crystalloid group: 5 ml/kg of multiple electrolyte sodium acetate injection (from Fresenius Kabi) was administered by infusion pump for 15 min; Updated Secondary Endpoints: --incidence of post-induction hypotension, --consumption of intraoperative vasoactive drugs, --SOFA score of postoperative day 1, --postoperative length of hospital stay --proportion of patients with optimal recovery, hospital mortality and all-cause mortality at 30 days, and renal replacement therapy (RRT) during the 30 days observation period;

		--Updated Interim Analysis Plan: We will conduct an interim analysis when 50% patients are enrolled and followed-up for 30 days with primary endpoints. We hypothesized that rapid infusion of colloid before induction of anesthesia is associated with a 20% relative risk reduction in postoperative complications within 30 days after surgery as compared to bolus infusion of crystalloids. Considering 10% drop-out rate, 1010 patients in each arms will have 90% power to detect above mentioned difference at a significance level of 0.05. A total of 2020 patients will be enrolled and randomized at 1:1 ratio to colloid or crystalloid group. --Updated Blinding Method: The intervention fluid will be provided by the coordinating center and the bag will be delabeled with only the test number.
07-07-2923	2.2	◆ Updated Crystalloid: Crystalloid group: 5 ml/kg of multiple electrolytes injection (PLASMA-LYTE A Injection from Baxter)

		was given before anesthesia induction within15 min. ◆ Updated Anesthesia Protocol Details: 5.2.2 Anesthetic intervention 3) Anesthesia maintenance: using intravenous, volatile or Combined anesthetics for manintenance 5) Multimodal analgesia: if no contraindications, give non-steroidal anti-inflammatory drugs 15 to 20 min before incision; Local incision infiltration or nerve block. Patient-controlled intravenous analgesia (PCA) was performed as required. ◆ Updated Blinding; The intervention fluid will be provided by the coordinating center and will be covered with a opaque bag.

ABSTRACT

Background

This a priori statistical analysis plan describes the relevant statistical considerations and analyzing methods for Colloid infusion for Optimal outcomes In Non-cardiac surgery (COIN) Trial.

Methods:

COIN trial aims to investigate whether the preoperative bolus administration of colloid before the induction of anesthesia reduces the postoperative complications of patients undergo non-cardiac surgery with general anaesthesia comparing to crystalloid bolus administration. The study is a parallel group, blinded, prospective, randomized controlled, multicenter trial. In total, 2020 adult (≥ 18 years old) participants scheduled for elective, non-cardiac surgery with ASA grade I-III will be enrolled. Eligible patients will be randomly assigned (at 1:1 allocation ratio) to infuse either colloid (5 ml/kg Hydroxyethyl Starch 130/0.4) or crystalloid (5 ml/kg of multiple electrolyte injection) before anaesthesia induction within 15 min.

The primary endpoint of interest is a composite measure of postoperative complications (defined as Clavien-Dindo Classification ≥ I) within 30 days after surgery. The trial will determine whether preoperative colloids infusion can reduce postoperative complications within 30 days.

Conclusions:

This document provides a detailed statistical analysis plan for COIN.

Funding:

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Trial registration:

ClinicalTrials.gov identifier: NCT05728645. Registered on 05, 02, 2023.

Keywords:

Preoperative fluid management; Fluid bolus administration, Postoperative complications; Colloid; Crystalloid; Post-induction Hypotension; Statistical Analysis Plan

BACKGROUND

Approximately 30%-40% of patients who underwent surgery under general anaesthesia have been reported to experience hypotension between the induction and the start of the surgical procedure [1]. This circumstance is mainly caused by relative or absolute blood volume insufficiency [2]. Such insufficiency can be directly attributed to preoperative blood fasting, vasodilation induced by some anesthetic drugs, and negative inotropic effects.

Studies have suggested that the 30-day mortality rate of patients who experience an intraoperative mean arterial pressure of less than 50 mmHg doubles compared to those with an intraoperative mean arterial pressure of no less than 80 mmHg [3]. Even transient hypotension has been shown to be associated with myocardial injury, stroke, and acute kidney injury, leading to a serious deterioration of patients' prognoses [2].

Thus, since it is almost certain that preoperative fasting and/or certain induction agents can lead to post-induction hypotension, the European Society of Anesthesiology guidelines recommend that adults consume clear fluids 2 hours before elective surgery and solid foods 6 hours before [4]. However, this recommendation is restricted due to multiple reasons, and in reality, fasting times are often extended [5]. The use of vasopressors and positive inotropes can relieve hypovolemia-induced hypotension, but it may further lead to an increased myocardial load and oxygen demand [6].

The general consensus remains that rehydration can compensate for hypovolemia at baseline just before surgery [7]. Preoperative fluid infusion has been shown to reduce post-induction hypotension by more than 50%, while also reducing the use of vasoactive drugs, improving the cardiac index (CI), and reducing the early stroke volume variation (SVV) during surgery [8].

Colloids have a 1:1 intravascular volume expansion effect, whereas crystals produce only a 20% to 25% expansion due to their extracellular distribution [9]. Despite both crystalloid and colloid fluids demonstrating stabilized hemodynamic effects during acute severe hypovolemic shock, the required dosage of colloid fluid was significantly lower than that of crystalloid [9]. The associated lower heart rate in patients using colloid fluid is also more conducive to maintaining the oxygen supply balance of the myocardium [10]. Patients who were given intravenous crystalloid boluses before the induction of general anaesthesia did not significantly impact haemodynamic instability [7].

Yet, there are very limited studies and no clear evidence regarding whether preoperative fluid infusion therapy can improve the postoperative prognosis of patients undergoing general anaesthesia. Considering the benefits achieved through preoperative infusion in relation to post-induction hypotension, we thus hypothesize that preoperative fluid infusion can have an impact on

postoperative complications. Additionally, whether the reduction in post-induction hypotension acts as a mediating effect will also be explored.

COIN (Colloid infusion for Optimal outcomes In Non-cardiac surgery(COIN): a randomized controlled trial. Rationale and Design) aims to investigate whether the preoperative colloid infusion before the induction of anesthesia can reduce the postoperative complications of patients planning to undergo non-cardiac surgery with general anaesthesia comparing to crystalloid. The study is a parallel group, blinded, prospective, randomised controlled, multicentre trial with 1 : 1 allocation ratio.

The trial commenced in July 12, 2023 and the estimated timeline for completion of patient accrual was Mar 31, 2025. The participants will be followed until 30 days after surgery. This statistical analysis plan details the pre-planned analyses and statistical considerations for COIN for transparency of data management and analyses procedures. The trial protocol has been submitted to *BMJ Open* (bmjopen-2025-100293).

STUDY OVERVIEW

Ethics and Study Design

The planned study is a parallel group, blinded, randomised, controlled, multi-centre trial conducted at seven tertiary teaching hospitals across China. The study protocol was initially approved by the institutional review board (IRB)

of the coordinating site (Xijing Hospital: KY20232058-F1) followed by institutional IRB approvals from all participating centres. The informed consent will be obtained from patients before enrollment. One interim analysis was plannned at 50% information rate (50% enrolled participants has primary endpoints at 30 days after surgery) with futility stopping rule.

Study Population

The study includes 2020 adults (≥ 18 years old) who are planning to undergo elective non-cardiac surgery with ASA grade I-III under general anesthesia that requires tracheal intubation. The trial excludes patients for whom the intervention fluids is contraindicated or should be withhold by the judgement of the attending physician (known allergy to hydroxyethyl starch and/or multiple electrolyte injection; presence of renal failure preoperatively (defined as eGFR < 30 mL/min/1.73m^2 and/or patient receiving renal replacement therapy); abnormal coagulation function (PLT < 100×10^9/L and/or PT <70% and / or aPTT> 35 s); severe electrolyte disorder (Na^+ > 160 mmol/L and/or <120 mmol/L); increased preoperative intracranial pressure requiring dehydration treatment). The trial also excludes patients with decompensate organ dysfunction or with systematic morbidities [cardiac dysfunction (EF < 35%); liver dysfunction (defined as Child-Pugh C); morbid obesity (BMI > 37.5 kg/m^2 or > 32.5 kg/m^2 with metabolic diseases)]. Patients with anticipated length of postoperative hospital stay less than 24 hours and patients scheduled for multiple operations during this hospitalization (e. g. burn patients) are also excluded from the study.

Randomisation, Allocation, Concealment and Blinding

Permute-blocked randomisation with random block sizes stratified on study sites is used. The randomisation procedure was realised using a web-based service (Research Electronic Data Capture, RedCap, developed by Vanderbilt University).

Eligible patients will be assigned to receive either colloid or crystalloid before anaesthesia induction at 1:1 ratio. Participants, caregivers, and investigators responsible for analysing data and assessing outcomes are unaware of the group assignments. Only one investigator will be unblinded and prepare the allocated intervention fluid. The blinding is achieved by covering the intervention fluid with opaque sterilized cloth bag. The fluid infusion will be conducted and finished through an infusion pump (Zhejiang Smith Medical instrument Co., Ltd., SY-1200 Infusion Pump) prior to induction of anesthesia. The unblinded investigator will not be involved in any other aspect of the surgery, anaesthesia, data recording, outcome assessment, or data analysis.

Interventions

Patients will be administered 5 ml/kg 6% Hydroxyethyl Starch 130/0.4 Electrolyte injection or 5 ml/kg multiple electrolyte injection before anaesthesia

induction. The infusion is required to be completed within 15 minutes. A detailed study flowchart can be found in Figure 1.

All participants will receive perioperative management in accordance to standard practices in each participant site. Mechanical ventilation is configured in the (IPPV mode, with a tidal volume 6 - 8 ml/kg and a respiratory rate f 10 - 15 breaths per minute) to maintain the end-tidal carbon dioxide ($EtCO_2$) level at 35 ± 5 mmHg. Any form of intravenous, inhaled, or compound anesthesia is permitted. Intraoperative monitoring encompasses vital signs such as mean arterial pressure (MAP), heart rate, peripheral capillary oxygen saturation (SpO2), temperature (either non-invasive or invasive arterial pressure), bispectral index (BIS) value (maintained between 40 and 60 during the operation), fluid volume, bleeding, urine output, as well as the use of intraoperative vasoactive and inotropic drugs. Other routine monitoring procedures include, but are not limited to, electrocardiogram (ECG), central venous pressure (CVP), cardiac output (CO), arterial blood gases, coagulation monitoring, and frequent routine laboratory examinations.

Nonsteroidal anti-inflammatory drugs (NSAIDs) will be administered 15 to 20 minutes prior to skin incision if no contraindications are used. Either local infiltration of the incision or a nerve block can be applied depending on the surgical site. Patient-controlled intravenous analgesia (PCA) is also allowed as

required. Based on the risk stratification of postoperative nausea and vomiting (PONV), double or triple therapy for postoperative nausea resistance should be provided. Postoperative muscle relaxant antagonism will be given when necessary, and the tracheal tube will be removed once the extubation requirements are met. All other anesthesia procedures will adhere to the institutional standard practices.

Data Collection and Management

Data will be collected prospectively at scheduled time points according to a pre-established case report form (CRF) and stored in REDCap. Baseline evaluation contains characteristic information such as demographics, comorbidies, chronic medications, preoperative lab tests and clinical evaluations, planned surgical procedures, blood pressure, oxygenation saturation before fluid bolus administration. Intraoperative anaesthesia information to be collected include monitored vital signs, anesthetic choice and dose, parameters for mechanical ventilation (tidal volume, positive expiratory pressure delivered, FiO_2), use of open labeled fluids and the use of inotropic drugs and vasopressors, intraoperative complications, procedure characteristics, etc. Postoperative management including the analgesia regimen, transition from the operating room to postoperative anaesthesia care unit (PACU), intensive care unit (ICU), or ward, and any complications of research interest will be documented.

The observation periods start from randomization to 30 days after surgery. Participants is closely monitored until hospital discharge. After discharge, follow-ups are conducted through either in-person hospital visit or telephone calls. Any postoperative complications will be recorded. The observation periods start from randomization to 30 days after surgery. Patients who experience adverse events (AEs) will be monitored until recovery or at least until having any indication of improvement in AE symptoms. All unresolved AEs must be followed up until the outcome is determined, or at least until the final follow-up visit.

All data will be meticulously recorded in CRFs. The principal investigator at each site is responsible for data accuracy. Original documents and test results will be verified before producing electronic versions. Data quality will also be monitored through random checks against original CRFs. An independent Data and Safety Monitoring Board (DSMB), composed of a statistician, CRC, and anesthesiology expert, will oversee the safety and scientific validity of the study.

STUDY OUTCOMES

Primary Endpoint

The primary endpoint is the composite of postoperative complications that occur within 30 days following surgery. Specifically, these complications are

evaluated based on the modified Clavien-Dindo Classification, with those classified as ≥ I (as detailed in Table 1) being considered.

Secondary Endpoint

1.Incidence of hemodynamic instability, which is defined as a mean arterial pressure (MAP) dropping below 65 mmHg or decreasing by more than 20% from the baseline within 20 minutes after the induction of anesthesia.

2. Intraoperative consumption of vasopressors.

3. Length of postoperative hospital stay, calculated as the time interval between the index surgery and the patient's discharge from the hospital.

4. Rate of ideal postoperative recovery, determined as uneventful discharge within 5 days after surgery (without major complications,classified as ≥ III according to the Clavien-Dindo classification, incision infection, and readmission);

5. Proportion of patients with Clavien-Dindo classification Grade IV complications, which is defined as life-threatening complications requiring ICU management, such as single organ dysfunction (including dialysis) or multiorgan dysfunction.

Exploratory outcomes

1. Each individual component of the composite primary endpoint (by organ system and by different Clavien-Dindo classification Grades)

2. 30-day all-cause mortality;
3. Incidence of unplanned ICU admission；
4. Incidence of unplanned reoperation；
5. Incidence of in-hospital complications；
6. Barthel index for activities of daily living (ADL) at 30 days after surgery.

Safety Outcomes

1. Incidence of acute kidney injury diagnosed by KDIGO criteria;[31]
2. Massive intraoperative bleeding (hemorrhage exceeds 1000 ml);
3. Episodes of intraoperative hypotension defined as SBP < 90 mm Hg or drop ≥ 30% of baseline lasted for 5 min;
4. Episodes of hypertension defined as SBP > 180 mm Hg or rise ≥ 30% of baseline lasted for 5 min;
5. Arrhythmia that consisted of bradycardia (heart rate < 40 beats per minutes), tachycardia (HR > 100bpm) or new onset of arrhymia that require anti-arrythmic drugs;
6. Airway hyper-responsiveness defined as a airway peak pressure > 40cm H_2O).

All outcomes will be discussed and evaluated by the endpoint assessment committee and documented as appropriate. All adverse events must be recorded in CRFs and documented. The reporting of SAE follows the

institutional requirement and local regulations.

STATISTICAL ANALYSIS PLAN

Scope of the Analysis plan

This Statistical Analysis Plan (SAP) presents the statistical consideration in design and analyses for COIN trial. The final manuscript will strictly follow this SAP.

Sample Sizes

In order to detect a 13% absolute reduction (from 33% to 26%) for the primary outcome of postoperative complications of Clavien-Dindo Grade ≥ I up to 30 days after surgery (a risk ratio of 0.8), with 90% power and an overall type I error rate of 5%, a total of 2020 patients (1010 per arm) are required, accounting for 10% drop-out rate.

Randomisation procedure

Randomisation will occur after obtaining informed consent from the eligible patients and shortly before the index surgical procedure is due to start (last-minute randomization). Patients will be centrally allocated to treatment arms in a 1:1 ratio by permuted block randomization stratified with participant centers. To enter a patient into the COIN trial, research staff at each participant site will log on to a secure web-based randomization platform of Redcap data

entry system and obtain a unique patient identification number and allocation assignment. This information will be only revealed to the unblinded investigator who prepare the intervention fluids.

Datasets for Analyses

All statistical analyses within this study will be performed following the intention-to-treat principle. This implies that patients will be analysed in accordance with the treatment groups to which they were initially assigned, as depicted in Figure 1. It is expected that there will be either no or very minimal losses to follow-up for primary and secondary outcomes considering the prospective feature. Patients with missing primary outcome data will be excluded from the analysis (complete-case analysis approach). Missing data for baseline covariates to be included in the analysis model will be accounted for using multiple imputation.

Participation of individual patient in the study will be terminated if they (or their trusted person) withdraw consent. However, if the investigator discontinues the patient's participation, either temporarily or permanently, for reasons in the patient's best interest, especially when serious adverse events are suspected to be related to the intervention, the patient will remain in the analysis to uphold the intention-to-treat principle. Their data will continue to be collected until 30 days after surgery, which marks the final follow-up.

Modified Intent-to-Treat (m-ITT) population excludes individuals who had their

surgical procedures canceled after randomization, patients who withdrew their consent. The as-treated population is defined by the treatment that was actually received during the trial. This takes into account any deviations from the initially assigned treatment regimen, such as crossovers to the other treatments. The Per-Protocol (PP) population consists of all patients who received the assigned treatment without significant deviations from the protocol. Specifically, the analysis will be restricted to those who completed the full-term intervention as it was initially assigned. Participants with treatment interruptions will be excluded from the PP analysis. The exclusion list will be verified by the steering committee prior to lock of the database. Analyses conducted on these dataset will be treated as supplementary analyses.

General analysis Principles

The COIN trial is designed to assess the impact of preoperative colloid infusion on the occurrence of postoperative complications in surgical patients undergoing non-cardiac surgery with general anesthesia. The estimand is the difference in the incidence of postoperative complications as defined by higher than grade I Clavien-Dindo classification at 30 days after surgery between Colloid bolus administration versus crystalloid bolus administration, in patients undergo elective non-cardiac surgery under general anesthesia. The target population is patients experienced surgery procedure. The patients have the planned surgery canceled after randomization will be excluded from the

primary analyses.

In general, categorical variables are to be compared using χ^2 test or Fisher's exact test. Continuous variables will be compared via t-test or Wilcoxon's rank-sum test. Variable normality will be assessed either via the Shapiro-Wilk test or QQ-plots and residual plots. Variable transformation such as natural logarithm or square root will be applied where necessary, or non-parametric methods (such as Wilcoxon rank sum test) shall be applied.

For the analyses of primary, secondary outcomes, and the process measures, the following information will be presented:

- The number of patients included in each analysis, by treatment arm
- A summary statistic of the outcome (such as, number (%), mean (sd), media (IQR), etc), by treatment arm
- The estimated treatment effect
- A 95% confidence interval for the estimated treatment effect
- A two-sided *P* value

For all analyses, a significance level of 5% will be used. Multiple comparisons will be conducted without Type I error correction and will be interpreted as exploratory.

Data Presentation and Baseline characteristics

Baseline characteristics will be summarized using descriptive statistics for whole patients cohort and for each treatment group by mean and standard

deviation or median and interquartile range for continuous variables, and the number, frequencies, and percent for categorical variables.

Durations According to Dates

For the indexed surgery, the date of randomization or admission to the intensive care unit corresponding to the surgery date will serve as day 1.

Take, for example, the calculation of the postoperative hospital stay (in days). The formula is: (Discharge date from hospital - Date of index surgery) + 1

Exact dates will be tracked and documented.

Analysis of the primary endpoints

The primary endpoint, incidence of postoperative complications as defined by higher than grade I Clavien-Dindo classification at 30 days after surgery will be analyzed using Chi-squared test as crude analysis. Unadjusted risk ratios with 95% confidence intervals will be estimated by two-by-two table with the use of log-Normal approximation or other approximation/numeric methods as appropriate. The effect size will be expressed as risk differences (95% confidence intervals) will be estimated using Wald's likelihood ratio approximation test or other methods appropriate, with the number needed to treat as the reciprocal of the risk difference, rounded to the nearest integer.

Secondary Analyses of the primary endpoint

To account for potential confounders, the adjusted analysis of primary endpoint will use a logistic regression model, wherethe primary endpoint as the dependent variable and independent variables to include study group (colloid fluid bolus group vs crystalloid fluid bolus group), adjusting for the relevant confounders (planned surgical procedure complexity grade, ASA grade, gender, age, baseline hemoglobin, and baseline creatinine, NPO duration, fluid administration within 12 hours prior to surgery). Odds ratios (95% confidence intervals) will be reported; for those ORs may potentially be biased approximation for RRs, estimates will be obtained via either binomial regressions or converted using bootstrap methods. We will also develop a logistic regression model accounting for the above variables plus any baseline characteristics that appear on visual review to be potentially imbalanced between the study groups.

To account for the center effects, we will fit a mix-effect model with the primary outcome as dependent variable, including group assignment as a fixed effect and participant center (stratification variable) as a random effect. Potential confounders that included in the model are the same as the logistic regression model. Alternative method to use if mixed-effect models fail to reach convergence:

- Include participant sites as a fixed-effect instead of random effect.
- Remove the fixed effect for participant sites
- Adjust for age, hemoglobin, creatinine, fasting duration, etc as a single

continuous variable.

- Remove the covariates in prespecified order to see if convergence reached: gender, hemoglobin, creatinine, age, surgical complexity, ASA grade.

To better interpret the composite endpoints with different levels of clinical importance. We will repeat analysis of primary outcome using a hierarchical global rank scale by using win ratio method. This method put the greater weight on the more patient centered outcomes with more clinical relevant outcomes (death, life threatening complications) than transient, self-limiting complications. In the present study, the complications with higher grade of Clavien-Dindo classification will be put on higher hierarchy. The global rank endpoint will be constructed by comparing each patient in the intervention group to each patient in the control group (a total of m x n comparisons where m is the total number of patients in the intervention group and n the number of patients in the standard care group) for the prespecified order of the endpoints. Based on which patient performs better in each pair, the group they belong to would be declared the ‘winner’. This would give us the total number of winners in each group and our test statistic would be based on this. In the case of the win-ratio method, for instance, the statistic would be the number of winners in the intervention group divided by the number of winners in the control group. A 95% confidence interval for the win ratio will be calculated with the bootstrap

method. To make the pairwise comparison, the priority order of endpoints are:

1. Clavien-Dindo grade V
2. Clavien-Dindo grade IVb
3. Clavien-Dindo grade IVa
4. Clavien-Dindo grade IIIb
5. Clavien-Dindo grade IIIa
6. Clavien-Dindo grade II
7. Clavien-Dindo grade I
8. No complications happened

Finally, We will repeat primary analysis on primary endpoints by using mITT, as-treated and PP data-sets.

For scenarios where events are rare in the defined order above, the following orders and composites shall be considered:

1. Clavien-Dindo grade V
2. Clavien-Dindo grade IV
3. Clavien-Dindo grade III
4. Clavien-Dindo grade II
5. Clavien-Dindo grade I
6. No complications happened

OR

1. Clavien-Dindo grade V
2. Clavien-Dindo grade III - IV

3. Clavein-Dindo grade I - II
4. No complications happened

Estimating the effect of the intervention for participants who undergo surgery under general anesthesia

The COIN trial is to evaluate whether colloid bolus infusion before anesthesia induction improves clinical outcomes compared to crystalloid bolus infusion in patients undergoing non-cardiac surgery under general anaesthesia. In clinical practice, in rare circumstance, surgery may be delayed or canceled, and the participant may not undergo surgery before the outcome is collected. Similarly, in rare instances, the surgery may be conducted under local anesthesia. These participants will be excluded and the left participants who undergo surgery will be analyzed as mITT datasets.

Protocol Deviations

The number and percent of patients with at least one protocol deviation will be summarized for each treatment arm. These include received wrong fluid, received wrong dose of fluid, or with infusion duration exceeds 15 min. These participants will be excluded and the left participants will be analysed as PP datasets.

Analysis of the secondary endpoints

Incidence of hemodynamic instability within 20min of anesthesia induction.

Incidence of post-induction hypotension will be analysed using a logistic regression model, adjusting for ASA grade, gender, age, NPO duration, fluid administration within 12 hours prior to surgery (y/n), history of hypertension.

Intraoperative consumption of vasopressors

Intraoperative consumption of vasopressors will be analyzed using a linear regression model, adjusting for ASA grade, gender, age, NPO duration, fluid administration within 12 hours prior to surgery (y/n), history of hypertension.

Length of postoperative hospital stay

Length of postoperative hospital stay will be analysed using a competing-risk time-to-event model, considering mortality as a competing risk for hospital discharge. The model will include adjustment for planned surgical procedure complexity grade, ASA grade, gender, age, baseline hemoglobin, and baseline creatinine. In case of convergence issues, singular matrix, or other numeric complexity, appropriate data transformation, or dimension reduction methods will be used.

For each treatment arm, we will present median and IQR for length of hospital stay for patients survived to hospital discharge. The number and percentage of patients survived to discharge and number and percentage of patients who died will also be reported.

Rate of ideal postoperative recovery within 5 days of surgery

Rate of ideal postoperative recovery within 5 days of surgery will be analysed using using a logistic regression model, adjusting for planned surgical procedure complexity grade, ASA grade, gender, age, baseline hemoglobin, and baseline creatinine. Similar will be conducted for as above for cases of computing complexities.

Analyses of exploratory outcomes

Each individual component of the composite primary endpoint (by organ system and by different Clavien-Dindo classification Grades)

This will be analyzed using the same approach as for the analysis of the primary outcome above. Unadjusted Chi - squared test will be used.

Thirty day all-cause mortality

The expected event rate for this endpoint is extremely low. Thus, descriptive statistics will be used. Fisher exact test will be used to compare between group difference.

Incidence of unplanned ICU admission；

This outcome will be compared either using Chi-square test or Fisher exact test as appropriate depending on rate.

Incidence of unplanned reoperation

This outcome will be compared either using Chi-square test or Fisher exact test as appropriate depending on rate.

Incidence of in-hospital complications

This outcome will be compared either using Chi-square test or Fisher exact test as appropriate depending on rate.

Barthel index for activities of daily living (ADL) at 30 days after surgery.

The ADL score will be analyzed using a linear mixed model, with a random intercept for participant centers and adjusting for planned surgical procedure complexity grade, ASA grade, age, gender, baseline hemoglobin, and baseline creatinine. For any computation complexities, variable transformations or dimension reduction methods will be used.

Clavien-Dindo Grade IV - V complications within 30 days of surgery

Clavien-Dindo Grade IV - V complications within 30 days of surgery will be analyzed using a logistic regression model, adjusting for planned surgical procedure complexity grade, ASA grade, baseline hemoglobin, and baseline creatinine.

The expected event rate for this endpoint is lower than for other outcomes, thus we reduce the number of covariates that included in the model.

Analysis of Safety outcomes

Safety outcomes will be analyzed using the same method as the analysis of primary endpoints.

Interim analyses and stopping rules

The data safety monitoring board (DSMB) will review the outcome data, safety data and recruitment data during the trial. The DSMB will recommend that the trial to stop early if:

1. There is overwhelming external evidence to convince a broad range of clinicians that one trial arm is clearly indicated or contraindicated, and this new evidence would influence patient management.
2. It becomes evident no clear outcome will be obtained.

In addition, one prespecified interim analysis for futility will be conduced a at halfway point of the trial, aka after enrollment of 1010 participant with 30-day follow-up visit for the primary endpoint. The stopping boundary for futility was designed based on O'Brien-Fleming spending function and the decisions will be made by an independent Data and Safety Monitoring Board (DSMB). The defined futility stopping conditions are either z-score > 0.263 or if one-sided p-value > 0.3962. No early efficacy stop was planned for this study as we do not intend to prematurely halt the study based on the observation of early positive results.

The DSMB will also formally evaluate the safety of the trial, The safety outcomes in each group will be reviewed by the DSMB. If the *P*-value for the difference between study groups in any of the safety outcomes is 0.05 or less using a Mann-Whitney rank-sum test and is concordant in direction with the point estimate for mortality, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point.

No adjustments to the primary analysis and the sample size will be made to account for any interim analysis performed for the DSMB. All unblinded analysis for the DSMB will be performed by an independent statistician not involved in the trial, so as to maintain blinding.

Subgroup analyses

Prespecified subgroup analyses using formal tests of statistical interaction in a logistic regression model will be performed for the primary outcome to assess whether prespecified baseline variables modify the effect of treatment group on the primary outcome intervention differs among subgroup population. The subgroup analyses will be performed using the same model as for the primary endpoint. Independent variables will include study group assignment, the potential effect modifier of interest, and adding an interaction term between the two, aka the potential effect modifier and the treat arm. The presence of interaction will be tested using a likelihood ratio test comparing the subgroup

analysis model with interaction term, to the primary analysis model without interaction term. The test will be considered significant at the 5% level. A *P* value for the interaction will be reported. *P* values less than 0.1 will be considered potential interaction, while values less than 0.05 considered to a confirmed interaction. Non-linearity for continuous variables will be explored and analyzed using smoothed methods such as splines and preferably consider 3-5 knots using a locally weighted regression or partial effects plots. Patients with complete outcome data will be included in the subgroup analysis. Within each subgroups, we will report summary statistics of the outcome by treatment arm, and a treatment effects and 95% confidence intervals. We will use a forest plot to display the effect of covariates. For presenting the continuous variables, they will be dichotomous for forest plot demonstration.

The pre-specified subgroups are:

- Participant center (1-7)
- age (continuous variable, and < 65 years vs ≥ 65 years)
- gender (male, female)
- BMI (continuous variable, and < 24 kg/m^2 vs ≥ 24 kg/m^2)
- ASA classification (I, II ,III)
- Surgical procedure (abdominal, reproductive and urogenital system, musculoskeletal and connective tissue, breast & thyroid, facial and orthognathic surgery and ophthalmology, nervous system, other)
- Surgical complexity grade (minor, moderate, major, complex)

- NSQIP any complication risk (continuous variable)
- Inferior Vena Cava Collapsibility Index (continuous variable)
- Baseline SBP (continuous variable)
- NPO duration (continuous variable)
- Fluid administration at 12 hours prior to surgery

In addition, we will perform exploratory analyses for additional effect modifiers that are collected after randomization and have the theoretical potential to be affected by the study group assignment:

- Surgical incision type (open, mini-invasive with endoscopy, endoscopic converted to open)
- Choice of sedatives (etomidate, ketamine, propofol, other).
- Use of vasopressor (yes/no)
- Post-induction hypotention (yes/no)
- SBP after fluid bolus infusion (continuous variable)

Handling of Missing Data

Considering the prospective feature of RCT studies and primary endpoints are short-term outcomes, we anticipate no missing primary outcomes and very rare missing values in other variables if any. All demographics and chronic medical history will be filled on site. Intraoperative data will be monitored and documented during surgeries in the operating rooms. Postoperative follow-ups

will be tracked from the electronic health records until discharge of hospital. Other 30-day follow-up data will be obtained via phone-calls, social media software, or updated medical records from any other medical units where available by trained CRCs. Therefore, missing data will not be imputed for the primary or secondary outcome. In adjusted analyses, missing data for covariates will be imputed by multiple imputation. We will combine estimates of the treatment effect and standard errors from the 10 imputed data sets on the log odds scale using Rubin's rules.

Outliers will be subject to confirmation queries to the investigators. In case of confirmation, no modifications will be made before taken into account during analyses.

Corrections for Multiple Testing

We will conduct a single primary analysis of a single primary outcome. Additional analyses are deemed exploratory and hypothesis-generating. No correction for multiple comparisons will be performed.

Table 1 Clavien-Dindo classification

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment, or surgical, endoscopic, and radiological interventions.

Grade	Definition
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including central nervous system complications) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

Figure 1 Study Flowchart