**Supplementary Online Content**

**eAppendix 1:** Study procedures

**eAppendix 2:** Statistical analysis plan

**eAppendix 1**

Patients were randomized to receive either goal-directed bolus administration of 250 mL lactated Ringer´s solution or 250 mL of hydroxethylstarch 6% (Voluven, Fresenius Kabi, Germany). We performed intraoperative goal-directed fluid management using esophageal Doppler monitoring (CardiacQ; Deletex Medical, Chicester, UK). Our fluid management was based on the algorithm published by Gan et al.1 All patients received a baseline lactated Ringer´s solution with an infusion rate of 2mL kg-1 IBW (ideal body weight) -1 h-1 . The infusion rate was increased to 3-5 mL kg IBW-1 h-1 as soon as viscera were exposed. IBW was calculated according to the Robinson formula as follows: Men: IBW (in kilograms) = 52kg + 1.9 kg for every 2.5cm over 150cm body size Women: IBW (in kilograms) = 49kg + 1.7 kg for every 2.5cm over 150cm body size. We placed the oesophageal Doppler probe after induction of anaesthesia. For fluid guidance we used corrected aortic flow time (FTc) and stroke volume (SV) derived from esophageal Doppler as previously descripted. A 250 mL aliquot of lactated Ringer solution or 6% hydroxyethyl starch was administered when the corrected Flow time (FTc) was less than 0.35s. If the stroke volume (SV) increased ≥ 10 % and FTc still remained below 0.35s, the bolus was repeated until no further increase in stroke volume was observed. If the FTc increased above 0.35s, no further fluid challenge was administered, and measurements were repeated after 10 minutes. If Ftc remained low after bolus administration and SV did not increase by ≥ 10%, no further bolus was administered, and measurements were repeated after 10 minutes. When we observed a further decrease in SV by at least 10% of the last value the fluid challenge was repeated. When mean arterial blood pressure decreased more than 20% of baseline value or was lower than 65 mmHg and was not improved by further fluid bolus administration or fluid administration was not indicated due to FTc greater than 0.35 s, intravenous bolus doses of vasopressors were administered (Phenylephrine 0.02-0.1 mg). Hemodynamic parameters were re-evaluated at least every 10 minutes (more frequently in case of significant hemodynamic changes, e.g. blood loss).

A study assistant, who was well trained in esophageal doppler monitoring, was in the OR throughout surgery to optimize the doppler derived signal. The study assistant further recorded hemodynamic data including doppler derived parameters, blood pressure, heart rate, and oxygen saturation every ten minutes. Furthermore, when a fluid bolus was administered, doppler derived parameters and blood pressure was recorded before and after the bolus was administered.

**eAppendix 2:**

**Hemodynamic Changes Following Crystalloid vs. Colloid Fluid Bolus During**

**Noncardiac Surgery**

**Statistical Analysis Plan**

Intraoperative hemodynamic and fluid management has a substantial impact on postoperative outcomes. Excessive or too restrictive fluid management during surgery is associated with increased morbidity and mortality. Goal-directed fluid therapy remains a more physiological approach as compared to a fixed dose regime. The effect on hemodynamic stability between using a crystalloid versus a colloid based goal-directed fluid regimen is still unknown.

Balanced crystalloid salt solutions are the most commonly used perioperative fluids because they are inexpensive, readily available, and relatively non-toxic. However, crystalloid solutions start to leave the intravascular space within minutes and thereafter provide little hemodynamic support. Crystalloids accumulate in tissues including lungs and incision sites, thus promoting edema, weight gain, and prolonged recovery.

Colloids, on the other hand, are more likely to stay intravascularly for hours, thus promoting hemodynamic stability. The higher osmotic pressure is provided by the high molecular weight. This makes it difficult for colloids to cross the glycocalyx barrier and the endothelium. Therefore, they are available longer in the in the intravascular space and might be better for circulatory support.

Besides maintaining intravascular volume, fluid bolus affects hemodynamic parameters like blood pressure and cardiac index. The differential effect of colloid versus crystalloid boluses on the cardiac index is not well known. It is also of great interest to evaluate the number of fluid boluses needed to reach the optimal cardiac output and moreover the duration of action before another fluid bolus is needed for hemodynamic stability.

Specifically, the hemodynamic effects of crystalloids versus colloids in patients with more comorbidities is still not known. Patients with higher preoperative risk factors are more susceptible to develop intraoperative hypotension and postoperative complications. In the overall study population in the main trial we did not observe a difference in postoperative minor and major complications with administration of either goal-directed colloid or goal-directed crystalloid administration. Furthermore, there was no difference in TWA-MAP between the groups, however there might be a difference in the within-patient variability of -MAP. It is thus important to evaluate in detail differences in pharmacokinetics as well as differences in hemodynamic parameters such as cardiac index. The goal-directed administration of colloids might result in a higher cardiac index and the duration of action is more sustainable as compared to crystalloids alone. Specifically, we want to know whether the increase (slope to reach a 20% higher FTC compared to the baseline value) in cardiac index is faster with colloids. In addition, we will evaluate the duration of time at which the cardiac index is at a specified level (defined as Ftc > 300ms).

Therefore, we will test the primary hypothesis that goal-directed colloid administration will increase TWA-CI compared to goal-directed crystalloid administration. Our secondary aims are to assess the effect of goal-directed colloid administration on 1) the net effect of a bolus administration on CI and the duration of action after each bolus given; and 2) the within-patient variability of MAP between the groups. In tertiary analyses we will assess the interaction between fluid strategy and baseline risk (high, low) on the primary and secondary outcomes.

**Study Aims**

**Primary Aim** –Evaluate whether goal-directed administration of colloids increases the TWA CI during surgery compared to the goal-directed administration of crystalloids.

*Primary Hypothesis* – Colloids have a higher molecular weight and therefore are more likely to increase CI than crystalloids.

*Primary Outcome* - The difference of TWA-CI between study groups.

**Secondary Aim 1** – Evaluate whether the goal-directed administration of colloids increases the immediate effect of bolus administration on CI compared to crystalloids.

*Secondary Hypothesis 1* – We assume that the immediate effect on CI is higher after a colloid bolus as compared to a crystalloid bolus.

*Secondary Outcome 1* – The difference of CI before and after each bolus administration for a patient given during surgery.

**Secondary Aim 2** - Evaluate whether the goal-directed administration of colloids increases the time between boluses compared to crystalloids. To the extent that the protocol was well followed, this will amount to a comparing of groups on duration of corrected flow time staying in desired range.

*Secondary Hypothesis 2* – The effect on the increased CI will be more sustainable after a bolus administration of colloids as compared to crystalloids.

*Secondary Outcome 2* – The time from ending of one bolus until the time of another bolus.

**Secondary Aim 3** – Assess whether colloids affect blood pressure variability.

*Secondary Hypothesis 3* – Blood pressure variability, measured as ARV-MAP, is lower with goal-directed colloid than crystalloid administration in patients having moderate- to high-risk abdominal surgery. Therefore, we evaluate differences in ARV-MAP, which is a marker of hemodynamic variability, between both study groups.

*Secondary Outcome 3* - Average real variability of mean arterial pressure for surgery between both groups. ARV-MAP will be calculated as the sum of absolute value of all changes across measurements divided by total time.

**Outcomes**

Primary Outcome: The time weighted average of cardiac index.

Secondary Outcomes 1: Change in CI after bolus administration.

Secondary Outcome 2: Duration of action of bolus administration.

Secondary Outcome 3: Average real variability of mean arterial pressure during surgery.

 **Measurements**

In the trial, cardiac output was measured intraoperatively at 10-minute intervals. They were also measured before and after a bolus administration however the exact timings of these measurements are not known. As a result, when computing the TWA of cardiac index, only the 10-minute interval measurements with timestamps will be used. Additionally, we will exclude any cardiac index measurements less than 0.8 L/min/m2 or greater than 8 L/min/m2 as they are likely to be recording errors.

The generalized average real variability (ARV) of mean arterial pressure will be computed as follows:



Where BPk is the kth MAP measurement and T is the total time between the first and last blood pressure measurement.

From the data, we know that approximately 8% of the patients had no cardiac output recorded at the prescribed 10 minute intervals. We will investigate the distribution of missing values between the two treatment groups as well as possible relationships with baseline variables. Assuming that no extreme associations with baseline variables or major differences between groups exist, the data will be considered missing at random and the principal population for this study will be the subset of the trial with at least one cardiac index measured.

 **Statistical Analysis**

*Confounder control*

From the previous trial, the randomized groups are known to be balanced on most of the demographic factors collected. The absolute standardized difference (ASD) for smoking status was 0.12 and all others had an ASD < 0.1. The primary and secondary analyses require us to subset the data to remove patients with missing outcome variables. Our strategy to control for confounding in all analyses will be as follows. If none of the baseline factors have an ASD > 0.1, no adjustments will be made. If only a small handful of the baseline factors are imbalanced, the imbalanced factors will be added to models. Otherwise, a propensity model will be created, and inverse probability of treatment weighting (IPTW) will be used when assessing the treatment effect on outcome variables.

*Propensity score (PS) model*. As needed, we will estimate propensity scores by fitting a logistic regression model predicting group assignment (colloids=1, crystalloids=0) as a function of all baseline potential confounding variables. A successful PS model will be achieved when ASD < 0.10 for all baseline variables. We will then use inverse probability of treatment weighting on the PS when comparing groups on outcome.

*Primary analysis (TWA of CI)*

We will assess the treatment effect on mean TWA of cardiac index using a 2-sample t-test either with or without inverse weighting by the PS. If that outcome is not normally distributed, we will attempt a transformation, and if not successful, will conduct a Wilcoxon rank-sum test. If only a few variables are imbalanced, the treatment effect may be assessed in a multivariable linear model while adjusting for the imbalanced variables.

A significance criterion of α=0.05 will be used for all analyses.

*Sensitivity analysis (imputed missing values)*

We will repeat the primary analysis using imputed values for the TWA of CI. Patients with missing outcomes will be imputed to the 75th percentile TWA CI if they are in the crystalloid group and the 25th percentile if they are in the colloid group. This imputation and analysis will be repeated using the largest and smallest observed values.

*Sensitivity analysis (repeated measures model)*

In addition to analyzing the aggregated cardiac index, we will also model the intraoperative cardiac index as a time series. A repeated measures model with an autoregressive (AR(1)) correlation structure will be fit to adjust for within-patient correlation. No imputation on missing outcomes will be done for this analysis.

*Secondary analysis 1 (immediate effect of bolus on CI)*

Differences between CI before and after bolus administrations will be computed. A repeated measures linear model with unstructured or AR(1) correlation will be used to account for correlation within a patient’s repeated measurements. The difference in mean changes in CI between groups will be tested.

Approximately 10% of patients had no bolus administrations and thus will be excluded from this analysis. After subsetting the population, we will attempt to control for confounding in the same manner as the primary analysis.

*Secondary analysis 2 (duration of effect of bolus on FTc)*

We will conduct a time to event analysis in order to assess differences in duration of the two fluid choices. We will collect the bolus administration timings for patients with at least one bolus administration. The last bolus for each patient will be considered right censored at the end of surgery. A Cox proportional hazard frailty model will be created to assess differences in time until the next bolus between groups. This model considers patient as a random effect in order to account for correlation in the repeated measurements within subjects. We will also assess the interaction between the bolus number and treatment group.

As with secondary analysis 1, if the subset of patients with at least one bolus administration is imbalanced on key characteristics, we will mitigate confounding with either adjustments to the model or inverse probability of treatment weights.

*Secondary analysis 3 (effect of fluids on ARV of MAP)*

We will assess the ARV of MAP between the two groups using a two-sample independent t-test if the groups are balanced, a linear model if we have a small number of imbalanced factors, and a weighted (IPTW) t-test if propensity score methods are required.

 **Sample size and power**

The sample size is fixed at the 1,057 patients from the trial (523 colloids and 534 crystalloids). In the primary analysis, the TWA of CI, we will be able to detect a Cohen’s d = 0.21 for TWA cardiac index with 90% power using a 2-sample t-test. A previous study by Szabó et al.1 found the standard deviation of cardiac index to be 0.71 which translates to 90% power to detect a difference in cardiac index of 0.14 L/min/m2.

**Citations**

1. Szabó B, Marosi EK, Vargová K, Nyolczas N (2018) Cardiac Index by Transthoracic Echocardiography (CITE) study. PLOS ONE 13(12): e0207269.