Comparison of Albumin and Ringer's Solution for Optimization of the Plasma Volume and Hemodynamics During Laparoscopic Surgery

1st July 2022

Statistical Analysis Plan

1. Statistics

1.1. Population to be analyzed

- In the protocol 20 patients are included in each group, with the goal to reach totally 60 evaluable patients (per protocol), defined as at least one infusion including 40 minutes of follow-up after termination of the infusion before end of surgery or converting the laparoscopic surgery to open surgery. If a patient is excluded before being counted as evaluable, the patient will be replaced.
  The number of patients missing in each group will be summarized for a new randomization, so that each group eventually will contain 20 patients. This implies that the total amount of initially randomized patients can exceed 60. Patients excluded from the study after randomization will be accounted for as dropouts.
- The study will be performed in Linköping and Norrköping, with approximate proportions 1:3. If one center has finished their part, studies will continue there, to support the other center, so both finish at the same time.

1.2. Statistical analysis

1.2.1. Statistical methods

- A two-sided test of significance will be used.
- After the last patient has been included an evaluation will be made if results are normally distributed. If so, parametrical statistical methods will be used i.e., ANOVA or T-test.
- If data are not normally distributed non-parametrical tests such as Mann-Whitney-U will be used.
- Maximum dilution of the plasma volume, and AUC (Area under the curve), i.e., dilution of hemoglobin over time will be evaluated. Moreover, the half-life for the dilution of hemoglobin will be determined.

The study contains three groups:

A. Infusion with acetated Ringer's (4 ml/kg), 20 patients
B. Infusion with albumin 5% (4 ml/kg), 20 patients
C. Infusion with albumin 20% (1 ml/kg), 20 patients

Statistical processing of the primary outcome measures only includes the first bolus for all patients.

1. In the first analysis all groups are studied as one group i.e., (A+B+C) 60 patients. The statistical difference (dilution/volume increase) between before the fluid infusion and directly after the fluid infusion for all the patients is evaluated.
   Method: paired T-test or Wilcoxon signed rank test .

2. In the second analysis, the dilution/plasma volume increase at 30 minutes after fluid infusion is compared for group A (acetated Ringer's), 20 patients, compared to a combined group B+C (both albumin groups) with 40 patients.

Methods: independent T-test or Mann-Whitney

3. In the last analysis (the first secondary outcome measure) the albumin groups are divided and compared for dilution/plasma volume expansion i.e., maximum during the entire trial, between the two albumin groups, group B (Alb 5%) 20 patients and group C (Alb 20%) 20 patients.
   B (20 patients) are compared with C (20 patients).
   Methods: T-test or Mann-Whitney

   Groups are compared in different combinations. Groups to be compared are not used twice. Thus, a correction for multiple comparisons is not needed.

   Dilution curves are seen as descriptive statistics.

1.2.2. Dropouts

- Dropouts, i.e., included patients who do not complete the first fluid infusion (including the 40 minutes follow up), will be accounted for. To make up for the dropouts, additional patients will be recruited and randomized to make up for the missing patients in each group.

1.3. Adjustment of significance and confidence

The primary outcome measurement is the dilution of hemoglobin and for this variable no correction for multiple comparisons has to be performed. All other measurement are secondary: thus no corrections for multiple comparisons will be done for these either. However, the issue will be considered in the interpretation of the results.

1.4. Calculation of sample size

- The sample calculation for the second primary outcome is based on a comparison between two groups, i.e., acetated Ringer's vs albumin 5% and albumin 20%. The albumin groups will have similar effects compared with acetated Ringer's, but less fluid is expected to be needed when Albumin 20% is infused.

- **Statistics:** With a desired P-value of < 0.05 and a power of 80 % with a difference (volume increase) of 35% and a standard deviation of 30% and a two-sided test, 16 individuals in each group are needed. At least 20 evaluable patients in each group will be recruited.