STATISTICAL ANALYSIS PLAN (SAP) FOR

Adverse effects of subcutaneous vs intravenous hydration on older acutely admitted patients: An assessor blinded RCT

Study group

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1. Study Synopsis

Subcutaneous (SC) hydration is often described as having a similar incidence of adverse effects as intravenous (IV) hydration[1–5]. Even though this is commonly stated in the literature, we believe it is a bold statement as only a few studies have examined this and only as a secondary outcome[6–9]. We wish to investigate if IV and SC hydration have a similar incidence of adverse effects. To examine this, we wish to perform an assessor-blinded, non-inferior RCT on older adults (>65 years) acute admitted to Aalborg University Hospital.

2. Study Objectives, Hypothesis, and Outcomes

2.1. Primary Outcome

Our primary objective is to determine if the risk of adverse effects with subcutaneous hydration is non-inferior to intravenous hydration on acutely admitted patients over 65 years of age who have a moderate need for parenteral fluid (1-2 liters over 24 hours). We have chosen a relatively short timeframe of 24 hours to reduce the number of dropouts and minimize the risk of violating the blinding. The primary outcome will be dichotomous (i.e., the occurrence of adverse effects: yes/no). Some of the adverse effects will require reinsertion of the needle, which will violate the assessor blinding; thus, we have chosen a dichotomous primary outcome rather than a total number of adverse effects as the occurrence of an outcome event potentially will compromise the blinding.

Three previous studies with short observation time (<48 hours) and a total number of 74 participants reported no serious adverse effects[7,10,11]. We, therefore, expect serious adverse effects to be uncommon in our study. Accordingly, we combine serious and minor adverse effects for the primary outcome.

We will use a non-inferiority limit of 20% when calculating the primary outcome, i.e., the incidence of adverse effects with SC hydration is less than 20% larger than the incidence of adverse effects with IV. This limit is based on a discussion in the author group and with relevant clinicians. A clinical trial on subcutaneous nutrition[12] and the PROSPERO protocol of a Cochrane review on achieving parenteral access in Ebola patients use a “clinically relevant difference of 20%” on achieving parenteral access in the power calculation of their meta-analysis[13]. The non-inferiority limit is based on the assumption that very few patients will experience serious adverse effects. A difference of 20% on the occurrence of serious adverse effects is not clinically acceptable. We believe this to be a reasonable assumption as no report of serious adverse effects have been reported in the trials we base the power calculation on.

Our null hypothesis (H_0) is therefore that the proportion of patients experience an adverse effect in the SC group (p_1) subtracted by the proportion of patients experience and adverse effects in the IV group (p_2) is equal to or larger than 20% (our non-inferiority margin):

H_0: $p_1 - p_2 \geq 0.2$

The alternative hypothesis (H_1) is that the proportion of patients experiencing an adverse effect in the SC group (p_1) subtracted by the proportion of patients experience and adverse effects in the IV group (p_2) is smaller than 20% (our non-inferiority margin):

H_1: $p_1 - p_2 < 0.2$

Definition of adverse effects outcome

We follow The Cochrane Handbook's definition of adverse effects: "An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility"[14]. In our study, we define serious adverse effects as any consequence of infusion requiring treatment. This includes prescription of medicine (e.g., diuretics, analgesic, and antibiotics), other medical treatment due to the fluid infusion, prolonged hospitalization, or persistent disability after the end of treatment, which is in line with the WHO definition of "serious" [15]. The clinical staff will grade the serious adverse effects on estimated relation to the infusion (almost certainly not related, properly not related, possibly related, and related).

We define minor adverse effects as any of the following:

- Reddening of the skin at infusion site larger than what is covered by dressing (approximately a 2 x 2 cm quadratic area over the infusion size)
- Painful swelling at the infusion site
- Prolonged swelling at the infusion site (more than two hours after the end of infusion)
- Itching
- Phlebitis without needing treatment (if treatment is required, it is a serious adverse effect)
- Patient complaining of infusion-related pain
- Failure of infusion
- Need for reinsertion of the infusion needle (Compromising the blinding)
- Accidental catheter removal by the patient (Compromising the blinding)
- Need for reduction of flow speed due to complaints from the patient.

We do not consider swelling at the infusion site, without discomfort or need for action, an adverse effect.

2.1.1 Further analysis of primary outcome

1. A superiority calculation of the primary objective.
   Reason: Based on our larger number of participants, we might find one of the techniques statistically superior to the other. This analysis will only be performed if non-inferiority is found.
2. A non-inferior calculation of the total number of adverse effects (continuous, not blinded), and if significant, a superiority calculation of the same.
   Reason: Despite this outcome not being blinded, it will add relevant information. We will be able to evaluate if the total number of adverse effects is spread out among patients or gathered on fewer patients with a higher number of adverse effects.

2.2. Secondary Objectives and Outcomes

2.2.1 Clinical effects

3. Compare death during hospitalization between groups.
   Reason: As with the latter, we do not expect a difference, but it would be highly relevant if found.
4. Number of delirious patients at the end of observation. The presence of delirium will be evaluated using CAM-score[16].
   Reason: Previous studies have shown a reduced incidence of agitation with SC hydration.

2.2.2 Subjective evaluation

5. Personal grading time spend on insertion for SC vs. IV (non-blinded)
   Reason: A selling point for SC hydration is "easy of insertion", but there is only limited evidence for this.
6. Patient evaluation of pain at insertion and annoyance during infusion (from both the IV and SC site on all patients. Non-blinded)
   Reason: Any experience by the patient is relevant.

2.3. Exploratory Objectives

2.3.1 Indebt analysis of adverse effects of SC hydration

7. Examine the risk of bleeding requiring attention, on patients prescribed anticoagulation medicine.
   Reason: We expect a few bleeding cases requiring attention, given that there theoretically could be a larger risk of this with SC.
8. An incidence rate of the different adverse effects on both IV and SC.
   Reason: The techniques' risk profile is relevant to inform patients of potential risks and increase awareness of expected adverse effects to reduce intervention response time.

2.3.2 Effect of infusion method on hydration status

9. A comparison of changes in hydration markers (albumin, creatinine, eGFR, urea, osmolality hemoglobin, sodium, potassium, blood pressure)
   Reason: Based on previous studies, we do not expect a difference in hydration status between the two groups.

2.4. Descriptive Objectives

Age, sex, admission diagnosis, Charlson comorbidity index[17].

3. Study Design

This study is a parallel-group non-inferiority, assessor-blinded, randomized controlled trial.

3.1. Sample Size

Previous trials on the subject with a short (<48 hours) observation time have reported an incidence of adverse effects of 17% in both SC and IV groups. No cases of serious adverse effects were reported[6,7].

With a significance level (alpha) of 5%, a power (1-beta) of 90%, and a non-inferiority limit of 20% (see Primary outcome for a reason behind this), a non-inferiority-sample-size-calculation with a binary outcome results in a total of 122 participants required[18]. We expect an attrition rate of 10% after inclusion. Giving us a total sample size of 135 patients.

3.2. Randomization and Blinding

Randomization will be done using REDCap version 7.0.11 hosted at Aalborg University Hospital[19].

To achieve assessor blinding, all patients will receive a sham catheter (opposite of the randomization). The sham catheter will not pierce the skin, and the catheter is placed on top of the skin, still covered by non-woven swabs before placement of the dressing. Infusion lines are primed with fluid and connected to both the active and the sham catheter. The infusion line connected to the active catheter is inserted into the fluid bag. The active and sham infusion lines are tangled under the infusion fluid bag. The tangle is then covered by gauze binding to concealed, which is connected to the infusion bag.

The outcome assessors (clinical nursing staff) will be asked to guess which intervention is active by choosing between three options: "SC", "IV", "Do not know". We will use James' Blinding index[20] to examine the degree of successful blinding of the outcomes assessors for data included in the primary outcome analysis.

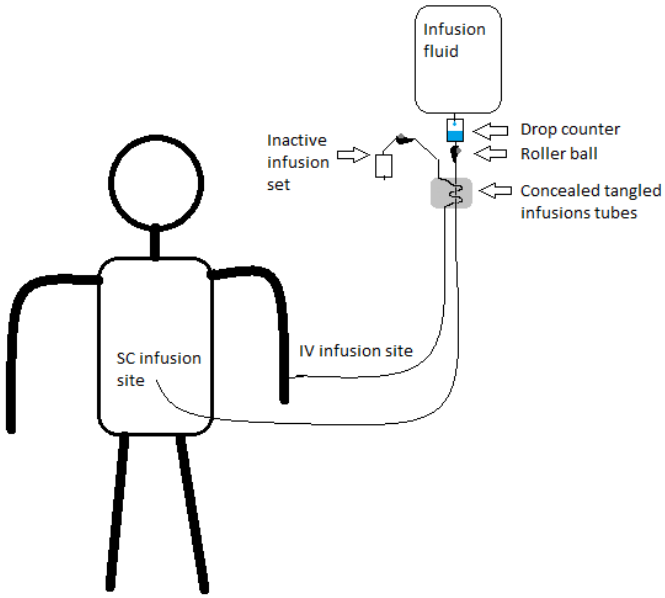

Figure 1. Experimental setup

4. Study Population

Inclusion Criteria:

1. Age >65 years old.
2. Medical patients admitted to the Acute Assessment Unit (AAU). (All internal medicine patients are admitted here first, except highly specialized patients (e.g., ketoacidosis or cardiology patients).
3. Orthopedic hip fracture patients admitted to the orthopedic ward.
4. A short-term care facility
5. Prescription of 0.5-2 liters of parenteral fluid over the next 24 hours.

Exclusion Criteria:

1. Red triage tag (severe ill patients)
2. Prescription of IV antibiotics or other treatments administrated intravenous hindering placement of another IC catheter.
3. Severe dehydration (fluid requirements over 2 liters over 24 hours)
4. Known strict fluid restriction (cannot receive ½ liters of fluid infusion)
5. Severe general edema
6. Unable to give informed consent

5. Data handling

The patient's assigned nurse will note all data obtained on a data collection sheet. The data will transfer the data to REDCap. All data collection sheets will be stored in a locked cabin if a validation of the data is needed.

6. Statistical Analysis

Table 1 | Variables, measures, and methods of analysis						
Variable/outcome	**Mode of assessing**	**Obtained by who**	**Variable type**	**Comment**	**Assumptions**	**Methods of analysis**
6.1 Primary outcome						
Adverse effects (Blinded, non-inferior)	Visual inspection	Nurse	Dichotomous			z-test[a] (non-inferior)[21]
Further analysis of primary outcome						
Adverse effects (Blinded, superiority calculation)	Visual inspection	Nurse	Dichotomous	Only if non-inferiority is found		One-sided Fisher's exact test
Adverse effects (total number, not blinded, non-inferior)	Visual inspection	Nurse	Discrete		We expect non-normal distribution	Wilcoxon rans sum test (Non-inferior)
Adverse effects (total number, not blinded, superiority calculation)	Visual inspection	Nurse	Discrete	Only if non-inferiority is found	We expect non-normal distribution	Wilcoxon rans sum test
6.2 Secondary outcomes						
Clinical effects						
Death during hospitalization	Retrieved from patient chart	Data manager	Dichotomous			Fisher's exact test
Delirium	CAM-score	Nurse	Dichotomous	Comparing incidence of delirium at end of observation.		Fisher's exact test
Subjective evaluation						
Time spend on insertion	On a scale of 1-6[b]	Nurse	Ordered categorical			Fisher's exact test[c]
Discomfort during insertion (patient evaluated)	VAS (0-100 scale)	Nurse	Discrete			Wilcoxon rans sum test[d] Alternative t-test
Discomfort during infusion (patient evaluated)	VAS (0-100 scale)	Nurse	Discrete			Wilcoxon rans sum test[d] Alternative t-test
Exploratory Objectives						**Table 1 continue**

Risk of bleeding on patients prescribed anticoagulation medicine in SC group.	Visual inspection	Nurse	Dichotomous	Comparing patients with/without anticoagulation		Fisher's exact test
Incidence rate of the different adverse effects on both IV and SC.	Visual inspection	Nurse	Discrete	Only to be examined visually in a box plot		
Descriptive Objectives						
Hydration markers[e]	Blood samples BT	Laboratory technician, nurse	This data will be displayed as mean + sd at baseline, endpoint and change. Data not normally distributed will be displayed median and 25/75 percentile.[f]			
Charlson comorbidity index, Age, Sex	Retrieved from the patient chart	Data manager	Displayed as baseline values only			

a) This is the z-test for non-inferiority: $Z = \frac{p_1 - p_2 - \pi}{\sigma}$, $\sigma = \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$. Where p_1 is the proportion of patients experience an adverse effect in the SC group, p_2 is the proportion of patients experience an adverse effects in the SC group, and π is the non-inferiority margin. With an alpha of 5%, we can reject H_0 if $z \geq 1.645$.

b) Nurses will estimate the time of insertion of the active infusion method into the following categories: 1: less than three minutes, 2: three to five minutes, 3: five to ten minutes, 4: ten to twenty minutes, If the primary nurse cannot achieve access, it will be noted if another ER nurse(5) or an anesthesiological nurse is needed (6).

c) We will combine rows (e.g., category 5 and 6 is combined into one) if there is a category with less than 1 observation or multiple with less than 5.

d) Previous studies on venous cannulation's discomfort found data to be non-normally distributed, even after log transformation.

e) The following parameters will be displayed albumin, creatinine, urea, osmolality, hemoglobin, sodium, potassium, blood pressure

f) We will refrain from performing statistical analysis on the effect of hydration. This is both due to the complexity of evaluating dehydration status on geriatric patients but also to avoid a type 1 error due to multiple comparisons.

7. Implementation of Analysis Plan

Data will be collected in REDCap and exported to STATA, where it will be analyzed. The primary investigator will analyze the data. The patient's allocation will be hidden from the primary investigator during data analysis, and the patient data will be pseudonymized to avoid violating the blinding. All statistical analyses will be performed with intention-to-treat (ITT). Only the primary outcome will be analyzed as non-inferior; the remaining analysis will be superiority calculations with an alpha of 5%.

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