Statistical Analysis Plan (SAP)

Title:

5 versus 10 units of insulin in hyperkalemia management: Prospective, Double blinded, randomized controlled trial, multicentre, non-inferiority.

(5/10 trial)

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Introduction

The objective of this research is to evaluate the effects of 5 units of intravenous insulin against 10 units in treating hyperkalemia at the Emergency Department of Sultan Qaboos University Hospital and Royal Hospital. This Statistical Analysis Plan (SAP) provides an in-depth overview of the study's endpoints and their respective analytical methods.

Study design

5 versus 10 units of insulin in hyperkalemia management: multi-center, prospective, double blinded, non-inferiority, randomized control trial in adult patients with age of 18 years and more at two emergency departments Sultan Qaboos university hospital and Royal hospital. We will include patients with potassium level 5.5 mEq/l and more. We will measure the mean reduction of insulin level among both groups at 2 hours from treatment. Written consent will be obtained from all patients. Eligible subjects will be enrolled. Control group will receive 10 units intravenous insulin with Dextrose 50 % 50 ml over 15 minutes and Salbutamol nebulization. Intervention group will receive 10 units intravenous insulin with Dextrose 50 % 50 ml over 15 minutes and Salbutamol nebulization.
Patient will be monitored and basic labs will be recorded. Blood sugar will be monitored at 0, 60 and 120 (2 hours) minutes. Potassium level will be measured at presentation and at 120 minutes (2 hours) from insulin administration.

Sample size calculation

We aim to study all hyperkalemia patients who come to the emergency departments of both hospitals. The sample size determination was influenced by a 2020 article in the Critical Care Explorations Journal titled "Comparison of IV Insulin Dosing Strategies for Hyperkalemia in the Emergency Department" authored by Kayvan Moussavi and colleagues. We expect an effect size of d=0.2, with an alpha error probability of 0.0250 (one-sided), a true power of 90, a standard deviation of 0.62, and a 1:1 allocation ratio. The sample size deduced is 320, split evenly between both groups. Anticipating a 5% attrition rate, we've adjusted our total sample to 336 participants, with 168 in each group

Aims and objectives

The aim of this study is to compare the efficacy of two insulin doses (5 units and 10 units) in reducing serum potassium level in patients receiving hyperkalemia treatment.

Outcomes

Primary outcome

- To study the efficacy of two intravenous insulin doses (5 units and 10 units) in reducing serum potassium level in patients receiving hyperkalemia treatment using the main laboratory measurements. (the aim of reduction of 0.6 mmol/l +/- 0.2 mmol/L) (1). Blood sample will be collected and send to the main laboratory for analysis at two hours from medications administration. The efficacy of the 2 doses will be measured at 2 hours from administration of medications by comparing the amount of changes in potassium level at two hours.

Secondary outcomes

1. Study the mean difference of the response to the anti-hyperkalemic measures based on the level of initial potassium (serum potassium before given any medications – At baseline) (the investigators will categorize potassium level into groups mild (5.5–6 mmol/l), moderate (6–6.5 mmol/l) and severe (>6.5 mmol/l) and will see the mean difference in reduction in potassium level in between the 2 doses).
2. Association of mean potassium reduction with initial blood sugar level (blood sugar level before given any medications – At Baseline) on potassium reduction (the investigators will categorize blood sugar into groups: Below 10mmol/L, 10.1-14.9 mmol/L, and 15 – 19.9mmol/L among each group the investigators will see the mean potassium reduction level).
3. Incidence of hypoglycemia (random blood sugar (RBS) ≤ 3.89 mmol/l in Diabetic patients and less than 3 mmol/l in non-Diabetic patients) (12). (and risk factor Characteristic of patients of higher risk of developing hypoglycemia (the investigators will investigate which group of patients will have a high risk of hypoglycemia ((e.g: initial Glucose level, initial creatinin/renal function, comorbidities, type of dialysis…).

Safety outcomes

Adverse events are reported at each visit.

Populations

Intention-to-treat (ITT)

All randomized study subjects. This will be seen as the primary population for the analysis.

Per Protocol (PP)

All randomized study subjects completing the whole study period (complete cases). For a specific analysis, study subjects with missing data on any of the variables in the model will be excluded from the analysis. Analyses of this population is seen as a sensitivity analysis to investigate whether conclusions are sensitive to assumptions regarding the pattern of missing data.

Statistical analysis

Primary outcome

The data analysis for the clinical trial will be conducted using IBM SPSS Statistics version 29.0. Categorized variables will be presented as percentages, and continuous variables will be presented as means with standard deviations or medians with interquartile ranges. The primary outcome, the reduction in serum potassium levels, will be analyzed using a linear mixed effect model that adjusts for baseline potassium levels. A p-value of <0.05 will be considered statistically significant.

The intention-to-treat (ITT) analysis will include all subjects who provide at least one post-baseline valid measurement. The per-protocol (PP) analysis will only include subjects who have completed the study according to the protocol and who have valid measurements for all time points. Non-inferiority will be concluded if both the ITT and PP analyses show that the difference in means between the two treatment groups is not statistically significant and lies above the margin of -20 units.

Secondary outcomes

Normally distributed continuous variables will be compared between the groups using Independent ‘t’ test or else with Mann-Whitney 'U' test and categorized levels will be compared using chi-square test. The incidence of hypoglycemia will be presented using percentage with 95% confidence interval. A p-value of <0.05 will be considered as statistical significance.