Study protocol

Title:

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

(5/10 trial)

Principal investigator:
Dr. Adnan Hussein Al-Ajmi , Oman medical speciality board, Emergency medicine resident.
Dr. Ibrahim Sabri Al-Hooti, Oman medical speciality board, Emergency medicine resident.

Authors:
Dr. Usama Al-Khalasi, Oman medical speciality board, Emergency medicine resident.
Dr. Suad Abdullah Al-Abri, Emergency medicine, senior consultant Sultan Qaboos University Hospital.
Dr. Abdullah Al Reesi, Emergency medicine, senior consultant Sultan Qaboos University Hospital
Dr. Saif Al-Ghafri, Emergency medicine, Consultant Sultan Qaboos University Hospital.
Dr. Ali Al-Lawati, Internal medicine, Nephrology Consultant, Sultan Qaboos University Hospital.
Dr: Abulmonim Al-Farsi, Emergency medicine, consultant, Royal hospital.

Corresponding Author: Dr. Suad Abdullah Al-Abri.

Ethical approval:
- Medical Research Ethics Committee (MREC), College of Medicine and Health Sciences, Sultan Qaboos University, MREC#2779. Date:1st june 2022.
- Sultanate of Oman, Ministry of Health Directorate General of Planning & Studies Centre of Studies and Research: MOH/CSR /23/26349. Date: 14/05/2023.

Version number: 003.
Date: 10/08/2023

Contents

1. Summary:

Introduction: Hyperkalaemia is a serum Potassium (K) level of more than 5.5 mEq/L. It is a common emergency medicine presentation and can be life-threatening. Because of the emergency in correcting hyperkalemia, different medications are used to reduce high potassium levels to normal as soon as possible. Salbutamol inhalers, Glucose solutions, and Insulin are the main medications for managing hyperkalemia. Insulin and Dextrose shift potassium ions into body cells by stimulating the sodium/potassium ATP pump. Its effect starts in less than fifteen minutes and can last up to sixty minutes. It usually reduces potassium up to 1.1 mEq/l. There are different recommendations for Insulin dose and rate of administration for patients with hyperkalemia.
Method: This will be a multi-center, prospective, double-blind, non-inferiority, randomized control trial. 336 hyperkalemia patients will be randomized to the intervention group 5 units of intravenous Regular insulin and 10 units of intravenous insulin groups with fifty ml of Dextrose Fifty percent. They will be enrolled once their potassium level is 5.5mEq/L or more. The attending physician/ investigator and patient will be blinded about the dose of insulin that the patient received. Serum potassium will be measured at 0 and at 120 minutes from the start of the medications. Random blood glucose will be measured at 0, 60, and 120 minutes by Glucometer. The safety of our patients will be assessed by documentation of all adverse events, vital signs, and clinical assessment before and after drug administration. The study will end at 2 hours from insulin administration.
Aim: Our research idea aims to compare two recommended doses of Insulin (5 Units vs. 10 Units of Regular insulin given intravenously over thirty minutes) in the management of patients with hyperkalemia.
Primary objective: Mean reduction in serum potassium level using the main laboratory results at two hours from medication administration.
Secondary objectives: effect of initial (baseline) potassium level on the mean potassium reduction, and frequency of hypoglycemia between the 2 groups. Does the initial (baseline) blood glucose level will affect the function of insulin/dextrose in lowering potassium levels?
Patient Population: Adult patients (Aged 18 years and older) who present to the Emergency department at Sultan Qaboos University and Royal Hospital for evaluation and are found to have potassium levels of 5.5 mEq/L and above.
Intervention: Single dose of 5 units of intravenous insulin over 30 minutes with 50 ml of Dextrose 50%.
Clinical Measurement: Mean reduction of potassium level using the main laboratory results at 2 hours from insulin/dextrose administration. We will follow serum potassium by blood sampling. Hypoglycemia will be followed by a bedside glucometer.
Outcome: reduction of potassium level at 2 hours from medication administration and medication safety**.**

2. Introduction: literature review and justification of the study.

Hyperkalaemia is the most dangerous and deadly electrolyte imbalance seen in all health institutions (1). Potassium is mainly an intracellular cation. The normal level of potassium is between 3.5 to 5.5 mEq/L (12). It is critical to identify and manage hyperkalemia as soon as possible. Hyperkalaemia can affect multiple systems including the central and peripheral nervous system, gastrointestinal system, renal system, and neuromuscular system including the cardiac muscles (2) The most dangerous effect of hyperkalemia is cardiac toxicity. Hyperkalaemia affects the heart by depressing it is electrical and muscular functions leading to cardiac arrhythmia and sudden cardiac death (1).
Potassium plasma level is determined by three main factors: the amount of potassium intake, the distribution of plasma between the extracellular fluid and the cells, and potassium excretion with urine (3).
There are different medications used for the treatment of hyperkalemia. The known regimen has 3 components (1) (4). The 1st group of treatment is cardiac muscle-stabilizing agents like Calcium gluconate (1) (4). The 2nd group is the medications that shift Potassium from the plasma to inside the cells like Insulin and Salbutamol (1) (4). The 3rd group of treatments is the ones that eliminate potassium from the body like dialysis and diuretics (1) (4). The standard dose of insulin is 10 units of Regular insulin as a bolus with dextrose 50% 50 to 100 ml (1) (4) (5). Some guidelines recommend an insulin dose between 5-10 units of Regular insulin as a bolus (2).
There are multiple studies done to monitor the efficacy and safety of potassium-lowering agents like insulin and other medications. A recent retrospective cohort study showed no difference between 5 Units and 10 units in lowering potassium levels (6).
Most of the studies done to compare insulin doses were retrospective studies and most of them were done on a patient with renal insufficiency (acute and chronic). These studies showed no difference in the efficacy of lowering potassium levels between 5 units of insulin and 10 units of insulin. They showed 5 units of insulin have the advantage of fewer hypoglycemia events compared to 10 units. As Bairbre A. McNicholas et al 2017, Heather A LaRue 2017, and Kayvan Moussavi 2021 (7) (8) (9) (10) showed the same finding

Ziv Harel and Kamel S. Kamel 2016 in their systemic review of articles that looked into the different doses of insulin found no difference in the efficacy of lowering potassium between 10, 12, and 20 units of insulin (11)

Kayvan Moussavi et al 2020 in their observation study showed that less than 10 units of insulin cause less incidence of hypoglycemia but the amount of potassium reduction was less in patients who received less than 10 units (8). But this study was a retrospective for patients who attended the emergency department in a single center. Although they mentioned less than 10 units have less efficacy but the doses of less than 10 units range from 3 units to 8 units as it will be difficult to conclude this range of values. (8).

The gap in the studies:

From these studies our question came. If 5 units of intravenous regular insulin reduce potassium level as effective as 10 units of insulin with less hypoglycemia why we do not use

it as our standard dose to avoid a possible complications and will be less cost as half the dose of insulin will be used in the future as standard.
Most of the studies were retrospective studies and a lot of confounders may affect the result, that's why this study will add much to the argument in regarding to the best dose in managing patient with hyperkalemia. Also the investigators will review the rate of hypoglycemia and who is more at risk to avoid this complication among those patients. In our secondary objective the investigators will analyse the effect of blood sugar level and potassium level in patient response to treatment.

3. Objectives and hypothesis of the study:

Primary outcome:

1. 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 outcome

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…).

Study hypothesis

No difference between 5 and 10 units of intravenous regular insulin in lowering potassium levels in patients with hyperkalemia at 2 hours.

4. Feasibility of the study

As hyperkalemia is very common our investigators can find a good number of cases. Also, it will be a multicentre study with the inclusion of emergency department patients in the study. The American College of Emergency Physicians (ACEP) recommends the use of both 5 units and 10 units of insulin as treatment of hyperkalemia published on their anti-hyperkalemia protocol in 2021 (13). With an average of 1 patient per day, the research team can achieve the target sample size within the timeline. Funding will be requested from the research council (Ministry of Higher Education, Research and Innovation) and Sultan Qaboos University fund.

5. Research Design and Methods

Study design

Prospective double blinded, randomized controlled clinical trial, in adults (from age 18) who presents to the emergency department (ED) at Sultan Qaboos University Hospital, and Royal Hospital, with hyperkalemia (potassium level >5.5 mEq/l, Written consent will be obtained from the patient. Eligible subjects will be enrolled (Appendix: Written informed consent).

Characteristics of study area and target population

This study will be conduct in 2 different hospitals, Sultan Qaboos University Hospital and Royal Hospitals both are tertiary hospitals in Muscat region. The research team might extend to other hospitals if noticed that we are short on patient number. Patient will be selected based on the potassium level in the main laboratory report. When potassium level ≥ 5.5 mEq/l the patient will be screened for inclusion and exclusion criteria. Our 5.5 mEq/l lab cut off came from Ministry of health protocol (see appendix: Ministry of health hyperkalemia management protocol) and ACEP protocol for hyperkalemia management (13).

Control Group

The patient will receive 10 U of regular insulin + Dextrose 50% over 30 minutes + salbutamol nebulization 10mg in 3ml normal saline over 15min, calcium gluconate will be given according to the physician responsible about the case.

Intervention Group

The patient will receive 5 U of regular insulin + Dextrose 50% over 30 minutes + salbutamol nebulization 10mg in 3ml normal saline over 15min, calcium gluconate will be given according to the physician responsible about the case.

Primary and secondary endpoints

Primary endpoint:

- Mean reduction in serum potassium level at 2 hours from insulin administration. Blood sample from the patient will be obtained for potassium measurement. The samples will be sent to the main laboratory for potassium level analysis.

Secondary endpoint:

- Mean difference of the response to the antihyperkalemic measures based of the baseline level of potassium.
- Incidence of hypoglycemia and risk factors characteristic of patients of higher risk of developing hypoglycemia.
- Association of mean potassium reduction with baseline blood sugar level.

Selection and withdrawal of subjects:

Inclusion and exclusion criteria

Inclusion criteria:

- Hyperkalemia patients with lab potassium levels equal to or more than 5.5 mEq/L (≥ 5.5 mEq/L)*.
- Adult: aged 18 years or more.
- Agreed to participate in the study.

* If a doctor/Investigator decided to start anti-hyperkalemia medications based on the VBG/ABG patient can be enrolled but if the main laboratory value is less than 5.5 mEq/L patients will be excluded

Exclusion criteria:

- Cardiac arrest
- Hyperglycemia with random blood sugar 20 mmol/L (13) or with acute diabetic complications like Diabetic Ketoacidosis / Hyperosmolar Hyperglycemic State.
- Hypoglycemia with random blood sugar (RBS) ≤ 3.89 mmol/l in Diabetic patients and less than 3 mmol/l in non-Diabetic patients.
- Allergies for any medication in the protocol.
- Pregnancy.
- Hemolyzed potassium level as reported by the main lab.
- Hemolysis, Tumor lysis syndrome, or Rhabdomyolysis due to the ongoing release of potassium.
- Acidosis with a pH less than 7.1 will require Sodium bicarbonate (NaHO3).
- A patient who will need urgent Furosemide (Lasix), and or dialysis during the study period of 2 hours.
- Refused to participate.

Withdrawal criteria

A subject/patient may be withdrawn from the study at any time for any reason and without penalty or prejudice. The following situations may be cause for a subject to be withdrawn from the study:

- Subject did not fulfil the inclusion or exclusion criteria.

- Subject experienced a significant complication, deemed due to the study treatment.
- Subject developed an inter-current illness, condition, or procedural complication that would interfere with continued participation.
- Subject voluntarily withdrew consent.
- Subject was in violation of the protocol.
- Treating Physician decided it is in the best medical interest of the subject to terminate involvement.

Upon occurrence of a serious adverse event or intolerable adverse event, the principal investigator will be notified. If a subject is discontinued from study treatment due to a serious adverse event, the event will be followed until resolution. The investigational staff must fill the withdrawal form (Appendix: Withdrawal form).

Sampling and sample size

Our target will be all patients with hyperkalemia presenting to the emergency departments in both hospitals. The Sample size was calculated based on a study published in Critical Care Explorations Journal 2020 with the article named *Comparison of IV Insulin Dosing Strategies for Hyperkalemia in the Emergency Department* by **Kayvan Moussavi** et al (8). The anticipated effect size d = 0.2 with alpha error prob = 0.0250 (one-side), actual power 90, Standard deviation of 0.62 and allocation ratio 1:1. The calculated sample size is 320 (160 in each arm). Our statistician estimated a 5% drop rate. So the sample size increasesd to 336 (168 in each arm).

6. Randomization

When a patient has hyperkalemia (K ≥ 5.5 mEq/L) our doctor/investigator will come to explain the research to the patient/relatives and after explaining all details a written consent will be signed. Our doctor/investigator will take a random envelope from the study box to randomize the patient between 5 units or 10 units of insulin with 50 ml of 50% Dextrose and salbutamol Nebulization. The doctor will take the envelope code and place it on the data collection sheet without looking into the instructions. The Doctor will give the nurse that envelope. Each envelope will have instructions about the medications administration route and dose (see appendix: medications administration form). The Nurse will administer the medications with the documentation of starting time. Then our doctor will follow the patients and lab results for 2 hours based on the ACEP and Ministry of Health/Royal hospital protocol.

Randomization codes will be done by an online free site for having unique codes (https://www.randomcodegenerator.com/en/generate-codes). Eligible participants after obtaining consent will be randomly assigned to either 5 units of Intravenous insulin or 10 units of intravenous insulin. The researcher and patient will not know the dose of insulin administered.

7. Study flow

The study protocol will be for a total of 2 hours. All groups will follow the same path except the dose of insulin administered. After the result of potassium level (≥ 5.5 mEq/L) patient will be screened for inclusion and exclusion criteria at the same time all other medications except insulin can be administered as the doses are fixed. Eligible patient will have to sign a

written consent if they agreed to be involved in our study. The initial data and basic labs will be collected before starting the study protocol. The incharge doctor/investigator will take the random code and write it on the data collection sheet of that patient from already prepared list/code and give the assigned nurse the medications administration card/form (see appendix: medications administration form).

Every patient will receive:

- Potassium lowering agent:
  - Intravenous Regular insulin 5 units ***OR*** 10 units with Glucose 50% water 50 ml over 30 minutes according to the randomization.
  - Salbutamol nebulization 10 mg in 3ml normal saline over 15 minutes.
- The physician will decide the need of cardiac stabilizing agents (e.g Calcium Gluconate) as indicated by the physician in-charge of the patient.

- Please see study flow chart in the attachment.

5 Units insulin group	10 units insulin group
Medications to be administered: • IV Insulin Regular 5 units with Dextrose 50 % 50 ml over 30 minutes. • Salbutamol 10 mg NEB over 15 minutes.	Medications to be administered: • IV Insulin Regular 10 units with Dextrose 50 % 50 ml over 30 minutes. • Salbutamol 10 mg NEB over 15 minutes.

Figure 1: Treatment. RBS: Random Blood sugar. IV: Intravenous. NEB: Nebulization.

Initial investigations will include:

ECG, Urea and electrolytes, Creatinine, eGFR, Random blood sugar, complete blood count, Magnesium level, bone profile, phosphate level, will be attached if not sent before.

Repeated labs will be with these frequencies:

Potassium level: 0 and 120 minutes from medications administration time.

Blood sugar: 0, 60 and 120 minutes from medications administration time.

The study will be over at 2 hours (120 minutes) or by patient decision to withdraw from the study.

		Post involvement	
Timeline (minutes) from medications administration	0	60	120
Eligibility screen	*		
Consent	*		
Randomization	*		
Basic labs: ECG, U&E, RBS, CBC, Mg, bone profile, PO4, VBG.	*		
Study Medication administration	*→		
Other medications as indicated	*→		
Serum Potassium measurement	*		*
Serum Glucose measurement	*	*	*

Figure 1: Schedule for evaluation time-line. ECG: electrocardiography, U&E: Urea and electrolytes, RBS: Random blood sugar, CBC: complete blood count, Mg: Magnesium, PO4: phospate, VBG: Venous Blood Gas.

8. Study treatment.

Medications for study treatment.

Regular insulin/ Dextrose 50%

Subjects in the emergency department with hyperkalemia will be administered regular insulin either 5 units or 10 units.

After identifying appropriate adult patients, obtaining written consent (Appendix: Written Informed consent), and labs confirmed that patient is having hyperkalemia. antihyperkalemic measures will be started, Regular insulin (5units or 10units) will be administered according to the steps below.

Method for Application of Intravenous Regular Insulin 5 units

1. Preform hand hygiene and don clean gloves.
2. Draw the 5 units of regular insulin.
3. Mix it with 50ml of dextrose 50%.
4. Connect to placed venous cannula.
5. Run it no less than 5 seconds (proposed 30 minutes)
6. Disconnect and discard all materials in their proper disposal bins.
7. Remove gloves and preform hand hygiene.

Method for Application of Intravenous Regular Insulin 10 units

1. Preform hand hygiene and don clean gloves.
2. Draw the 10 units of regular insulin.
3. Mix it with 50ml of dextrose 50%.
4. Connect to placed venous cannula.
5. Run it no less than 5 seconds (proposed 30 minutes)
6. Disconnect and discard all materials in their proper disposal bins.

7. Remove gloves and preform hand hygiene.

Salbutamol

Method for Application of Salbutamol Nebulization

1. Preform hand hygiene and don clean gloves.
2. Take 10 mg of insulin.
3. Mix it with 3 ml of Sodium Chloride 0.9%.
4. Put it on Nebulization devise.
5. Run it for 15 minutes
6. Disconnect and discard all materials in their proper disposal bins.
7. Remove gloves and preform hand hygiene.

9. Storage, Handling, and Administration

The principle investigator and co-investigators will ensure that:

- The study treatment is handled and stored safely and properly.
- The study treatment is only dispensed to study subjects in accordance with the protocol.
- The study treatment will be stored in accordance to product labelling.
    - o Exposure to light, freezing and extreme heat should be avoided.
    - O Will Be stored the at pharmacy in controlled room temperature.
- There will be only one use per ampule of treatment per subject.
- The study treatment will be checked for expiration dates prior to use.

Packaging and Labelling

A calculated sample size equivalent both insulin doses 5 units VS 10 units will be prepared and set ready to be used based on randomization blocks. Each package has its own unique number corresponding to (case and control) sampling.

Each package contains:

- **Envelope with:**
    - o Data collection sheet with unique generated number.
    - o Consent form.
    - o Instructions sheet
    - o Medication administration form (for the nurses).

Blood investigation will be sent to biochemistry lab for potassium level and other investigations, and it's the only acceptable way in the study. The study investigators will verify that study treatments are received intact and in the correct amounts.

10.Variable definitions and measurements

Intravenous Regular Insulin will be used for our intervention. Potassium level will be measured by the main laboratory. Our outcome will be measured based on amount of potassium level reduction.

Hypoglycemia will be defined as (random blood sugar (RBS) ≤ 3.89 mmol/l in Diabetic patients and less than 3 mmol/l in non-Diabetic patients).

Data collection tools and methods

All data will be collected from the hospital information system. Data will be kept in secured files with encryption keys/password to maintain all patients' privacy. Only who is involved in the study will be able to access the files.

Data quality

In each site there will be a focal point. A physician will be responsible for that site. Before the study starts our investigators will do training sessions about the study and will clarify all the details that the site physicians inquire. Research assistances will be hired for data collections to facilitate the process of data collection and to monitor the flow of the study protocol in each site.

Data analysis

Statistical Package for the Social Sciences (SPSS) applications version 29 will be used for our analysis.

11.Ethical considerations

Ethical approval will be needed from both hospitals before starting our research. Any adjustment advised by all ethical committees the research team will apply it to ensure patient safety. At any time during our study if the investigator noticed any increase risk on the patient safety the investigator will stop our study protocol.
Because the study will not deviate from what is practiced by some physician and what is recommended by some guidelines our researchers team do not anticipate major harm on the patients. Even with this our investigator will follow our patients/participants and will stop the study if any indicator for harm rose at any time of the study. Our study will help if it proved no difference in the effect of both doses in 2 main things. The 1st one less hypoglycemia for the patients in the future and the 2nd main point cost effect as less doses of the same medication will be required to achieve the same goal.
By the end of the study all participants will be contacted and our investigators will share the results with them and how their contribution helped the advancement of medical field.

12.Conflict of interest:

No conflict of interest

13.Incentives:

No incentives of any kind will be given to the participants.

14.Results Dissemination

After completing the study the research team will publish the results in international journals and will have poster presentations.

15.Management and monitoring of the research activities:

The full team will manage the study flow. Each researcher will be responsible for a hospital work flow at a certain time then the researchers will swab after a period of time. Daily monitor will be done for all the cases via direct visit or follow up via the phone or Virtual meeting. Once enough sample collected the investigators will start our initial analysis of them.

16.Limitations and difficulties of the study:

The large sample size will need to be followed and all data must be kept and organised all time.
Multicentre will have some difficulties as 2 different HIS used in these hospitals.
Funding will be needed for to cover all the logistics and facilitate the flow of the research..

17. Safety Assessments

Adverse Events

All adverse events will be documented on serious adverse event case log. All serious adverse events should be immediately reported to the primary investigator. Any serious, adverse event will be reported immediately to the Institutional Review Board.

An Adverse Events is considered serious if it causes a threat to the patient's life or functioning. The U.S. Food and Drug Administration (FDA) define a serious adverse event (SAE) as any untoward medical occurrence that:

- Results in death.
- Life threatening (places the patient at risk of death).
- Requires hospitalization or prolongs an existing hospitalization.
- Causes persistent or significant disability or incapacity.
- Requires medical intervention to prevent one of the above outcomes.

18.Rationale for subject selection and recruitment.

This is a prospective efficacy, safety and tolerability trial in adults. Active treatment (a single dose of intravenous insulin 5 units or 10 units) will be used. The population selected for this study, adult patients is a patient population that may benefit from the use of insulin. This is a population in whom intravenous 5 units of insulin has been approved for and in whom insulin has been shown to be safe and effective when used for hyperkalemia management, specifically renal failure patient. This is also a population in whom other dose insulin, 10 units of insulin have been shown to be efficacious and safe. Therefore, it seems highly likely that the intravenous 5 units of insulin, is an appropriate dose and it will also be effective, safe and well tolerated.

19. Efficacy and safety assessment.

Efficacy Variables

Primary Efficacy Variable

The primary efficacy variable is the assessment of reduction of the potassium level after intravenous regular insulin dose (either 5 units or 10 units) at 2 hours from medication administration. Blood sample will be collected from the patient and will be sent to the main laboratory for analysis.

Secondary Efficacy Variables

The secondary efficacy measurement of risk of hypoglycemia event and the risk factors of hypoglycemia.

Safety Variables

The safety variables are the occurrence of adverse events.

20. Statistical analysis:

Subgroup analyses planned.

No subgroup analyses planned.

Number of subjects to be enrolled.

336 subjects will be needed (168 in each arm).

Rationale for the choice of sample size

The Sample size was calculated based on a study published in Critical Care Explorations Journal 2020 with the article named Comparison of IV Insulin Dosing Strategies for Hyperkalemia in the Emergency Department by Kayvan Moussavi et al (8). The anticipated effect size d = 0.2 with alpha error prob = 0.0250 (one-side), actual power 90, Standard deviation of 0.62 and allocation ratio 1:1. The calculated sample size is 320 (160 in each arm). Our statistician estimated a 5% drop rate. So the sample size increased to 336 (168 in each arm).

Planned interim analyses.

Interim analyses will be done after collecting 50% of the data.

21. Criteria for terminating the study.

A subject/Patient who is enrolled in the study and for whom study treatment is prematurely terminated will be discontinued from study treatment. After discontinuation/early release from the study, the subject/patient will receive standard-of-care treatment as per the treating clinician. End of Study Efficacy and Safety assessments will be performed, if appropriate and whenever possible.

The study will be terminated when 336 subjects are enrolled, and all data is obtained and documented on the data collection sheet and transferred to Epi-Data program.

22. Quality control and quality assurance.

Preparation quality

• A study approval from the Royal Hospital and Sultan Qaboos University hospital review board obtained.

• Ensure that all required documents (data collection sheet, informed consent), randomization packages are in order and easily accessible for the investigators.

- o **Investigator's brochure**

▪ To document that relevant and current scientific information about the investigational product has been provided to the investigator.

- o **Signed protocol.**
- o **Informed consent form.**
- o **Subject Deviation/Unanticipated Problem Case Log.**
- o **Serious Adverse Event (SAE) Case Log.**
- o **Withdrawal log.**

- **Nurses and physicians who are involved in the date collection will be trained in the following areas:**
    - o Full description of the attended study and the way to obtain research consent.
    - o Obtaining potassium level from official biochemistry lab result
    - o Preparing Intravenous insulin/Dexstrose 50% + Salbutamol Nebulization.
    - o Measurement of possible side effected and secondary outcomes.

During research progress regular visits from the principle investigator will be done ensuring the following:

- Informed Consent forms are properly completed and up to date.
- Participants are appropriately screened and enrolled.
- Inclusion and exclusion criteria are applied properly.
- Randomization procedures are followed, and the blind is maintained.
- Trial assessments and treatment are conducted in compliance with the protocol.
- All source documents are attributable, legible, contemporaneous, original, accurate, and complete.
- Medication dosing and documentation are following the protocol.
- All adverse events and serious adverse events have been documented and appropriately reported to the principle Investigator and Institutional review board.
- Reviewing drug accountability records for completeness and accuracy.
- Checking for protocol deviations/violations that may have occurred.
- Following up on unresolved issues from previous visits.
- Providing, or arranging for, additional staff training in problem areas.

23. Data handling and record keeping.

Subject/patient information obtained because of this study is considered confidential and disclosure to third parties is prohibited. Medical information may be assessed only after approval from the subject/patient to the Investigator. The investigator will not disclose any confidential information regarding subjects during performance of study duties without justifiable reasons. The investigator affirms the subject's right to protection against invasion of privacy. All data collection sheets are collected in a locked and secured box in the emergency department and no access is allowed except for investigators. Any electronic file containing patient data will be protected by a complicated password. No data will be shared though any social platforms including WhatsApp. Data can be shared between investigators only by password protected Google Drive account. After termination of the study and finishing data analysis, data will be stored for a period of 3 year and will be discarded safely and securely.

24. Procedures for reporting deviations from the original plan.

- **Definition of Protocol Violation:** A protocol violation refers to any non-compliance with the study protocol, procedures, or approved amendments. This can include, but is not limited to, enrollment of ineligible participants, missed study visits, incorrect drug administration, or failure to obtain informed consent.

- **Identification of Violation:** All study personnel should be vigilant in identifying potential protocol violations. Regular audits and monitoring visits will also serve as a mechanism to identify and address violations.

- **Immediate Action:** Upon identification of a potential protocol violation, immediate corrective action should be taken to ensure the safety and rights of the study participants.

- **Documentation:** All protocol violations, regardless of perceived significance, must be documented in details. This documentation should include the nature of the violation, the date it occurred, the individuals involved, and any corrective actions taken.

- **Notification:** The Principal Investigator (PI) must be informed of all protocol violations within 24 hours of discovery. Depending on the severity and nature of the violation, the Institutional Review Board (IRB) and the study sponsor may also need to be notified.

- **Analysis and Reporting:** The PI, in collaboration with the study team, will analyze the cause of the violation and determine its potential impact on the study's integrity and participant safety. A report detailing the violation, its cause, potential impact, and corrective actions will be submitted to the IRB and study sponsor as required.

- **Preventive Measures:** Based on the analysis, preventive measures will be implemented to avoid recurrence of similar violations. This may include additional training for study personnel, revision of study procedures, or increased monitoring.

- **Follow-Up:** All protocol violations will be reviewed during regular study team meetings to ensure that corrective and preventive actions are effective. Any trends in violations will be addressed promptly.

- **Transparency:** All protocol violations and their resolutions will be transparently reported in the study's final publication to ensure the scientific community is aware of any potential biases or limitations in the study results.

Study Protocol Violation Algorithm:

Step 1: Detection
Monitor study activities regularly.
Review data collection sheets, informed consent forms, and other study-related documents for inconsistencies or missing information.

Step 2: Classification
Classify the detected issue: Is it a minor deviation or a major violation?
Refer to the study protocol for definitions and examples.

Step 3: Immediate Action
For minor deviations: Correct the issue immediately, e.g., obtain a missing signature on a consent form.
For major violations: Pause the affected study activity and ensure the safety of the participant.

Step 4: Documentation
Record the violation in the "Subject Deviation/Unanticipated Problem Case Log."
Include details such as the nature of the violation, date, individuals involved, and corrective actions taken.

Step 5: Notification
Inform the Principal Investigator (PI) within 24 hours of discovery.
If severe, notify the Institutional Review Board (IRB) within 14 working days.

Step 6: Analysis
The PI and study team analyze the cause and potential impact of the violation.
Determine if the violation affects participant safety, data integrity, or participant willingness to continue.

Step 7: Report Compilation
Compile a detailed report of the violation, its cause, potential impact, and corrective actions.
Submit the report to the IRB and any other relevant bodies.

Step 8: Preventive Measures
Implement measures to prevent recurrence based on the analysis.
This could include additional training, revision of study procedures, or increased monitoring.

Step 9: Follow-Up
Review all protocol violations in regular study team meetings.
Address any trends or repeated violations promptly.

Step 10: Transparency & Publication
Ensure all protocol violations and resolutions are transparently reported in the study's final publication.

Anticipated Protocol Violations:

Informed Consent Issues:

1. Missing original signed and dated consent form.
2. Use of an incorrect version of the informed consent form.
3. Missing pages from the executed consent form.
4. Inappropriate documentation of consent, such as missing signatures or the individual obtaining consent not being listed on the IRB approved application.

Timing Issues:

1. The subject/patient falls outside of the window of time indicated by the protocol.

Recruitment and Enrollment:

2. Implementation of unapproved recruitment procedures.
3. Enrollment of participants who do not meet the inclusion and exclusion criteria.

Treatment and Assessment:

1. Incorrect drug administration or dosage.
2. Failure to maintain the study's blind.
3. Not following randomization procedures.
4. Trial assessments not conducted in compliance with the protocol.

Documentation and Data Handling:

1. Inaccurate or incomplete source documents.
2. Medication dosing and documentation not following the protocol.
3. Adverse events not being documented or reported to the PI and IRB.

25. Anticipated results

The antihyperkalemic measure effect of intravenous regular insulin 5units is not inferior to intravenous regular insulin 10 units and there will be fewer side effects.

26.References:

1. **Ron M. Walls, MD.** Hyperkalemia. *Rosen emergency medince Concepts and Clinical practice.* 9th. Philadelphia : Elsevier, 2018, 117, pp. 1516 - 1519.
2. **Judith E. Tintinalli, MD, MS.** Hyperkalemia. *Tintinalli's Emergency Medicine a comprehensive study guide.* 9th. s.l. : McGraw-Hill Education, 2020, 17, p. 89.
3. **David B Mount, MD.** Causes and evaluation of hyperkalemia in adults. *Uptodate.* [Online] May 26, 2020. [Cited: October 29, 2021.] https://www.uptodate.com/contents/causes-and-evaluation-of-hyperkalemia-in-adults?search=hyperkalemia&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.
4. —. Treatment and prevention of hyperkalemia in adults. *Uptodate.* [Online] October 29, 2021. [Cited: October 30, 2021.] https://www.uptodate.com/contents/treatment-and-prevention-of-hyperkalemia-in-adults.
5. **Eleanor Lederer, MD, FASN.** Hyperkalemia Treatment & Management. *Medscape.* [Online] [Cited: October 30, 2021.] https://emedicine.medscape.com/article/240903-treatment#d8.
6. *A comparison of insulin doses for treatment of hyperkalaemia in intensive care unit patients with renal insufficiency.* **Miranda Verdier PharmD, Joshua M.DeMott PharmD, MSc, Gary D.PeksaPharmD, MBA.** 6, s.l. : ELSEVIER, June 21, 2021, Australian Critical Care, Vol. 34.
7. *Treatment of Hyperkalemia With a Low-Dose Insulin Protocol Is Effective and Results in Reduced Hypoglycemia.* **Bairbre A. McNicholas, Mai H. Pham, Katrina Carli, Chang Huei Chen, Nancy Colobong-Smith, Arthur Eric Anderson and Hien Pham.** october 23, 2017, KI reports, pp. 328–336. https://www.researchgate.net/publication/320590998_Treatment_of_Hyperkalemia_With_a_Low-Dose_Insulin_Protocol_Is_Effective_and_Results_in_Reduced_Hypoglycemia.
8. *Comparison of IV Insulin Dosing Strategies for.* **Kayvan Moussavi, PharmD, BCCCP, et al., et al.** s.l. : Wolters Kluwer Health, Inc, 2020, Critical Care Explorations Jaurnal, Vol. 2.
9. *A Comparison of Insulin Doses for the Treatment of Hyperkalemia in Patients with Renal Insufficiency.* **Heather A. LaRue, Gary Daniel Peksa, Shital C. Shah.** 12, December 2017, American college of clinical pharmacy, Vol. 37, pp. 1516-1522.
10. *Reduced alternative insulin dosing in hyperkalemia: A meta-analysis of effects on hypoglycemia and potassium reduction.* **Kayvan Moussavi, Joshua Garcia, Eglis Tellez-Corrales, Scott Fitter.** 7, s.l. : American College of Clinical Pharmacy, May 16, 2021, Vol. 41, pp. 598-607. https://accpjournals.onlinelibrary.wiley.com/doi/10.1002/phar.2596.
11. *Optimal Dose and Method of Administration of Intravenous Insulin in the Management of Emergency Hyperkalemia: A Systematic Review.* **Ziv Harel, Kamel S. Kamel.** [ed.] Sao

Paulo State University, BRAZIL Pasqual Barretti. may 5, 2016, PLOS ONE. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0154963.
12. **Adrian Vella, MD.** Hypoglycemia in adults without diabetes mellitus: Diagnostic approach. *Up-To-Date.* [Online] July 23, 2020. [Cited: December 31, 2022.] https://www.uptodate.com/contents/hypoglycemia-in-adults-without-diabetes-mellitus-diagnostic-approach?search=hypoglycemia%20&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
13. **ames Neuenschwander, MD, FACEP (co-chair) Matthew Weir, MD (co-chair) Terra Armstead DNP, RN, CEN Jason J. Bischof, MD Joanna Hudson, PharmD W. Frank Peacock, MD, FACC, FESC, FACEP Zubaid Rafique, MD, FACEP.** Hyper K recognition and treatment of Hyperkalemia in the ED. *American College of Emergency Physicians.* [Online] 05 08, 2022. [Cited: 08 05, 2022.] https://www.acep.org/patient-care/hyperk/.
14. *Reduced Versus Conventional Dose Insulin for hyperkalemia Treatment.* **Joshua Garcia, PharmD, BCPS1,2, Megan Pintens, PharmD, BCPS, BCCCP2, Amanda Morris, PharmD, BCPS, BCCCP2, Paul Takamoto, PharmD2, Laura Baumgartner, PharmD, BCPS, BCCCP2,3, Chelsea L. Tasaka, PharmD, BCPS, BCCCP2,4.** 3, 2020, Journal of Pharmacy practice, Vol. 33, pp. 262 - 266.
15. **Baig, Dr Tom Pickett & Israr.** Treatment guideline : Hyperkalemia. *NHS Gloucestershire Hospitals.* [Online] NHS, February 2021. [Cited: 10 26, 2022.] https://www.gloshospitals.nhs.uk/gps/treatment-guidelines/hyperkalaemia/.
16. *Comparison of IV Insulin Dosing Strategies for Hyperkalemia in the Emergency Department.* **Kayvan Moussavi, PharmD, BCCCP, et al., et al.** s.l. : Wolters Kluwer Health, Inc, 2020, Critical Care Explorations Jaurnal, Vol. 2.

27.Appendix:

Data collection sheet

Patient hospital ID						
Study Code:						
Demographics						
Hospital						
Location (ED/Inpation)						
Gender						
Age						
DM type						
HTN						
IHD						
ESRD						
Last Dialysis session (if any)						
Other comorbidities						
Home Medications						
Suspected cause of Hyperkalemia						
CBC	Hb:	WBC:	Plat:			
UE	AG:	HCO3:	Creat:	GFR:	Na:	K:
Mg serum						
Follow up /time line (minutes)	0	60	120			
Potassium						
Blood sugar						
Total amount of Intravenous fluid received during the study period / type of IV fluid						
Other medications adminestered						
Urine output (if any)						
Needed another antihyperkalemic messures?						
Needed Urgent/Emergent Dialysis?						

Written informed consent

5 versus 10 units of insulin in hyperkalemia management: Double Blinded, Randomized Clinical Trial

5/10 trial

Introduction:
We are researchers from Oman medical speciality board (OMSB) conducting a research on the efficacy and safety of different insulin doses (5 units versus 10 units of regular insulin) in management of hyperkalemia. Hyperkalemia is the most common electrolytes imbalance, and it has significant side effects on the heart. This consent will include all the information about our study and the protocol in addition to the rationale of our study.

The aim of the study
Hyperkalemia is a life threatening electrolyte imbalance and needs immediate management. Different medications are used to treat hyperkalemia. One of these medications is insulin. Different doses of insulin are used in treating hyperkalemia depending on the physician's judgment and patient condition. No previous prospective study done to compare the doses of insulin in hyperkalemia. Insulin is associated with hypoglycemia as a side effect especially with high doses. Our investigators will allocate you into one of two groups of doses (5 units vs 10 units) of insulin and will follow the effect on reducing potassium level, in addition following up blood sugar level. At the same time. At the same time, You also will receive dextrose IV to prevent you from hypoglycemia**.**

Type research intervention:
Comparing between two doses of insulin in lowering hyperkalemia.

Participant collection:
All patients above 18 years, whom having hyperkalemia will be evaluated to participate in the study.

Voluntary participation:
Your participation in this research is entirely voluntary. It is your choice whether to participate or not. All the services you receive at this hospital will continue and nothing will change If you choose not to participate in this research project, you will be offered the same treatment but without registering your data, as it is the same treatment offered in this hospital for hyperkalemia. You may change your mind later and stop participating even if you agreed earlier**.**

Information about the study
This study will start after identifying hyperkalemia, and the treating physician identifies you as a candidate for the treatment. You will be randomised in 2 different groups of insulin doses, and will be followed and monitored throughout the entire study period. All other antihyperkalemic medications will be started the same with no change from the routine treatment. At the same time, You also will receive dextrose IV to prevent you from hypoglycemia.
.

Study Procedure:
Because till now no prospective study has been done to compare the 2 doses of insulin in lowering hyperkalemia, and the increase of risk of hypoglycemia with the high dose of insulin. This study aims to select the proper and the safest dose for our patients.
The patient will follow the routine path of clinical evaluation and management. If a patient is found to have hyperkalemia more than or equal 5.5 mEq/L he/she will be screened for inclusion and exclusion criteria. The patient or the family member who can give consent for the patient will be informed about the study. After explaining all the details for the patients/relative a written consent will be taken with an Arabic and English copy will be provided for further details.
Once consent is signed a physician will randomise the patient into one of the two different groups of insulin doses. One group will receive 5 units of insulin regular and the second group will receive 10 units of insulin regular. At the same time, You also will receive dextrose IV to prevent you from hypoglycemia.
. The group selection will be randomised before the start of the study, and the physician will not decide which patient will join which group to maintain good randomization and to have proper results from the study. Serial labs will be collected at different time intervals to monitor the patient and his response. Labs will be collected at 0, 120 minutes to trace potassium level. Blood sugar will be monitored by Glucometer at 0, 60, 120 minutes or as indicated by the treating physician according to your symptoms. Patients will receive all treatments for hyperkalemia without change from the hospital followed protocol except for the dose of insulin. If there is any concern at any point during the study feel free to contact me or to contact the treating physician for any clarification. If there is any concern regarding your safety during the study you can stop at any time and the local protocol/guidelines will be followed for your management.

Risk:
Risk of hypoglycemia as a side effect of higher insulin dose, but it is managed by the sugar that is given with insulin at the start of the study. All side effects will be monitored as per the protocol, and medications side effects will be traced, and will be treated as soon as possible once identified.

Benefit
This will help us to clarify the proper dose of insulin in treating hyperkalemia with the least side effect to patients. Your participation will improve the next patient care once the data analyses.

Reimbursements
You will not be given any other money or gifts to take part in this research.

Confidentiality
The information that collected by our investigators from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers/investigators will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers/investigators will know what your number is, and the information will be lock up with a lock and key.

Sharing the Results
The knowledge that our investigators get from doing this research will be shared with you through community meetings before it is made widely available to the public. Confidential

information will not be shared. There will be small meetings in the community, and these will be announced. After these meetings, our research team will publish the results in order that other interested people may learn from our research.

Right to Refuse or Withdraw
You do not have to take part in this research if you do not wish to do so and refusing to participate will not affect your treatment at this emergency department in any way. You will still have all the benefits and you may stop participating in the research at any time that you wish without losing any of your rights as a patient here. Your treatment at this hospital will not be affected in any way.

Alternatives to Participating
If you do not wish to take part in the research, you will be provided with the established standard treatment available at the hospital.

Contact information

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it. Any questions that I asked, they have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research.

Authorised to consent name	**Relationship to the patient**	**Signature**	**Date**

Researcher/Doctor:
Signature:
Date:

Subject ID: ☐☐☐☐☐ **D** ☐☐/☐☐/☐☐☐☐

Month **Day** **Year**

Withdrawal form

Date subject went Off Study: ☐☐ ☐☐ ☐☐☐☐

Month **Day** **Year**

INDICATE OFF STUDY REASON: (select only one)

☐ **Study Activities Completed**

If the subject was withdrawn prior to completing the study (i.e. early withdrawal), select one of the following:

- ☐ **Subject withdrawn – by Subject PRIOR to enrollment****
- ☐ **Subject withdrawn – by Subject AFTER enrollment****
- ☐ **Subject withdrawn – by PI PRIOR to enrollment****
- ☐ **Subject withdrawn – by PI AFTER enrollment****
- ☐ **Death**
- ☐ **Other****

If the subject was withdrawn, indicate specific reason(s): (select all that apply)

- ☐ **Subject lost to follow-up**
- ☐ **Subject refused follow-up**
- ☐ **Due to adverse events or complications**
- ☐ **Other…**

****Additional explanation required:**

_____

_____

Form Completed by:

Medications administration form:

Medications administration card

(Insulin 5 units group)

- The doctor **must not know** the dose of insulin received by the patient.
- Give the patient the following medications:
  - Insulin Regular 5 units with Dextrose 50 ml of 50 % concentration intravenously (IV) over 30 minutes.
  - Salbutamol 10 mg Nebulization over 15 minutes.

Please repeat potassium level after 120 minutes from the time insulin/dextrose infusion

Repeat RBS: 60 and 120 minutes.

	60 minutes	120 minutes
Serum Potassium measurement		*
*RBS via glucometer	*	*

- If a patient become hypoglycemic (random blood sugar (RBS) ≤ 3.89 mmol/l in Diabetic patients and less than 3 mmol/l in non-Diabetic patients) inform the Doctor/Research assistant.
- Example: if you start insulin/Dextrose at 02:00 the infusion till 02:30 so repeat RBS at 03:00 and 04:00. Repeat U&E at 04:00.
- *RBS: Random blood sugar. U&E: urea and electrolytes.

==========

Medications administration card

(Insulin 5 units group)

- The doctor **must not know** the dose of insulin received by the patient.
- Give the patient the following medications:
  - Insulin Regular 5 units with Dextrose 50 ml of 50 % concentration intravenously (IV) over 30 minutes.
  - Salbutamol 10 mg Nebulization over 15 minutes.

Please repeat potassium level after 120 minutes from the time insulin/dextrose infusion

Repeat RBS: 60 and 120 minutes.

	60 minutes	120 minutes
Serum Potassium measurement		*
*RBS via glucometer	*	*

- If a patient become hypoglycemic (random blood sugar (RBS) ≤ 3.89 mmol/l in Diabetic patients and less than 3 mmol/l in non-Diabetic patients) inform the Doctor/Research assistant.
- Example: if you start insulin/Dextrose at 02:00 the infusion till 02:30 so repeat RBS at 03:00 and 04:00. Repeat U&E at 04:00.
- *RBS: Random blood sugar. U&E: urea and electrolytes.

Study Flow chart:

STUDY FLOW

Patient diagnosed in the ED with hyperkalemia, K ≥ 5,5 mEq/l from official Laboratory test, will Start all antihyperkalemic measures, Ca gluconate need will be decided by the treating physician .

Patient in whom K level was checked from VBG and found to be ≥ 5.5 mEq/l

They will go through the same process.

If the official lab K level result below 5.5mEq/l, or hemolyzed patient will be excluded from the study.

↓

Attending physician

1. Patient will receive Salbutamol nebulization 10 mg in 3ml normal saline over 15 minutes.
2. ((The physician will decide the need of cardiac stabilizing agents (e.g Calcium Gluconate) as indicated by the physician in-charge of the patient.))
3. Will screen inclusion and exclusion criteria.
4. Explain all study procedure to the patient.
5. Obtain informed consent with signature.

↓

Randomization

1. Open study envelope.
2. Take the included code in that envelope and stick it to the patient data collection sheet.
3. Give medication instructions card to the nurse in-charge of the patient

↙ ↘

5 IU of Insulin

10 IU of Insulin

↘ ↙

Assessment

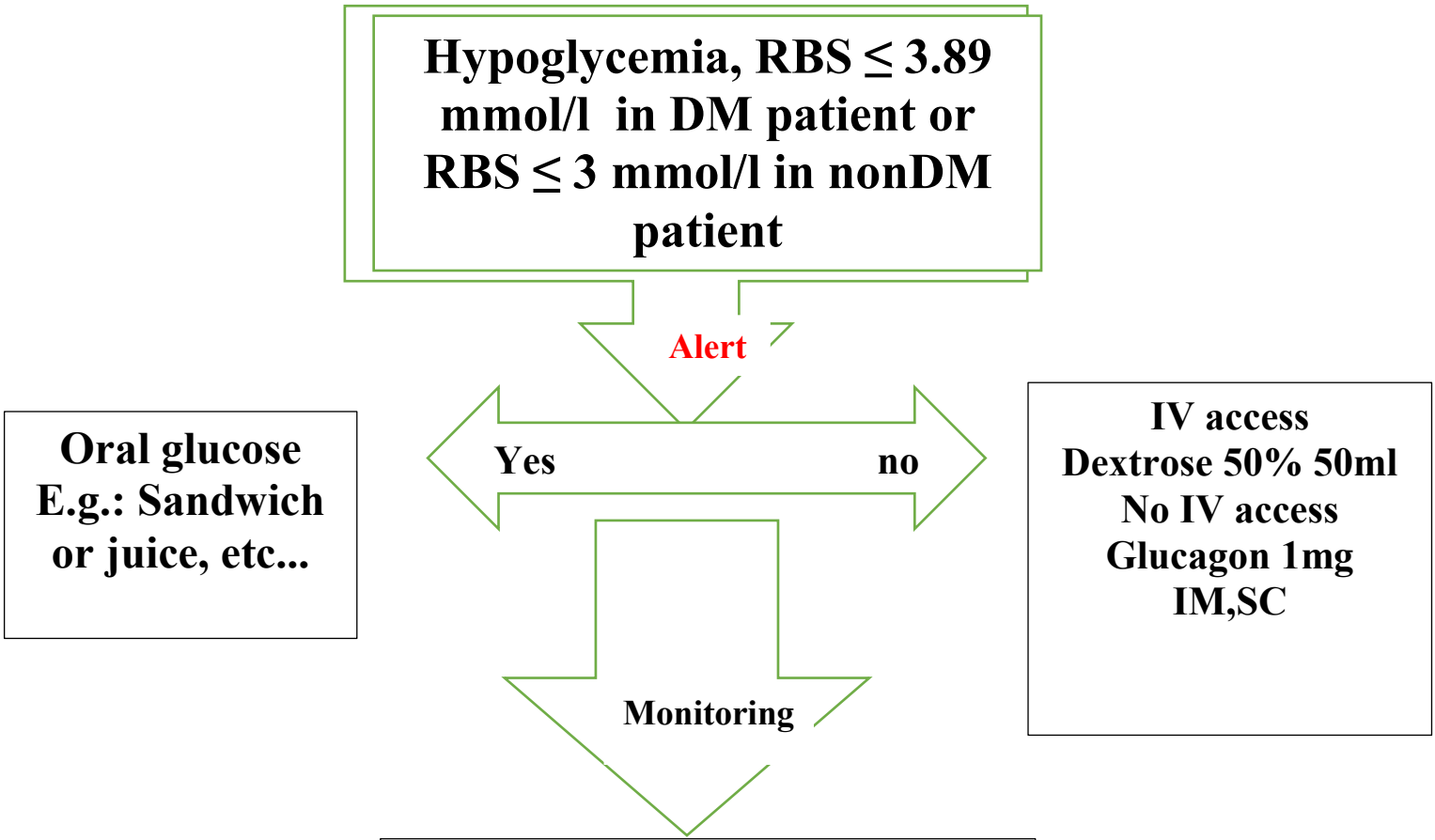
Potassium level: 0 and 120 minutes.
Blood sugar: 0, 60 and 120 minutes.
Report any adverse event

↓

Termination

The study will be over at 120 min from medication administration

Hypoglycemia management flow chart

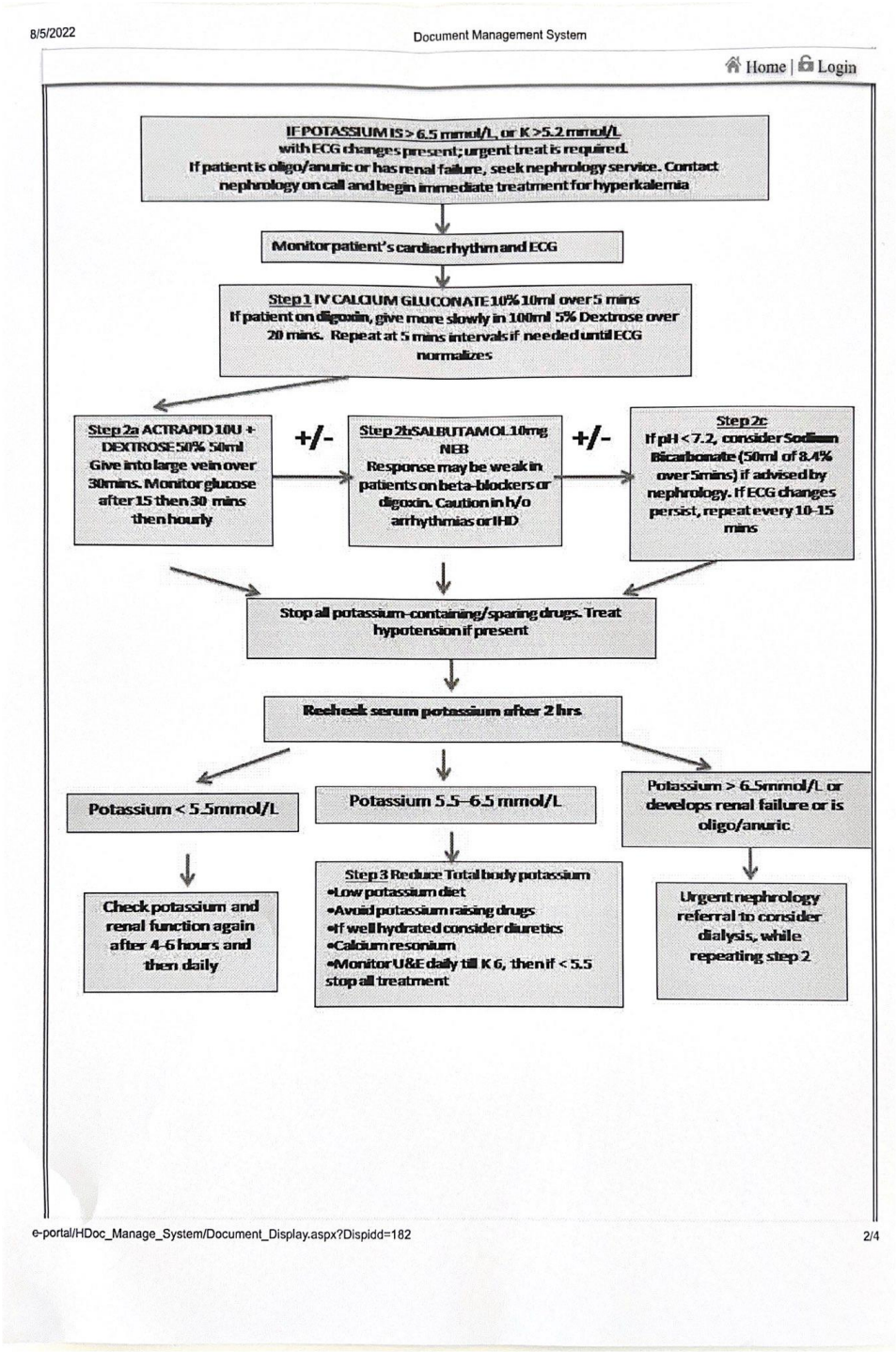


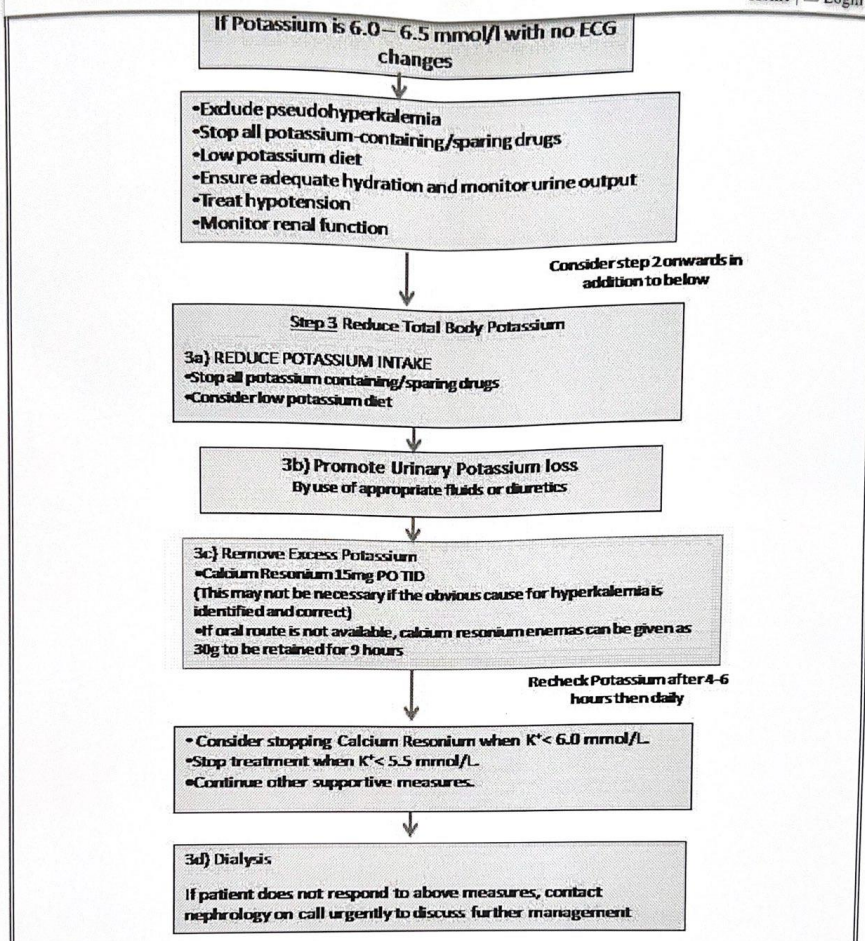
Disposition

Consider discharge after 4h uneventful observation if,

- Hypoglycemia fully and rapidly reversed without continuous infusion of dextrose
- Tolerated a full meal in ED
- Clear and innocuous cause identified with recurrence unlikely
- Adequate patient understanding, home support/monitoring, and ability to detect/prevent recurrence with close primary care follow-up

Ministry of Health hyperkalemia management:





Reference:

Support C. Guideline for the Management of Acute Hyperkalaemia in Adults Guideline for the Management of Acute Hyperkalaemia in Adults Guideline for the Management of Acute Hyperkalaemia in Adults Summary – Management of Acute Hyperkalaemia This guideline covers the. 2013;(April):1-12.

Written by: Dr.Wessam Osman Specialist, AMAU
Checked by: Dr. Adil Al Lawati Consultant, AMAU.
Authorized by: HISHAM ABDULLAH MOHD AL DHAHAB

Back

Serious Adverse Event (SAE) Case Log

Principal Investigator: _____

IRB Number: _____ Protocol Number: _____ Subject ID# | | | | | |

Short Protocol Title: _____

SAE Number	SAE Description	Adverse Event* *(Select from Safety Profiler)*	SAE Classification	Event Start Date	Event End Date	Date Site Became Aware of Event (Reported Date)	Grade	Unexpected (Y or N)	Attribution	Outcome

*look up corresponding AE at: https://safetyprofiler-ctep.nci.nih.gov/

SAE Classification	Grade	Attribution	Outcome
1 - Fatal (resulted in death)	1 - Mild	0 – Definite	0 – Fatal
2 - A life-threatening occurrence	2 - Moderate	1 – Probable	1 – Not recovered/not resolved
3 - Requires inpatient hospitalization or prolongation of existing hospitalization	3 - Severe	2 – Possible	2 – Recovered w/sequelae
4 - Results in persistent or significant disability/incapacity	4 - Life Threatening	3 – Unlikely	3 – Recovered w/o sequelae
5 - Results in congenital anomaly/birth defect	5 – Death (Fatal)	4 – Unrelated	4 – Recovering/Resolving
6 - A significant medical incident that, based upon appropriate medical judgment, may jeopardize the subject and require medical or surgical intervention to prevent one of the outcomes listed above.			

Subject Deviation/Unanticipated Problem Case Log

Subject Deviation/Unanticipated Problem Case Log

Principal Investigator: _____

IRB Number: _____ Protocol Number: _____ Subject ID# ☐☐☐☐☐

Short Protocol Title: _____

#	Start Date	End Date	Description	Category (see below)	Does the deviation/UP have the potential to:			Reported to IRB	PI Initials	Date of PI Initials
					Impact Subject Safety*	Affect Data Integrity*	Affect Subject's Willingness to Participate?*			
					☐ Yes ☐ No ☐ Not Applicable	☐ Yes ☐ No ☐ Not Applicable	☐ Yes ☐ No ☐ Not Applicable	__/__/____ ☐ Not Applicable		
					☐ Yes ☐ No ☐ Not Applicable	☐ Yes ☐ No ☐ Not Applicable	☐ Yes ☐ No ☐ Not Applicable	__/__/____ ☐ Not Applicable		

**If one or more is answered yes for any event, it must be reported to the IRB promptly (14 business days from notification of or becoming aware of the event).*

Category:

1. Consent Deviation
2. Drug/Device Administration/Accountability
3. Enrollment Deviation
4. Procedural Deviation
5. Loss of Confidentiality
6. Other (describe)