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BMJ Open Insulin glucose infusion versus nebulised salbutamol versus combination of salbutamol and insulin glucose in acute hyperkalaemia in the emergency room: protocol for a randomised, multicentre, controlled study (INSAKA)

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ABSTRACT

Introduction Hyperkalaemia is a common electrolyte disorder and can be life-threatening. In the emergency room (ER), interventions aim to protect patients from the immediate dangers of elevated serum potassium by redistributing potassium ions from the bloodstream into the cells via intravenous insulin or nebulised beta2-agonists. However, to date, evidence for acute management of hyperkalaemia is limited. The aim of this randomised controlled trial is therefore to compare three strategies, namely insulin/glucose intravenous infusion, nebulised salbutamol or a combination of nebulised salbutamol and insulin/glucose intravenous infusion to reduce serum potassium concentration at 60 min as a first-line treatment in patients admitted to the ER with serum potassium concentrations superior or equal to 6 mmol/L.

Methods and analysis INSAKA is a prospective, multicentre, controlled, open-label, parallel-group, randomised in a 1:1:1 ratio clinical trial. Patients will be eligible for randomisation if they have serum potassium concentrations superior or equal to 6 mmol/L measured in the ER. Patients will receive either: (1) 10 mg of nebulised salbutamol, (2) 10 units of short-acting insulin in an intravenous bolus with 500 mL of 10% glucose or (3) 10 units of short-acting insulin in an intravenous bolus with 500 mL of 10% glucose combined with 10 mg of nebulised salbutamol. The primary endpoint will be the mean change in the absolute serum potassium level from baseline to 60 min measured in mmol/L. We plan to include 525 patients.

Ethics and dissemination The INSAKA trial will be conducted in accordance with the International Council on Harmonization Good Clinical Practices. All trial documents and procedures have been reviewed and approved by the Ethics Committee Sud Méditerranée III (approval ID number: 19.07.16.36428). The results will be actively disseminated through peer-reviewed journals, conference presentations, social media, broadcast media, print media and the internet.

Strengths and limitations of this study

- This multicentre trial assesses acute management of hyperkalaemia in the emergency room with treatments that have not been well evaluated.
- The trial evaluates three different first-line treatments available in the emergency room: beta2-agonists, insulin-dextrose or both.
- The outcome chosen, serum potassium level is objective.
- A limitation of the trial is its open-label design.

Trial registration EudraCT number: 2019-002710-39, Clinicaltrials.gov identifier: NCT04012138.

INTRODUCTION

Hyperkalaemia is a frequent electrolyte disorder in patients admitted to the emergency room (ER).¹ Patients with chronic pathology such as diabetes mellitus, hypertension, heart failure or chronic kidney disease are especially at risk of developing acute hyperkalaemia.² Hyperkalaemia is a potentially life-threatening electrolyte disturbance that can impair cardiac function.²⁻³ Studies have established the association between hyperkalaemia and all-cause mortality.⁴⁻⁷ Decreasing serum potassium to normal values can be performed by reducing potassium intake from external sources, redistributing potassium ions from the bloodstream into the cells, increasing potassium removal from the body or a combination of the above. First-line treatment is based on pharmacological interventions in the ER.⁸ A threefold approach to

the treatment of hyperkalaemia is currently being adopted by clinicians: (1) stabilising the cardiac membranes with intravenous calcium, (2) redistribution of potassium with intravenous insulin or beta2-agonist and (3) elimination of potassium from the body via haemodialysis in patients with severe renal failure when first-line treatment fail.⁹

However, solid evidence is lacking to guide the emergency management of patients with hyperkalaemia and the effectiveness of therapeutic strategies remains unclear.¹⁰ Consequently, emergency treatment for hyperkalaemia is highly variable from patient to patient within an institution and variations in recommendations for treatment of hyperkalaemia have been observed.¹¹ A recent study reported that insulin/glucose was frequently used to treat hyperkalaemia in the ER, but that overall, 43 different treatment combinations have been employed within the first 4 hours.¹² Furthermore, a Cochrane systematic review found that evidence for acute pharmacological management of hyperkalaemia is poor and strikingly incomplete with several methodological biases detected.¹³ Finally, the latest Kidney Disease: Improving Global Outcomes (KDIGO) statement on hyperkalaemia proposes a therapeutic algorithm encompassing 'IV insulin and glucose and/or salbutamol', acknowledging that 'insulin and albuterol may have an additive effect'.¹⁴

Therefore, a rigorous evaluation of first-line treatments of hyperkalaemia in the ER is warranted to reliably trigger recommendations for clinical practice.

Aim

The primary objective of our study will be to compare three commonly used strategies, namely insulin/glucose intravenous infusion, nebulised salbutamol or combination of nebulised salbutamol and insulin/glucose intravenous infusion to reduce serum potassium concentration at 60 min as first-line treatment in patients admitted to the ER with serum potassium concentrations superior or equal to 6 mmol/L. The secondary objectives of the trial will be to: (1) compare the three treatment groups for reduction in serum potassium concentrations at 180 min and 24 hours; (2) compare the proportion of patients with normokalaemia (from 4 to 4.9 mmol/L) at 60, 180 min and 24 hours; (3) compare the proportion of patients who require second-line treatment or dialysis at 60 and 180 min; (4) compare selected adverse reactions at 60 and 180 min; (5) compare, on a standard 12-lead ECG, the proportion of patients with heart rhythm disorders or high-grade atrioventricular bloc that require urgent medication during the first 180 min; (6) compare other ECG abnormalities at 60, 180 min and 24 hours; and (7) compare the rates of major cardiovascular events at 60, 180 min and 24 hours.

METHODS AND ANALYSIS

Trial design

INSAKA is a prospective, multicentre, controlled, randomised, open-label, parallel-group trial, comparing

insulin/glucose intravenous infusion, nebulised salbutamol or combination of nebulised salbutamol and insulin/glucose intravenous in patients admitted to the ER with serum potassium concentrations superior or equal to 6 mmol/L. The trial will be conducted in 15 ERs in France.

Subjects meeting all eligibility criteria will be randomly assigned to one of the three treatment groups in a 1:1:1 ratio based on a computer-generated randomisation list prepared before the beginning of the study. Randomisation will be performed using permuted blocks of random sizes. The block sizes will not be disclosed to study investigators. Randomisation will be centralised via a web interface. Randomisation will be stratified: (1) according to the serum potassium level at baseline (6 to <6.5 mmol/L and superior or equal to 6.5 mmol/L). We chose these thresholds based on the European Resuscitation Council that recommends the stratification of hyperkalaemia into moderate (6.0–6.4 mmol/L) and severe (>6.5 mmol/L)¹⁵; and (2) according to the prescription or not of intravenous diuretics during the 6 hours prior to randomisation. Patients will then be randomised to receive either: (1) 10 mg of salbutamol nebulised in 30 min or (2) 10 units of regular short-acting insulin in an intravenous bolus with 500 mL of 10% glucose administered over a 30-min period or (3) 10 units of regular short-acting insulin in an intravenous bolus with 500 mL of 10% glucose administered over a 30-min period and 10 mg of salbutamol nebulised in 30 min. Serum potassium will be then measured at 60 min. If the patient still has hyperkalaemia at 60 min, the patient will receive a second-line treatment, left to the discretion of the physician in charge. Serum potassium will be then measured again at 180 min and 24 hours. Importantly, serum potassium levels will be measured at local laboratories at baseline and 60, 180 min and 24 hours. They will perform a visual inspection and a validated semiquantitative test on each blood sample as an assessment for haemolysis. In case of hemolysis, serum potassium will be measured again.

The trial has been designed on the basis of the Consolidated Standards of Reporting Trials (2010) guidelines,¹⁶ and a Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) figure is provided (figure 1). A SPIRIT checklist file is attached (online supplementary file 1).

Sample selection

Consecutive adults (18 years and older) admitted to the ER will be enrolled in the study if local laboratory serum potassium levels are superior or equal to 6 mmol/L. Criteria for non-inclusion will be: haemolysis of blood samples or thrombocytosis $>10^6/\text{mm}^3$ or hyperleucocytosis $>10^5/\text{mm}^3$ on the first blood sample that could be pseudohyperkalaemia, acute complications of diabetes (diabetic ketoacidosis and hyperosmolar hyperglycaemic syndrome), pregnant or lactating women, women with childbearing potential who have not had effective contraception, patients expected to require emergency

TIMEPOINT	Inclusion visit	Randomisation visit	Follow up visits			Close-out
	-t ₁	0	t ₁ 60 minutes	t ₂ 180 minutes	t ₃ 24 hours	T ₄ 36 hours
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Potassium level measurement, other baseline characteristics and blood samples		X				
Randomisation		X				
INTERVENTIONS:						
Insulin/dextrose OR B2-agonist OR both		X	If needed	If needed		
Calcium salt, other treatments (bicarbonate, diuretics, dialysis)			If needed	If needed		
ASSESSMENTS:						
Potassium level, glycemia, magnesemia			X	X	X (only potassium level)	
Evaluation of Adverse events and the need for re-treatment or dialysis		X	X	X	X	X
electrocardiogram		X	X	X	X	X
Safety evaluations		X	X	X	X	X

Figure 1 SPIRIT figure for the INSAKA trial. SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

intubation and ventilation, patients expected to require dialysis within the first 60 min, patients expected to require diuretics within the first 60 min, patients expected to require intravenous sodium bicarbonate within the first 60 min, patients with heart rhythm disorders or high-grade atrioventricular bloc that require urgent medication on ER admission, hypersensitivity to the tested active substance or to the excipients of salbutamol or insulin treatment, acute coronary syndrome, patients not on a health insurance plan, patients under guardianship, curatorship or the safeguard of justice.

Importantly, the senior ER physician in charge of the patient will obtain informed consent. Patients who meet all of the inclusion will be randomly assigned to one of the three groups after signing an informed consent form (online supplementary file 2).

Measurement and planned outcomes

The primary endpoint will be the mean change in serum potassium levels from baseline to 60min measured in mmol/L. The secondary endpoints will be: (1) the mean change in the serum potassium levels from baseline to 180min and 24hours; (2) the proportion of patients with serum potassium levels of 4mmol/L to <4.9mmol/L at 60, 180min and 24hours; (3) the proportion of patients who

require retreatment or dialysis at 60, 180 min and 24hours; (4) the proportion of patients with adverse effects at 60 and 180 min, including hypokalaemia (serum potassium levels <3.5 mmol/L and <4mmol/L), hypomagnesaemia (serum magnesium levels of <0.58mmol/L), hypoglycaemic (serum glucose levels<4.0mmol/L), hyperglycaemic (serum glucose levels >10.0mmol/L), the proportion of patients with gastrointestinal disorders, including diarrhoea, nausea, vomiting, the proportion of patients with tachycardia >130/min; (5) the proportion of patients with heart rhythm disorders or high-grade atrioventricular bloc who require urgent medication during the first 180min; (6) the proportion of patients with electrocardiographic abnormalities, at 60, 180min and 24hours, including auricular extrasystoles, ventricular extrasystoles, atrioventricular block, QRS interval prolongation (>120ms), QT interval prolongation (>500ms) ; (7) the proportion of patients with major cardiovascular events at 60, 180min and 24hours, including cardiac arrest, stroke, acute heart failure, complete atrioventricular block, ventricular fibrillation and ventricular tachycardia.

All ECGs will be reviewed by two cardiologists who are experts in ECG interpretation at a core electrocardiographic laboratory. The core electrocardiographic laboratory will provide centralised assessment of all ECGs including assessment of heart rhythm, RR interval, PR interval, QRS duration, QT interval and QTc interval. In addition, for each ECG, the core electrocardiographic laboratory will provide an assessment of whether the ECG findings are consistent with hyperkalaemia or hypokalaemia. All ECGs will be reviewed blinded to the treatment group. In case of discordant interpretation of an ECG between the two cardiologists, another cardiologist will interpret the ECG.

An independent adjudication committee will adjudicate all events including ECGs and clinical events as defined in the secondary endpoints. This critical event committee will review blinded data during the study in order to adjudicate these events and will provide an assessment of whether death is related to the treatment prescribed. The critical committee will use electronic Case Report Form (eCRF), safety reports and all files submitted to support the declaration of these events (ECG, biological parameters, hospitalisation records, and so on). In addition, the critical event committee will formally assess whether individual ECG findings identified by the core electrocardiographic laboratory are related to a potassium disorder. Cardiovascular events will be adjudicated based on the recognised, standardised definitions for cardiovascular endpoint events in clinical trials.¹⁷

Data collection

Prior to the beginning of the trial, study personnel will undergo training sessions on data collection and will be individually tested on data entry as well as outcome assessments. Study data will be collected and managed using Ennov Clinical electronic data capture tools at Nantes University Hospital. Ennov Clinical is a secure, web-based application designed to support data capture for research



studies, providing: (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Study personnel with their own access rights to the study database will enter/capture data from source documents corresponding to a subject in the protocol-specific eCRF.

Sample size

The estimated number of participants calculated is based on an analysis of superiority of one of the strategies tested, the combination of salbutamol and insulin/dextrose versus insulin/dextrose intravenous infusion alone or nebulised salbutamol alone. On the basis of the Ngugi *et al*¹⁸ study, the minimum relevant difference between treatment given alone and combined treatments was 0.25 mmol/L. With an SD of 0.66, a sample size of 175 patients per group of treatment will enable a 90% power to detect this difference with a two-sided t-test with a type I error of 0.025.

Data analysis

Statistical analysis will be performed at the end of the study. No interim analysis is planned. The intention-to-treat principle will be applied. The number of participants with missing data for each variable of interest will be indicated. Baseline characteristics will be reported per group using descriptive statistics. No statistical test will be performed on baseline measures. The primary endpoint will be analysed via analysis of variance (ANOVA) to explain this outcome by the randomised group (three different groups) and the variables used to stratify the randomisation (serum potassium level at baseline and the prescription or not of intravenous diuretics during the six previous hours). The superiority of the combination salbutamol and insulin/dextrose compared with the two other treatments (insulin/dextrose or salbutamol alone) will be proven if the decrease in serum potassium in the salbutamol group and insulin/dextrose is significantly greater than the decrease in each of the two other groups with a significant level considered at 2.5% (5%/2). For the secondary outcomes, comparisons will be performed using ANOVAs for continuous outcomes and logistic regression for binary outcomes. As independent variables, we will consider in each model only the randomisation group and the variables used to stratify randomisation (serum potassium level at baseline and the prescription or not of intravenous diuretics during the six previous hours). The analyses will be performed using Stata software (Stata Corp, Texas, USA).

Patient and public involvement

No patients were involved in the design process of this study, setting the research question or the outcome measures nor were they involved in the analysis, interpretation and writing of the results. Our findings from the trial will be shared with

all participants, who will be provided with a lay abstract of our study and access to the full manuscript.

DISCUSSION

Hyperkalaemia is a commonly encountered, and a potentially life-threatening condition that requires prompt treatment in the ER. However, to date, evidence for acute management of hyperkalaemia in the ER is limited. Up to the present, the choice to use insulin with glucose, or nebulised beta2-agonist, or the combination of insulin with glucose and nebulised beta2-agonist has not been supported by robust trials. Furthermore, the adverse effects of treatments have not been well evaluated and are poorly communicated in previous studies. Our trial is designed to compare these three strategies in terms of efficacy and safety. Our trial will have the power to answer several outstanding issues: which treatment is the most effective to reduce potassium levels—beta2-agonists, insulin-dextrose or both? Which treatment is the most effective to reduce serious adverse events (ie, arrhythmias)? Which treatment has the fewest adverse effects? When should potassium be rechecked? When is retreatment needed? Our trial will have practical consequences and may lead to a change in the management of patients admitted to ERs with hyperkalaemia.

In our trial, patients will receive either: (1) 10 mg of salbutamol nebulised in 30 min, (2) 10 units of regular short-acting insulin in an intravenous bolus with 500 mL of 10% glucose administered over a 30-min period or (3) 10 units of regular short-acting insulin in an intravenous bolus with 500 mL of 10% glucose administered over a 30-min period and 10 mg of salbutamol nebulised in 30 min. Sterns *et al*¹⁹ found that the most commonly recommended regimen for emergency treatment of severe hyperkalaemia is a bolus intravenous injection of 10 U of regular insulin. Recently, the KDIGO Controversies Conference recommended to use 10 units of insulin,¹⁴ based on a systematic review by Harel and Kamel, who reported that the administration of 10 units of insulin resulted in comparable lowering of potassium as the administration of 20 units, while use of the larger dose was associated with a higher risk for hypoglycaemia.²⁰ They also recommend to use salbutamol 10 mg nebulised.¹⁴

A limitation of the trial is its open-label design. We considered the possibility of performing the INSAKA trial with a double-blind protocol but it is not feasible for one principal reason: it is not possible to blind for 500 mL of dextrose just as it is not ethical to give 500 mL of normal saline (0.9% NaCl solution). Indeed, this massive supply of normal saline could be very harmful to patients with chronic heart failure or to elderly patients. This could lead to acute heart failure without benefit for the patients in the blind procedure. Moreover, the increase in serum chloride due to normal saline intake could increase serum potassium levels. Given this issue, we decided to perform INSAKA as an open-label trial. We chose an outcome (serum potassium level) that is objective in order to minimise the risk of bias. The open-label design of our study will not bias our primary objective evaluation to any extent. To reinforce this, in the systematic

review by Batterink *et al*²¹ they classified the lack of blinding of participants and personnel (performance bias) as a low risk of bias, concluding that the risk of bias was probably low given the objective nature of the primary outcome which was a change in potassium levels—the same outcome chosen in our trial.

Ethics and dissemination

The INSAKA trial is supported by a grant from the French Ministry of Health (PHRC 2018 API 18-0191) and will be conducted in accordance with the International Council on Harmonization Good Clinical Practices that adhere to the ethical principles of the Declaration of Helsinki (1964 and subsequent amendments). The funding source will have no role in the study design, data collection, data analysis, data interpretation or report writing.

All authors have agreed to submit for publication. All trial documents and procedures have been reviewed and approved by the Ethics Committee (CPP SUD MEDITERRANEE III, 7 October 2019, approval ID number: 19.07.16.36428). Written informed consent will be obtained from all patients before admission to the trial.

The results of our trial will be actively disseminated through peer-reviewed journals, conference presentations, social media, broadcast media, print media and the internet.

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Contributors All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval to the version to be published. EM devised the study concept and drafted the manuscript. EM, PR and ML designed the study in collaboration. JBH build the statistical plan. LL provided substantial scientific contribution and critical revision of important intellectual content.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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