COMPARING THE EFFICACY OF SUBCUTANEOUS INTERMITTENT SOLUBLE INSULIN VERSUS INTRAVENOUS CONTINUOUS SOLUBLE INSULIN INFUSION IN THE TREATMENT OF DIABETIC KETOACIDOSIS IN AN EMERGENCY DEPARTMENT SETTING.

Esmail Dawood Sangey

MMed (Emergency Medicine) Dissertation
Muhimbili University of Health and Allied Sciences
October, 2013

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By

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A dissertation submitted in (partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Emergency Medicine) of Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences
October, 2013

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled ***Comparing the efficacy of subcutaneous intermittent soluble insulin versus intravenous continuous soluble insulin infusion in the treatment of Diabetic Ketoacidosis in an Emergency Department setting***, in partial fulfillment of the requirements for the degree of Master of Medicine, (Emergency Medicine) of the Muhimbili University of Health and Allied Sciences (MUHAS).

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DECLARATION

AND

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I, **Esmail Dawood Sangey**, declare that this dissertation is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

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DEDICATION

This work is dedicated to my parents; in whose footsteps I hope to follow

And

To all the patients who suffer the burden of chronic diseases

TABLE OF CONTENTS

Title page……..... i
Certification on award.....ii
Declaration and Copyright iii
Acknowledgement.....iv
Dedication.....vi
Table of Contents.....vii
List of tables.....ix
List of Abbreviations.....x
ABSTRACT.....xii
1.0 INTRODUCTION AND LITERATURE REVIEW……. 1
2.0 PROBLEM STATEMENT …….. 5
3.0 STUDY RATIONALE ……. 6
4.0 STUDY OBJECTIVES …… 7
5.0 METHODOLOGY ……... 8
5.1 Study design …… 8
5.2 Study population ……... 8
5.3 Study site ……...8
5.4 Study duration ……...…8
5.5 Study sample ……...…..8
5.6 Inclusion criteria ……...…….9
5.7 Exclusion criteria ……...……..10
5.8 Resolution criteria ……..10
5.9 Recruitment and management of study participants ……...……11
5.10 Data collection and instruments ……..13

5.11 Laboratory investigation and measurements……14

5.12 Research assistant and training ……...…15

5.13 Data analysis……15

6.0 ETHICAL CONSIDERATIONS ……16

7.0 RESULTS……17

7.1 Patient characteristics on presentation ……17

7.2 Response to Insulin therapy ……18

7.3 Association of precipitating factors of DKA

in response to outcomes after insulin therapy ……20

7.4 Laboratory parameters on presentation and resolution of DKA ……..…21

8.0 DISCUSSION……..22

9.0 LIMITATION ……25

10.0 CONCLUSION……26

11.0 RECOMMENDATION ……..27

12.0 REFERENCES…….28

13.0 APPENDICES ……32

Appendix A: Ethics clearance letter…….....32

Appendix B: Consent form in English…….33

Appendix C: Consent form in Kiswahili ……36

Appendix D: Intravenous insulin protocol in treatment of DKA ……...39

Appendix E: Subcutaneous insulin protocol in treatment of DKA ……43

LIST OF TABLES

Table 7.1: Patient characteristics on presentation.....17

Table 7.2: Response to Insulin Therapy 19

Table 7.3: Association of precipitating factors of DKA
in response to outcomes after insulin therapy 20

Table 7.4: Laboratory parameters on presentation and resolution of DKA 21

LIST OF ABBREVIATIONS

BS	Blood Slide
BUN	Blood Urea Nitrogen
Cl	Chloride
Cr	Creatinine
DKA	Diabetic Ketoacidosis
DNS	5% Dextrose, 0.9% Normal Saline
ECG	Electrocardiogram
ED	Emergency Department
EMD	Emergency Medicine Department
FBP	Full Blood Picture
HCO3	Bicarbonate
HHS	Hyperosmolar Hyperglycemic Syndrome
IM	Intramuscular
IV	Intravenous
K	Potassium
KCl	Potassium chloride
mls	Millilitres
mmol/L	millimoles per litre
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health & Allied Sciences
Na	Sodium
NaCl	Sodium chloride
NS	0.9% Normal Saline

pCO2	Partial pressure of carbon dioxide
pO2	Partial pressure of oxygen
RBG	Random blood glucose
SC	Subcutaneous
VBG	Venous blood gas

ABSTRACT

Background: As the prevalence of diabetes increases in both industrialized and developing countries, the incidence of diabetic ketoacidosis (DKA) is also increasing. DKA is a potentially fatal condition, but is highly treatable and has an excellent prognosis when timely intervention is available. Mainstay treatment for DKA includes intravenous fluids and low-dose fast-acting insulin regardless of the route of administration (IV infusion or intermittent IM/SC). Intravenous infusion of insulin, however, requires extra resources such as infusion pumps, monitored beds, and additional training for personnel, and may be associated with an increased rate of adverse events if not monitored. While many guidelines recommend treatment of DKA with continuous IV infusion, to date there is no definitive study establishing the superiority of either IV infusion or intermittent SC administration of insulin for the treatment of DKA. Current inpatient treatment at Muhimbili National Hospital (MNH) is based on intramuscular administration of insulin, while current Emergency Medical Department (EMD) practice includes both continuous IV infusion and intermittent subcutaneous (SC) administration of insulin, based on equipment availability and provider preference.

Aim of the study: To compare the efficacy of SC intermittent soluble insulin over IV continuous soluble insulin infusion in the treatment of DKA in a randomized open-label trial carried out at the MNH EMD**.**

Methodology: This was a randomized controlled open-label clinical trial study that was carried out at the MNH Emergency Department in patients diagnosed with DKA. 30 patients were randomly assigned to one of two groups. One group had 14 patients who were treated with IV continuous regular soluble insulin and other group had 16 patients

who were treated with SC intermittent regular soluble insulin. Data collected included vital signs, RBG every 1 hour, and VBG every 2 hours. All data were collected in EMD by the trained doctors and nurses till to the resolution of ketoacidosis using a guided DKA management protocol algorithm (see attached). The data was collected into a guided flow chart and analyzed in response to therapy by duration of treatment to resolution of DKA as a primary outcome. A difference of $\geq$ 2 hours between two groups of treatment was considered as clinically significant. Secondary outcomes included amount of insulin administered, and rate of glucose drop per hour until resolution of DKA, adverse events (hypoglycemia and/or hyperkalemia/hypokalemia), and precipitating factors for DKA with either group of insulin therapy. All data was expressed as means or proportions with Standard deviation (SD).

Results: The demographic, clinical and biochemical parameters on presentation to the EMD were similar and not statistically significantly between the two groups of treatment. There was no statistical difference between patients treated with IV continuous infusion and SC intermittent of regular soluble insulin in mean time to resolution of DKA (14.9 $\pm$ 7.9 and 16.4 $\pm$ 5.0 hours); total amount of insulin required for resolution of DKA (66.5 $\pm$ 45.7 and 50.4 $\pm$ 27.0 units); rate of glucose drop per hour (1.3 $\pm$ 1.2 and 1.3 $\pm$ 1.0 mmol/L), respectively. The hypoglycemic events were higher in IV infusion group than in SC group. The number of hypokalemic events was slightly higher in patients treated with SC intermittent regular soluble insulin than IV infusion. There were no statistical significant differences in either of the treatment group (IV or SC) for both precipitating factors (infection and poor compliance/out of medication) based on time to resolution of

DKA, total amount of insulin used till resolution of DKA and rate of glucose drop per hour.

Conclusion and Recommendation: This study suggests that even severe DKA can be managed using SC intermittent low dose regular soluble insulin therapy and this regimen is as effective as and possibly safer than IV infusion of regular soluble insulin. SC intermittent regular soluble insulin administration can be managed effectively even where infusion pumps and rapid acting insulin analogues are not available.

1.0: INTRODUCTION AND LITERATURE REVIEW

Diabetic ketoacidosis (DKA) is a potentially life-threatening complication in patients with diabetes mellitus. DKA occurs more often in those with type 1 diabetes, but can occur in those with type 2 diabetes during the catabolic stress of acute illness or interruption of medical maintenance therapy.(1),(2) DKA is caused by reduced insulin levels or increased insulin resistance, decreased glucose utilization in the peripheral tissues, and increased gluconeogenesis and glycogenolysis from elevated counter regulatory hormones, including catecholamines, glucagon, and cortisol while lipolysis increases serum free fatty acids which catabolizes to acidic intermediate and end metabolites. These processes result in the production of acidic ketone bodies which, in combination with hyperglycemia, cause most of the symptoms and complications. (3),(4),(5)

The main metabolic issues in DKA are hyperglycemia, hypovolemia, and absolute or relative insulinopenia. Hyperglycemia usually overwhelms the renal glucose reabsorption threshold, leading to glycosuria and osmotic diuresis, resulting in water and electrolyte (sodium, potassium, phosphorus and magnesium) losses, which then deplete intravascular volume causing impaired kidney perfusion, further compromise of renal glucose excretion, and worsening hyperglycemia.(6) Deficiency in insulin secretion accelerates catabolism of fats into free fatty acids, and the consequent increase in ketones (beta-hydroxybutyrate and acetoacetate) from hepatic oxidation is largely responsible for DKA related metabolic acidosis.(7) In addition, hypovolemia due to osmotic diuresis decreases peripheral perfusion and leads to accumulation of lactic acids in the tissues, which can also contribute to metabolic acidosis to a lesser degree.(8)

A diagnosis of DKA is made by the presence of classical features such as polyuria, polydipsia, fatigue, moderate to severe dehydration, and Kussmaul's breathing, supported by plasma glucose concentration above 14 mmol/L, a pH level of less than 7.30, and a bicarbonate level of 15mmol/L or less.(6),(9),(10),(11) The resolution of DKA is evidenced by a venous pH≥7.30, HCO3≥18mmol/L, and a calculated anion gap ≤12 mEq/L.(6),(9) Serum beta-hydroxybutyrate is the preferred quantitative measurement of degree of ketosis, and can serve to monitor response to therapy but is not available in our setting. Urine ketones do not accurately reflect the timing of response to therapy and resolution of DKA.(12)

Insulin and fluid replacement are the mainstays of therapy for DKA, and careful monitoring of potassium levels is crucial. Phosphorous and magnesium may also need to be replaced.(4),(6),(8) Overly-rapid correction with intravenous fluid should be avoided as it may result in cerebral edema, though this complication is more often a concern in children rather than adults. Treatment for cerebral edema includes fluid restriction and administration of mannitol.(13) Bicarbonate therapy is rarely indicated in the management of DKA because it further lowers levels of potassium, has been associated with the development of cerebral oedema,(12),(14),(15) and may also increase hepatic ketone production.(16) Infection, insulin omission, and other problems that could have precipitated ketoacidosis should be treated accordingly.

The epidemiology of DKA varies considerably based on geographic location. While DKA occurs more commonly in patients with type 1 diabetes, patients with type 2 diabetes are susceptible to DKA under stressful conditions, such as trauma, surgery, or infections.(17) In the developed world, the annual incidence of DKA in the general population was

estimated to be 12.9 per 100,000 in 2007, being higher in males than in females (14.4 versus 11.4 per 100,000).(18) In developing countries such as Tanzania, the annual incidence of DKA has been estimated to be 1.5 per 100,000 populations for both sexes in the year 1993.(19) One Tanzanian study showed that at onset of type 1 diabetes, 75% of children presented with DKA and 89.8% had at least one episode of DKA.(20)

Kenyan studies reported that DKA occurred in about 8% of hospitalized diabetic patients and that it was a major cause of morbidity and mortality. The main precipitant factors for DKA were infections and poor insulin compliance due to social and economic factors, including limited access to health care and limited availability of insulin in many centers,(21) In another study of Ethiopian children, the mortality rate was 6% in cases of DKA occurring in previously undiagnosed diabetics.(22) The study done in South Africa showed that more juveniles were admitted for multiple DKA episodes (65%) than non-juveniles (35%), whereby 23% of them presented with new onset of type 1 diabetes. Infection was present in 40% of type 1 DM patients with single DKA episodes, and in 45% of type 1 DM patients with multiple DKA episodes. A total of 23.2% and 32% of all admissions for single DKA and multiple DKA episodes respectively involved non-compliance with medication usage.(23)

There is increasing recognition of the prevalence of DKA and its regionally-specific precipitating factors in Sub Saharan Africa. These factors include limited or no access to health care, lack of availability of insulin or use of less effective alternative therapies, and a high rate of infectious disease, such as malaria, urinary tract infections, tuberculosis and pneumonia.(24),(25)

Several guidelines are currently available for the management of DKA in both adults and children, with therapeutic goals of fluid and electrolyte replacement to correct dehydration and metabolic acidosis, replacement of insulin to lower hyperglycemia and reverse ketogenesis, and management of precipitating or co-morbid conditions.(26) The mainstay of treatment of patients with DKA involves administration of low doses of regular insulin by continuous intravenous infusion of regular insulin or by frequent subcutaneous injections of rapid acting insulin analogs.(4),(12) Although many reports have shown that low dose insulin therapy is effective regardless of the route of administration, some guidelines favor continuous intravenous infusion of regular insulin over subcutaneous insulin until resolution of ketoacidosis because of the potential delay in onset of action and longer duration of effect of subcutaneously given regular insulin.(26),(27) There is no definitive published evidence, however, that intravenous regular insulin infusion is superior to subcutaneous routes for the treatment of DKA.(3),(10),(11) The prognosis of properly treated patients with DKA is excellent, especially in younger patients if concurrent infections are absent. Hypothermia, oliguria, and the presence of coma at the time of diagnosis are signs of poor prognosis. The worst prognosis usually is observed in older patients with severe concurrent illnesses (e.g., myocardial infarction, sepsis, or pneumonia), especially when these patients are treated outside an intensive care unit.(4)

2.0: PROBLEM STATEMENT

There are several international consensus guidelines that recommend treatment of DKA with continuous IV infusion of insulin, but there is no definitive published evidence stating that intravenous insulin infusion is superior to subcutaneous routes for the treatment of DKA.(3),(10),(11) Intravenous insulin requires additional resources such as infusion pumps, trained personnel, and additional monitoring, and may be associated with increased risk of hypoglycemia.

DKA patients receiving continuous IV infusion of insulin should be admitted to an ICU setting for continuous close monitoring, and this may be difficult to achieve in an environment with a limited number of ICU beds. Currently at MNH, many patients are treated initially in the ED with intravenous or subcutaneous insulin and subsequently admitted to the general medical ward for continued intramuscular therapy based on the inpatient protocol. Because infusion pumps are not available on the wards and because there are limited personnel available for monitoring, any patients receiving intravenous insulin infusion must be held in the ED until completion of intravenous treatment. Treatment of DKA with subcutaneous insulin in the EMD represents a cost-effective and technically simplified procedure that obviates the need for infusion pumps and ICU admission.(3) But it is not known whether this is as safe and effective as intravenous infusion route.

3.0: STUDY RATIONALE

This study was comparing the efficacy and safety of two regimens for the treatment of DKA. To our knowledge, this is the first study to comparatively evaluate the use of regular insulin administered subcutaneous. This is the only type of insulin available at MNH and at many sites in Tanzania.

The findings provide valuable information to guide clinicians in the efficient and effective management of DKA in this region. A systematic emergency department protocol derived from these results will improve overall care and reduce the morbidity and mortality associated with DKA. If subcutaneous administration of insulin were shown to be as effective as IV infusion and/or associated with a lower rate of adverse events, this would support the establishment of an emergency department subcutaneous protocol that would consume fewer equipment and personnel resources and potentially be safer for patients.

4.0: OBJECTIVES

4.1: Broad objective

To compare efficacy and safety of SC intermittent soluble insulin over IV continuous soluble insulin infusion in the treatment of DKA in patients seen in MNH Emergency department.

4.2: Specific objectives

1. To compare time to resolution of DKA in EMD patients treated with a SC intermittent insulin protocol and those treated with continuous IV infusion.
2. To compare the amount of soluble insulin required for resolution of DKA in EMD patients treated with a SC intermittent insulin protocol and those treated with continuous IV infusion.
3. To compare rate of glucose drop per hour in EMD patients treated with a SC intermittent insulin protocol and those treated with continuous IV infusion.
4. To determine the rates of adverse events, such as episodes of hypoglycemia and, hypokalemia/hyperkalemia in EMD patients treated with a SC intermittent insulin protocol and those treated with continuous IV infusion.
5. To determine whether precipitating factors for DKA are associated with differences in response to therapy or outcomes in patients treated with a SC intermittent insulin protocol and those treated with continuous IV infusion.

5.0: METHODOLOGY

5.1: Study Design

This was an open-label randomized clinical trial carried out at the MNH Emergency department whereby consecutive patients presenting with DKA were randomly assigned to a treatment protocol based on continuous IV infusion of soluble insulin; or a treatment protocol derived from on the current MNH inpatient protocol and based on SC intermittent soluble insulin. For the purpose of this study, all patients in both groups were held and treated in the EMD until resolution of DKA.

5.2: Study population

Patients presenting with DKA to MNH EMD, Dar es Salaam.

5.3: Study site

Muhimbili National Hospital Emergency Medicine Department, Dar es Salaam.

5.4: Study duration

The study was carried out from April 2012 to October 2012

5.5: Study Sample

Sample size for this study was calculated according to the equation as follows:

$$N = (Z_{\alpha/2} + Z_{\beta})^2 (\sigma_1^2 + \sigma_2^2) / (\mu_1 - \mu_2)^2$$

where N is the number of participants for the study; $Z_{\alpha/2}$ is the standard normal deviate for α (if alternative hypothesis is two-sided, $Z_{\alpha/2} = 1.96$ when $\alpha = 0.05$); Z_{β} is the standard

normal deviate for β (Z_β = 0.84 when β = 0.20 ➔ 1 – β = power = 0.80); Based on prior literature σ1 was the standard deviation for time to resolution of DKA in regular IV insulin group, σ_2 was the standard deviation for time to resolution of DKA in SC insulin group.(3) ($\mu_1 - \mu_2$) is the expected mean of time to resolution of DKA in IV insulin group and SC insulin group respectively, which we aimed to detect a difference of at least 2 hours between the two groups.

Thus, Sample size N = $(1.96 + 0.84)^2$ (1.62 + 2.22) / $(2)^2$ = 15 patients in each group

(Total sample size = 30 patients)

Null hypothesis for this study is that there is no difference in the time to resolution of DKA in the two groups.

5.6: Inclusion criteria

All patients diagnosed with DKA had met all of the following criteria during their arrival at MNH Emergency as inclusion criteria into the study (6),(9)

- plasma glucose concentration ≥ 14mmol/L
- pH level < 7.30
- bicarbonate level ≤ 15mmol/L
- presence of ketones on urine dipstick ≥ 2+
- Age ≥ 12 years

5.7: Exclusion criteria

Patients with any of the following conditions after being diagnosed with DKA were excluded from the study

- Severe anemia (Hb ≤ 6g/dl)
- Malnutrition
- Known heart failure
- Known severe renal failure or persistently elevated serum creatinine>250 micromoles per liter after initial 2 liter bolus.
- Known hepatic failure

5.8: Resolution criteria

After the intervention with either SC intermittent or IV continuous infusion soluble insulin, all of the following criteria were used to define resolution of DKA(6),(9) and time to resolution was recorded.

- venous pH ≥ 7.30
- HCO3 ≥ 18mmol/L
- Anion gap ≤ 12mmol/L

5.9: Recruitment and management of study participants

Patients presenting to the MNH EMD with DKA were consented via the process described in the ethics section below and assigned to a group based on simple randomization via online randomization program (www.random.org) using True Random number generator. A doctor and a nurse on the shift at EMD managed the patient on a guided DKA management protocol algorithm for either SC intermittent or IV continuous infusion (see the attached management protocol) derived and adopted from Kitabchi and associates.(28)

Both group of patients were treated similarly with IV fluids (0.9% Normal saline), potassium replacement using KCl, and also treated for the underlying cause such as infections (malaria, UTI, cellulitis, abscess) or out of medication/poor compliance. Initially patient received IV fluids of 2000mls in 1 hour which was directed towards intravascular expansion, establishing good urine output with good renal perfusion and reverse insulin resistance and deficiency(9), then subsequently reduced to 1000mls per hour in 3 hours to 500mls hour in 3 hours and then 250mls per hour till to the resolution of DKA. Changing of IV fluids from 0.9% Normal Saline to 5% Dextrose 0.9% Normal Saline (DNS) took place when RBG levels were less than 14mmol/L. Potassium chloride (KCl) was added into the IV fluid to run for 1 hour if serum potassium level were less than 5.0mmol/L. The dose of KCl was between 10-40mmol and was added into the IV fluids based on the potassium levels. No patient received bicarbonate therapy in this study.

Both group of patients received the same form of soluble insulin (a human recombinant insulin analogue) which is the only fast acting insulin available at MNH pharmacy. Insulin therapy in both groups was initiated after an initial fluid bolus of 2 liters over 1 hour.

Patients treated with IV soluble insulin received an initial 0.15U/kg IV bolus followed by continuous IV infusion drip of soluble insulin at a rate of 0.1U/kg/hr until RBG level ≤ 14mmol/L. At this level, IV soluble insulin dose rate was reduced to 0.05U/kg/hr and IV fluids changed to DNS ran at 250ml/hr to maintain RBG levels below 14mmol/L until resolution of DKA. At any point, if the RBG level was raised above 14mmol/L despite IV insulin dose 0.05U/kg/hr and IV DNS, the patients were switched back to IV insulin dose of 0.1U/kg/hr and IV fluids of Normal saline.

Patients treated with SC soluble insulin received an initial 0.2U/kg IV bolus and 0.2U/kg SC followed by 0.1U/kg/hr of soluble insulin every 2 hours until RBG level reached ≤ 14mmol/L. At this level, soluble insulin dose was reduced to 0.05U/kg SC given every 2 hours and IV fluids changed to DNS ran at 250ml/hr to maintain RBG levels below 14mmol/L until resolution of DKA. At some point, if the RBG level was raised above 14mmol/L despite SC insulin dose 0.05U/kg and IV DNS, the patients were switched back to SC insulin dose of 0.1U/kg and IV fluids of Normal saline.

Hypoglycemic event is one of the side effects of insulin therapy and it was defined in this study as RBG ≤ 3mmol/L. This was treated with 25g of Dextrose either using 10% Dextrose 250mls or 50% Dextrose 50mls based on the availability in the hospital pharmacy.

In both of the treatment groups when resolution criteria values were achieved, insulin administration was discontinued 1 hour after the resolution of DKA as to prevent recurrence hyperglycemia and ketoacidosis. After resolution of DKA, patients were admitted to the general wards.

The precipitating factors such as malaria, sepsis, UTI, cellulitis, and abscess were treated accordingly. Patients were kept in the EMD for the duration of treatment, until resolution of DKA as defined above.

5.10: Data collection and instrument

After random assignment to treatment group, the appropriate management protocols for DKA were used by the EMD doctor to guide management of DKA. The data then were collected by the treating doctor and recorded into the attached guided flow chart. The flow chart (see attached) had the following components:

- Demographic and background information
- Vitals: temperature, blood pressure, pulse rate, respiratory rate, oxygen saturation
- Mental status each hour: Recorded as Alert, Drowsy, Stupor, Comatose
- Bedside biochemical tests including: blood glucose, urine ketones using dipsticks, electrolytes (sodium, potassium, chloride, bicarbonate), pH, pO2, pCO2, BUN, and Cr.
- Insulin given and route
- Amount and type of intravenous fluids given each hour.
- Output: hourly urine output recorded in milliliters (ml)

5.11: Laboratory investigation and measurements

DKA was diagnosed in EMD based on above mentioned inclusion criteria using bedside biochemical Abbott® I-STAT/Siemen® ABG rapidlab machine, blood glucose machine and urine dipsticks. Venous blood obtained from a DKA patient were inserted into I-STAT reagent cartridge or ABG rapidlab machine and analyzed for five minutes to get automated results. These results included values of Na, K, Cl, AG, Glu, BUN, pH, pCO2, HCO3, Cr. Bedside VBG investigations were done every two hourly for both group of patients until the resolution of DKA.

Random blood glucose was measured at the EMD every one hourly using bedside blood glucose machine by finger pricking the patient using a sterile lancet after cleansing the skin with an alcohol swab.

All patients with DKA were catheterized with an indwelling Foley's urinary catheter and initial urine sample were obtained to measure urine ketones using urine dipstick.

Other laboratory investigations such as BS for malaria parasite, FBP, and urine samples were obtained after the diagnosis of DKA was made. The samples were taken to the MNH laboratory with urgent request to rule out infection or malaria as precipitating factor and treated accordingly with broad spectrum antibiotic or antimalarial medications respectively.

5.12: Research assistant and training

A nurse and a doctor at EMD were selected as a research assistant for this study. They were trained by the principal investigator on the study objectives, patient recruitment, and administration of consent. In addition, they were responsible in administrating of medications (fluids, insulin, potassium, antibiotics), recording values from glucose machine and ABG machine routinely, timing, monitoring vitals, clinical evaluations and when to stop the study based on resolution criteria.

5.13: Data analysis

Data were entered and analysed using SAS (Statistical Applied Software) version 9.3. A multi-variable logistical analysis on predictor variables was conducted to evaluate differences between groups. Patient's characteristics on presentation were summarized using frequency distribution table where some of the initial biochemical continuous data were expressed as means or median $\pm$ Standard deviation (SD) and the rest of the tables were expressed by means $\pm$ Standard deviation (SD). Means and medians were compared using students' t test and ANOVA (analysis of variance). Association between categorical variables was tested by use of fishers' exact tests. Primary outcome of this study was time to resolution of DKA. A difference of $\geq$ 2 hours between groups was considered as clinically significant difference in the primary outcome and computed with *p-value* where if less than 0.05, it was considered to be statistically significant. Secondary outcomes included amount of insulin administered, rate of glucose drop per hour, and adverse effects (hypoglycemia and/or hyperkalemia/hypokalemia)

6.0: ETHICAL CONSIDERATION AND CLEARANCE

All patients presenting to the EMD with DKA were offered the opportunity to participate in the study. The study was explained to patients with alert mental status wishing to participate and they were asked to provide informed written consent. For patients with abnormal mental status, an accompanying proxy was allowed to provide consent. Data was initially collected on unaccompanied patients with abnormal mental status as the EMD treatment protocol was the same in all patients. Patient's condition and results were explained to all patients and families. All data collected were treated with strict confidence and stored in locked cabinets and on encrypted computers.

Ethical clearance to carry out this study was obtained from the Research and Publications Committee of MUHAS and the director of clinical services of MNH

7.0: RESULTS

7.1: Patient characteristics on presentation:

This study took place from April 2012 to October 2012. 30 patients were diagnosed with DKA at EMD and randomized where by 14 patients were enrolled into IV group and 16 patients were enrolled into SC group. The demographic, clinical and biochemical parameters on presentation were similar and not statistically significant between the two groups of treatment.

The RBG was computed as median rather than mean due to some data reading 'HI' on glucose machine used, thus HI was considered as value more than 35mmol/L (see Table 7.1). With the use of median, there was no significant difference between IV and SC group.

Table 7.1: Patient characteristics on presentation:

	IV	**SC**	***p-value***
Number of patients (n)	14	16	
Age (years) [mean $\pm$ SD]	23 $\pm$ 10	30 $\pm$ 16	0.20
Sex: Male	8 (57%)	7 (44%)	0.22
Female	6 (43%)	9 (56%)	0.22
New onset diabetes mellitus	7 (50%)	8 (50%)	1.00
Duration of diabetes mellitus (in years)	1.8 $\pm$ 2.8	2.4 $\pm$ 4.4	0.63
Precipitating factor:			
- Infection	11 (79%)	12 (75%)	0.33
- Out of medication/poor compliance	2 (14%)	3 (19%)	0.36
- Both Infection and out of med/poor compliance	1 (7%)	1 (6%)	0.51
Mental status: - Alert group	5 (36%)	2 (12%)	0.12

- Altered group (drowsy, stupor, coma)	9 (64%)	14 (88%)	0.31
RBG (in mmol/L) (Median value ± SE)	30.8 ± 2.1	26.1 ± 1.9	0.81 *
MAP (mm Hg) (Mean value)	88 ± 17	89 + 18	0.91
PR (beats per minute)	120 ± 12	120 ± 20	0.93
RR (breaths per minute)	28 ± 6	25 ± 11	0.53
SPO2 (in Room air)	13 (93%)	13 (81%)	0.53
SPO2 (on oxygen)	1 (7%)	3 (19%)	0.07
Sodium (mmo/L)	140 ± 8	138 ± 15	0.70
Potassium (mmol/L)	4.8 ± 1.3	5.2 ± 2.0	0.47
Chloride (mmol/L)	104 ± 9	106 ± 18	0.67
Bicarbonate (mmol/L)	8.2 ± 4.6	7.4 ± 3.5	0.58
Venous pH	7.092 ± 0.123	7.081 ± 0.138	0.83
Partial pressure of carbon dioxide (pCO2)	18.7 ± 10.7	21.0 ± 6.3	0.48
Calculated Anion gap (mmol/L)	27.3 ± 7.9	24.1 ± 9.4	0.32

* using median instead of mean, thus ANOVA is used with Wilcoxon *p-value*

7.2: Response to Insulin Therapy

The time to resolution of DKA in IV group was 14.9 ± 7.9 hours and in SC group was 16.4 ± 5.0 hours. This suggested there were not clinically and statistically significant *(p = 0.53).* The prior study done by Umpierrez et al (2004), they arbitrarily estimated a difference between groups ≥ 4 hours to resolve ketoacidosis as clinically significant.() Comparatively with this study, we used ≥ 2 hours as clinically significant.

The total amount of insulin used till the resolution of DKA in IV group was 66.5 ± 45.7 units and in SC group was 50.5 ± 27.0 units. This had no statistical difference *(p=0.24).* Clinically IV group utilized more insulin for the treatment of DKA than the SC group.

During the insulin therapy, the glucose drop per hour in IV group was 1.3 $\pm$ 1.2 mmol/L whereas for SC group was 1.3 $\pm$ 1.0 mmol/L. This as well had no statistical difference *(p=0.91)*

There were 2 (7%) episodes of hypoglycemia seen in IV group where as SC group had no any hypoglycemic episodes. This revealed no statistical difference between IV and SC group but had clinical significance to IV infusion of insulin causes more hypoglycemic episodes than the SC group.

For hypokalemic episodes, SC group had more hypokalemic events (43%) than the IV group of patients (30%), which was also suggested no statistical difference between these two treatment groups. (See Table 7.2)

Table 7.2: Response to Insulin Therapy

	IV	**SC**	***p-value***
Time to resolution of DKA (hrs)	14.9 $\pm$ 7.9	16.4 $\pm$ 5.0	0.53
Total amount of insulin required for resolution of DKA (units)	66.5 $\pm$ 45.7	50.4 $\pm$ 27.0	0.24
Rate of glucose drop per hour (mmol/L)	1.3 $\pm$ 1.2	1.3 $\pm$ 1.0	0.91
Number of patients with Hypoglycemia	2 (7%)	0	0.21
Number of patients with Hypokalemia	9 (30%)	13 (43%)	0.19

7.3: Association of precipitating factors of DKA in response to outcomes after insulin therapy

Two forms of precipitating factors were identified in this study where by 23 patients had infection as a precipitating factor to DKA (malaria, sepsis, cellulitis, UTI) and 5 patients had poor compliance/out of medication as their precipitating factor. 2 patients had both infection and poor compliance/out of medication as their precipitating factor.

There were no statistical significant differences in either of the treatment group (IV or SC) for both precipitating factors (infection and poor compliance/out of medication) based on time to resolution of DKA, total amount of insulin used till resolution of DKA and rate of glucose drop per hour. (See Table 7.3)

Table 7.3: Association of precipitating factors of DKA in response to outcomes after insulin therapy

Precipitating factors	**IV**	**SC**	***p-value***
Infection: (N)	**11**	**12**	
- Time to resolution of DKA (hrs)	15.5 $\pm$ 8.1	17.0 $\pm$ 5.1	0.59
- Amount of insulin required for resolution of DKA (units)	71.1 $\pm$ 47.7	51.5 $\pm$ 28.8	0.24
- Rate of glucose drop per hour	1.1 $\pm$ 1.0	1.3 $\pm$ 1.1	0.66
Out of medication/Poor compliance: (N)	**2**	**3**	
- Time to resolution of DKA (hrs)	14.0 $\pm$ 11.3	14.0 $\pm$ 5.3	1.00
- Amount of insulin required for resolution of DKA (units)	49.5 $\pm$ 57.3	39.5 $\pm$ 22.6	0.79
- Rate of glucose drop per hour	2.6 $\pm$ 2.7	0.9 $\pm$ 0.7	0.44

NB: 2 patients, one in each group report both precipitating factors and therefore not included into this table

7.4: Laboratory parameters on presentation and resolution of DKA

The resolution biochemical parameters for the two groups are presented in Table 7.4. They were not significantly different between IV and SC treatment groups.

Table 7.4: Laboratory parameters on presentation and resolution of DKA

	IV		**SC**		
Parameters	**At time of presentation with DKA**	**At time of resolution of DKA**	**At time of presentation with DKA**	**At time of resolution of DKA**	***p-value* at time to resolution of DKA**
RBG (mmol/L) *	30.8 ± 7.7	13.3 ± 7.0	26.2 ± 7.5	13.9 ± 4.5	0.92
Sodium (mmol/L)	140 ± 8	144 ± 10	138 ± 15	147 ± 14	0.24
Potassium (mmol/L)	4.8 ± 1.3	3.8 ± 0.5	5.2 ± 2.0	3.6 ± 0.5	0.96
Chloride (mmol/L)	104 ± 9	116 ± 11.5	106 ± 18	120 ± 13	0.64
HCO3 (mmol/L)	8.2 ± 4.6	18.1 ± 0.6	7.4 ± 3.5	18.7 ± 1.8	0.24
pH	7.092 ± 0.123	7.330 ± 0.044	7.081 ± 0.138	7.331 ± 0.030	0.15
pCO2	18.7 ± 10.7	32.8 ± 4.2	21.0 ± 6.3	30.3 ± 3.9	0.75
Calculated Anion gap (mmol/L)	27.3 ± 7.9	9.3 ± 2.6	24.1 ± 9.4	9.4 ± 2.0	0.90

* p-value computed using median values of RBG

8.0: DISCUSSION

DKA is one of the endocrine emergency crisis encountered in the busy emergency department. The morbidity and mortality from DKA remains high in Sub-Saharan Africa due to poor health system and occasioned by unavailability and unaffordabilty of insulin. Improvement in the healthcare systems and reliable insulin supply can reverse the trend to a large extent (24)

This study showed that 50% of patients in both treatment groups presented with DKA as newly diagnosed diabetes which was similar to the study done in Kenya by Mbugua PK et al(21) but however they have reported 23.4% of patients with infections and 34% had missed insulin as their precipitating cause to DKA. In this study, about 79% in IV group and 75% in SC group had infection as a cause to DKA whereas about 14% in IV group and 19% in SC group had out of medication/poor compliance as cause to DKA. This could be because of geographical and economical differences between Kenya and Tanzania in terms of infection such as malaria which is a huge burden in Tanzania.

The results from this study suggest that SC intermittent low dose insulin therapy is as effective as treatment with IV continuous drip of low dose insulin. The time to resolution of DKA, total amount of insulin required till resolution of DKA and rate of glucose drop per hour were similar between two treatment groups. The study done by Karoli R et al(3) and Umpierrez et al(11) used insulin lispro and insulin aspart respectively in SC group of patients compared with patients received regular (soluble) insulin in IV continuous form, they reported with similar results as SC insulin analogues 1-2 hourly given was as effective as treated with IV continuous drip. They concluded with that SC therapy can be managed in step down unit or even in the general ward. They had included patients in their study

with mild to moderate DKA. Severe DKA patients were excluded due to thought of bicarbonate therapy had a role in the management. In this study all 3 forms (mild, moderate and severe) of DKA were included and randomized into either IV or SC treatment group without using bicarbonate therapy. Both treatment groups used regular soluble insulin. This showed with no statistically significant difference in the time to resolution of DKA with 14.9 $\pm$ 7.9 and 16.4 $\pm$ 5.0 hours respectively *(p = 0.53)*. This suggested that even severe DKA can be managed with low dose SC regular soluble insulin therapy as alternative to IV insulin continuous drip in a limited resource set up and the significance is that regular soluble insulin is widely available than other insulin analogues. Thus, use of SC regular soluble insulin can be cost effective mode of treatment compared to IV form of treatment which usually requires infusion pumps and well trained health personnel. Viallon A et al(14),15),(29) and Green SM et al showed no promising benefit in the use of bicarbonate therapy in DKA, even in the severe form. Thus in this study bicarbonate therapy was not used.

This study has observed number of hypoglycemic events which was relatively more in IV group than in SC group. This was similarly seen relatively in the study done by Karoli et al.(3) This study suggested that using SC regular soluble insulin has minimal complication as hypoglycemia as compared to IV infusion which requires attentive intensive care monitoring on blood glucose.

The percentage of patients with hypokalemic events have been observed slightly higher in SC than in IV groups. This was also seen in the study done by Dieterlen P et al (30) showed similar episodes. SC therapy with insulin tends to release into the blood circulation in sustained amount which initiates additional movement of potassium from extracellular

to the intracellular compartment leading to further hypokalemia. Hypokalemia is fatal condition that can lead to cardiac arrhythmia and in some circumstances to respiratory failure.(31)

This study has observed increased level of Sodium (Na) and Chloride (Cl) after resolution of DKA in both IV and SC treatment groups with the standard available IV fluids in the EMD MNH i.e. 0.9% Normal saline or 5% Dextrose 0.9% Normal saline. These lead in both IV and SC treatment groups with non-anion gap hyperchloremic acidosis (116 $\pm$ 11.5 and 120 $\pm$ 13 mmol/L respectively). In fact, hyperchloremic acidosis developed in the patients with the better hydration status.(32) This was due to excretion of ketone anions as to normalize the bicarbonate levels along with an increasing level of Chloride concentration with ultimately on fluid administration.(33) Hyperchloremia retards the increase in bicarbonate and pH and, consequently tends to prolong IV insulin infusion time and thus prolonged hospital stay(34) and in our set up would be prolonged stay in the EMD. There have been number of published recommendations in the prevention of hyperchloremic acidosis with the use of 0.45% Sodium chloride IV solution and in the aim of early resolution of DKA.(35) The recent study done looking at usefulness of Balanced Electrolyte Solution (BES) comprising of Plasma-Lyte A pH 7.4; Baxter International, Deerfield, IL versus 0.9% Normal saline. They showed good DKA resuscitation results with the use BES solution in terms of lower serum chloride and higher bicarbonate levels compared to the use of 0.9% Normal saline, consistent in the prevention of hyperchloremic acidosis.(36)

9.0: LIMITATIONS

The main limitation of this study was that it had small sample size which was constrained by a fixed data collection period. A larger sample size might have been able to detect smaller differences between two groups of treatment.

In this study, patients were retained in the EMD till they resolve their ketoacidosis even the severe forms. This required throughout monitoring of the patient in the busy EMD by the doctors and nurses. At some point timely monitoring of laboratory values were difficult due to huge volume of new patients in the resuscitation room.

10.0: CONCLUSION

This study suggested that DKA can be managed using SC intermittent low dose regular soluble insulin therapy and that this regimen is as effective as and possibly safer than IV infusion of regular insulin. This supports the idea that DKA management can be well initiated in a set up of good supervision and can be managed effectively where infusion pumps and rapid acting insulin analogues are not available.

11. RECOMMENDATION

The DKA treatment with rapid acting soluble insulin using subcutaneous represents simplified method and low cost of treatment as patient would not require infusion pumps, thus no need of admission into intensive care unit. The Emergency Department at MNH and other hospitals should impart in the development of treatment protocols of DKA using subcutaneous route as this is considered as safe and easy to implement.

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APPENDICES

Appendix A: Ethics clearance letter

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
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Ref. No. MU/PGS/SAEC/Vol. VI/

21st May, 2012

Dr. Esmail Dawood Sangey,
MMed.Emergency Medicine,
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED "COMPARING THE EFFICACY OF SUBCUTANEOUS INTERMITTENT SOLUBLE INSULIN VERSUS INTRAVENOUS CONTINUOUS SOLUBLE INSULIN INFUSION IN THE TREATMENT OF DIABETIC KETOACIDOSIS IN AN EMERGENCY DEPARTMENT SETTING"

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has on behalf of the Senate approved ethical clearance for the above-mentioned study.

Thus ethical clearance is granted and you may proceed with the planned study.

Please liaise with bursar's office to get your research fund.

Prof. Z. Premji
DIRECTOR, POSTGRADUATE STUDIES

/emm

c.c. Vice Chancellor, MUHAS
c.c. Deputy Vice Chancellor – ARC, MUHAS
c.c. Dean, School of Medicine - MUHAS

Appendix B: Consent form in English

TITLE OF THE STUDY: COMPARING THE EFFICACY OF SUBCUTANEOUS INTERMITTENT SOLUBLE INSULIN VERSUS INTRAVENOUS CONTINUOUS SOLUBLE INSULIN INFUSION IN THE TREATMENT OF DIABETIC KETOACIDOSIS IN AN EMERGENCY DEPARTMENT SETTING.

My name is Dr. Esmail Sangey, a 2nd year resident in the department of Emergency Medicine at Muhimbili University of Health and Allied Sciences (MUHAS).
I am conducting a study with the above title as part of my study program.

Aims of the study:

This study aims to compare efficacy of SC intermittent soluble insulin over IV continuous soluble insulin infusion in the treatment of DKA in patients seen in MNH Emergency department based on its time to resolution. In addition, this will give us information on which of the route of administration would support the establishment of an emergency department protocol.

Participation in this study:

A diagnosis of DKA in all patients arriving at EMD will be made and will be requested in the enrolment into the study. Patient him/herself or the next of kin if the patient has altered mental status can give a written consent as to be enrolled into the study. The study involves treatment of DKA using soluble insulin either Subcutanoues (SC) or Intravenous (IV) infusion route. If you agree to be enrolled into this study, you will be randomly enrolled into either form of treatment (SC or IV infusion) and treated at EMD until resolution of your/your patient's DKA. After the resolution of DKA, you/your patient will be moved to their respective inpatients ward for further management.
In addition, during this study finger prick one hourly and venopuncture two hourly will be obtained for blood glucose and biochemical parameters respectively.
If you choose not to participate in this study, you/ your patient will continue to receive the normal care at the EMD and will not be compromised in any way.

Risks:

Mainstay treatment of DKA is intravenous fluids and insulin regardless of the route of administration. However, there is risk of hypoglycemia in either group of treatment (SC or IV infusion) as one the side effects of insulin which is reversible and monitored carefully.

Benefits:

If you agree to participate in this study, you or your patient will benefit in the treatment of DKA regardless of group of treatment enrolled in (SC or IV infusion). The patient will not incur in any cost of medical service given at EMD even for the file registration. The results from this study will be used for building up EMD protocol in the management of DKA.

Confidentiality:

All data collected will be treated with strict confidence and stored in locked cabinets and on encrypted computers and will not be revealed to anybody outside the research team.

Cost:

You will not be required to make any payments to participate in this study and no payment will be made to you.

For further information, questions or queries, you can contact:

1. The Principal Investigator,
   Dr. Esmail Sangey,
   Department of Emergency Medicine,
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2. Prof. Victor Mwafongo,
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4. Prof. M. Aboud,
   Director of Research and Publications,
   MUHAS.
   Tel No: +255 22 2150302-6.

I, _____, have read/been told of the contents of this form and have understood its meaning. I agree to participate in this study.

OR

I,_____, husband/wife/father/mother/_____ have read/been told of the contents of this form and have understood its meaning. I agree to enroll _____ (patient's name in full) in this study

Signature of patient/Next of kin_____
Signature of Researcher _____ Date _____

Appedix C: CONSENT FORM IN KISWAHILI

FOMU YA RIDHAA YA KUSHIRIKI KATIKA UTAFITI

Jina langu ni Dr. Esmail Sangey, mwanafunzi wa udaktari bingwa wa mahututi (Emergency Medicine) katika chuo kikuu cha afya na sayansi shirikishi Muhimbili (MUHAS). Ninafanya utafiti kuangalia utofauti ya matibabu ya kisukari hatari (kisukari ketoacidosis) kwa kutumia insulini kwa njia aidha ya ngozi au mshipa na kuangalia muda mpaka kupona kwa mgonjwa anapofikia idara ya mahatuti katika hospitali ya Taifa, Muhimbili, Dar es Salaam.

Madhumuni ya utafiti:

Utafiti huu unalenga kujua insulini gani kati ya kutumia njia ya ngozi au mshipa ni bora kwa kumtibu mgonjwa na kisukari hatari (kisukari ketoacidosis) na kuangalia muda wa kupona kwao kati ya hizo njia mbili tofauti. Pia, utafiti huu utajadili njia bora kati ya hizo kwa kutumia insulini kutumika tiba itifaki katika idara ya mahututi.

Ushiriki katika utafiti:

Utambuzi wa kisukari hatari (kisukari ketoacidosis) itafanyika kwa wagonjwa wote kwa kutumia vigezo maalum ya kitaamu na watashauria kuingia kwenye utafiti huu kwa hiari. Mgonjwa au mbadala wa mgonjwa (kama kwa mgonjwa hayupo kwenye akili yake timamu) ataidhini kwa maandishi ili mgonjwa apate matibabu wakati yupo ndani ya utafiti. Hiyo utafiti inahusu tiba ya kisukari hatari kwa kutumia insulini kwa aidha njia ya ngozi au mshipa. Kama kati ya wewe au mbadala mmekubali tiba ya utafiti, kwa hiyo mgonjwa atapangiwa tiba ya insulini kati njia ya ngozi au mshipa na matibabu yatafanyika hapo idara ya mahututi (emergency department) mpaka kupona kwa mgonjwa. Baada kupona kutoka kisukari hatari, mgonjwa anahamishiwa wodini ili kuendelea na matibabu.

Pia, wakati wa matibabu ya utafiti, mgonjwa atachukuliwa sampuli ya damu kutoka kidole ili kujua kiasi ya sukari kila baada ya saa mmoja na sampuli ya damu kiasi kidogo nyingine kutoka mshipa mkubwa inaonekana ili kujua madini na acidosis mwilini kila baada ya masaa mawili.

Kama ukiamua kutoshiriki katika utafiti huu, wewe au mgonjwa wako ataendelea kupata huduma ya kawaida hapo idarani na hataathirika kwa njia yeyote.

Hatari:

Tiba ya kisukari hatari ni maji kwa njia ya mshipa na insulini aidha njia ya ngozi au mshipa. Kuna madhara ya kushukiwa sukari kiwago cha chini kwa kutumia insulini aidha iwe kwa njia ya ngozi au mshipa na kwa hayo inawezekana kuweka sukari ya mwilini kwenye kiwango cha kawaida na kufuatiliwa kwa makini.

Faida za utafiti:

Kwa kushiriki katika utafiti huu, wewe au mgonjwa wako atapata faida ya kutibiwa kisukari hatari kwa njia ya insulini iwe kati ya aidha njia ya ngozi au mshipa. Mgonjwa hatalipa chochote kwa matibabu yake hapo idara ya mahututi na pia gharama ya kufungua faili yake yatalipiwa.

Usiri:

Taarifa zote zitakazokusanywa katika utafiti huu zitakuwa siri, hivyo ushiriki wako hautajulikana na mtu. Taarifa hizi zitajulikana kwenye timu ya watafiti tu.

Malipo:

Kwa kushiriki kwenye utafiti huu, hautalipwa wala hautalipa chochote.

Ukiwa na swali au tatizo lolote, unaweza kuwasiliana na wafuatao:

1. Mtafiti Mkuu,
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4. Prof. M. Aboud,
   Director of Research and Publications,
   MUHAS.
   Simu: +255 22 2150302-6.

Mimi, _____, nimesoma/nimesomewa maelezo yote yaliyomo kwenye fomu hii na nimeelewa.

AU

Mimi, _____, mume/mke/baba/mama/_____ nimesoma/nimesomewa maelezo yote yaliyomo kwenye fomu hii na nimeelewa. Nakubali mgonjwa wangu ashiriki katika utafiti huu.

Sahihi ya mzazi/mbadala _____
Sahihi ya Mtafiti _____
Tarehe _____

Appendix D: Intravenous insulin protocol in treatment of DKA

INTRAVENOUS INSULIN PROTOCOL IN TREATMENT OF DKA

Date:_____ Patient Name:_____ Reg No.:_____

Sex: M / F Age:_____ Onset of diabetes: [ ] New onset [ ] Duration of diabetes_____mo/yr

Precipitating DKA factor [ ] Infection [ ] Out of Meds/non compliance [ ] Other _____

Actual time TIME

[ ] Hr 1

Mental Status

[ ] Alert

[ ] Drowsy

[ ] Stupor

[ ] Coma

INCLUSION CRITERIA - PATIENT MUST MEET ALL 5 CRITERIA

[ ] RBG >14 mmol/L	Value: _____
[ ] pH < 7.3	Value: _____
[ ] Bicarbonate < 15 mmol/L	Value: _____
[ ] Ketonuria ≥ 2+	Value: _____
[ ] > 11 years of age	Value: _____

ORDER

[ ] I-Stat/VBG Q2H [ ] INSERT 2 LARGE BORE IV CANNULAS [ ] INSERT URINARY CATHETER

[ ] RBG Q1H [ ] FBP once

[ ] VITALS **Weight:** _____ **Kg**

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

INTIAL I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr_____

IV FLUIDS + POTASSIUM

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour

[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour

[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour

[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

[ ] In addition to above, ALL PATIENTS SHOULD RECEIVE AN ADDITIONAL 1 L of NS

reasses UOP/hydration status Fluid given this hour _____

Urine Output this hr:_____

Actual time Time

[ ] Hr 2 RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 2nd I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr _____

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

CONTINUE IV FLUIDS + POTASSIUM IF NECESSARY

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour
[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour
[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour
[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

reasses UOP/hydration status

Fluid given this hour _____
Urine Output this hr:_____

START INSULIN PROTOCOL

[ ]HOLD INSULIN PROTOCOL FOR K < 3.0 mmol/L or RBG < 3.0 mmol/L, UNTIL CORRECTED
[ ]IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS
[ ]IF RBG > 14 FOLLOW INSULIN PROTOCOL BELOW:

IV SOLUBLE INSULIN PROTOCOL

[ ] 0.15 units/kg IV STAT, followed by
[ ] 0.1 units/kg/HOUR continuous drip

Dose given: _____
Insulin Drip Rate: _____units/hr

Actual time Time

[ ] Hr 3 RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

CONTINUE IV FLUIDS + POTASSIUM IF NECESSARY

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour
[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour
[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour
[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

reasses UOP/hydration status

Fluid given this hour _____
Urine Output this hr:_____

[ ] Hr 4 [ ] RBG _____ [ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] IF RBG > 14 continue INSULIN AT 0.1 UNITS/KG/HR

[ ] GIVE 500 ML/NS IV BOLUS

ml given: _____
Urine Output this hr: _____
Insulin Drip Rate: _____units/hr

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 3rd I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr _____

REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.0 mmol/L

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

[ ] Hr 5	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	[ ] GIVE 500 ML/NS IV BOLUS					
[ ] Alert						
[ ] Drowsy				Fluid given this hour _____		
[ ] Stupor				Urine Output this hr: _____		
[ ] Coma				Insulin Drip Rate: _____units/hr		
[ ] HR 6	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	[ ] IF RBG > 14 continue INSULIN AT 0.1 UNITS/KG/HR			Fluid given this hour _____		
[ ] Alert	[ ] GIVE 500 ML/NS IV BOLUS			Urine Output this hr: _____		
[ ] Drowsy				Insulin Drip Rate: _____units/hr		
[ ] Stupor	[ ] VITALS					
[ ] Coma	BP: _____mmHg	PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min		***STOP STUDY IF:***
	[ ] 4th VBG					
	Na _____	K _____	Cl _____	AG _____	Glu _____	***pH ≥ 7.3, AND***
	BUN _____	pH _____	pCO2 _____	HCO3 _____	Cr_____	***Bicarb ≥ 18, AND***
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L					***Anion Gap ≤ 12***

Actual time Time						
[ ] Hr 7	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	[ ] GIVE 500 ML/NS IV BOLUS					
[ ] Alert						
[ ] Drowsy				Fluid given this hour _____		
[ ] Stupor				Urine Output this hr: _____		
[ ] Coma				Insulin Drip Rate: _____units/hr		
[ ] Hr 8	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	[ ] IF RBG > 14 continue INSULIN AT 0.1 UNITS/KG/HR			Fluid given this hour _____		
[ ] Alert	[ ] 250 mls/hr of NS IV			Urine Output this hr: _____		
[ ] Drowsy				Insulin Drip Rate: _____units/hr		
[ ] Stupor	[ ] VITALS					***STOP STUDY IF:***
[ ] Coma	BP: _____mmHg	PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min		
	[ ] 4th VBG					***pH ≥ 7.3, AND***
	Na _____	K _____	Cl _____	AG _____	Glu _____	***Bicarb ≥ 18, AND***
	BUN _____	pH _____	pCO2 _____	HCO3 _____	Cr_____	***Anion Gap ≤ 12***
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L					

[ ] Hr 9	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	[ ] continue 250 mls/hr of NS IV					
[ ] Alert						
[ ] Drowsy					Fluid given this hour _____	
[ ] Stupor					Urine Output this hr: _____	
[ ] Coma					Insulin Drip Rate: _____units/hr	

[ ] Hr 10	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	**[ ] IF RBG > 14 continue INSULIN AT 0.1 UNITS/KG/HR**				Fluid given this hour _____	
[ ] Alert	**[ ] continue 250 mls/hr of NS IV**				Urine Output this hr: _____	
[ ] Drowsy					Insulin Drip Rate: _____units/hr	
[ ] Stupor	[ ] VITALS					
[ ] Coma	BP: ____mmHg	PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min		
	[ ] 4th VBG					***STOP STUDY IF:***
	Na _____	K _____	Cl _____	AG _____	Glu _____	
	BUN _____	pH _____	pCO2 _____	HCO3 _____	Cr _____	***pH ≥ 7.3, AND***
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L					***Bicarb ≥ 18, AND***
						Anion Gap ≤ 12
[ ] Hr 11	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	**[ ] continue 250 mls/hr of NS IV**				Dose Given: _____	
[ ] Alert						
[ ] Drowsy					Fluid given this hour _____	
[ ] Stupor					Urine Output this hr: _____	
[ ] Coma					Insulin Drip Rate: _____units/hr	
[ ] Hr 12	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*				
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG/HR IV CONTINUOUS					
Status	**[ ] IF RBG > 14 continue INSULIN AT 0.1 UNITS/KG/HR**				Fluid given this hour _____	
[ ] Alert	**[ ] continue 250 mls/hr of NS IV**				Urine Output this hr: _____	
[ ] Drowsy					Insulin Drip Rate: _____units/hr	
[ ] Stupor	[ ] VITALS					
[ ] Coma	BP: ____mmHg	PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min		***STOP STUDY IF:***
	[ ] 4th VBG					
	Na _____	K _____	Cl _____	AG _____	Glu _____	***pH ≥ 7.3, AND***
	BUN _____	pH _____	pCO2 _____	HCO3 _____	Cr _____	***Bicarb ≥ 18, AND***
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L					***Anion Gap ≤ 12***

4 HOUR FOLLOW UP AFTER EMD. ***TIME_____*** ***RBG_____*** ***MENTAL STATUS***

[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

ADDITIONAL NOTES/DEVIATIONS FROM PROTOCOL:

_____

_____

_____

_____

_____

Appendix E: Subcutaneous insulin protocol in treatment of DKA



SUBCUTANEOUS INSULIN PROTOCOL IN TREATMENT OF DKA

Date:_____ Patient Name:_____ Reg No.:_____

Sex: M / F Age:_____ Onset of diabetes: [ ] New onset [ ] Duration of diabetes_____mo/yr

Precipitating DKA factor [ ] Infection [ ] Out of Meds/non compliance [ ] Other _____

Actual time TIME

[ ] Hr 1

Mental Status

[ ] Alert

[ ] Drowsy

[ ] Stupor

[ ] Coma

INCLUSION CRITERIA - PATIENT MUST MEET ALL 5 CRITERIA

[ ] RBG >14 mmol/L	Value: _____
[ ] pH < 7.3	Value: _____
[ ] Bicarbonate < 15 mmol/L	Value: _____
[ ] Ketonuria ≥ 2+	Value: _____
[ ] > 11 years of age	Value: _____

ORDER

[ ] I-Stat/VBG Q2H [ ] INSERT 2 LARGE BORE IV CANNULAS [ ] INSERT URINARY CATHETER

[ ] RBG Q1H [ ] FBP once

[ ] VITALS **Weight:** _____ **Kg**

BP: ____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

INTIAL I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr _____

IV FLUIDS + POTASSIUM

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour

[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour

[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour

[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

[ ] In addition to above, ALL PATIENTS SHOULD RECEIVE AN ADDITIONAL 1 L of NS

reasses UOP/hydration status Fluid given this hour _____

Urine Output this hr:_____

Actual time Time

[ ] Hr 2 RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 2nd I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr_____

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

CONTINUE IV FLUIDS + POTASSIUM IF NECESSARY

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour
[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour
[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour
[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

reasses UOP/hydration status

Fluid given this hour _____
Urine Output this hr:_____

START INSULIN PROTOCOL

[ ]HOLD INSULIN PROTOCOL FOR K < 3.0 mmol/L or RBG < 3.0 mmol/L, UNTIL CORRECTED
[ ]IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H
[ ]IF RBG > 14 FOLLOW INSULIN PROTOCOL BELOW:

SC SOLUBLE INSULIN PROTOCOL

[ ] 0.2 units/kg IV STAT, followed by Dose given: _____
[ ] 0.2 units/kg SC STAT Dose given: _____

Actual time Time

[ ] Hr 3 RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

CONTINUE IV FLUIDS + POTASSIUM IF NECESSARY

[ ] K < 3.3 mmol/L --> start 1 LITER NS + 40 mmol of KCL over 1 hour
[ ] For K=3.3 - 3.9 mmol/L --> start 1 LITER of NS + 20 mmol of KCL over 1 hour
[ ] For K=4 - 4.9 mmol/L --> start 1 Liter of NS + 10 mmol of KCL over 1 hour
[ ] For K ≥ 5 mmol/L -- > do NOT replace potassium, give 1 L NS

reasses UOP/hydration status

Fluid given this hour _____
Urine Output this hr:_____

[ ] Hr 4 [ ] RBG _____ [ ]IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] IF RBG > 14 give SOLUBLE INSULIN 0.1 units/kg SC ml given: _____

[ ] GIVE 500 ML/NS IV BOLUS Urine Output this hr: _____

Insulin Dose Given: _____

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 3rd I-Stat/VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr_____

REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.0 mmol/L

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

_____ Hr 5	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*	
Mental	[ ]IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H		
Status	**[ ] GIVE 500 ML/NS IV BOLUS**		
[ ] Alert			
[ ] Drowsy		Fluid given this hour _____	
[ ] Stupor		Urine Output this hr: _____	
[ ] Coma			
_____ HR 6	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*	
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H		
Status	**[ ] IF RBG > 14 give SOLUBLE INSULIN 0.1 units/kg SC**	Fluid given this hour _____	
[ ] Alert	**[ ] GIVE 500 ML/NS IV BOLUS**	Urine Output this hr: _____	
[ ] Drowsy		Insulin Dose Given: _____	
[ ] Stupor	[ ] VITALS		
[ ] Coma	BP: _____mmHg PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min
	[ ] 4th VBG		
	Na _____ K _____	Cl _____	AG _____ Glu _____
	BUN _____ pH _____	pCO2 _____	HCO3 _____ Cr _____
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L		

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb > 18, AND
Anion Gap ≤ 12

Actual time Time			
_____ Hr 7	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*	
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H		
Status	**[ ] GIVE 500 ML/NS IV BOLUS**		
[ ] Alert			
[ ] Drowsy		Fluid given this hour _____	
[ ] Stupor		Urine Output this hr: _____	
[ ] Coma			
_____ Hr 8	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*	
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H		
Status	**[ ] IF RBG > 14 give SOLUBLE INSULIN 0.1 units/kg SC**	Fluid given this hour _____	
[ ] Alert	**[ ] 250 mls/hr of NS IV**	Urine Output this hr: _____	
[ ] Drowsy		Insulin Dose Given: _____	
[ ] Stupor	[ ] VITALS		
[ ] Coma	BP: _____mmHg PR: _____	RR: _____	SPO_2: ____ RA/O_2 ___ L/min
	[ ] 4th VBG		
	Na _____ K _____	Cl _____	AG _____ Glu _____
	BUN _____ pH _____	pCO2 _____	HCO3 _____ Cr _____
	REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L		

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

_____ Hr 9	[ ] RBG _____	*FOR RBG < 2.5 mmol/L give D10% or D50% STAT*	
Mental	[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H		
Status	**[ ] continue 250 mls/hr of NS IV**		
[ ] Alert			
[ ] Drowsy		Fluid given this hour _____	
[ ] Stupor		Urine Output this hr: _____	
[ ] Coma			

Hr 10 [ ] RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H
[ ] IF RBG > 14 give SOLUBLE INSULIN 0.1 units/kg SC
[ ] continue 250 mls/hr of NS IV

Fluid given this hour _____
Urine Output this hr: _____
Insulin Dose Given: _____

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 4th VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr_____

REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

Hr 11 [ ] RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H
[ ] continue 250 mls/hr of NS IV

Fluid given this hour _____
Urine Output this hr: _____

Hr 12 [ ] RBG _____ *FOR RBG < 2.5 mmol/L give D10% or D50% STAT*

Mental Status
[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

[ ] IF RBG ≤ 14 START MAINTENANCE DNS @ 250 ml/hr + INSULIN 0.05 UNITS/KG SC Q2H
[ ] IF RBG > 14 give SOLUBLE INSULIN 0.1 units/kg SC
[ ] continue 250 mls/hr of NS IV

Fluid given this hour _____
Urine Output this hr: _____
Insulin Dose Given: _____

[ ] VITALS

BP: _____mmHg PR: _____ RR: _____ SPO_2: ____ RA/O_2 ___ L/min

[ ] 4th VBG

Na _____ K _____ Cl _____ AG _____ Glu _____

BUN _____ pH _____ pCO2 _____ HCO3 _____ Cr_____

REPLETE POTASSIUM AS NECESSARY, HOLD INSULIN FOR K <3.3 mmol/L

STOP STUDY IF:

pH ≥ 7.3, AND
Bicarb ≥ 18, AND
Anion Gap ≤ 12

4 HOUR FOLLOW UP AFTER EMD. ***TIME***_____ ***RBG***_____ ***MENTAL STATUS***

[ ] Alert
[ ] Drowsy
[ ] Stupor
[ ] Coma

ADDITIONAL NOTES/DEVIATIONS FROM PROTOCOL:

_____

_____

_____

_____

_____