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Comparing the Efficacy of Subcutaneous Intermittent Soluble Insulin versus Intravenous Continuous Soluble Insulin Infusion in the Treatment of Diabetic Ketoacidosis in an Emergency

Esmail Dawood Sangey, Teri Reynolds, Victor Mwafongo, Zahra Khan* and Abdul Rafey Usmani

Muhimbili University Health Allied and Science(MUHAS), Tanzania.

***Correspondence:**
Zahra Khan, Muhimbili University Health Allied and Science (MUHAS), Tanzania.

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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); 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.*

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. A difference of ≥ 2 hours between two groups of treatment was considered as clinically significant.*

Results: *The demographic, clinical and biochemical parameters on presentation to the EMD 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. 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 can be managed effectively even where infusion pumps and rapid acting insulin analogues are not available.*

Keywords

Diabetic Ketoacidosis (DKA), Diabetes Mellitus, Subcutaneous Insulin, Intravenous Insulin Infusion, Regular Soluble Insulin.

Introduction

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 [3-5]. The main metabolic issues in DKA are hyperglycemia, hypovolemia, and absolute or relative insulinopenia. 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]. 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 [10].

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 [11,12]. 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) [13]. 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 [14]. One study in Tanzania showed that 75% of children with early onset of type 1 DM presented with DKA and 89.8% had at least one episode of DKA [15]. There are increased prevalences of DKA and its precipitating factors in regions within Sub Saharan Africa [16,17]. 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 [16,17].

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 [18]. 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 [7,19,20]. 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 [12,21,22].

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 [4,7,19]. The resolution of DKA is evidenced by a venous pH≥7.30, HCO3≥18mmol/L, and a calculated anion gap ≤12 mEq/L [6,7]. Urine ketones do not accurately reflect the timing of response to therapy and resolution of DKA [20].

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 [23]. Treatment for cerebral edema includes fluid restriction and administration of mannitol [24]. 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 [20,23,25] and may also increase hepatic ketone production [26]. Infection, insulin omission, and other problems that could have precipitated ketoacidosis should be treated accordingly [8,24].

There is no definitive published evidence, however, that intravenous regular insulin infusion is superior to subcutaneous routes for the treatment of DKA [3,8,9].

Methodology

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 MNH inpatient protocol and based on SC intermittent soluble insulin.

Duration: The study was carried out from April 2012 to October 2012.

Sample size: were calculated according to the equation as follows:

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

Where: **N** is the number of participants for the study; $\mathbf{Z_{\alpha/2}}$ is the standard normal deviate for **α** (if alternative hypothesis is two-sided, $\mathbf{Z_{\alpha/2}} = 1.96$ when $\boldsymbol{\alpha} = 0.05$); $\mathbf{Z_{\beta}}$ is the standard normal deviate for **β** ($\mathbf{Z_{\beta}} = 0.84$ when $\boldsymbol{\beta} = 0.20$ □ **1 – β** = power = 0.80); Based on prior literature $\boldsymbol{\sigma_1}$ was the standard deviation for time to resolution of DKA in regular IV insulin group, $\boldsymbol{\sigma_2}$ was the standard deviation for time to resolution of DKA in SC insulin group [3]. $(\boldsymbol{\mu_1 - \mu_2})$ 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 $\mathbf{N} = (1.96 \pm 0.84)^2 (1.62 \pm 2.22) / (2)^2 = 15$ patients in each group (Total sample size = 30 patients).

Criteria: Patients with DM age 12yrs and above, who came in with DKA had met all of the criteria's for DKA: plasma glucose concentration ≥ 14mmol/L, pH level < 7.30, bicarbonate level ≤ 15mmol/L, presence of ketones on urine dipstick ≥2+, otherwise patient with Severe anemia (Hb ≤ 6g/dl), Malnutrition, Known heart, renal and liver failures were excluded, Resolution of DKA [6,7] and time to resolution were recorded based on venous pH ≥ 7.30, HCO_3 ≥ 18mmol/L, and an Anion gap ≤ 12mmol/L.

Technique

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.

The KCl solution was priscribed based on the potassium levels at the dose of 10-40mmol. No patient received bicarbonate therapy in this study. 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.

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. All these were diagnosed in EMD using bedside biochemical Abbott® I-STAT/Siemen®, ABG rapidlab machine, blood glucose machine and urine dipsticks other sepsis biomarkers were sent to main laboratory.

Ethical 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.

Data analysis

Data were entered and analysed using SAS version 9.3. Means and medians were compared using students' 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 and Secondary outcomes includes rate of glucose drop per hour and adverse effects (hypoglycemia and/or hyperkalemia/hypokalemia) with P <0.05.

Results

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. (Table 1).

Table 1: Patient characteristics on presentation.

Characteristic	IV	SC	p-value
Number of patients (n):	**14**	**16**	
Age (years) [mean ± SD]	23 ± 10	30 ± 16	0.2
Sex: Male	8 (57%)	7 (44%)	0.22
Female	6 (43%)	9 (56%)	0.22
New onset diabetes mellitus	7 (50%)	8 (50%)	1
Duration of diabetes mellitus (in years)	1.8 ± 2.8	2.4 ± 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
SPO_2 (in Room air)	13 (93%)	13 (81%)	0.53
SPO_2 (on oxygen)	1 (7%)	3 (19%)	0.07
Sodium (mmo/L)	140 ± 8	138 ± 15	0.7
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 (pCO_2)	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

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 (p = 0.53). 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 (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 ± 1.2 mmol/L whereas for SC group was 1.3 ± 1.0 mmol/L (p=0.91). There were 2 (7%) episodes

of hypoglycemia seen in IV group whereas SC group had no any hypoglycemic episodes, SC group had more hypokalemic events (43%) than the IV group of patients (30%) (Table 2).

Table 2: Response to Insulin Therapy.

	IV	SC	p-value
Time to resolution of DKA (hrs)	14.9 ± 7.9	16.4 ± 5.0	0.53
Total amount of insulin required for resolution of DKA (units)	66.5 ± 45.7	50.4 ± 27.0	0.24
Rate of glucose drop per hour (mmol/L)	1.3 ± 1.2	1.3 ± 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

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

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 (Table 3).

Table 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 ± 8.1	17.0 ± 5.1	0.59
Amount of insulin required for resolution of DKA (units)	71.1 ± 47.7	51.5 ± 28.8	0.24
Rate of glucose drop per hour	1.1 ± 1.0	1.3 ± 1.1	0.66
Out of medication/Poor compliance: (N)	2	3	
Time to resolution of DKA (hrs)	14.0 ± 11.3	14.0 ± 5.3	1.00
Amount of insulin required for resolution of DKA (units)	49.5 ± 57.3	39.5 ± 22.6	0.79
- Rate of glucose drop per hour	2.6 ± 2.7	0.9 ± 0.7	0.44

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

Laboratory parameters on presentation and resolution of DKA

The resolution biochemical parameters for the two groups are presented in Table 4. They were no significantly different between IV and SC treatment groups.

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 [16].

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. [12], 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., [9] 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 our 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

Table 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
pCO_2	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.

treatment groups used regular soluble insulin. This showed with no statistically significant difference in the time to resolution of DKA with 14.9 ± 7.9 and 16.4 ± 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., [10,25,27] and Green SM et al., [24] 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., [28] 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 [29].

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 ± 11.5 and 120 ± 13 mmol/L respectively). In fact, hyperchloremic acidosis developed in the patients with the better hydration status [30]. 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 [31]. Hyperchloremia retards the increase in bicarbonate and pH and, consequently tends to prolong IV insulin infusion time and thus prolonged hospital stay [32] 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 [33]. 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 [34].

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. At some point timely monitoring of laboratory values were difficult due to huge volume of new patients in the resuscitation room.

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.

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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