Efficacy and Safety of Subcutaneous Insulin Analogue Versus Intravenous Insulin Infusion Among Patients with Mild to Moderate Diabetic Ketoacidosis at the University of Santo Tomas Hospital

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Abstract

Introduction: Diabetic ketoacidosis (DKA) remains a significant complication of diabetes in the world and is associated with high rates of hospital admissions. In mild, uncomplicated cases of DKA a subcutaneous regimen of newer rapid-acting insulin analogues has been proposed as a safe and effective alternative to intravenous regular insulin in prospective, randomized trials. Our primary objective is to compare the efficacy and safety of intermittent subcutaneous (SC) rapid insulin administration with continuous intravenous (IV) regular insulin infusion in the treatment of mild to moderate DKA.

Methodology: A retrospective chart review of all adult Filipino patients admitted for mild to moderate DKA at UST Hospital private and clinical divisions from 2012 – 2015 was done. Chart cases were divided into two groups, namely: group one who received IV infusion of regular insulin and group two who received SC rapid insulin analog as treatment. The clinical and biochemical characteristics of the patients on admission were obtained. Efficacy and safety of both treatment regimens were compared as to the duration of time and amount of insulin administered from admission until resolution of DKA was achieved, occurrence of hypoglycemia and hypokalemia, mortality and length of hospitalization.

Results: Twenty-one chart cases were included, twelve in the continuous IV insulin infusion group and nine in the intermittent SC rapid insulin group. The baseline characteristics of patients were almost similar. There was no significant difference between the treatment groups in the duration of time and amount of insulin administered to achieve DKA resolution, occurrence of hypoglycemia, and death. Hypokalemia occurred more frequently and hospital stay was longer in the IV insulin group.

Conclusion: Intermittent subcutaneous rapid insulin regimen is an effective, safe, and potentially cost-effective alternative to continuous intravenous insulin infusion for treatment of mild to moderate cases of DKA.

Keywords: Diabetic ketoacidosis, rapid insulin analogue, regular insulin infusion, efficacy and safety

Introduction

Diabetic ketoacidosis (DKA) remains a significant complication of diabetes in the world and is associated with high rates of hospital admissions.[1] At our institution, six to twelve cases of DKA were admitted yearly for the past four years. Thus, it is important for us physicians to be able to manage this crisis. Though management of DKA has followed a set of algorithm for many years, we now have new alternatives on the horizon such as subcutaneous insulin analogues for mild to moderate cases of DKA.[1]

Rapid insulin analogues have been available for clinical use over the last two decades and have proven to be beneficial in reducing the incidence of hypoglycemia while providing better control of post-prandial hyperglycemia with less weight gain and offering a possible little better overall glycemic control in terms of HbA1c reduction.[1] DKA, resulting from absolute insulin deficiency and counter-regulatory hormone excess, can potentially lead to increased morbidity and fatal complications.[2] The increased morbidity and death among patients with DKA, in turn, are most often due to poor hospital care and the severity of the underlying factor which precipitated DKA.[2] The mainstay of treatment includes hydration to restore adequate circulating volume, correction of electrolyte deficits, insulin administration to reverse ketosis and promote gradual reduction in blood sugar levels and identification of precipitating events.[1] Implementation of effective standardized treatment protocols and timely identification and treatment of precipitating causes and co-morbidities are important factors affecting outcome. Experts have recommended intravenous insulin infusion as

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the treatment of choice in the intensive care setting, as it is a predictable means of administration allowing for maximal peak insulin within the first hour of treatment.[1] Continuous intravenous insulin infusion with hourly blood sugar monitoring can become more costly compared to a regimen of subcutaneous rapid insulin analogue administered every two hours with two-hourly blood sugar monitoring. Refusal of the patient to be admitted into the intensive care unit of the hospital can become a limiting factor in administering continuous intravenous insulin infusion. One major barrier is inadequacy of nursing staff on general ward floors to implement the strict monitoring protocol. In mild cases of DKA, a subcutaneous regimen of newer rapid-acting insulin analogues (aspart, lispro, glulisine) has been proposed as a safe and effective alternative to the use of intravenous regular insulin in prospective, randomized trials.[2,3,4,5,6] In the Philippines, a developing country where health insurance coverage is limited and where patients would have to shoulder almost all medical expenses, use of a less expensive treatment that would still offer quality medical care would be of great benefit to our diabetic patients. Treatment of mild to moderate DKA using a regimen of subcutaneous rapid-acting insulin analogue with a loading dose of 0.3 units/kg body weight followed by 0.1 unit/kg/hour or 0.2 units/kg every two hours until blood glucose level reached 200 to 250 mg/dL could be more cost-effective than continuous intravenous insulin infusion in patients without major co-morbidities.[3] There has been no recently published study in the Philippines comparing treatment outcomes of patients with mild to moderate DKA treated with continuous intravenous insulin infusion versus intermittent subcutaneous rapid insulin analogue. Therefore, the primary objective of this study is to compare the efficacy and safety of intermittent subcutaneous rapid insulin regimen with continuous intravenous insulin infusion in the treatment of mild to moderate DKA as to the length of time and amount of insulin administered to achieve resolution of DKA, occurrence of hypoglycemia and hypokalemia, length of hospital stay, and mortality. Secondary objectives are to describe the baseline clinical and biochemical characteristics of patients admitted for mild to moderate DKA and to estimate costs of treatment for twenty-four hours at the private and clinical divisions of UST Hospital using both insulin regimen. Clinical and biochemical profile include the age on admission, gender, precipitating factors, co-morbidities, initial blood glucose, arterial blood pH, bicarbonate and serum potassium levels.

Methods

Study Design and Population

Approval of the UST Hospital institutional review board was secured prior to commencement of the study. Review of in-patient hospital records of all adult Filipino patients with admitting diagnosis of diabetic ketoacidosis at the UST Hospital Private and Clinical Divisions from January 2012 up to December 2015 was done. Chart cases which fulfilled the criteria for mild to moderate DKA and given either continuous intravenous regular insulin infusion or intermittent (one to two hourly) subcutaneous rapid-acting insulin analogue were screened further. Diagnostic criteria for mild DKA[1] are blood glucose elevation of > 250 mg/dL, arterial pH of 7.25 to 7.30, serum bicarbonate of 15 to 18 meq/L, anion gap of >10, positive blood and/or urine ketones and an alert mental state. Moderate DKA,[1] meanwhile, is defined by blood glucose of > 250 mg/dL, positive blood and/or urine ketones, arterial pH of 7.0 to 7.24, serum bicarbonate of 10 to < 15 meq/L, anion gap of > 12, and drowsiness. Chart cases classified under severe DKA, characterized by a blood glucose of > 250 mg/dL, arterial pH of < 7.00, serum bicarbonate of < 10 meq/L, anion gap of > 12 with stupor or coma, and those with severe, persistent hypotension defined as systolic blood pressure of less than 90 mmHg requiring vasopressor, acute and chronic decompensated liver disease with serum transaminase levels more than three times the upper limit of normal range, chronic kidney disease with estimated creatinine clearance of less than 15 cc/min using the Cockroft-Gault formula, decompensated heart failure, dementia, coma, steroid use, pregnant at the time of admission, and initially treated using combined intravenous and subcutaneous insulin were excluded. Chart cases were classified into two groups. The first group consisted of subjects who were given continuous intravenous insulin infusion while the second group consisted of those who were given intermittent subcutaneous rapid insulin analogue. To assess the response to therapy in both groups, the following data were gathered from in-patient hospital records: length of time and amount of insulin administered from admission until resolution of DKA was achieved as defined by blood glucose of less than 200 mg/dL plus two of the following: arterial pH of >7.3, plasma bicarbonate level of >15 meq/L, and calculated anion gap of <12 meq/L,[1] occurrence of hypoglycemia defined as capillary blood or plasma glucose level of <70 mg/dL, occurrence of hypokalemia with serum potassium level of <3.5 meq/L, length of hospital stay and mortality. The clinical and biochemical characteristics of patients on admission were likewise recorded such as age, gender, diabetes duration, precipitating factors, co-morbid conditions, blood glucose, serum potassium, arterial pH, and bicarbonate levels.

Statistical analysis

The age on admission, initial blood glucose, serum potassium, arterial pH, and plasma bicarbonate levels, total amount of insulin administered and length of time to achieve DKA resolution are expressed as mean and standard deviation in continuous variables. Diabetes duration and length of hospitalization are reported in median and range while gender, precipitating factors,

co-morbid conditions, hypoglycemia, hypokalemia, and mortality are reported in frequency and percentage. Chi-square analysis was used for comparison of categorical variables and Mann-Whitney U Test for numerical (continuous) variables. A total sample size of 20 patients was needed, ideally 10 in each group, to achieve a power 0.80 given an α error of 0.05, computed using the G*Power Software.

Results

A total of thirty charts with admitting diagnosis of DKA were retrieved from the medical records of our institution from January 2012 up to December 2015. Of these, nine charts were excluded from the study: three charts with severe DKA, two with incomplete data, two with initial treatment using combined subcutaneous and intravenous insulin, one with end-stage renal disease, and another one with concomitant steroid use.

Twenty-one chart cases fulfilled the inclusion and exclusion criteria, of which, nine received subcutaneous rapid insulin analogue every two hours and twelve received continuous intravenous insulin infusion until the DKA resolved.

The age on admission, diabetes duration, co-morbid conditions and precipitating causes of DKA did not differ significantly between the two treatment groups (Table I). Age on admission was 58.00 ± 12.31 years in the intravenous infusion group and 50.33 ± 19.08 years in the subcutaneous insulin group. Majority of patients were male. In the intravenous insulin infusion group, nine (75%) had associated co-morbidities, of which hypertension (67%) was most common followed by coronary artery disease (33%), obesity (17%), urolithiasis (1.0%), and polycystic ovarian syndrome (1.0%). Five (42%) had newly diagnosed diabetes mellitus. Five (56%) in the subcutaneous rapid insulin group had associated co-morbidities with hypertension being the most common (33%) followed by obesity (22%) and coronary artery disease (11%). Only one (11%) had newly-diagnosed diabetes. The most common precipitating cause of DKA was infection, which was recorded in eight patients for both groups (67% and 89% for IV insulin infusion group and SC rapid insulin group, respectively). Urinary tract infection and pneumonia were most common followed by skin, soft tissue (cellulitis/diabetic foot/abscess), and intra-abdominal (acute cholecystitis) infection. Another precipitating cause of DKA was omission of insulin treatment. Others presented with DKA as the initial manifestation of their diabetes.

The biochemical characteristics of patients on admission were almost similar, satisfying the criteria for mild to moderate DKA (Table II). Mean blood glucose was 451.55 ± 75.61 vs. 390.57 ± 93.54 mg/dL (P-value 0.171), with arterial pH of 7.250 ± 2.19 vs. 7.230 ± 0.07, plasma bicarbonate of 13.58 ± 2.63 vs. 15.00 ± 3.35 meq/L, and potassium of 4.59 ± 0.85 vs. 4.06 ± 0.56 meq/L, for the IV and SC insulin groups, respectively.

Table I. Clinical profile of patients on admission

	IV insulin infusion group N=12	SC insulin analogue group N=9
Age (years)*	58.00 ± 12.31	50.33 ± 19.08
Sex*		
Male	4 (33)	7 (78)
Female	8 (67)	2 (22)
Diabetes duration (years)*	6 (0-22)	5 (0-15)
Co-morbidities*		
Coronary artery disease	4 (33)	1 (11)
Hypertension	8 (67)	3 (33)
Obesity	2 (17)	2 (22)
Others	2 (17)	0 (0)
Precipitating factors*		
Infection	8 (67)	8 (89)
Missed insulin	2 (17)	0 (0)
New-onset diabetes	5 (42)	1 (11)

** Data are expressed as mean or median ± standard deviation or frequency (%) or range (years)*

Table II. Biochemical profile of patients on admission

	IV insulin infusion group N=12	SC insulin analogue group N=9	P-value+
Blood glucose level (mg/dL)*	451.55 ± 75.61	390.57 ± 93.54	0.171
Arterial pH (units)*	7.250 ± 2.19	7.230 ± 0.07	0.642
Arterial plasma bicarbonate level (meq/L)*	13.58 ± 2.63	15.00 ± 3.35	0.399
Serum potassium level (meq/L)*	4.59 ± 0.85	4.06 ± 0.56	0.126

** Data are expressed as mean ± standard deviation*
+ Significant difference if P value is <0.05

There was no significant statistical difference between IV and SC rapid insulin in the length of time and in the amount of insulin administered to achieve resolution of DKA as shown in Table III. DKA resolved within 44 hours in both groups with mean duration of 26 hours for the IV insulin group and 24 hours for the SC insulin group. Total insulin given was 89.08 units ± 25.99 (1.49 ± 0.57 units/kg body weight) for the IV insulin group and 85.13 ± 28.37 units (1.19 ± 0.66 units/kg body weight) for the SC insulin group. Length of hospital stay was significantly shorter by a mean of six days for those on the SC insulin group compared to those on the IV insulin group.

The occurrence of hypoglycemia during insulin therapy was similar between the two groups (Table IV). Two patients (17%) in the IV insulin group and one patient (11%) in the SC insulin group developed hypoglycemia. The lowest blood sugar level recorded was 62 mg/dL and none required the assistance of a medical personnel to administer glucose. Hypokalemia occurred more frequently in the IV insulin group compared with the SC insulin group and this difference was statistically significant. None developed arrhythmia during the course of therapy.

One patient died in the SC insulin group due to septic shock secondary to a hospital-acquired infection which he developed several days after resolution of the ketoacidosis and hyperglycemia. No mortality was reported in the IV insulin group.

The estimated cost of therapy for 24 hours at the private and clinical division of UST hospital showed higher cost with IV regular insulin infusion compared to SC rapid insulin analogue regimen (Table V and Table VI).

Discussion

Our study showed that intermittent subcutaneous rapid insulin regimen is equally effective, safe, and potentially cost-effective alternative to continuous intravenous insulin infusion for treatment of mild to moderate cases of DKA.

Several studies done internationally compared the efficacy and safety of intermittent administration of subcutaneous rapid insulin analogue with continuous intravenous insulin infusion in the treatment of mild to moderate DKA. Similarly, both studies of Umpierrez GE et al,[2,4] which compared intermittent subcutaneous aspart or lispro with intravenous regular insulin infusion, did not show significant statistical difference between the treatment groups in the length of time and in the amount of insulin administered until the ketoacidosis resolved as well as in the occurrence of hypoglycemia, and death. Furthermore, there was a significant decrease in medical care costs in the subcutaneous insulin group.

Ersoz HO et al[5] did a similar prospective, randomized, open trial in a Turkish population comparing hourly subcutaneous lispro with intravenous insulin infusion for mild to moderate DKA. Similar to the first two studies, the duration of time from the onset of DKA until normoglycemia was achieved did not differ significantly between the subcutaneous and intravenous insulin group.

Lastly, an Indian study by Prasad A. and Gupta A,[6] which compared the efficacy and safety of intermittent (hourly and two-hourly) subcutaneous aspart and continuous intravenous regular insulin among patients with mild to moderate DKA, showed no significant statistical difference among the three groups in the mean duration of time to achieve resolution of ketoacidosis, length of hospital stay, occurrence of hypoglycemic episodes, and mortality.

Table III. Comparison of efficacy of IV and SC insulin in mild to moderate DKA

	IV insulin infusion group N=12	SC insulin analogue group N=9	P-value+
Time from admission until resolution of DKA (hours)*	25.67 ± 8.56	24.11± 7.70	0.668
Amount of insulin administered from admission until resolution of DKA (units)*	89.08 ± 25.99	85.13 ± 28.37	0.757
Amount of insulin administered from admission until resolution of DKA (units/kg BW)*	1.49 ± 0.57	1.19 ± 0.66	0.320
Length of hospital stay (days)*	11.42 (4-28)	5.22 (3-11)	0.027

** Data are expressed as mean or median ± standard deviation range(days)*
+ Significant difference if P value is <0.05

Table IV. Comparison of safety of IV and SC insulin in mild to moderate DKA

	IV insulin infusion group N=12	SC insulin analogue group N=9	P-value+
Occurrence of hypoglycemia*	2 (17)	1 (11)	0.719
Occurrence of hypokalemia*	6 (50)	1 (11)	0.072
Number of deaths*	0 (0)	1 (11)	0.231

** Data are expressed in frequency (%)*
+ Significant difference if P value is <0.05

Table V. Estimated cost of therapy (in peso) of mild to moderate DKA for 24 hours with continuous IV insulin infusion and intermittent (two-hourly) SC rapid insulin analogue at the UST Hospital Private division

	IV insulin infusion group		SC insulin analogue group			
Frequency of blood sugar monitoring	Every hour		Every two hours			
Type of insulin	Insulin regular vial A	Insulin regular vial B	**Insulin aspart**	Insulin glulisine	Insulin lispro pen	**Insulin lispro vial**
	1938.20	766.50	1063.00	1070.00	1175.00	2276.75
Glucose meter strip	1164.00		582.00			
Lancet	144.00		72.00			
Pen needle	NA*		312.00			NA*
Insulin syringe	NA*		NA*			180.00
Daily rental of infusion set	1350.00		NA*			
Infusion set	1337.00		NA*			
TOTAL:	**P 5933.20**	**P 4761.50**	**P 2029.00**	**P 2036.00**	**P 2141.00**	**P 3110.75**

**NA – not applicable*

Table VI. Estimated cost of therapy (in peso) of mild to moderate DKA for 24 hours with continuous IV insulin infusion and intermittent (two-hourly) SC rapid insulin analogue at the UST Hospital Clinical division

	IV insulin infusion group		SC insulin analogue group			
Frequency of blood sugar monitoring	Every hour		Every two hours			
Type of insulin	Insulin regular vial A	Insulin regular vial B	**Insulin aspart**	Insulin glulisine	Insulin lispro pen	**Insulin lispro vial**
	1536.75	613.25	843.00	850.75	940.00	2276.75
Glucose meter strip	930.00		465.00			
Lancet	144.00		72.00			
Pen needle	NA*		312.00			NA*
Insulin syringe	NA*		NA*			180.00
Daily rental of infusion set	925.00		NA*			
Infusion set	420.00		NA*			
TOTAL:	**P 3955.75**	**P 3032.25**	**P 1692.00**	**P 1699.75**	**P 1789.00**	**P 2993.75**

**NA – not applicable*

In our study, the clinical and biochemical characteristics of patients on admission were almost similar except that majority of our patients were male. Infection was the most common precipitating cause of DKA while omission of insulin and new-onset diabetes accounted for the rest. These findings were similar to the study of Prasad et al in India[6] but somewhat different from that of Umpierrez GE et al,[2] which showed that omission of insulin and new-onset diabetes were more common precipitating causes of DKA than infection. Hypertension, obesity and coronary artery disease were the most common underlying co-morbid conditions. None had hypokalemia on admission, reflecting the insulin-deficient state of DKA. Occurrence of hypoglycemia during the course of insulin therapy was similar using either regimen, which is consistent with the results of other studies.[2,4,6] However, hypokalemia during insulin treatment occurred with greater frequency in those given IV insulin. None of the prospective, randomized trials[2,4,5,6] comparing IV insulin infusion with intermittent SC rapid insulin for treatment of mild to moderate DKA used hypokalemia as one of the measures of safety of therapy. Hospital stay was longer for those on IV insulin than those on SC insulin, in contrast to studies done by Umpierrez GE et al[4] and Prasad A and Gupta A,[6] wherein length of hospitalization was similar among treatment groups. The underlying co-morbidities and precipitating cause of DKA including the severity of infection could have contributed largely to the longer duration of hospital stay of patients on IV insulin more than the insulin regimen used to achieve resolution of hyperglycemia and ketoacidosis. Lastly, mortality was low and not significantly different in both groups, similar to results from other studies.[2,4,5,6]

Based on these results, a regimen using intermittent subcutaneous rapid insulin administered every two hours is equally effective and probably safer, with less occurrence of hypokalemia, in achieving resolution of hyperglycemia and ketoacidosis in mild to moderate DKA with the additional advantage of potentially lower cost because of less strict monitoring protocols and admission to the general ward instead of the intensive care unit, which is very appropriate in our clinical setting where financial resources are limited.

However, a greater number of subjects is needed to derive stronger conclusions from this study and prospective, randomized trials in adult diabetic Filipino patients would have been a better research endeavor compared to a retrospective chart review. Also, performing cost-effectiveness analysis can provide a more objective assessment of the cost and health effects of these particular types of therapy.

Conclusion

Intermittent subcutaneous rapid insulin regimen is an effective, safe, and potentially cost-effective alternative to continuous intravenous insulin infusion for treatment of mild to moderate DKA.

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