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Evaluation of Insulin Infusion Rates for the Treatment of Diabetic Ketoacidosis in the Emergency Department

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Abstract

Introduction: There is minimal literature to support the appropriate dosing for the initiation of IV regular insulin therapy in DKA patients. A 0.1 unit/kg bolus followed by 0.1 units/kg/hour or 0.14 units/kg/hour is commonly utilized and recommended in guidelines. **Objective:** We sought to assess clinical and safety outcomes associated with various insulin infusion starting doses in patients diagnosed with DKA in the emergency department in an effort to help guide prescribing. **Methods:** A retrospective cohort study was conducted within an academic emergency department and included patients who received continuous infusion regular insulin with an ICD-10 code for DKA between January 2016 and January 2019. A predictive regression model was applied to test if predefined lab values influenced the starting insulin infusion rates. Clinical and safety outcomes were evaluated by starting insulin infusion rate. Data was analyzed based on starting insulin infusion rates. **Results:** 347 patients met inclusion criteria with 92 (26.5%) patients receiving <0.07 units/kg/hr, 123 (35.4%) patients receiving 0.07 to 0.099 units/kg/hr, 123 (35.4%) patients receiving 0.10 to 0.139 units/kg/hr, and 9 (2.6%) patients receiving ≥0.14 units/kg/hr. After adjusting for baseline labs, glucose was the only significant predictor of the initial infusion rate ($p < 0.001$). For every 100 mg/dL increase in the baseline glucose value, the initial infusion rate increased by 0.005 units/kg/hr. There was no difference between insulin starting infusion rates and length of stay, rates of hypoglycemia, hypokalemia, or dysrhythmias. **Conclusion:** Glucose levels significantly influenced the insulin starting infusion rate, with no identified differences in adverse effects or clinical outcomes.

Keywords

Diabetic Ketoacidosis, Regular Insulin, Intravenous Insulin, Dose, Infusion

Rates

1. Introduction

Positive therapeutic responses have previously been established with the use of intravenous (IV) insulin therapy in adult patients with diabetic ketoacidosis (DKA) [1] [2] [3]. There is minimal literature to support the appropriate dosing for the initiation of IV insulin therapy in these patients. The role of insulin in the inhibition of ongoing lipolysis, suppression of further glucose production from the liver, and providing insulin for adequate glucose uptake into cells is widely understood and accepted. What is yet to be established is the impact of the starting insulin infusion rate that achieves all of the above metabolic functions while also down trending the glucose in a manner that is conducive to optimal time to gap closure and mitigation of risk associated with the infusion. Safety concerns, specifically cerebral edema and the rate of serum glucose reduction, have been identified and are associated with bolus doses of insulin prior to starting the infusion [4] [5]. A previous small prospective cohort study concluded that a bolus dose of insulin is not required if an adequate dose of regular insulin, defined as 0.14 units/kg/hour, is administered as a continuous infusion. Utilizing this insulin dosage strategy resulted in no difference in time to pH, bicarbonate, and glucose control. However, patients who received a starting dose of 0.07 units/kg/hour with no bolus were identified as not adequate to get the same response to insulin therapy [2]. Similarly, Goyal *et al.* also concluded that a bolus insulin dose was not associated with significant benefit in adult patients with DKA, and showed increased rates of hypoglycemic episodes [6]. While the data to support no bolus initiation in these patients has become a more common practice, the appropriate starting infusion rate without a bolus remains variable and controversial even in various national guidelines [4] [5] [7] [8] [9] [10].

Our large academic medical center emergency department has a provider pathway that reflects an initial starting infusion rate of IV regular insulin at 0.14 units/kg/hour with no associated bolus. Despite this dose embedded in the pathway, the dose that is chosen to start patients' on varies tremendously based on patient specific factors as well as pharmacist and provider specific practices. Some patient specific factors commonly mentioned as being evaluated include baseline lab values to help classify DKA severity (including pH, bicarbonate, anion gap, and glucose), lab values associated with safety (potassium), diabetes mellitus type (type I, II, or other) and known insulin history, including being insulin naive or insulin resistant. There is a wide range of providers and pharmacists that work within the emergency department which naturally lends itself to variability in these practices.

We aimed to evaluate patients presenting to a large, academic emergency department for treatment of DKA receiving IV regular insulin via continuous infu-

sion. The goal of this study was to assess descriptive characteristics, clinical outcomes, and safety of various starting insulin infusion rates (units/kg/hour) for the treatment of DKA within the emergency department. A predictive regression model was applied to test if predefined lab values influenced the starting insulin infusion rates.

2. Methods

A retrospective cohort study utilizing electronic medical records was conducted from January 2016 through January 2019 within a large, academic medical center's emergency department. Our research was approved by the Colorado Multiple Institutional Review Board (COMIRB #19-2060). Health Data Compass was utilized to pull medication, lab, and encounter data from the electronic health record for each patient meeting defined inclusion criteria. Health Data Compass is a local, enterprise health data warehouse that integrates patient clinical data from the electronic health record [11]. Inclusion criteria were defined as patients 1) between 18 and 89 years old; 2) administration of continuous infusion regular insulin with or without a bolus within the UCH emergency department; and 3) an ICD-10 diagnosis code for DKA during the same encounter (Table 1).

Data was analyzed based on starting insulin infusion rates < 0.07 units/kg/hr, 0.07 - 0.099 units/kg/hr, 0.1 - 0.139 units/kg/hr, and ≥0.14 units/kg/hr. DKA severity was defined as mild, moderate, or severe to help categorize the population in the study (Table 2). A predictive regression model was applied to test if initial lab values influenced the starting insulin infusion rates. The regression model accounted for baseline lab values of glucose, potassium, anion gap, pH, and bicarbonate. These covariates were analyzed for multicollinearity. Other analyzed outcomes included duration of insulin infusion and mean ICU and hospital length of stay. In order to assess metabolic outcomes, time to goal values were assessed

Table 1. Inclusion diagnoses by defined ICD-10 code.

Code	Description
E13.11	Other specified diabetes mellitus with ketoacidosis with coma
E10.10	Type I (juvenile type) diabetes mellitus with ketoacidosis, uncontrolled
E13.10	Type II or unspecified type diabetes mellitus with ketoacidosis, uncontrolled
E08.1	Diabetes mellitus due to underlying condition with ketoacidosis
E08.11	Diabetes mellitus due to underlying condition with ketoacidosis with coma
E10.11	Type 1 diabetes mellitus with ketoacidosis with coma

Table 2. Diabetic ketoacidosis severity definitions (baseline).

DKA Category	Blood Glucose (mg/dL)	pH	Bicarbonate
Mild	>250	7.25 - 7.30	15 - 18
Moderate	>250	7.00 - 7.24	10 - (<15)
Severe	>250	<7.00	<10

including time to blood glucose ≤ 250 mg/dL, pH ≥ 7.3, bicarbonate ≥ 15 mmol/L, and anion gap ≤ 12 mmol/L. Hypoglycemia, dysrhythmias, and hypokalemia were defined by documented ICD-10 codes within 0 to 48 hours of starting insulin therapy.

Descriptive analyses were completed for baseline population characteristics. The Chi-squared test or Fisher's Exact Test were used to analyze categorical variables and student's t-test or the Kruskal Wallis test for continuous data. The analysis for this project was generated using SAS software, Version 9.4 of the SAS System for Windows. Copyright © 2016 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

A total of 347 patients met inclusion criteria with 92 (26.5%) patients in the <0.07 units/kg/hour cohort, 123 (35.4%) patients in the 0.07 to 0.099 units/kg/hour cohort, 123 (35.4%) patients in the 0.10 to 0.139 units/kg/hour cohort, and 9 (2.6%) patients in the ≥0.14 units/kg/hour cohort. Patient demographics are shown in Table 3. Of note, patients in the <0.07 units/kg/hour cohort had a statistically higher mean weight compared to other starting infusion rate cohorts and the mean infusion rate in units/kg/hour was statistically different between cohorts as expected. Although mean infusion duration was not statistically different between cohorts, there were 42 patients with insulin infusion discontinuation in 8 hours or less, with a mean pH of 7.15. Table 4 shows a significant difference was found in the distribution of patients by starting insulin infusion rate and DKA severity ($p < 0.001$).

After adjusting for other baseline lab values, glucose was the only significant predictor of the initial insulin infusion rate ($p < 0.05$). For every 100 mg/dL increase in the baseline glucose value, the initial infusion rate increased by 0.005 units/kg/hr. A higher anion gap was correlated with a higher initial infusion rate and a higher bicarbonate and pH were correlated with a lower initial infusion rate, though not statistically significant. No multicollinearity was found among covariates. For all values associated with the linear regression, see Table 5. Time

Table 3. Demographics.

Characteristic	<0.07 units/kg/hr (n = 92)	0.07 - 0.099 units/kg/hr (n = 123)	0.10 - 0.139 units/kg/hr (n = 123)	≥0.14 units/kg/hr (n = 9)	P-Value
Sex, N (%)					
Male	51 (55.4%)	70 (56.9%)	65 (53.3%)	5 (55.6%)	0.864
Female	41 (44.6%)	53 (43.1%)	57 (46.7%)	4 (44.4%)	
Mean Weight, kg	90.7 ± 31.9	75.4 ± 20	68.4 ± 16.7	69.1 ± 9.2	<0.001
Mean infusion rate, units/kg/hr	0.04 ± 0.03	0.09 ± 0.02	0.11 ± 0.02	0.13 ± 0.03	<0.001
Mean infusion duration, hours	38.2 ± 43.2	48.7 ± 56.5	48.9 ± 46	41.8 ± 32.2	0.153

Table 4. Diabetic ketoacidosis baseline severity by starting insulin drip rate.

Starting Insulin Drip Rate by DKA Category	Mild DKA (n = 102)	Moderate DKA (n = 121)	Severe DKA (n = 115)	P-value
Number of patients, n (%)				
<0.07 units/kg/hr	38 (45.2%)	34 (40.5%)	12 (14.3%)	
0.07 - 0.099 units/kg/hr	39 (31.7%)	41 (33.3%)	43 (40%)	<0.001
0.10 - 0.139 units/kg/hr	23 (18.9%)	42 (34.4%)	57 (46.7%)	
≥0.14 units/kg/hr	2 (22.2%)	4 (44.5%)	3 (33.3%)	

Table 5. Linear regression model for baseline labs and starting insulin infusion rate.

Variable	Parameter Estimate	Standard Error	P-value
Intercept	0.28660	0.16317	0.08
Anion Gap	0.00014	0.00050	0.77
Glucose	0.00005	0.00001	<0.0001
Bicarbonate	−0.00096	0.00062	0.12
Potassium	−0.00033	0.00260	0.90
pH	−0.03031	0.02295	0.19

to goal glucose less than or equal to 250 mg/dL was statistically different between starting infusion rate cohorts (p = 0.006), with no significant difference identified for time to bicarbonate, pH, or anion gap goals (Figure 1). There was no significant difference in ICU length of stay or total hospital length of stay between starting infusion rate cohorts (p = 0.095 and 0.06 respectively, Table 6). Safety outcomes of dysrhythmia, hypoglycemia, and hypokalemia were also not different between starting infusion rates (Table 6).

4. Discussion

Insulin administration, in addition to fluid and electrolyte management, continue to be the mainstay of treatment for DKA, and emergency departments have continued to develop protocols in line with national guidelines [4] [12]. Despite the large number of annual emergency department visits for DKA management, there is minimal literature to support the wide range of dosing strategies used to initiate continuous infusion regular insulin therapy. While some protocols call for a standard starting infusion rate for all patients regardless of individual patient characteristics, the current process followed within our site facilitated the ability to study ordering trends occurring with interdisciplinary collaboration between the emergency department providers and pharmacists to determine starting insulin infusion rates [13]. To our knowledge, this type of model has never been assessed in this setting for DKA management.

This retrospective cohort study showed similar trends to previous literature, with no statistically significant difference between clinical or safety outcomes associated with starting IV insulin infusion rate [1] [3] [8] [9] [10]. Although

Table 6. Clinical and safety outcomes by starting insulin infusion rate.

Characteristic	<0.07 units/kg/hr (n = 92)	0.07 - 0.099 units/kg/hr (n = 123)	0.10 - 0.139 units/kg/hr (n = 123)	≥0.14 units/kg/hr (n = 9)	P-Value
Total hospital Length of Stay, Days	1.18 ± 0.38	1.09 ± 0.29	1.07 ± 0.26	1 ± 0	0.06
ICU Length of Stay, Minutes	202.9 ± 489.3	347.7 ± 591.8	393.4 ± 669.5	415.9 ± 420.5	0.095
Dysrhythmia, n (%)	12 (14%)	22 (17.9%)	20 (16.3%)	3 (33.3%)	0.42
Hypoglycemia, n (%)	5 (5.4%)	10 (8.1%)	18 (14.6%)	1 (11.1%)	0.13
Hypokalemia, n (%)	30 (32.6%)	25 (20.3%)	28 (22.8%)	0 (0%)	0.055

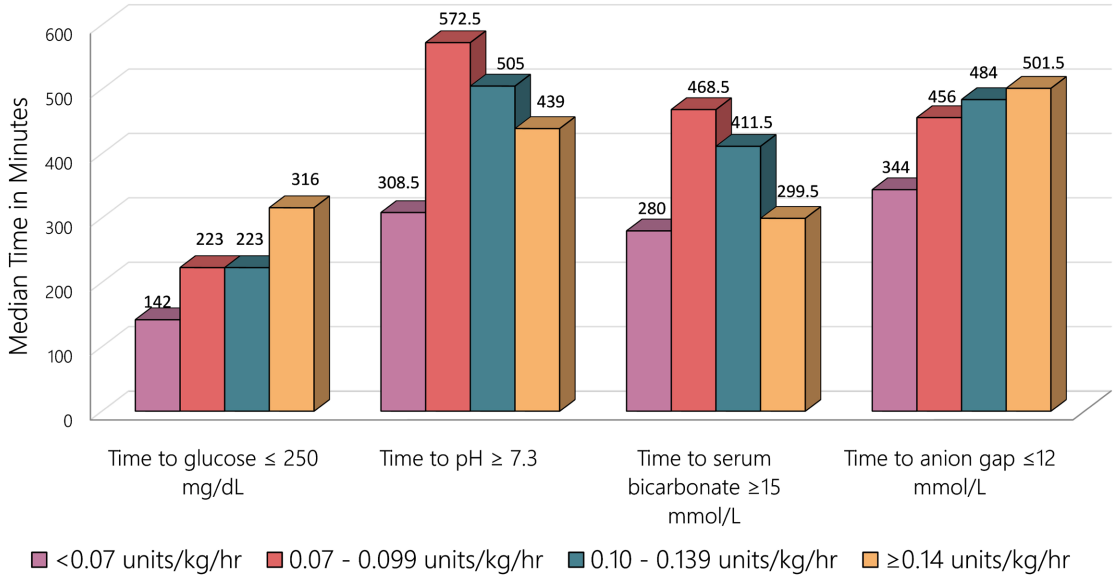

Figure 1. Median time to lab outcome in minutes based on starting insulin drip rate.

time to glucose goal less than or equal to 250 mg/dL was statistically different, this is not unexpected as the baseline glucose value was statistically different between groups. The linear regression model supports that baseline glucose level is the only significant predictor for insulin starting infusion rate in our interdisciplinary collaboration model of ordering. Only nine patients over several years were initiated on the starting insulin infusion rate of 0.14 units/kg/hour. This indicates that a change to our emergency department DKA pathway is indicated to better represent the majority of insulin infusion ordering practices. This seems particularly relevant as there are minimal safety or efficacy data available for this cohort of higher starting insulin infusion rates. Another interesting finding from this study was the lack of significant difference in mean insulin infusion duration between starting infusion rate cohorts. Although our current protocol does not support early administration of long acting insulin to help facilitate transition off of infusion to subcutaneous therapy, this is a future consideration for our pathway and population based on newer literature showing

potential benefit, particularly in mild-moderate DKA patients [10] [14] [15] [16]. As the starting insulin infusion rate does not appear to impact duration of infusion, it would be interesting to assess the addition of long acting insulin to this outcome in a future pathway. Lastly, the 42 patients who had their insulin infusions discontinued within 8 hours had a clear pH association of ≥7.15 with this early discontinuation. This finding has directly led to changes in our practice for the management of patients with mild to moderate DKA, partially defined as having a pH ≥ 7.15, being treated in our observation unit utilizing a subcutaneous insulin regimen.

5. Limitations

This study had several limitations. First, it was a single site, retrospective analysis with data obtained from a large database warehouse, and as a result could be impacted by missing data and selection bias. Additionally, with only a small cohort of patients in the initial infusion rate cohort of ≥0.14 units/kg/hour, our results and data analysis for this cohort are unable to provide any sound clinical conclusions about this cohort. Lastly, we calculated time to goal lab values based on previous studies and clinically relevant endpoints. We analyzed our endpoints based on the initial and final lab values from the patients' stay. While these are important to being able to assess disease severity and time to resolution, the progression of disease and clinical implications of the infusion rates may benefit with analysis of the changes between these values as well.

6. Conclusion

There is a wide range of starting insulin infusion rates utilized in patients with DKA. Glucose levels significantly influenced the insulin starting infusion rate, with no identified differences in adverse effects or clinical outcomes between starting infusion rate cohorts.

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Conflicts of Interest

The authors report no conflicts of interest related to this work.

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