Intravenous fluid bolus rates and pediatric diabetic ketoacidosis resolution

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ABSTRACT

Background: Recent data have challenged the notion that rapid intravenous fluid administration results in adverse neurologic outcomes in children with diabetic ketoacidosis (DKA). While many physicians still administer a cautious 10 cc/kg bolus of intravenous fluids for pediatric DKA patients, there may be benefits to using a larger bolus.
Methods: This was a retrospective chart review of all pediatric patients with DKA presenting to a single emergency department (ED) between 2013 and 2015. Patients who received a bolus of 10 cc/kg or less in the ED were compared to patients who received >10 cc/kg of fluids. The primary outcome was the difference in hospital length-of-stay between the two groups. Secondarily, we compared groups with regards to the time to bicarbonate normalization.
Results: In sum, 170 pediatric DKA ED visits were analyzed. Patients who received a 10 cc/kg bolus or less of fluids in the ED had a mean hospital length-of-stay > that was 0.38 days longer (95% CI: 0.006 to 0.75 days) than those who received >10 cc/kg. On multivariable regression analysis, the difference between groups was diminished and no longer statistically significant. The time to bicarbonate normalization was 0.12 days longer (95% CI -0.029 to 0.27) in the 10 cc/kg or less group than the >10 cc/kg group.
Conclusions: After adjustment for confounders, no statistically significant differences in outcomes were seen in pediatric DKA patients who received a 10 cc/kg bolus or less compared to those who received a larger initial bolus.

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1. Introduction

Previously, many experts believed that the rapid administration of intravenous (IV) fluids in patients with diabetic ketoacidosis (DKA) could result in brain swelling and, potentially, neurologic injury as a result of reduced serum osmolality [1,2]. These beliefs were supported by retrospective studies [3,4]. Consequently, many treatment protocols for pediatric DKA patients recommend a relatively small bolus of isotonic fluids (often 10 cc/kg), rather than the typical 20 cc/kg used for other dehydration states in pediatrics. However, the results of a recent randomized, controlled trial suggest that the concerns that rapid fluid administration can lead to neurologic damage in pediatric DKA are likely unwarranted as the study found that neither the rate of administration nor the

sodium chloride content of intravenous fluids influenced neurologic outcomes in these patients [5].

If IV fluids were previously being withheld in pediatric DKA patients for fear of causing cerebral edema, it may now be time to reassess the size of the initial bolus of IV fluids given for these patients. Indeed, DKA patients are dehydrated, and dehydration leads to a stress response that can worsen insulin resistance; so there is potential benefit to a more aggressive, early administration of IV fluids [6]. Interestingly, while not statistically significant, the previous study mentioned by Kuppermann, et al. [5] found lower rates of adverse events for patients who received a "fast" administration of IV fluids (20 cc/kg in boluses and then replacement of additional fluid deficits over 24 h) compared to those who received "slow" IV fluids (a 10 cc/kg bolus followed by the replacement of additional fluid deficits over 48 h).

Thus, we performed a retrospective chart review to compare the outcomes of pediatric DKA patients who received an IV fluid bolus of 10 cc/kg or less in the emergency department (ED) compared to those who received a larger fluid bolus. In particular, we sought to

determine if patients who received larger fluid boluses recovered faster from their DKA compared to those who received just a 10 cc/kg bolus.

2. Materials and methods

2.1. Study design and setting

This was a retrospective analysis of pediatric DKA patients presenting to the ED of a single regional tertiary medical center in Baton Rouge, Louisiana. All pediatric patients admitted from the ED with a diagnosis of DKA from January 1st, 2013, to December 31st, 2015, were analyzed for eligibility. This study was approved by the xxx Institutional Review Board (IRB).

2.2. Selection of participants

Patients were initially identified using International Statistical Classification of Disease and Related Health Problems (ICD) Ninth and Tenth Revision codes. Patients could be included if they were 18 years of age or younger and were diagnosed with DKA as defined by International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria [7]. Patients were excluded if they did not receive continuous weight-based insulin infusion per American Diabetes Association (ADA) and ISPAD recommendations, if they had received treatment at another medical facility prior to arrival at our hospital, or if there was missing documentation such that the outcomes could not be assessed.

2.3. Data collection

Patient information was abstracted from the electronic medical records using a standardized form by a single physician abstractor who was unaware of the study hypothesis. A selection of 10% of data entries were crosschecked for reliability. Data was collected from initial ED presentation until the time of hospital discharge. The abstracted data included basic patient demographics, metabolic panel results, initial pH, disposition location and times, treatments administered, and adverse neurologic outcomes (cerebral edema or intubation).

2.4. Data analysis

The DKA patients were divided into two groups: those who received a bolus of 10 cc/kg or less of IV fluids in the ED and those who received more than a 10 cc/kg bolus of IV fluids in the ED. The primary outcome for this study was the difference in hospital length of stay between these two groups. Secondarily, we compared the two groups with regards to the time to bicarbonate normalization (defined as a bicarbonate of 15 mEq/L or greater). We used t-tests to compare the two treatment groups for continuous variables, and we used chi-square tests for categorical variables. Initially, groups were assessed with univariate analyses. We then used the clinical characteristics with statistically significant differences between groups on univariate analysis as variables in a multivariable regression analysis to adjust for confounders.

3. Results

Initial screening identified 276 patient charts with an ED diagnosis of DKA. Of these charts, 66 did not meet ISPAD diagnostic criteria, and thus were not included. Additionally, 40 patient encounters were excluded as 9 had received treatment at another medical facility before arrival in our ED, 26 did not receive a weight-based continuous insulin infusion, and 5 had missing doc-

Table 1
Comparison of the clinical characteristics for DKA patients receiving a bolus of 10 cc/kg or less compared to those receiving >10 cc/kg.

Clinical characteristic	10 cc/kg or less	>10 cc/kg	p-Value
Mean Age	11.7 years	15.1 years	p < 0.0001
% Male	31.3	57.1	p = 0.003
Mean Body Mass Index	20.0 kg/m^2	21.4 kg/m^2	p = 0.16
% with Fever[a]	1.6	2.4	p = 0.73
Mean Initial Glucose	566 mg/dL	614 mg/dL	p = 0.33
Mean Initial Sodium	133.3 mEq/L	133.4 mEq/L	p = 0.86
Mean Initial Potassium	4.9 mEq/L	5.3 mEq/L	p = 0.04
Mean Initial Creatinine	1.35 mg/dL	1.64 mg/dL	p = 0.001
Mean Initial pH	7.10	7.09	p = 0.60
Median Initial Bicarbonate	7 mEq/L	6 mEq/L	[b]
% Admitted to ICU	74.2	88.1	p = 0.06
Mean Volume of Bolus	9.8 cc/kg	20.6 cc/kg	p < 0.0001

[a] Fever = temperature of at least 100.4° F.
[b] The p-value cannot be calculated for the initial bicarbonates because some of the lab values are listed as "<5".

umentation such that the outcomes could not be assessed. The remaining eligible encounters included 170 ED visits made by 91 patients.

Overall, the average patient presenting to the ED with DKA was 12.5 years of age; 106 (62,4%) were female, and 64 (37.6%) were male. In total, 55.3% of patient encounters were by African Americans, 41.8% by Caucasians, 2.4% by Asians, and 0.6% by Hispanics. All cases of pediatric DKA in this study were admitted to the hospital.

In total, a 10 cc/kg bolus or less was administered in 128 cases (75.3%), and a bolus larger than 10 cc/kg was administered in 42 cases (24.7%). The fluid used for all boluses was normal saline. Patient clinical characteristics for each of the treatment groups are detailed in Table 1.

Regarding the primary outcome, for those receiving a 10 cc/kg bolus or less of IV fluids, the mean hospital length-of-stay was 2.74 days. For those receiving higher than a 10 cc/kg bolus, the mean hospital length-of-stay was 2.36 days. The between groups difference was 0.38 days (95% CI: 0.006 to 0.75 days), with p = 0.043. However, as demonstrated in Table 1, there were significant differences between groups with regards to age, gender, initial creatinine, and initial potassium. Thus, a multivariable regression analysis was conducted to adjust for the differences in these variables between groups. After this analysis, the reduction in hospital length of stay associated with the larger IV fluid bolus group became just 0.02 days, and the between groups difference was no longer statistically significant (p = 0.92).

With regards to secondary outcomes, the time to bicarbonate normalization was 0.76 days in the 10 cc/kg bolus or less group, compared to 0.64 days in the >10 cc/kg group. The difference between groups is 0.12 (95% CI -0.029 to 0.27). There were two patients treated with mannitol for suspected cerebral edema (2.2%). Both of those patients had received a bolus of 10 cc/kg. No patients required intubation or vasopressor support. Additionally, there were no deaths and no patients had neurologic deficits upon discharge.

Finally, as a side note, a magnesium was ordered on 169 of the 170 patient encounters in this study. The mean was 2.3 mEq/L; the median was 2.2 mEq/L (IQR: 2.0 to 2.5 mEq/L). In zero of the 169 cases was the magnesium low.

4. Discussion

This is the largest study to date to attempt to determine if the size of the initial fluid bolus in pediatric DKA patients is associated with the rapidity of improvement. One prior retrospective study

found the amount of fluid administered did not correlate with the rapidity of patient recovery, but the study analyzed just 42 DKA patients [8]. One small randomized, controlled trial with 50 total patients found that patients who received 20 cc/kg had more rapid normalization of pH and bicarbonate compared to those who received 10 cc/kg [9]. Although there could be a modest benefit of giving a larger fluid bolus to pediatric DKA patients as suggested in that study, our results suggest that the size of the initial fluid bolus (at least in the range of 10–20 cc/kg) does not have a large impact on the patient's outcome.

It should be emphasized that no patients in this study died or had neurologic disability at the time of hospital discharge. This is consistent with prior recent data demonstrating low mortality for pediatric DKA [10], and confirms that with modern day therapy, major adverse outcomes in pediatric DKA are extremely rare. Therefore, we believe that pediatric DKA studies should now focus more on outcomes other than mortality or neurologic disability. This is why we chose hospital length of stay as our primary outcome.

Despite recommendations that for years have allowed pediatric DKA patients to receive an initial bolus of 20 cc/kg [11], and the fact that average water losses in pediatric DKA have been estimated to be 70 cc/kg [12], most patients in this study received a 10 cc/kg bolus. This was especially true for younger pediatric patients and females. This preference for a smaller initial fluid bolus may be partially explained by local practice preferences, as the pediatric DKA order set at this facility recommends an initial bolus of 10 cc/kg. (That being said, this order set is primarily used by the admitting providers, after the diagnosis of pediatric DKA has been confirmed). However, the data from this study precede the publication of trial results by Kuppermann, et al. [5], and thus the high percentage of patients receiving a 10 cc/kg bolus may reflect a fear of causing cerebral edema. It is hoped that with the new data available, emergency physicians will at least feel comfortable giving an IV bolus that is standard for other dehydration states — 20 cc/kg.

Although the primary aim of this study was to evaluate the association of IV fluid bolus amounts and outcomes in pediatric DKA, we had one incidental outcome that is worth discussing further. Despite the fact that a magnesium was ordered on >99% of DKA patient encounters, there were no identified cases of hypomagnesemia. Although experts often recommend the routine ordering of magnesium in pediatric DKA patients [13], our study appears to be convincing evidence that it is not necessary to do so.

The present study has several limitations to consider. As a retrospective study it is subject to confounding. Indeed, the clinical characteristics of the two treatment groups were quite different, making them difficult to compare. Although we performed a multivariable regression analysis to adjust for confounders, there may have been additional confounders that were not taken into account. In particular, many patients were likely treated prior to arrival in the ED with insulin (at home) or with IV fluids from emergency medical services; these treatments were not accounted for. Additionally, the study was performed at a single facility, which weakens the external validity. In particular, the local prac-

tices (such as the consistent use of normal saline rather than lactated ringers) may not be the same at other facilities.

5. Conclusion

A multivariable regression analysis demonstrated that pediatric DKA patients who received an initial IV bolus of 10 cc/kg or less had similar hospital lengths of stay and rates of bicarbonate normalization compared to patients who received larger initial IV fluid boluses. There were zero cases of hypomagnesemia in our group of pediatric DKA patients, and a magnesium level should not be routinely ordered in these patients.

Support

Declaration of interest

We have no conflicts of interest to report.

Prior presentations

None.

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