The Journal of Emergency Medicine, Vol. 50, No. 4, pp. 551–559, 2016

0736-4679/$ - see front matter

ELSEVIER

http://dx.doi.org/10.1016/j.jemermed.2015.12.003

Original Contributions

EFFECT OF VOLUME OF FLUID RESUSCITATION ON METABOLIC NORMALIZATION IN CHILDREN PRESENTING IN DIABETIC KETOACIDOSIS: A RANDOMIZED CONTROLLED TRIAL

Katherine Bakes, MD,* Jason S. Haukoos, MD, MSC,*† Sara J. Deakyne, MPH,‡ Emily Hopkins, MSPH,* Josh Easter, MD,* Kim McFann, PHD,§ Alison Brent, MD,|| and Arleta Rewers, MD, PHD||

*Department of Emergency Medicine, Denver Health Medical Center, University of Colorado, School of Medicine, Denver, Colorado, †Department of Epidemiology, Colorado School of Public Health, University of Colorado, Aurora, Colorado, ‡Department of Research Informatics, Children's Hospital Colorado, Research Institute, Aurora, Colorado, §Colorado School of Public Health, University of Colorado, Aurora, Colorado, and ||Section Emergency Medicine, Department of Pediatrics, University of Colorado, School of Medicine, Aurora, Colorado

Reprint Address: Katherine Bakes, MD, Department of Emergency Medicine, Denver Health Medical Center, 777 Bannock Street, Mail Code 0132, Denver, CO 80204

☐ **Abstract—Background: The optimal rate of fluid administration in pediatric diabetic ketoacidosis (DKA) is unknown. Objective: Our aim was to determine whether the volume of fluid administration in children with DKA influences the rate of metabolic normalization. Methods: We performed a randomized controlled trial conducted in a tertiary pediatric emergency department from December 2007 until June 2010. The primary outcome was time to metabolic normalization; secondary outcomes were time to bicarbonate normalization, pH normalization, overall length of hospital treatment, and adverse outcomes. Children between 0 and 18 years of age were eligible if they had type 1 diabetes mellitus and DKA. Patients were randomized to receive intravenous (IV) fluid at low volume (10 mL/kg bolus + 1.25 × maintenance rate) or high volume (20 mL/kg bolus + 1.5 × maintenance rate) (n = 25 in each). Results: After adjusting for initial differences in bicarbonate levels, time to metabolic normalization was significantly faster in the higher-volume infusion group compared to the low-volume infusion group (hazard ratio [HR] = 2.0; 95% confidence interval [CI] 1.0–3.9; $p = 0.04$). Higher-volume IV fluid infusion appeared to hasten, to a greater extent, normalization of pH (HR = 2.5; 95% CI 1.2–5.0; $p = 0.01$) than normalization of serum bicarbonate (HR = 1.2; 95% CI 0.6–2.3; $p = 0.6$). The length of hospital treatment HR (0.8; 95% CI 0.4–1.5; $p = 0.5$) and time to discharge HR (0.8; 95% CI 0.4–1.5; $p = 0.5$) did not differ between treatment groups. Conclusions: Higher-volume fluid infusion in the treatment of pediatric DKA patients significantly shortened metabolic normalization time, but did not change overall length of hospital treatment. ClinicalTrials.gov ID NCT01701557.** © **2016 Elsevier Inc.**

☐ **Keywords—pediatric diabetes; ketoacidosis; DKA; fluid resuscitation; acidosis; bicarbonate; ketones**

INTRODUCTION

The optimal volume and rate of initial intravenous (IV) fluid replacement in diabetic ketoacidosis (DKA) in the pediatric population is controversial. In the setting of DKA, the presence of hyperglycemia leads to osmotic urinary diuresis with subsequent dehydration. Dehydration in turn stimulates a stress response with counter-regulatory hormone production, leading to greater insulin resistance, thus perpetuating a cycle of hyperglycemia and further fluid loss. In an attempt to truncate the production of counter-regulatory hormone production, some authors have advocated for more aggressive fluid rehydration for patients in DKA (1).

RECEIVED: 28 January 2015; FINAL SUBMISSION RECEIVED: 19 November 2015;
ACCEPTED: 13 December 2015

In 1989, Adrogue et al. published a small prospective study evaluating the effect of initial volume of fluid administration in adults presenting with DKA (2). Their data suggested that more modest amounts of infused fluids in the first 4 h of treatment resulted in a more rapid recovery of acid–base status and shorter hospital stay, which correlated with a reduction in medical costs. One theoretical explanation for these findings is depletion of keto-anion salts in the urine among normotensive patients with DKA treated with aggressive amounts of intravenous fluids (3). Keto-anions serve as substrates for bicarbonate regeneration, but administration of IV saline leads to keto-anion excretion in the urine with replacement by chloride anions. As a result, a non-anion gap metabolic acidosis ensues, resulting in an acid–base imbalance, which takes longer to correct (4). This could explain the longer time to recovery and length of treatment in patients given larger volumes of IV fluids.

Despite their universal need for intravascular volume repletion, patients with DKA are rarely hemodynamically unstable. Furthermore, clinicians often overestimate their extent of dehydration, often resulting in excessive fluid replacement (5,6). Rapid fluid administration may have potential harmful effects in pediatric populations, where alterations in fluid balance have been implicated in the development of cerebral edema (7,8). Moreover, despite conflicting evidence for the role of rapid fluid replacement in the development of cerebral edema, this concern continues to influence management recommendations in treatment of pediatric DKA (9). Few pediatric studies have directly evaluated optimal fluid replacement protocols in DKA. One retrospective study of children with DKA found that children who received 0.45% (i.e., half normal) saline received longer durations of insulin therapy and thus had longer intensive care unit stays (10). Consensus clinical practice guidelines for treatment of DKA in children call for 10–20 mL/kg 0.9% (i.e., isotonic or normal) saline in the first 1–2 h after presentation (11,12). However, the optimal amount and rate of fluid administration within this wide range is unclear. We hypothesized that in pediatric patients presenting with DKA, low-volume fluid infusion, as compared with the higher-volume fluid infusion, would result in a greater relative availability of ketones as a substrate for bicarbonate production, and thus more rapid metabolic normalization.

METHODS

We used the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement to report methodology and results (13).

Study Design

We performed a randomized clinical trial of two different IV fluid regimens for pediatric patients with DKA. After obtaining consent, patients were assigned to a study arm using a concealed randomization list generated in SAS Version 9.3 (SAS Institute, Inc., Cary, NC). Clinicians, nurses, research assistants, patients, or family of patients were not blinded to the intervention.

Study Setting and Population

This study was conducted in the pediatric emergency department (ED) and inpatient units of an academic freestanding children's hospital. The study interval was from December 2007 until June 2010. The cohort consisted of a convenience sample of 50 patients who were enrolled when an ED research assistant was available. The treating attending physician identified potential subjects, followed by laboratory confirmation of DKA. Children were eligible for participation if they were between 0 and 18 years of age, had type 1 diabetes mellitus plus the presence of DKA, as defined by glucose >250 mg/dL, presence of ketone bodies in the blood, and metabolic acidosis (venous pH < 7.30 or serum bicarbonate < 15 mmol/L). Patients were excluded from the study if they 1) required additional fluid resuscitation for treatment of hemodynamic instability, given at the discretion of the treating attending physician; or 2) weighed >70 kg. This study was approved by the Colorado Multiple Institutional Review Board and written informed consent was obtained from the parent or guardian and assent from each participant before randomization.

Interventions

The current nationally accepted consensus guidelines for the treatment of DKA in children recommend 10–20 mL/kg of 0.9% saline in the first hour after presentation followed by IV infusion of solution with tonicity >0.45% saline at 1–2 times maintenance rates (12). To study volume differences, we chose two fluid volumes that were furthest apart in volume differences, but still within the nationally recommended, as well as our institution's, treatment guidelines. Group I, the high-volume IV fluid group, received a 20 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.5 times maintenance, whereas Group II, the low-volume IV fluid group, received a 10 mL/kg of IV 0.9% saline bolus over the first hour followed by 0.675% saline + potassium replacement at 1.25 times maintenance (0.675% saline, or three-quarters isotonic saline, was used per standard hospital