Editorial

Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis

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Diabetic ketoacidosis (DKA) is a profound derangement in metabolism due to deficiency of insulin. The metabolic derangement is exaggerated by counter regulatory stress hormone effects leading to hyperglycemia, dehydration, and ketone production. This leads to the classic presentation of polyuria, polydipsia, and weight loss. DKA is the initial presentation in as many as 30–50% for children with diabetes (1). Younger children are more likely to present with DKA, and are more at risk for cerebral edema (CE). In children with DKA, CE is the major cause of mortality and morbidity accounting for 60–90% of all DKA deaths (2).

Contemporary guidelines for fluid resuscitation of children with DKA designed to minimize the risk of CE are not evidence-based, but support the notion that rapid resuscitation might lead to cellular edema of the brain, the osmolar hypothesis. Current guidelines by the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend following an intravenous bolus of 10–20 mL/kg body weight 0.9% saline, the remaining deficit of 7–10% body weight is evenly provided over 48 hours (1). Numerous case series have failed to support the osmolar hypothesis (3,4) and more recent studies have suggested that hypoperfusion followed by reperfusion, along with neuroinflammation, may be causal (5). This would explain the occasional case of CE developing before intravenous fluid administration.

The multicenter study by Kuppermann *et al.* (6) compares what had been the typical regimen of two 10 mg/kg 0.9% saline boluses followed by half the deficit in the next 12 hours and the remaining deficit during the subsequent 24 hours using either 0.9% or 0.45% saline to the slow administration over 48 hours after a single bolus using either 0.9% or 0.45% saline (2). 1,389 DKA episodes in 1,255 children 0–18 years old were randomly assigned to one of these 4 regimens. Primary endpoint was a decline in Glasgow Come Scale (GCS) scores of <14 during treatment for DKA. Secondary outcomes included clinically apparent brain injury during treatment, short term memory during treatment, and IQ 2–6 months after recovery from DKA. The study found 48 (3.5%) episodes of decline in GCS <14 and 12 (0.9%) episodes of clinically apparent brain injury in the 1,389 episodes of DKA. The results confirmed what numerous case series of the past suggested, that neither the rate nor the sodium chloride content of intravenous fluids influenced neurologic outcomes during treatment for DKA. Specifically, fast resuscitation in DKA did not lead to increased rates of neurological decline, and the data showed a trend towards, though not statistically significant, faster improvement cognitively and fewer episodes of clinically apparent brain injury (6). Even in the subjects presenting in severe DKA, there was no difference in rates of clinically apparent brain injury among the 4 groups, and the fast resuscitation groups trended to have faster improvement in cognitive function. The clinical importance of faster improvement in cognitive function is uncertain, as this did not change the length of hospital stay and resolution of DKA between groups.

A limitation of this study is that providers were not blinded. The multicenter nature of the study could introduce bias if subjects were on a rate or NaCl

composition much different than prescribed by the protocol. Another limitation is the potential variation and subjectivity of GCS scoring. This study was powered for change in GCS <14 during DKA treatment, not detecting clinically apparent brain injury (CE). Because CE is a rare event, designing a study with the number required is not feasible. This study did have a similar incidence of clinically apparent brain injury in DKA, 0.9%, which occurs in 0.5% to 1.5% of episodes of DKA in children (7).

As the only controlled study to verify the observations of clinical series, this is an important contribution.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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