DEM Journal Club

Article Appraisal

Article: Kuppermann et al. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis, in NEJM 2018

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Background and Study Objective(s):

In pediatric diabetic ketoacidosis (DKA) there has been retrospective research that has shown an association between large amounts of fluid resuscitation with cerebral edema and clinically apparent brain injury. Among patients without obvious neurologic decline during treatment for DKA, subtle neurologic alterations are often present after recovery, including deficits in memory, attention, and IQ.

Despite there being a low incidence of this, it has been widely documented as a complication of DKA management and presents as acute decline in neurological status. More well-done retrospective and prospective studies have not shown this association between fluid volume and cerebral edema. Newer studies have also shown that patients can have cerebral edema both clinically and on imaging before treatment begins, and that the treatment is not associated with worsening edema on imaging. We know that clinically apparent brain injuries can occur in children with DKA, originally presumed to be caused by rapid administration of IV fluids that reduces serum osmolality causing a cerebral edema mechanism (by shifting fluid intracellularly). The mechanism for clinically apparent brain injury in DKA is now thought to occur through many ways, and may mostly be from cerebral hypoperfusion and alterations in the blood brain barrier, with less mechanism of osmotic shifts occurring than previously thought. The reason the authors undertook this study was because there seems to be significant clinical equipoise regarding types and rates of fluid used for resuscitation of volume deplete children with DKA, which is why there is significant practice variation for rehydration therapy.

The objective of this 13-center RCT was to investigate differences in fluid and fluid infusion rates for pediatric DKA, with respect to neurological outcomes.

Study Design:

Pediatric patients presenting or transferred to 13 large urban center Emergency Departments in the USA in the PECARN Network, who were between 0 and 18 years of age with DKA (blood glucose >16.7mmol/L and either venous pH <7.25 or serum bicarbonate of <15 mmol/L. Exclusion criteria were underlying disorders that could affect neurocognitive evaluation, concurrent EtOH and drug use, head trauma, DKA for which patient had already received substantial treatment, or if treating physician determined a specific fluid therapy was necessary. Participants with GCS <14 were excluded from the primary analysis. Children with GCS <12 were excluded in year 2 of the trial, due to

not wanting to randomize these patient's treatment. Study was limited to patients being enrolled twice, but two patients were entered into the study three times. From February 2011 through September 2016, 1389 episodes of DKA were reported in 1255 children.

The 1255 children were randomly assigned to one of four treatment groups in a 2x2 factorial design for either 0.9% or 0.45% sodium chloride content, and either rapid or slow rate of administration. Group 1: Fast administration of 0.45 % NaCl; Group 2: Fast administration of 0.9 % NaCl; Group 3: Slow administration of 0.45 % NaCl; Group 4: Slow administration of 0.9% NaCl.

Fast: 10 mL/kg 0.9 % NaCl bolus, with additional 10 ml/kg bolus if physician thought the patient was under perfusing. Fluid deficit: 10% BW. During the initial 12 hours, half the fluid deficit was replaced, plus maintenance fluids. The remaining deficit, plus maintenance fluids, were replaced during the subsequent 24 hours.
Slow: 10 ml/kg 0.9 % NaCl bolus, no additional bolus. Fluid deficit: 5 % BW. Deficit plus maintenance fluids replaced evenly over a period of 48 hours.

0.9 % NaCl group: 0.9 % NaCl used for replacement of fluid deficit and maintenance fluids.
0.45 % NaCl group: 0.45 % NaCl used for replacement of fluid deficit and maintenance fluids.
Aside from the experimental intervention, all groups were treated equally: Insulin infusion at 0.1 unit/kg/hr, initiated after fluid bolus. Dextrose infusion (5-10%) was added when blood glucose fell below 11.1-16.7 mmol/L, to keep blood glucose between 5.6-11.1 mmol/L. Potassium was replaced as needed (initially KCl 20 meq/L and Kphos 20 meq/L, then adjusted to maintain potassium levels). Maintenance fluid rate calculated using 4:2:1 equation.
Primary outcome in this study was deterioration of neurologic status as evidenced by two consecutive Glasgow Coma Scale scores of <14 during any hour within the first 24 hours of treatment for diabetic ketoacidosis).
Secondary outcomes included short-term memory during treatment for diabetic ketoacidosis (forward and backward digit-span recall; clinically apparent brain injury (defined as a deterioration in neurologic status leading to initiation of hyperosmolar therapy or endotracheal intubation or resulting in death) during treatment for diabetic ketoacidosis; and short-term memory, contextual memory, and IQ 2 to 6 months after the episode of diabetic ketoacidosis.

The primary analyses were performed according to the intention-to-treat principle. They also performed secondary analyses in the per-protocol population. The trial was not stopped early.

Of note, there was no industry funding for the trial. In addition, the entire methodology was published in advance online in a different journal.

Results:

GCS declined to less than 14 in 48 episodes (3.5 %). They found no statistically significant difference in the % of episodes among the 4 groups where the GCS decreased to < 14. Incidence of a GCS decline <14 & clinically apparent brain injury was actually lower in fast rehydration groups (21 vs 27 & 4 vs 8 episodes respectively), but both were not statistically significant. Memory assessed by forward and backward digit-span scoring and IQ test results did not significantly differ between the 4 groups.

Clinically apparent brain injury occurred in 12 episodes (0.9 %). There were no differences between groups. It should be noted that patients with clinically apparent brain injury presented with severe acidosis and hypocapnia. Out of the 12 patients with clinically apparent brain injury 1 patient died, and the other 11 recovered without overt neurological deficits.

Serious adverse events were rare and did not differ between groups.

Validity of Results:

This was a well done, single blinded multi-center RCT. There are some limitations to the validity of the results. Patients with GCS <12 were excluded from this study, as they had already met the primary outcome. These patients are more likely to have adverse neurological outcomes and may be the ones we are most interested in. As well

clinicians were able to exclude patients before randomization due to fluid preference, and 289 of these patients were excluded whom also were likely the sicker of the cohort. This study was underpowered to find their primary outcome, which was initially powered for a 20 % difference, but only occurred 3.5 % of cases. It was also underpowered to find a difference in clinically apparent brain injury which occurred in 0.9 % of cases. Finally, 30 % of patients were lost to follow up for the follow up neurocognitive testing, which limits the validity of the results.
In terms of the statistical analysis, Cochran–Mantel–Haenszel tests were used to test the effects of the rate of administration and of the sodium chloride content of the fluid. This test allows for the comparison of two binary variables, while controlling for other confounding variables. Thus, it can compare fast vs slow (within groups of different fluid concentrations and stratified by site), and also compare different fluid concentrations (within the groups of fast and slow and stratified by site).

It would have been nice to see the results stratified by risk factors known to contribute to cerebral edema in DKA, such as younger age of the patient and how recently they were diagnosed with DKA. Also, a significant proportion of patients (about 290) were withdrawn by the treating clinician, with no explanation or description of these patients.

Generalizability of Results:

This study was done in large urban centers in the USA, similar to ones that we work in. In BC, we perhaps have a slightly smaller Hispanic population than that in Table 2. Overall, these results are generalizable to the pediatric DKA patients that we see.

However, we know that children with significant electrolyte issues are more likely to have severe DKA, so it would have been better that they didn't exclude these patients so we could apply these conclusions to all comers. More studies might be necessary to determine if fluid infusion rates make a difference in those most likely to deteriorate neurologically (low GCS, significant electrolyte abnormalities, very low pH, etc.). They also excluded 67 patients who are more likely to have cerebral edema (GCS < 12), which limits the generalizability.

The Bottom Line:

1. Among pediatric patients who presented with a GCS of 14 or 15, neither the rate of administration nor the sodium chloride content of intravenous fluids significantly influenced neurologic outcomes in children with diabetic ketoacidosis.

2. Clinically apparent brain injury in DKA is rare, and due to study size this study does not provide definitive evidence that clinically apparent brain injury is not caused by fluid rate/composition. Few children who were less than six years old, who are at higher risk of poor outcomes, were included in this study (~12 %). Also, many of the sickest kids were excluded from this trial (exclusion of patient who were GCS <12, and patients being taken out of randomization based on clinician's judgement).

3. This protocol is similar to or more aggressive than our BCCH pediatric DKA protocol, so we may be comfortable that we are likely not causing poor neurological outcomes using this protocol. Feel free to bolus patients if necessary to improve perfusion, and set them on the right course to be managed by our consultants. The journal club consensus was that in at least some children with DKA (the not-so-sick ones), a more liberal approach to IV fluid resuscitation (with either a second 10 cc/kg bolus and/or faster maintenance IV fluid rates) is unlikely to cause cerebral edema. It may even improve neurological outcomes.