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Effects of Fluid Rehydration Strategy on Correction of Acidosis and Electrolyte Abnormalities in Children With Diabetic Ketoacidosis

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OBJECTIVE

Fluid replacement to correct dehydration, acidosis, and electrolyte abnormalities is the cornerstone of treatment for diabetic ketoacidosis (DKA), but little is known about optimal fluid infusion rates and electrolyte content. The objective of this study was to evaluate whether different fluid protocols affect the rate of normalization of biochemical derangements during DKA treatment.

RESEARCH DESIGN AND METHODS

The current analysis involved moderate or severe DKA episodes (*n* = 714) in children age <18 years enrolled in the Fluid Therapies Under Investigation in DKA (FLUID) Trial. Children were assigned to one of four treatment groups using a 2 × 2 factorial design (0.90% or 0.45% saline and fast or slow rate of administration).

RESULTS

The rate of change of pH did not differ by treatment arm, but P_{CO_2} increased more rapidly in the fast versus slow fluid infusion arms during the initial 4 h of treatment. The anion gap also decreased more rapidly in the fast versus slow infusion arms during the initial 4 and 8 h. Glucose-corrected sodium levels remained stable in patients assigned to 0.90% saline but decreased in those assigned to 0.45% saline at 4 and 8 h. Potassium levels decreased, while chloride levels increased more rapidly with 0.90% versus 0.45% saline. Hyperchloremic acidosis occurred more frequently in patients in the fast arms (46.1%) versus the slow arms (35.2%).

CONCLUSIONS

In children treated for DKA, faster fluid administration rates led to a more rapid normalization of anion gap and P_{CO_2} than slower fluid infusion rates but were associated with an increased frequency of hyperchloremic acidosis.

Diabetic ketoacidosis (DKA) is a life-threatening complication of type 1 diabetes. In the U.S., DKA affects ∼30–60% of children and youth at diagnosis of type 1 diabetes (1–3) and occurs at a rate of 7–10% per year among those with established type 1 diabetes (4–6). Brain injuries associated with DKA increase acute morbidity, mortality, and costs (7–9) and result in adverse long-term neurological outcomes

(10–14). Children who present with DKA at the time of diagnosis of type 1 diabetes also have worse long-term glycemic control (15,16), increasing the risk of microvascular complications.

Fluid replacement to correct dehydration, acidosis, and electrolyte abnormalities is the cornerstone of treatment of DKA. However, the optimal volume, rate of infusion, and sodium content of intravenous (IV) fluid replacement have been controversial (17–19). A recent large randomized controlled trial, the Pediatric Emergency Care Applied Research Network (PECARN) Fluid Therapies Under Investigation in DKA (FLUID) Trial, found that neither the rate of administration nor the NaCl content of IV fluids significantly influenced neurological outcomes in children with DKA (20). Recommendations from the FLUID Trial are part of the current Clinical Practice Consensus Guidelines of the International Society for Pediatric and Adolescent Diabetes (21). The guidelines suggest that fluid management should be based on the patient's hydration status and may be administered at rates as high as those used in the FLUID Trial.

Liberalization of fluid treatment protocols may have occurred as a result of the FLUID Trial data; however, little is known about the effects of IV fluid administration rate and NaCl content on the rates of change in glucose and electrolytes and metabolic normalization during treatment of DKA in children. A small randomized controlled trial in adults with DKA and modest fluid deficits suggested that smaller volumes of IV fluid administration lead to faster normalization of bicarbonate concentrations and shorter hospitalizations (22). In contrast, a small randomized controlled trial in children with DKA (23) showed faster metabolic normalization in those receiving larger volumes of IV fluids. The FLUID Trial was designed, in part, to provide definitive answers in this area of controversy. The goal of the current study was to investigate the effect of IV fluid administration rate and NaCl content on the rate of change in pH, P_{CO_2}, glucose, anion gap, glucose-corrected sodium, chloride, and potassium levels as well as time to metabolic normalization in children randomized to one of four DKA fluid treatment protocols in the PECARN FLUID Trial.

RESEARCH DESIGN AND METHODS

Study Design

The PECARN FLUID Trial evaluated the effects of fluid rehydration rate and NaCl content on neurocognitive outcomes in 1,255 children <18 years old with 1,389 episodes of DKA between February 2011 and September 2016 (20). This randomized controlled trial was conducted in 13 children's hospitals within PECARN. Written informed consent was obtained from the parents or guardians of all enrolled patients. This study was approved by the local institutional review board at each study site. Assent was obtained from patients whose age met the minimum age for assent according to their local institutional review board. Exclusion criteria were previously described (24) and consisted of conditions unrelated to DKA that may affect mental status or cognitive abilities or receipt of substantial treatment for DKA prior to transfer to the study center. DKA was defined as a blood glucose level of >300 mg/dL [16.7 mmol/L] and either a venous pH of <7.25 or a serum bicarbonate level of <15 mEq/L.

In the current post hoc analysis of data from the PECARN FLUID Trial, we excluded DKA episodes in which the child withdrew (n = 43, 3%), was later found to be ineligible (n = 8, 1%), or did not receive treatment according to protocol for nonclinical reasons (n = 102, 7%). Patients in this last group either *1*) received <80% or >125% of the expected amount of total protocol-prescribed fluid or *2*) received a majority (>50%) of nonbolus fluid that did not match the protocol-prescribed sodium concentration. Children whose treatment was changed for clinical reasons (adverse events or other clinical conditions that required changes in treatment) were not excluded from the current analyses. Finally, we included only moderate or severe DKA episodes defined as serum glucose >300 mg/dL and venous pH <7.20 or serum bicarbonate <10 mEq/L. Mild DKA episodes (522 of 1,389, 38%) were excluded because DKA often resolved rapidly, frequently ending before the 4- or 8-h time points, making analyses of biochemical trends difficult and irrelevant. The current analyses, therefore, included 714 (51%) moderate to severe DKA episodes.

Procedures

The PECARN FLUID Trial compared four fluid rehydration protocols frequently used in the U.S. to treat children with DKA (24) (Supplementary Table 1). In the current analysis, we compared biochemical trends among children randomized to each treatment arm. Fluid infusion rate was classified as either fast or slow, and NaCl content was classified as either 0.90% or 0.45% NaCl according to randomization arm. Patients received a fluid bolus of 0.90% saline, with the amount of bolus fluid dictated by the randomization group. Fluid boluses could be repeated at the discretion of the clinician if additional boluses were felt to be clinically necessary. For all enrolled children, insulin was administered as an IV infusion at 0.1 units/kg/h. Potassium replacement was included in IV fluids after the initial fluid boluses. Combinations of potassium salts used for replacement varied somewhat among sites as a result of a shortage of potassium phosphate during the study period; however, analyses were stratified by site to account for this variability. Dextrose was added to the IV fluids when the serum glucose concentration was 200–300 mg/dL to maintain the serum glucose concentra-

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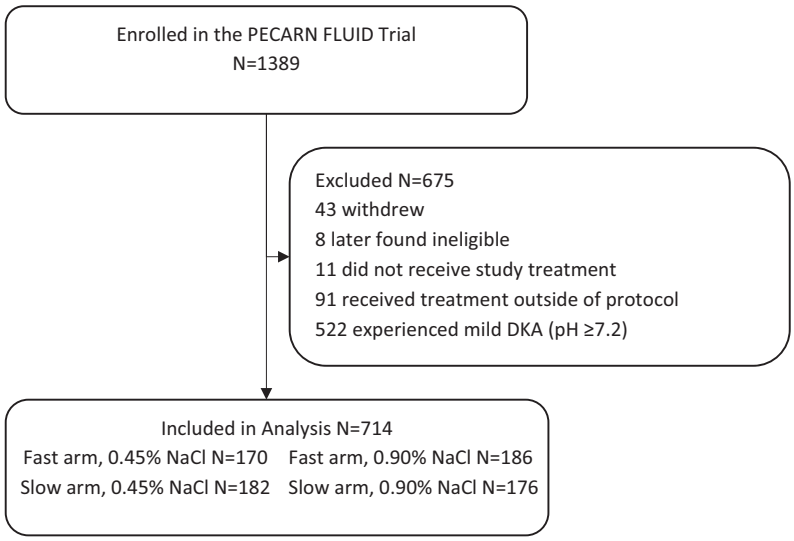

Figure 1—Study flow diagram.

tion between 100 and 200 mg/dL. A detailed description of patient enrollment can be found in the study flow diagram (Fig. 1). Primary outcomes included the rates of change in pH, P_{CO_2}, anion gap, glucose, glucose-corrected sodium, chloride, and potassium during treatment. Rates of change in biochemical measures were determined by calculating the differences between the initial laboratory values and the values measured 4- or 8-h after initiation of protocol-prescribed IV fluids (±1 h). This difference was divided by the time from DKA treatment initiation (typically the first study fluid bolus) until the time of the hour 4 or 8 laboratory measurements to determine the hourly rate of change. We used the first value measured within 60 min of DKA treatment initiation as the initial value. Data from complete electrolyte panels were used preferentially. Time to metabolic normalization in hours was determined for pH, P_{CO_2}, glucose, and anion gap. Those outcomes were calculated as the time from the initial laboratory measurement until the first normal value (pH $\geq$7.32; P_{CO_2} $\geq$38 torr; anion gap $<$12 mEq/L; glucose $\leq$200 mg/dL). Time of transition to subcutaneous insulin was used as a surrogate for normalization time if the above-listed laboratory values were not achieved by 8 h of treatment.

Secondary outcome measures included rates of adverse events related to changes in glucose and electrolytes. Hyperchloremic acidosis during DKA was defined as either an anion gap $\leq$12 mEq/L and low age-specific bicarbonate level (in mEq/L, $<$18 for age 1–3 years, $<$19 for 4–5 years, $<$20 for 6–7 years, $<$21 for $\geq$8 years) at any time between randomization and DKA resolution or a reported adverse event of hyperchloremic acidosis. Hypernatremia was defined as a glucose-corrected sodium level $>$155 mEq/L.

Statistical Analyses

We used the van Elteren test to analyze treatment differences for the following continuous outcomes: rate of change in pH, P_{CO_2}, anion gap, glucose, sodium, chloride, and potassium concentrations between treatment initiation and 4 or 8 h after treatment initiation as well as time to normalization of pH, P_{CO_2}, anion gap, and serum glucose concentration. We used the Mantel-Haenszel test to assess differences in rates of hyperchloremic acidosis and hypernatremia as well as frequency of administration of additional fluid boluses beyond that dictated by the study protocol. Statistical analyses were stratified by study hospital. For comparisons of fluid infusion rate, tests were further stratified by fluid NaCl content. For comparisons of fluid NaCl content, tests were further stratified by fluid infusion rate. Both linear regression and conditional logistic regression models were used to test for treatment interactions, adjusting for study hospital. Two-tailed tests with a significance level of 0.05 were used to evaluate outcomes for all treatment comparisons. No corrections were made for multiple comparisons. We conducted all analyses using SAS/STAT 9.4 statistical software (SAS Institute, Cary, NC).

RESULTS

Comparisons were based on 714 episodes of moderate or severe DKA among 667 study participants. Baseline demographic characteristics of participants and baseline laboratory values (Table 1) did not differ by treatment arm. Children in the slow infusion arms received more than the prescribed IV fluid bolus more often than those in the fast infusion arms ($P <$ 0.001).

The primary study outcomes by treatment assigned are compared in Table 2. We did not find significant differences in rates of change in pH among study arms. Increases in P_{CO_2} between treatment initiation and 4 h after treatment initiation were more rapid in children in the fast infusion arms compared with those in the slow infusion arms. However, rates of change in P_{CO_2} between treatment initiation and 8 h after treatment initiation were not significantly different among arms. Mean time to normalization of pH and P_{CO_2} also did not differ significantly among the arms (Table 2).

The rate of decrease in anion gap was more rapid in children treated with fast fluid infusion compared with those treated with slow fluid infusion at both 4 and 8 h after treatment initiation. There were no significant differences in rates of change in anion gap between the 0.90% and 0.45% NaCl arms. The mean time to normalization of anion gap was significantly shorter in children assigned to fast infusion arms compared with those assigned to slow infusion arms.

The rates of decline in glucose concentrations from treatment initiation to 4 and 8 h after treatment initiation were more rapid in children treated with slow fluid infusion compared with those treated with fast fluid infusion. In addition, the mean time from treatment initiation to glucose normalization was significantly shorter among children assigned to slow infusion arms compared with those assigned to fast infusion arms. Rates of change in glucose concentrations did not differ between the 0.45% and 0.90% NaCl arms. In a sensitivity analysis, we removed $\sim$6% of the study subjects who did not achieve glucose concentrations $<$200 mg/

Table 1—Demographic and baseline laboratory characteristics of the study participants

Characteristic	Treatment arm assigned				Overall (*N* = 714)
	Fast 0.45% (*n* = 170)	Fast 0.90% (*n* = 186)	Slow 0.45% (*n* = 182)	Slow 0.90% (*n* = 176)	
Age (years)	11.7 ± 4.1	12.3 ± 3.9	12.2 ± 3.8	12.1 ± 3.9	12.1 ± 3.9
Male sex	75 (44.1)	87 (46.8)	89 (48.9)	81 (46.0)	332 (46.5)
Race					
White	110 (64.7)	111 (59.7)	123 (67.6)	116 (65.9)	460 (64.4)
Black or African American	40 (23.5)	55 (29.6)	43 (23.6)	37 (21.0)	175 (24.5)
Multiracial	10 (5.9)	6 (3.2)	5 (2.7)	10 (5.7)	31 (4.3)
American Indian/Alaska Native	0 (0.0)	2 (1.1)	2 (1.1)	2 (1.1)	6 (0.8)
Asian	1 (0.6)	0 (0.0)	1 (0.5)	1 (0.6)	3 (0.4)
Native Hawaiian or other Pacific Islander	1 (0.6)	0 (0.0)	1 (0.5)	2 (1.1)	4 (0.6)
Unknown	8 (4.7)	12 (6.5)	7 (3.8)	8 (4.5)	35 (4.9)
Ethnicity					
Hispanic or Latino	26 (15.3)	36 (19.4)	26 (14.3)	36 (20.5)	124 (17.4)
Not Hispanic or Latino	138 (81.2)	142 (76.3)	150 (82.4)	135 (76.7)	565 (79.1)
Unknown	6 (3.5)	8 (4.3)	6 (3.3)	5 (2.8)	25 (3.5)
New-onset diabetes	72 (42.4)	77 (41.4)	77 (42.3)	69 (39.2)	295 (41.3)
pH	7.11 ± 0.07 (155)	7.10 ± 0.09 (168)	7.10 ± 0.08 (165)	7.09 ± 0.09 (163)	7.10 ± 0.08 (651)
P_{CO_2} (mmHg)	25.0 ± 7.6 (155)	25.8 ± 7.0 (168)	25.2 ± 7.7 (164)	26.1 ± 7.4 (161)	25.5 ± 7.4 (648)
Glucose (mg/dL)	541 ± 161 (167)	540 ± 165 (179)	525 ± 166 (177)	537 ± 163 (175)	536 ± 163 (698)
Glucose-corrected sodium (mEq/L)	142.8 ± 5.0 (165)	141.5 ± 5.6 (177)	142.0 ± 5.2 (170)	142.3 ± 6.0 (170)	142.1 ± 5.5 (682)
Chloride (mEq/L)	99.4 ± 5.7 (165)	98.2 ± 7.1 (171)	99.3 ± 5.4 (165)	99.5 ± 6.4 (171)	99.1 ± 6.2 (672)
Bicarbonate (mEq/L)	7.4 ± 2.8 (164)	7.3 ± 2.5 (175)	7.6 ± 3.2 (170)	7.4 ± 2.8 (168)	7.4 ± 2.8 (677)
Potassium (mEq/L)	4.9 ± 0.9 (166)	5.1 ± 1.2 (173)	5.1 ± 1.1 (169)	5.1 ± 1.1 (171)	5.0 ± 1.1 (679)

Data are mean ± SD or *n* (%). Number of DKA episodes with responses are shown for characteristics with item nonresponse. No differences by fast vs. slow or 0.45% vs. 0.90% NaCl were found.

dL prior to initiation of subcutaneous insulin. This analysis found similar results, with continued significant differences between treatment groups in glucose normalization.

Glucose-corrected sodium concentrations decreased gradually during the initial 4 and 8 h of treatment in children randomized to 0.45% NaCl infusion but did not change appreciably in those randomized to the 0.90% NaCl infusion arms. The rate of rehydration had a smaller effect on glucose-corrected sodium concentrations, but this effect was significant at the 8-h time point. Chloride concentrations increased and potassium concentrations decreased more rapidly in the 0.90% NaCl vs. 0.45% NaCl arms during both 4 and 8 h of treatment. Changes in concentrations of electrolytes and glucose during DKA treatment are presented in Fig. 2.

Secondary Outcome Measures (Adverse Effects)

Hyperchloremic acidosis developed in 164 of 356 (46.1%) children in the fast fluid infusion arms compared with 126 of 358 (35.2%) in the slow fluid infusion arms ($P = 0.002$). There was a smaller effect of NaCl concentration, with hyperchloremic acidosis developing in 157 of 362 (43.4%) children in the 0.90% NaCl arms vs. 133 of 352 (37.8%) in the 0.45% NaCl arms ($P = 0.06$). Rates of hypernatremia did not differ by treatment arm.

CONCLUSIONS

In this large randomized controlled trial of fluid treatment in pediatric DKA, we analyzed differences in the rates of correction of acidosis and normalization of electrolytes with variable fluid infusion rates and fluid NaCl concentrations. More rapid fluid administration led to more rapid increases in P_{CO_2} during the first 4 h of treatment and more rapid normalization of the anion gap, which occurred ∼2–3 h earlier in the fast fluid infusion arms. In contrast, pH did not normalize more rapidly with faster fluid infusion rates, possibly as a result of frequent development of hyperchloremic acidosis in the fast fluid infusion arms. We also observed modest effects of fluid infusion rate on changes in potassium and glucose-corrected sodium concentrations; however, these small differences were unlikely to be clinically relevant.

Our results demonstrate that ketoacidosis resolves more quickly with more rapid fluid infusion; however, hyperchloremic acidosis is also more frequent. Our findings are similar to results of an earlier very small trial in children with DKA (23) but contradict another report (22) that showed more rapid correction of bicarbonate levels and shorter hospital stay after receiving smaller amounts of IV fluids in adults treated for DKA.

We found, rather unexpectedly, that faster fluid administration led to a slower decline in glucose concentrations, after adjusting for potential confounders. The difference was small (∼3 mg/dL/h on average), with children in the slower infusion arms reaching a blood glucose concentration of ≤200 mg/dL on average 1 h earlier than those in the fast infusion arms. This minor effect may have been related to lower glucose load per hour in patients receiving dextrose-containing fluids at slower

Table 2—Primary outcomes by treatment assigned

	Treatment arm assigned				*P* value	
	Fast 0.45% (*n* = 170)	Fast 0.90% (*n* = 186)	Slow 0.45% (*n* = 182)	Slow 0.90% (*n* = 176)	Fast vs. slow	0.45% vs. 0.90%
4-h rate of change in pH (units/h)	0.02 ± 0.02 (87)	0.02 ± 0.01 (102)	0.02 ± 0.02 (84)	0.03 ± 0.02 (90)	0.26	0.73
8-h rate of change in pH (units/h)	0.02 ± 0.02 (79)	0.02 ± 0.01 (91)	0.02 ± 0.01 (79)	0.02 ± 0.02 (87)	0.13	0.98
Time from treatment initialization until pH reaches ≥7.32 (h)	15.5 ± 7.1 (170)	15.2 ± 6.5 (186)	15.7 ± 8.2 (182)	16.6 ± 8.3 (176)	0.24	0.60
4-h rate of change in P_{CO_2} (mmHg/h)	0.4 ± 1.2 (85)	0.6 ± 1.2 (102)	0.1 ± 1.3 (85)	−0.0 ± 1.5 (88)	**0.003**	0.33
8-h rate of change in P_{CO_2} (mmHg/h)	0.8 ± 1.3 (83)	0.7 ± 1.2 (89)	0.7 ± 0.9 (79)	0.7 ± 0.9 (84)	0.44	0.92
Time from treatment initialization until P_{CO_2} reaches ≥38 (h)	14.8 ± 7.6 (170)	14.9 ± 8.0 (186)	15.9 ± 8.3 (182)	16.0 ± 9.8 (176)	0.35	0.59
4-h rate of change in anion gap (mEq/L/h)	−2.2 ± 0.8 (128)	−2.5 ± 1.1 (116)	−2.0 ± 0.9 (120)	−2.0 ± 0.9 (109)	**<0.001**	0.06
8-h rate of change in anion gap (mEq/L/h)	−2.1 ± 0.7 (120)	−2.2 ± 1.1 (107)	−1.9 ± 0.7 (121)	−1.9 ± 0.9 (109)	**<0.001**	0.89
Time from treatment initialization until anion gap <12 (h)	14.8 ± 6.3 (170)	14.4 ± 7.2 (186)	16.7 ± 9.3 (182)	17.8 ± 11.9 (176)	**0.002**	0.40
4-h rate of change in glucose (mg/dL/h)	−51 ± 28 (116)	−57 ± 39 (119)	−57 ± 34 (120)	−59 ± 32 (111)	**0.02**	0.10
8-h rate of change in glucose (mg/dL/h)	−46 ± 42 (93)	−49 ± 43 (87)	−51 ± 38 (86)	−51 ± 39 (67)	**0.04**	0.36
Time from treatment initialization to glucose ≤200 mg/dL or subcutaneous insulin (h)	8.8 ± 5.3 (170)	8.2 ± 4.5 (186)	7.6 ± 4.8 (182)	7.1 ± 4.1 (176)	**0.003**	0.26
4-h rate of change in glucose-corrected sodium (mEq/L/h)	−0.5 ± 0.5 (140)	−0.0 ± 1.1 (137)	−0.3 ± 0.6 (135)	−0.1 ± 0.6 (123)	0.07	**<0.001**
8-h rate of change in glucose-corrected sodium (mEq/L/h)	−0.4 ± 0.4 (132)	−0.0 ± 1.0 (134)	−0.3 ± 0.5 (139)	−0.1 ± 0.6 (125)	**0.046**	**<0.001**
4-h rate of change in chloride (mEq/L/h)	1.7 ± 0.7 (137)	2.3 ± 1.0 (130)	1.7 ± 0.8 (126)	2.0 ± 0.8 (119)	0.32	**<0.001**
8-h rate of change in chloride (mEq/L/h)	1.2 ± 0.6 (126)	1.7 ± 0.8 (124)	1.2 ± 0.5 (130)	1.4 ± 0.5 (122)	0.37	**<0.001**
4-h rate of change in potassium (mEq/L/h)	−0.06 ± 0.12 (137)	−0.14 ± 0.18 (135)	−0.11 ± 0.18 (133)	−0.10 ± 0.21 (121)	0.15	**0.001**
8-h rate of change in potassium (mEq/L/h)	−0.07 ± 0.08 (132)	−0.12 ± 0.12 (131)	−0.10 ± 0.10 (137)	−0.12 ± 0.11 (126)	**0.04**	**<0.001**

Data are mean ± SD (*n*). Treatment interaction effects were present for rate of change in chloride at 4 h ($P = 0.02$) and 8 h ($P = 0.02$) as well as for 4-h rate of change in potassium ($P = 0.005$) according to linear regression models. *P* values reported are from Van Elteren test stratified by treatment and study hospital. Boldface type indicates significance at $P < 0.05$.

infusion rates while continuing to receive insulin at the same dosage as those receiving higher fluid infusion rates.

The choice of 0.45% vs. 0.90% NaCl solution as the rehydration fluid had a substantial effect on the rate of change in glucose-corrected sodium, chloride, and potassium concentrations. Children treated with 0.45% NaCl had declines in glucose-corrected sodium concentrations in contrast to those receiving 0.90% NaCl, whose average glucose-corrected sodium concentrations did not decrease during the 8-h observation period. These findings are similar to those reported in a previous small retrospective study (25). Chloride levels increased less in the 0.45% NaCl arms compared with the 0.90% NaCl arms, resulting in lower rates of hyperchloremic acidosis. Finally, potassium levels decreased less rapidly in the 0.45% NaCl arms. This effect was more substantial in children receiving fast fluid replacement rates, where a significant interaction between treatment effects

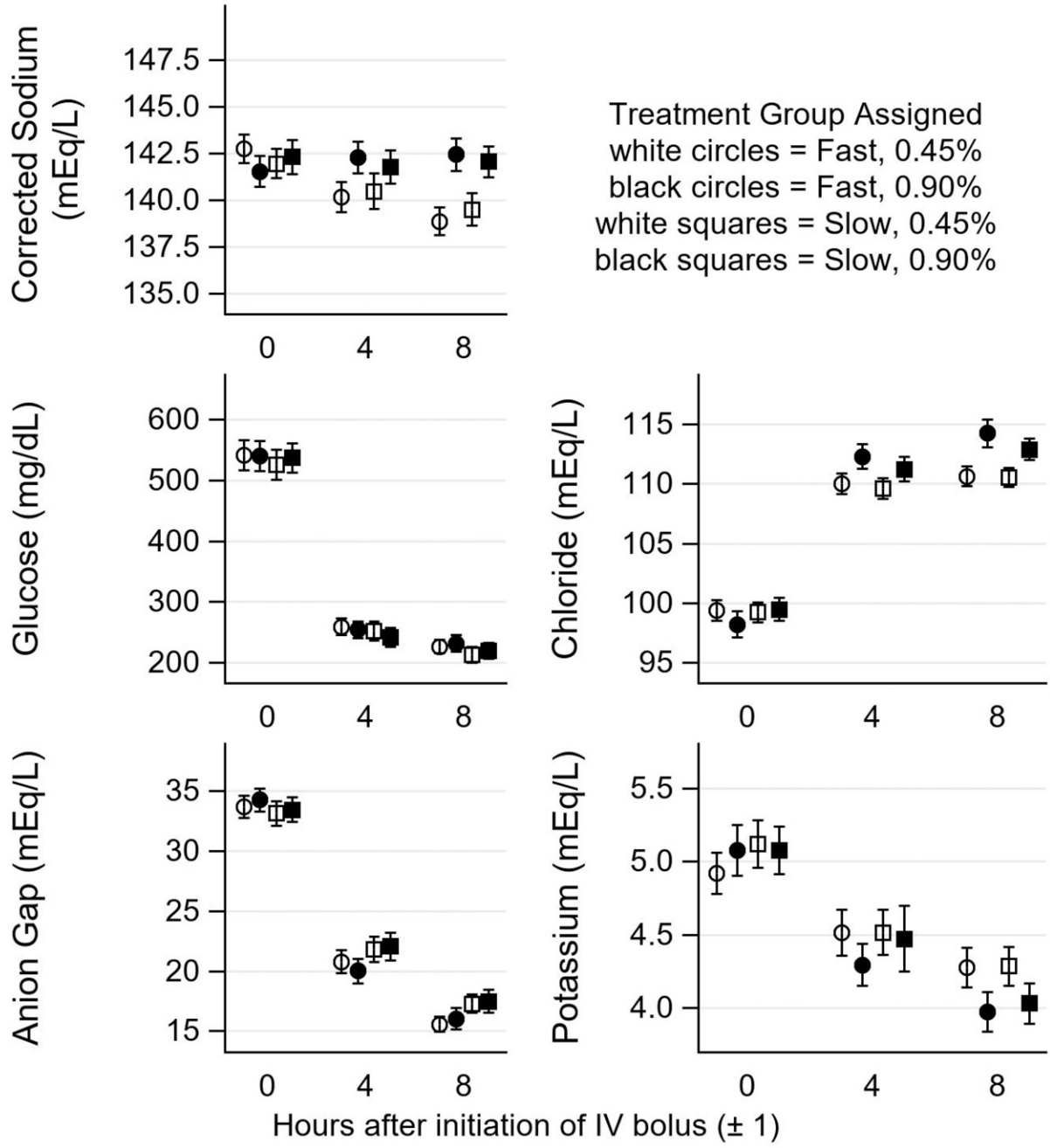

Figure 2—Changes in electrolyte and glucose concentrations during DKA treatment. Means and 95% CIs are shown by treatment group assigned.

was noted. These differences likely result from increased sodium delivery to the renal tubules, with more rapid infusion or higher sodium content fluids causing increased aldosterone-stimulated sodium reabsorption and potassium secretion.

Preferential renal excretion of ketones over chloride ions in DKA, in addition to infusion of large amounts of NaCl, may lead to hyperchloremic metabolic acidosis during treatment for DKA (25–27). Although hyperchloremic acidosis resolves spontaneously, this metabolic derangement may mask recognition of resolution of ketoacidosis when total base deficit or bicarbonate levels are used to monitor biochemical improvement (28,29). To avoid this misinterpretation, the International Society for Pediatric and Adolescent Diabetes guidelines recommend measurement of bedside β-hydroxybutyrate concentrations to monitor DKA resolution (21). In the current study, more rapid fluid administration resolved DKA more quickly (normalization of anion gap) but with an increased risk of hyperchloremia, especially if 0.90% NaCl was used. Potassium replacement in our study was given as an equal mixture of potassium chloride and potassium phosphate, which further increased the chloride load. The development of hyperchloremic acidosis could be mitigated by using 0.45% NaCl rather than 0.9% NaCl and by using potassium salts other than potassium chloride.

The current study was a post hoc analysis, and the results should therefore be interpreted with several limitations in mind. The generalizability of our results may be somewhat limited for patients at the extremes of the spectrum of pediatric DKA. We excluded a small subset of patients presenting with Glasgow Coma Scale scores ≤11. We also excluded patients with mild DKA. It is possible that results may have differed for these subsets of patients. In addition, the fluid infusion rates used in our study were selected to represent the upper and lower ends of DKA protocols used in the U.S. Results may differ for other protocols previously proposed for this patient population (30).

To our knowledge, this is the largest randomized clinical trial evaluating the effect of different fluids rates and sodium content on changes in electrolyte levels and metabolic normalization in children treated for DKA. We found that faster fluid administration normalized the anion gap 2–3 h earlier than slower fluid infusion rates. Previous analyses also demonstrated that faster fluid infusion rates were not associated with greater risk of mental status changes or clinical diagnoses of cerebral injury in the full study population and resulted in improved mental status during DKA treatment in some patient subgroups (20). Although more rapid fluid rates were associated with an increased frequency of hyperchloremic acidosis, this complication is generally benign and could be mitigated by using 0.45% NaCl and potassium salts other than potassium chloride for potassium replacement. In conclusion, on the basis of our findings, we recommend treating pediatric DKA using fluid infusion rates similar to the fast infusion rates used in this study.

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References

1. Rewers A, Dong F, Slover RH, Klingensmith GJ, Rewers M. Incidence of diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado youth, 1998-2012. JAMA 2015;313:1570–1572
2. Alonso GT, Coakley A, Pyle L, Manseau K, Thomas S, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes in Colorado children, 2010-2017. Diabetes Care 2020;43:117–121
3. Jensen ET, Stafford JM, D'Agostino RB Jr., et al. Rapid increase in prevalence of DKA at diagnosis among youth with type 1 diabetes: the SEARCH for Diabetes in Youth study. Oral presentation at the 55th European Association for the Study of Diabetes Annual Meeting, 16–20 September 2019, Barcelona, Spain
4. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. JAMA 2002;287:2511–2518
5. Cengiz E, Xing D, Wong JC, et al.; T1D Exchange Clinic Network. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes 2013;14:447–454
6. Maahs DM, Hermann JM, Holman N, et al.; National Paediatric Diabetes Audit and the Royal College of Paediatrics and Child Health, the DPV Initiative, and the T1D Exchange Clinic Network. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care 2015;38:1876–1882
7. Glaser N, Barnett P, McCaslin I, et al.; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk factors for cerebral edema in children with diabetic ketoacidosis. N Engl J Med 2001;344:264–269
8. Edge JA, Jakes RW, Roy Y, et al. The UK case-control study of cerebral oedema complicating diabetic ketoacidosis in children. Diabetologia 2006;49:2002–2009
9. Patel A, Singh D, Bhatt P, Thakkar B, Akingbola OA, Srivastav SK. Incidence, trends, and outcomes of cerebral edema among children with diabetic ketoacidosis in the United States. Clin Pediatr (Phila) 2016;55:943–951
10. Ghetti S, Lee JK, Sims CE, Demaster DM, Glaser NS. Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes. J Pediatr 2010;156:109–114
11. Cameron FJ, Scratch SE, Nadebaum C, et al.; DKA Brain Injury Study Group. Neurological consequences of diabetic ketoacidosis at initial presentation of type 1 diabetes in a prospective cohort study of children. Diabetes Care 2014;37:1554–1562
12. Semenkovich K, Bischoff A, Doty T, et al. Clinical presentation and memory function in youth with type 1 diabetes. Pediatr Diabetes 2016;17:492–499
13. Aye T, Mazaika PK, Mauras N, et al.; Diabetes Research in Children Network (DirecNet) Study

Group. Impact of early diabetic ketoacidosis on the developing brain. Diabetes Care 2019;42:443–449
14. Ghetti S, Kuppermann N, Rewers A, et al.; Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study Group. Cognitive function following diabetic ketoacidosis in children with new-onset or previously diagnosed type 1 diabetes. Diabetes Care 2020;43:2768–2775
15. Fredheim S, Johannesen J, Johansen A, et al.; Danish Society for Diabetes in Childhood and Adolescence. Diabetic ketoacidosis at the onset of type 1 diabetes is associated with future HbA1c levels. Diabetologia 2013;56:995–1003
16. Duca LM, Wang B, Rewers M, Rewers A. Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control. Diabetes Care 2017;40:1249–1255
17. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988;113:10–14
18. Harris GD, Fiordalisi I, Harris WL, Mosovich LL, Finberg L. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. J Pediatr 1990;117:22–31
19. White PC. Optimizing fluid management of diabetic ketoacidosis. Pediatr Diabetes 2015;16:317–319
20. Kuppermann N, Ghetti S, Schunk JE, et al.; PECARN DKA FLUID Study Group. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. N Engl J Med 2018;378:2275–2287
21. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19(Suppl. 27):155–177
22. Adrogué HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use in patients without extreme volume deficit. JAMA 1989;262:2108–2113
23. Bakes K, Haukoos JS, Deakyne SJ, et al. Effect of volume of fluid resuscitation on metabolic normalization in children presenting in diabetic ketoacidosis: a randomized controlled trial. J Emerg Med 2016;50:551–559
24. Glaser NS, Ghetti S, Casper TC, Dean JM; Pediatric Emergency Care Applied Research Network (PECARN) DKA FLUID Study Group. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. Pediatr Diabetes 2013;14:435–446
25. Basnet S, Venepalli PK, Andoh J, Verhulst S, Koirala J. Effect of normal saline and half normal saline on serum electrolytes during recovery phase of diabetic ketoacidosis. J Intensive Care Med 2014;29:38–42
26. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. Nephron 1990;54:1–6
27. Adrogué HJ, Wilson H, Boyd AE 3rd, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982;307:1603–1610
28. Taylor D, Durward A, Tibby SM, et al. The influence of hyperchloraemia on acid base interpretation in diabetic ketoacidosis. Intensive Care Med 2006;32:295–301
29. von Oettingen JE, Rhodes ET, Wolfsdorf JI. Resolution of ketoacidosis in children with new onset diabetes: evaluation of various definitions. Diabetes Res Clin Pract 2018;135:76–84
30. White PC, Dickson BA. Low morbidity and mortality in children with diabetic ketoacidosis treated with isotonic fluids. J Pediatr 2013;163:761–766