Kuppermann 2018

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Bibliographic Reference	Kuppermann, Nathan; Ghetti, Simona; Schunk, Jeff E; Stoner, Michael J; Rewers, Arleta; McManemy, Julie K; Myers, Sage R; Nigrovic, Lise E; Garro, Aris; Brown, Kathleen M; Quayle, Kimberly S; Trainor, Jennifer L; Tzimenatos, Leah; Bennett, Jonathan E; DePiero, Andrew D; Kwok, Maria Y; Perry, Clinton S 3rd; Olsen, Cody S; Casper, T Charles; Dean, J Michael; Glaser, Nicole S; PECARN DKA FLUID Study, Group; Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis.; The New England journal of medicine; 2018; vol. 378 (no. 24); 2275-2287

Study details

Study type	**Randomised controlled trial (RCT)** **2-by-2 factorial design**
Study location	USA
Study setting	13 emergency departments
Study dates	February 2011 through September 2016
Duration of follow-up	Glasgow Coma Scale scores were assessed at enrolment and hourly thereafter. Glasgow Coma Scale scores of less than 14 were confirmed by repeating the test 15 minutes later. For children 3 years of age or older, digit-span tests were conducted at enrolment and every 4 hours thereafter during normal waking hours. Glasgow Coma Scale and digit-span assessments continued for 24 hours or until resolution of diabetic ketoacidosis (as defined by the transition to subcutaneous insulin) if diabetic ketoacidosis resolved before the 24-hour time point. Patients 3 to 18 years of age were asked to return 2 to 4 months after discharge from the hospital for neurocognitive assessment but were allowed to return up to 6 months after discharge.
Sources of funding	Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grant U01HD062417) and the Emergency Medical Services for Children Network Development Demonstration Program of the Maternal and Child Health Bureau, Health Resources and Services Administration, under cooperative agreement
Inclusion criteria	Children aged between 0 and 18 years of age and had a diagnosis of diabetic ketoacidosis
Exclusion criteria	underlying disorders that could affect mental status testing or neurocognitive evaluation; concurrent alcohol or narcotics use, head trauma, or other conditions that could affect neurologic function; diabetic ketoacidosis for which the patient had already received substantial treatment; known pregnancy; or factors for which treating physicians determined that a specific fluid and electrolyte therapy was necessary. Children who presented with a Glasgow Coma Scale score of 11 or lower (on a scale ranging from 3 to 15, with lower scores indicating worse mental status) were excluded after year 2 because many participating clinicians believed that fluid regimens for such children should not be determined on the basis of randomization.
Sample size	1389 participants
Condition specific characteristics	Ketoacidosis defined as a blood glucose level of >300 mg per deciliter [16.7 mmol per liter] and either a venous pH of <7.25 or a serum bicarbonate level of <15 mmol per liter)
Interventions	**Fast administration of 0.45% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter).

Study type	**Randomised controlled trial (RCT)** **2-by-2 factorial design**
	Additional intravenous fluid bolus: 10 ml per kilogram of 0.9% sodium chloride solution **Assumed deficit:** 10% of body weight. **Process of replacement of deficit:** During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours. **Fluid used for replacement of deficit:** 0.45% sodium chloride solution. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites. **Slow administration of 0.45% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter). **Additional intravenous fluid bolus:** No additional bolus. **Assumed deficit:** 5% of body weight. **Process of replacement of deficit:** Replace deficit, plus maintenance fluids, evenly during a period of 48 hours. **Fluid used for replacement of deficit:** 0.45% sodium chloride solution. Replacement of potassium was provided with the use of an equal mixture of potassium chloride and potassium phosphate or an equal mixture of potassium acetate and potassium phosphate. Potassium salts used for replacement were identical among the groups at each site but varied among the trial sites. **Fast administration of 0.9% sodium chloride** **Standard initial bolus:** 10 ml per kilogram bolus of 0.9% sodium chloride solution. Initial fluid bolus volumes were subtracted from the fluid deficit that was used to calculate the rate of fluid replacement. Fluid boluses could be repeated at the discretion of the treating physician to restore peripheral perfusion and hemodynamic stability. Insulin treatment was initiated after the initial intravenous fluid boluses as a continuous intravenous infusion at a rate of 0.1 U per kilogram of body weight per hour. Dextrose was added to the intravenous fluids when the serum glucose level declined to below 200 to 300 mg per deciliter (11.1 to 16.7 mmol per liter) to maintain the serum glucose level between 100 and 200 mg per deciliter (5.6 to 11.1 mmol per liter). **Additional intravenous fluid bolus:** 10 ml per kilogram of 0.9% sodium chloride solution. **Assumed deficit:** 10% of body weight. **Process of replacement of deficit:** During the initial 12 hours, replace half the fluid deficit, plus maintenance fluids. Then replace remaining deficit, plus maintenance fluids, during the subsequent 24 hours.

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Outcome measures	**Confirmed decline in Glasgow Come Scale Score** as evidenced by two consecutive Glasgow Coma Scale scores of <14 during any hour within the first 24 hours of treatment for diabetic ketoacidosis **Clinically apparent brain injury** defined as a deterioration in neurologic status leading to initiation of hyperosmolar therapy or endotracheal intubation or resulting in death **IQ** IQ was evaluated with the use of the Wechsler Abbreviated Scale of Intelligence (in patients 6 years of age or older) and the Wechsler Preschool and Primary Scale of Intelligence short form (in patients 3 to 5 years of age) **Renal failure** **Death** **Time to DKA resolution** time from randomisation until transition to subcutaneous insulin administration if within 24 hours; time until anion gap ≤ 12 if transition to SC was after 24 hours; time until transition to SC insulin in anion gap ≤12 not documented **Time to hospital discharge (hours)**

Study arms

Fast administration of 0.45% sodium chloride solution (N = 344)
Slow administration of 0.45% sodium chloride solution (N = 345)
Fast administration of 0.9% sodium chloride solution (N = 351)
Slow administration of 0.9% sodium chloride solution (N = 349)

Characteristics

Arm-level characteristics

	Fast administration of 0.45% sodium chloride solution (N = 344)	Slow administration of 0.45% sodium chloride solution (N = 345)	Fast administration of 0.9% sodium chloride solution (N = 351)	Slow administration of 0.9% sodium chloride solution (N = 349)
Age (years)	11.5 (4.06)	11.6 (4.09)	11.8 (4.26)	11.6 (3.89)
Mean/SD				
Age < 6 years	n = 43; % = 12.5	n = 42; % = 12.2	n = 42; % = 12	n = 35; % = 10
No of events				
% Female	n = 179; % = 52	n = 187; % = 54.2	n = 187; % = 53.3	n = 186; % = 53.3
No of events				
Previous diagnosis of diabetes	n = 174; % = 50.6	n = 185; % = 53.6	n = 182; % = 51.9	n = 192; % = 55
No of events				

Cochrane risk of bias tool 2.0 (RoB 2.0)		
Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Cochrane risk of bias tool 2.0 (RoB 2.0)		
intended interventions (effect of assignment to intervention)		
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
	Overall Directness	Directly applicable For all other outcomes Indirectly applicable (Outcome brain injury not specified in review protocol but the authors hypothesised that rapid administration of IV fluids results in brain injury.)