Management of Pediatric Diabetic Ketoacidosis – a Comparison between a Conventional Protocol and a Novel Osmolality Control Protocol

Running title: Comparison of two pediatric DKA protocols

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Abstract

Background: Diabetic ketoacidosis (DKA) is conventionally treated using a single line for administration of ready-made dextrose and saline solutions for rehydration. For some patients this results in poor control of plasma glucose, sodium, and effective osmolality.

Objective: Management of pediatric DKA requires close monitoring and frequent titration of fluids, electrolytes, and dextrose. Because there is no consensus on the safest DKA protocol, treatment is challenging. We developed a novel treatment protocol for DKA that allows precise titration of dextrose and of the plasma sodium concentration and fluid volume by adjusting the infusion rates of three separate lines.

Methods: We conducted a retrospective single-center study of 60 consecutive pediatric DKA patients (age 7 months to 16 years) treated in a tertiary hospital in Turku, Finland. The first 26 patients were treated with the conventional and the following 34 patients with the novel protocol. We collected and analyzed clinical and laboratory data, timing of medical interventions and clinical outcomes from the electronic patient record system.

Results: Plasma effective osmolality remained more stable when the patient was treated according to the novel protocol than the conventional protocol ($p < 0.001$) and plasma sodium levels were higher ($p = 0.018$). Recovery from acidosis was also faster. Two patients on the conventional protocol needed intracranial pressure monitoring and ventilator support, none on the novel protocol. There were no deaths in either protocol.

Conclusions: Our novel protocol allows more precise control of the effective plasma osmolality and appears to be as safe as the conventional protocol.

Keywords: pediatric, children, diabetes, diabetic ketoacidosis

Introduction

The incidence of type 1 diabetes among children aged 0–14 years in Finland is 57.6/100.000 – highest in the world (2). Most alarmingly, the incidence is increasing globally, especially among the youngest children, those aged 0–4 years (3–5). For children, diabetic ketoacidosis (DKA) is more detrimental than for adults (6). Mortality among children with DKA is 0.15–0.3%, but if DKA-associated cerebral edema (CE) is present, mortality rises to 20–25% (7). Since the subdural space of children is narrower than of adults, the osmolytic balance in plasma needs to be controlled stringently during rehydration (8). Also, other autoregulatory mechanisms are not as well developed in children as in adults (7).

Management of DKA requires close monitoring and frequent titration not only of the fluid replacement therapy, but also of the administration of electrolytes and dextrose. DKA is treated by rehydration and, to normalize hyperglycemia, with insulin. However, the timing of treatment and the composition of the rehydration solutions is controversial (9,10). The consensus guidelines of the International Society for Pediatric and Adolescent Diabetes (ISPAD) (11) recommend to initiate dextrose infusion, when plasma glucose falls to approximately 14-17 mmol/L or sooner if the rate of fall is very rapid. Furthermore, use of 5-12.5% dextrose may be necessary to prevent hypoglycemia. Still, the range of fluid administration is wide, which leaves patient-specific guidance ambiguous.

ISPAD acknowledge that the plasma sodium concentration should increase throughout treatment for DKA. The sodium concentration of the rehydration solution seems to be an independent factor influencing plasma sodium levels and, hence, the effective osmolality of the plasma (12). Previous results suggest that keeping the

effective osmolality stable is one of the most important factors affecting patient outcome (13,14). Young age, new-onset diabetes and a prolonged duration of symptoms have been associated with CE. Also a small, rather than a swift, increase in the plasma sodium concentration during therapy and treatment included administration of bicarbonate solution has been correlated with a higher incidence of CE (11). Furthermore, mortality is lower when patients with DKA are treated with isotonic instead of hypotonic solutions (12)(15).

Many hospitals have their own treatment practices for DKA, which makes it difficult to compare the outcomes of DKA treatment across institutions and countries. Since there is no consensus on the safest DKA protocol, treatment is challenging.

We conducted a retrospective study to evaluate the conventional one-line protocol traditionally used in Turku University Hospital to our novel protocol consisting of separate infusions of concentrated 50% dextrose, a balanced electrolyte solution, hypertonic 3% saline and insulin. We hypothesized that meticulous titration of dextrose, sodium and fluid volume by adjusting the infusion rates separately improves patient outcome by better maintenance of the stability of the effective plasma osmolality. Our aim was also to implement a more adaptable and flexible tool for maintaining effective plasma osmolality. The primary outcome measure was effective plasma osmolality and the secondary outcome measures were duration of acidosis, plasma sodium, potassium, chloride and glucose levels, volume of replacement therapy and neurological status of the patient.

Methods

Patients

This retrospective study included all patients younger than 16 years who were admitted because of DKA and were treated between January 1, 2013 and December 31, 2017 in the pediatric intensive care unit (PICU) at the Turku University Hospital, Turku, Finland. Patients were identified consecutively from our electronic patient record system (Centricity Critical Care Clinisoft 8.0, GE Electronics, Helsinki, Finland) and Uranus (CGI, Montreal, Canada) by the ICD-10 code E10.1 (type 1 diabetes mellitus with ketoacidosis). We included the patients who fulfilled the criteria for DKA by the ISPAD guidelines 2018: hyperglycemia (glucose >11mmol/L [>250 mg/dL]), venous pH <7.30 or serum bicarbonate <15 mmol/L, and ketonemia (blood β-hydroxybutyrate ≥3 mmol/L) or moderate or severe ketonuria. Mild, moderate and severe DKA were defined as pH <7.3 or HCO3 <15 mmol/L, pH <7.2 or HCO3 <10, and pH <7.1 or HCO3 <5 mmol/L, respectively (11).

All patients who were diagnosed with DKA were transferred immediately from the emergency room to the PICU and treatment started immediately with the DKA protocol used at that time. Throughout the study, patients were treated by the same physicians, nurses, pediatric intensive care specialists and endocrinologist consultants in the PICU.

Recorded data

Age, height and weight of the patients were collected from the electronic patient records. The total amount of insulin, fluids, dextrose, sodium, potassium and chloride administered during DKA treatment in the PICU were recorded, as were clinical data, timing of medical therapies and clinical outcomes.

Appropriate analyses of pH, bicarbonate, base excess, glucose, sodium, potassium and chloride were made with blood gas analyzer (ABL800 FLEX, Radiometer Medical ApS, Brønshøj, Denmark) and recorded in the patient records from which they were transferred for analysis of the data for this report. Both the laboratory measures and point of care tests were included in our analyses. The effective plasma osmolality (P_{Osmol}) was calculated from plasma glucose (P_{Gluc}) and sodium (P_{Na}) levels using the equation: $P_{Osmol} = P_{Gluc} + 2 \times P_{Na}$. The following clinical data were also recorded: somnolence, nausea, headache, pediatric Glasgow Coma Scale (pGCS) score, cerebral edema, need for intracranial pressure measurement and ventilation therapy.

Treatment protocols

Both protocols were based on common guidelines and instructions by ISPAD (10). The aim of both protocols was to maintain effective plasma osmolality stable during the first 18 hours of treatment while steadily correcting dehydration, acidosis, plasma glucose and electrolyte levels. In both protocols, a glucose decrease of no more than 3 mmol/L/h was considered optimal and glucose was not allowed to decrease under a concentration of 10 mmol/L before ketosis was resolved.

The conventional treatment protocol (Protocol 1, Group 1) follows the practice of using multiple ready-made dextrose and saline solutions to achieve an optimal total solution concentration (Figure 1). We used 5% dextrose with 0.9% saline and 0–60 mmol/L potassium replacement in Protocol 1, depending on plasma potassium levels. Insulin was administered intravenously at a rate of 0.075–0.1 IU/kg/h. If plasma sodium decreased concomitantly with plasma glucose, causing a sharp decrease in effective osmolality and patient showed symptoms of CE, hypertonic 3%

saline infusion was administered at a rate of 0.1–1 mL/kg/h as judged by the responsible physician.

Protocol 2 (Group 2) is a novel protocol developed at our institution. It is based on three separate infusions: 50% dextrose, a balanced electrolyte solution (BES, Plasma-Lyte 148®, Baxter, Deerfield, IL, USA) and hypertonic 3% saline, each adjusted individually through separate infusion pumps (Figure 1). An insulin infusion (0.05 IU/kg/h) was started at the same time. 50% dextrose, infused together with BES, was started at a low infusion rate to give the total concentration of 3.3% dextrose. The infusion rate of dextrose was adjusted to the rate of plasma glucose decline; e.g. in case of undesirably rapid glucose decrease, dextrose infusion rate was increased according to guidelines set by our institution. Because 50% dextrose is highly hyperosmolar, it was always infused alongside BES. Also, a safety protocol was followed where all infusions were stopped during the time the infusions were adjusted. Hypertonic 3% saline was infused only if the plasma sodium level did not rise sufficiently during treatment to maintain effective osmolality. In practice, the sodium concentration of the overall infusion was initially raised from 131 to at least 154 mmol/L initially, but if necessary, even higher. Potassium phosphate was added to the BES at a standard concentration of 35 mmol/L after initial resuscitation to meet the need of potassium and phosphate. Appropriate rates of the infused fluids were documented in a spreadsheet program (written by the authors; Excel 2013, Windows, Microsoft, U.S), which visualized the contents of each fluid used. The goal of this protocol was to maintain effective plasma osmolality constant during the first 12–18 hours after which it was slowly allowed to decrease.

Rehydration

Fluid resuscitation of the patient was started with 360 mL/m^2/30 min under the assumption that the patients were 7% dehydrated. If the patient still was after the first fluid resuscitation hemodynamically unstable, the resuscitation was repeated in both protocols. The resuscitation fluid was 0.9% saline in Protocol 1 and BES in Protocol 2. The rate of the fluid replacement during rehydration in both protocols was kept constant during the first two 6-hour periods after treatment start (during the first 6-hour period the infusion rate was 1800 mL/m^2 and during the second 6-hour period 900 mL/m^2). During the third and fourth 6-hour periods the infusion rate was 480 in Protocol 1 and 600 mL/m^2 in Protocol 2, respectively. If a patient needed all four 6-hour treatment periods, the total infused volume was 4020 and 4260 mL/m^2/24 h in Protocols 1 and 2, respectively.

In both protocols, fluid loss via diuresis was replaced only when excessive diuresis resulted in a negative fluid balance and slow correction of acidosis. Polyuria was compensated with 5% dextrose and added electrolytes based on the urine analysis in Protocol 1 and with BES in Protocol 2.

Statistical analyses

The sample size was based on previous experience in similar retrospective studies. The primary outcome measure was effective osmolality at 18 hours after the start of treatment. Secondary outcome measures were duration of acidosis, plasma sodium, potassium, chloride and glucose levels, the amount of insulin and crystalloids infused and neurological status. Data were evaluated for normality of distribution using probit plots and Shapiro-Wilk's W-test. The data was analyzed first as one group for descriptive statistics, after which the patients were allocated into two treatment

groups based on the DKA treatment protocol to analyze the effect of treatment protocol. Continuous variables were compared with one-way ANOVA, while categorical data was compared with the Kruskal-Wallis test. Data were log-transformed prior to ANOVA analysis, but non-transformed results are reported. Levene's test for homogeneity of variances was used prior to ANOVA. The results are expressed as mean values and SD, except for categorical and time-related parameters that are reported as medians and interquartile range (IQR). The statistical significance level was set at $p < 0.05$. R software (version 3.6.1) (16) and ggplot2 (version 3.3.2)(17) were applied for statistical analysis and graphics.

Results

There were no differences between the Groups 1 and 2 in demographic data nor baseline laboratory values (Table 1). The evolution of primary and secondary outcome measures and controllability of effective plasma osmolality is shown in Figure 2. The laboratory measures showing the correction of acidosis (BE, HCO3 and pH) are shown in Figure 3. The amounts of infused fluids, electrolytes and insulin are shown in Table 2 and in Figure 4.

Patients

The total number of patients who fulfilled the entry criteria over the five-year period 2013–2017 was 60. There were 26 consecutive patients in Group 1 and 34 in Group 2. DKA was mild in 12 (40%), moderate in nine (30%) and severe in nine (30%) patients in Group 1, whereas DKA was mild in 17 (57%), moderate in eight (27%), and severe in five (17%) patients in Group 2.

Controllability of effective plasma osmolality

In Group 1, the ***effective plasma osmolality*** (mean and SD) decreased from a mean baseline value of 294 mosm/L (11.3) to 291 mosm/L (6.24) in 6 hours and to 288 mosm/L (6.81) in 12 hours. In Group 2, the corresponding figures were 295 mosm/L (11.9), 294 mosm/L (11.9) and 296 mosm/L (11.6).

In Group 1, the average (SD) ***plasma sodium*** was 134 (5.4) mmol/L at baseline, 137 mmol/L (2.84) at 6 hours and 138 mmol/L (3.35) at 12 hours. In Group 2, the corresponding values were 135 mmol/L (4.46), 138 mmol/L (3.79) and 140 mmol/L (4.18).

The mean (SD) ***plasma glucose*** decreased in Group 1 from a baseline value of 24.3 mmol/L (6.32) to 17.8 mmol/L (5.63) in 6 hours and 13.7 mmol/L (6.0) in 12 hours. In Group 2 the corresponding values were 23.3 mmol/L (6.32), 18.0 mmol/L (5.63) and 15.6 mmol/L (6.0) (Figure 3).

In Group 2, plasma sodium and osmolality levels remained significantly higher throughout the treatment period than in Group 1 ($p = 0.018$ and $p < 0.001$, respectively). During the treatment, plasma glucose decreased less from baseline and exhibited less dispersion of values during the first 24 hours in Group 2 than in Group 1 (Figure 2).

Resolution of acidosis

In Group 1, ***plasma bicarbonate*** increased from a mean (SD) baseline value of 13.1 mmol/L (3.78) to 16.7 mmol/L (3.98) in 6 hours and to 19.2 mmol/L (2.99) in 12 hours. In Group 2, the corresponding values were 11.7 mmol/L (3.31), 19.5 mmol/L (3.57) and 21.9 mmol/L (2.39), at 0, 6 and 12 hours, respectively. In Group 1, the ***base excess*** (BE) changed from a mean (SD) baseline value of -15.9 (13.9) to -9.8 (6.11) in 6 hours and to -6.46 (4.11) in 12 hours. In Group 2, BE the corresponding values were -17.3 (5.16), -6.25 (4.33) and -3.15 (3.76).

In Group 1, ***pH*** changed from a mean (SD) baseline value of 7.20 (0.11) to 7.29 (0.06) in 6 hours and 7.34 (0.43) and 12 hours. In Group 2, the corresponding values were 7.18 (0.12), 7.35 (0.06) and 7.38 (0.04) (Figure 3). One patient in Group 1 received sodium bicarbonate to treat acidosis, but in Group 2 no one needed it.

Total amounts of fluids and dextrose infused

Table 2 sums and Figure 4 shows the total amount of therapeutics administered to the patients. In Group 2 the patients were infused 39% less insulin during the

treatment period than in Group 1 (1.6 vs 0.9 IU/kg, 95% CI –1.028 to -0.256 IU/kg, p = 0.003).

The total amount of fluids infused did not differ significantly between the two groups. In Group 1 and Group 2, a mean (SD) of 147 (131) and 141 (79) mL/kg of fluids was infused during treatment, respectively. The average total amount of fluids was 4128.00 and 4073.50 mL in Group 1 and Group 2, respectively (p = 0.773).

The level of acidosis affected the administered fluid volume. The patients in Group 1 and Group 2 received on average 104.2 vs 127.5 mL/kg of fluids in mild, 162.6 vs 133.3 mL/kg in moderate and 188.7 vs 173.3 mL/kg in severe acidosis, respectively. Due to the small sample size, statistical inference was not assessed. The total amount of dextrose administered did not differ between the groups. On average, the patients in Group 1 received 8.9 (11.9) g/kg of dextrose and the patients in Group 2 received 7.4 (5.5) g/kg (p = 0.807).

Total amounts of electrolytes infused

The average (SD) amount of infused sodium was 15.7 (11.7) mmol/kg in Group 1 and 18.3 (9.7) mmol/kg in Group 2 (p = 0.033). The mean amount of potassium was 4.5 (4.5) and 5.0 (5.1) mmol/kg and that of chloride 15.5 (11.2) and 15.3 (10.1) mmol/kg in Group 1 and 2, respectively. The amount of potassium and chloride administered did not differ between the groups (p = 0.589 and 0.971, respectively).

Clinical outcome

All patients recovered from the DKA. Two patients in Group 1 needed ventilator support due to worsening of neurological symptoms. The intracranial pressure of these two patients was also monitored, and the intracranial pressure of one of them was high (44 mmHg, reference <15 mmHg). In Group 2 intracranial pressure

monitoring was not needed in any of the patients and neurological symptoms, when present, were mild. One patient in Group 2 was sedated with dexmedetomidine to treat anxiety. Plasma creatinine was monitored only once at the beginning of treatment, but based on urinary output, none of the patients in either group had acute kidney injury.

Conclusions

We conducted a retrospective study of 60 consecutive pediatric patients treated at our hospital to compare two protocols used to treat DKA. Our main interest was to study the controllability of effective osmolality, but we were also interested in whether there was a difference between the time it takes for acidosis to resolve and safety matters. We have experienced previously that we need new tools to keep plasma osmolality steady during the treatment. We hypothesized that more precise titration of dextrose, sodium, and fluid volume by adjusting the infusion rates separately could improve outcomes by providing more stability to the level of effective plasma osmolality. 2-line and 3-line methods have been previously described in the literature (18) (19), but this is the first time, to our knowledge, that all properties of the infusions used to treat DKA are adjusted individually and precisely as desired. Patient-specific needs may vary widely during treatment. To achieve an accurate concentration, we used a spreadsheet pre-programmed with the contents of the solutions to evaluate the effects of any changes we made to the concentrations of the infusion solutions. The use of a more concentrated dextrose solution (50%) made it easier to control and modify the concentration of the infused electrolytes.

Effective osmolality was maintained stable during the first 12 hours after treatment start with the novel protocol (Protocol 2), but this was not the case with the conventional protocol (Protocol 1) where the effective osmolality decreased steadily. Protocol 2 resulted in better control of the effective plasma osmolality than Protocol 1 (Figure 2 and 3). It has been suggested that effective osmolality should remain stable for approximately 15 hours from the start of treatment and then slowly decline (14). If the effective osmolality is to remain unchanged, the factors affecting it, i.e., changes in plasma glucose and sodium, must be controlled carefully.

During treatment, the plasma glucose decreased more gradually on Protocol 2 than Protocol 1, and there was less dispersion in the glucose concentration. Without dextrose, plasma glucose levels fell steeply during the insulin infusion and this resulted in unstable effective plasma osmolality levels in Protocol 1. In both protocols, we used dextrose-containing infusions to manage the decrements in plasma glucose concentrations. The amount of dextrose in Protocol 2 could be fine-tuned to match the desired decrement rate of the plasma glucose concentration, but in Protocol 1 the amount of dextrose was bound to the concentrations of the ready-made dextrose solutions and did not fully meet the need for dextrose.

In Protocol 2, a hypertonic 3% saline infusion was added to the treatment of the patients whose sodium levels did not rise sufficiently. With hypertonic saline infusion, the aim was to increase the plasma sodium concentration of the overall fluid infusion from 131 to 154 mmol/L or even higher. This technique was usually effective for controlling sodium levels, and, by the end of treatment, plasma sodium levels were significantly higher on Protocol 2 than Protocol 1. In a previous study (12), a too modest increase in the plasma sodium concentration reduces osmolality and CE symptoms emerge concomitantly with reduced plasma glucose concentrations. On Protocol 2, we recorded no signs of elevated intracranial pressure, but on Protocol 1 two patients showed signs of increased intracranial pressure and required invasive intracranial pressure monitoring. None of the patients died.

Acidosis was corrected significantly faster on Protocol 2 than Protocol 1: the median time for resolution of acidosis was 6 hours and 12 hours, respectively. On Protocol 2 the insulin infusion rate (usually 0.05 IU/kg/h) was lower than on Protocol 1 (0.1 IU/kg/h), and thus ketone elimination does not explain the difference in the time to acidosis correction. Nor is faster recovery of lactate levels during rehydration

probable, since the total amount of fluids infused did not differ between the groups. The amount of chloride in the fluids used in the protocols was the same, but the buffers (acetate, gluconate, and lactate) metabolized to bicarbonate were not: saline in Protocol 1, BES in Protocol 2. Thus, BES might correct pH faster than chloride-based fluids. This is, however, inconsistent with the results of the SPinK trial (20), where the time to resolution of DKA was similar (14.5 h in BES and 16 h in the saline group). On the other hand, the total amount of fluids was lower than in our protocols.

The recent PECARN DKA Fluid Study did not find differences in the rate of mental decline in patients whose dehydration was treated with fluids with different sodium contents administered at different rates (21). This is in line with a previous report on protocols using different tonicity and fluid volumes (22). The authors of neither study reported data on effective osmolality and deterioration of pGCS values or brain injury. Obviously, more studies are needed to establish the effect of sodium concentration on maintenance of effective osmolality when treating DKA of pediatric patients.

One of the strengths of our study is the comparability of the data. There were only few non-protocol variables since both protocols have been followed in the same hospital. The data were extracted from an electronic patient information system, which allowed us to use accurate time points for laboratory values.

This study has the drawbacks of being retrospective in design. Despite a relatively small number of patients, significant differences were recorded. Also, the data were unevenly distributed between the groups, with the number of mild DKA cases being as high as severe and moderate. Some data series were incomplete, as expected for a retrospective study: The exact time for ketone removal was not determined, pGCS

was not recorded systematically and the length of stay (LOS) at the PICU was not determined because the transfer to the pediatric ward after resolving of DKA depends on non-protocol factors such as the time of day and degree of occupancy of the pediatric wards.

In summary, we present a novel protocol for treating DKA appears to be significantly better than the conventional protocol for controlling the effective osmolality of plasma. Acidosis resolution takes only half the time, and this substantially shortens the duration of treatment. Benefits in terms of reduced morbidity are difficult to assess – this would require a much bigger number of patients – but might be substantial if the novel protocol would be used widely. Improved acidosis clearance seems to reflect easy adaptability of the novel protocol; it meets the patient's individual needs more precisely at any given moment of the first 12–18 hours of DKA treatment.

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Table 1 - Demography and baseline laboratory values during admission of patients treated with the conventional and new protocol.

	Conventional Protocol Group 1 (n=34)	New Protocol Group 2 (n=26)	p-value
Age (years)	11.1 (1.0, 15.7)	12.0 (0.67, 16.4)	0.363
Weight (kg)	39.5 (19.6)	42.1 (21.6)	0.756
P-glucose (mmol/L)	24.3 (6.32)	23.3 (6.32)	0.485
P-sodium (mmol/L)	135 (4.9)	135 (4.5)	0.438
P-osmolality (mosm/L)	294 (11.3)	295 (11.9)	0.704
P-pH	7.22 (6.90, 7.29)	7.20 (6.88, 7.30)	0.340
P-bicarbonate (mmol/L)	13.1 (3.8)	11.7 (3.31)	0.534
P-OHBut (mmol/L)	6.6 (1.8)	6.2 (2.1)	0.423

Data are shown as means (SD), except for age and pH, which are given as median and range. The Kruskall-Wallis test was used for statistical inference. P, plasma; OHBut, beta-hydroxybutyric acid.

Table 2 - Total amounts of fluids, insulin, glucose and electrolytes infused during the first 18 hours of DKA treatment.

	Conventional protocol (Group 1)	Novel protocol (Group 2)	p-value
Infusion fluids (mL/kg)	113.0 [90.2, 149.3]	120.1 [85.2, 162.9]	0.773
Insulin (IU/kg)	1.6 [1.2, 2.2]	0.9 [0.6, 1.4]	0.003
Glucose (g/kg)	6.5 [4.1, 8.8]	5.6 [3.6, 10.4]	0.807
Sodium (mmol/kg)	10.8 [8.3, 16.4]	14.8 [11.3, 23.1]	0.033
Potassium (mmol/kg)	2.7 [1.6, 5.0]	3.4 [2.0, 7.1]	0.589
Chloride (mmol/kg)	11.9 [8.5, 16.4]	12.2 [8.2, 16.7]	0.971

Data are shown as as median and interquartile range. IU, international units.

Figure 1

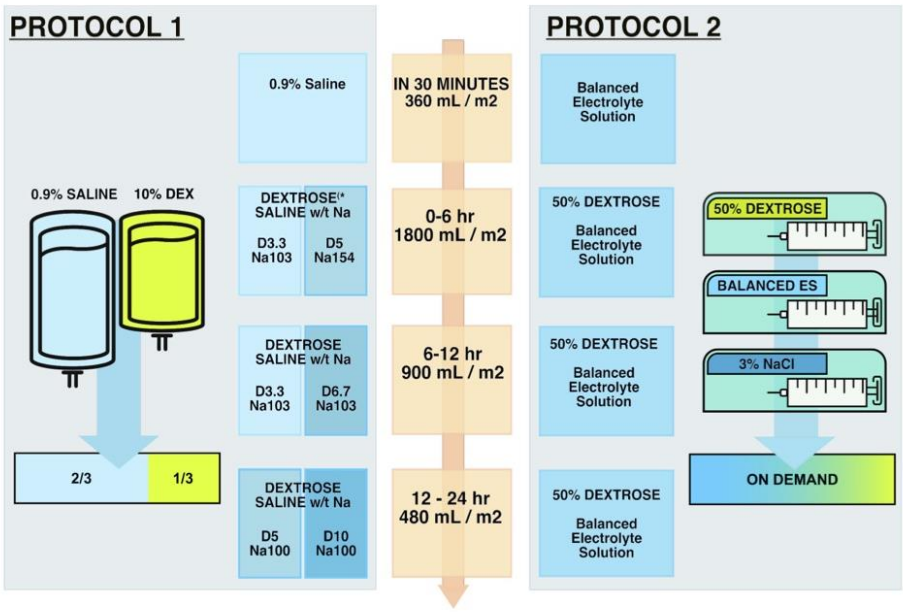

Figure 1. Treatment protocols. Protocol 1 (left). Dextrose and saline were infused with varying concentrations as shown (*). Concentrations were adjusted every six hours, but also during each period if necessary (*in blue*). However, the relative proportions of saline (2/3) and 10% dextrose (1/3) volumes were kept constant. Potassium concentration of the replacement fluid varied from 0 to 60 mmol/L based on plasma potassium levels. In addition, constant insulin infusion of 0.1 IU/kg was administered until plasma glucose decreased below 15 mmol/L, after which the rate was adjusted to 0.075 IU/kg. Renal losses were replaced with 5% dextrose supplemented with sodium and potassium, which were adjusted based on urine analysis. DEX, dextrose. Protocol 2 (right): Dextrose, a balanced electrolyte solution (BES, Plasma-Lyte 148®, Baxter, Deerfield, IL, USA) and hypertonic 3% saline were each adjusted individually through separate infusion pumps. The proportion of BES and 50% dextrose were adaptively adjusted according to the plasma glucose levels and effective osmolality values. If necessary, the sodium concentration of the

solution was increased with 3% NaCl-solution. Constant insulin infusion of 0.05 IU/kg was administered throughout the treatment. 35 mmol/L potassium was added to BES. Replacement of renal losses was performed by increasing the rate of BES infusion. Infusion rates and total volumes during each period are shown in the middle (*in orange*). In Protocol 2, the total volume and infusion rate of the 12–24-hr period was 600 mL/m^2.

Figure 2

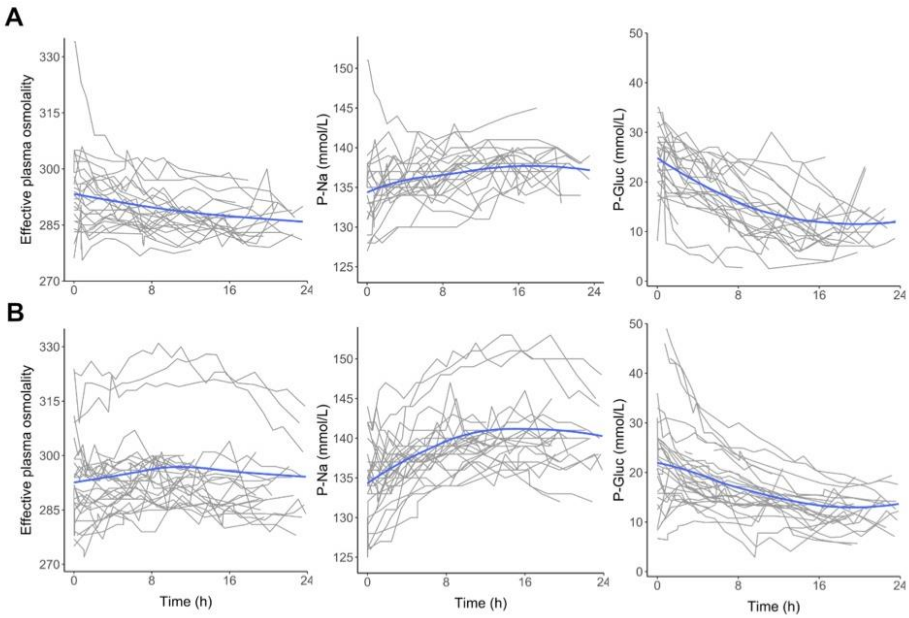

Figure 2. Individual measured plasma glucose, sodium and osmolality (mosm/L) levels during the study. Each gray line represents one patient, and the blue line represents the LOESS-smoother. Upper panel (A) shows Group 1 and lower panel (B) Group 2. LOESS, locally estimated scatterplot smoothing. In Group 2, plasma sodium and osmolality levels were significantly higher during the whole treatment period than in Group1 ($p= 0.018$ and $p=<0.001$, respectively).

Figure 3

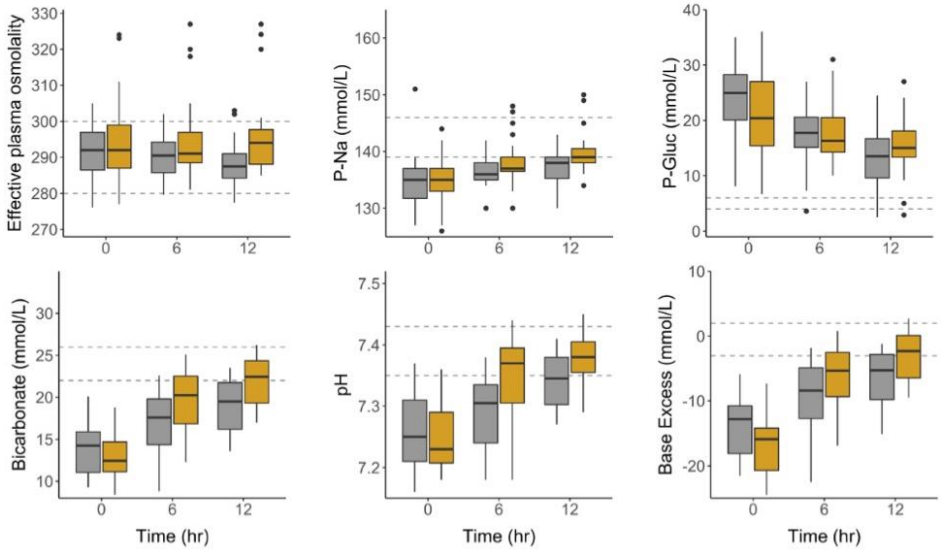

Figure 3. Time course of plasma glucose, sodium and osmolality (mosm/L) in Group 1 (*gray*) and Group 2 (*orange*) during the first 12 hours after start of treatment of DKA. Box plots show the median and 25–75th percentiles, and the whiskers show the minimum and maximum.

Figure 4

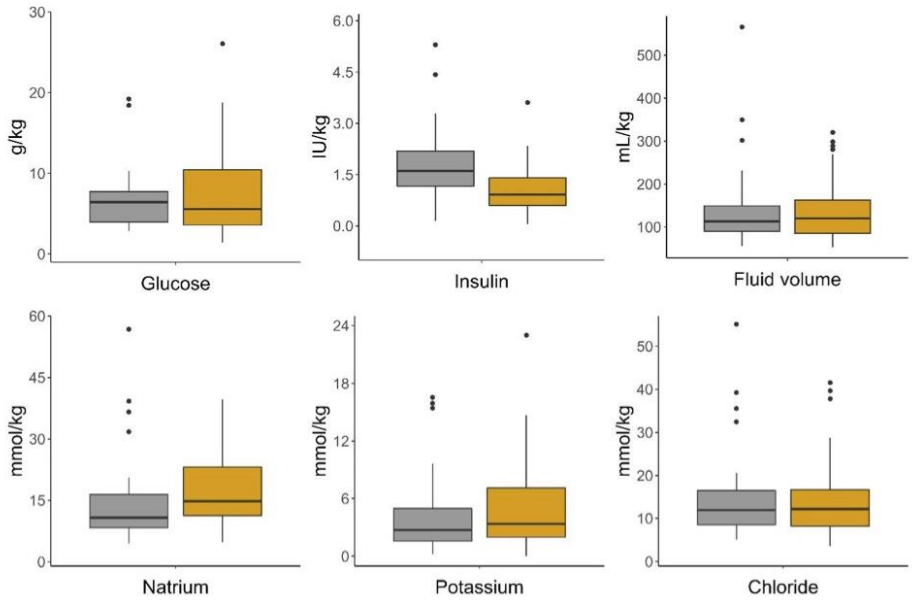

Figure 4. Total amounts of electrolytes and fluids administered during the study in Group 1 (*grey*) and Group 2 (*orange*). Box plots show the median and 25–75th percentiles, and the whiskers show the minimum and maximum.