Evaluation of the Effect of Fluid and Electrolyte Therapy on Electrolytes and Acidosis Resolution Time in Diabetic Ketoacidosis

Diyabetik Ketoasidoz Hastalarında Sıvı ve Elektrolit Tedavisinin Elektrolit Düzeyleri ve Asidoz Düzelme Süresine Etkisi

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ABSTRACT

Objective: Fluid replacement and insulin infusion are the cornerstones of treatment of diabetic ketoacidosis, but the optimal volume, rate of infusion, and electrolyte content of fluid replacement have been controversial. The aim of this study was to investigate the effects of treatment on pH, bicarbonate (HCO_3), anion gap, chloride, and potassium levels as well as time to resolution of acidosis in children with diabetic ketoacidosis.

Material and Methods: Ninety-six episodes with diabetic ketoacidosis between January 2015-December 2017 were evaluated.

Results: The mean resolution time of acidosis was 13.4±7.1 hours. Anion gap was returned to normal in 68 (70.8%) episodes at the 4th hour of treatment with a mean of 11±4.2 mmol/L. Episodes with potassium phosphate (KPO_4) replacement resulted in a faster increase in pH and a significantly shorter resolution time of acidosis (p<0.001). Acidosis persisted at the 16th hour of treatment in episodes with lower pH, lower serum bicarbonate (HCO_3) and higher white blood cell (WBC) counts on admission (p<0.001, p=0.003 p=0.033, respectively). Hyperchloremia (Cl/Na ratio > 0.79) was observed in 97% of cases after 8 hours of treatment.

Conclusion: Although the value of the anion gap in predicting acidosis is controversial, severe DKA episodes and high white blood cell count at admission; potassium replacement with high amounts of chloride and KCl containing fluids given during treatment have been associated with a longer recovery time of acidosis.

Key Words: Acidosis, Diabetic ketoacidosis, Hypopotassemia, Pediatric, Type 1 Diabetes

ÖZ

Amaç: Sıvı replasmanı ve insülin infüzyonu Diyabetik Ketoasidoz DKA tedavisinin temel taşlarıdır, ancak sıvı replasmanının optimal hacmi, infüzyon hızı ve elektrolit içeriği hala tartışmalı olan bir konudur. Bu çalışmanın amacı, diyabetik ketoasidozlu çocuklarda tedavinin pH, bikarbonat (HCO_3), anyon açığı, klorür ve potasyum düzeyleri üzerindeki etkilerinin yanı sıra asidozun düzelme süresini araştırmaktı.

Gereç ve Yöntemler: Ocak 2015-Aralık 2017 tarihleri arasında diyabetik ketoasidoz tanısı ile takip edilen 93 hasta (toplam 96 DKA atağı) retrospektif olarak değerlendirildi.

Bulgular: Asidozun ortalama düzelme süresi 13.4±7.1 saatti. Anyon açığı 68 (%70.8) atakta tedavinin 4. saatinde ortalama 11±4.2 mmol/L ile normale döndü. Potasyum fosfat (KPO_4) replasmanı yapılan hastalarda pH artışı daha hızlı ve asidoz düzelme süresi daha kısa olarak saptandı (p<0.001). Başvuruda daha düşük pH, daha düşük serum bikarbonat (HCO^3) ve daha yüksek beyaz küre sayısı olan ataklarda tedavinin 16. saatinde asidozun devam ettiği görüldü (sırasıyla p<0.001, p=0.003 p=0.033). Hiperkloremi (Cl/Na oranı > 0.79) tedavinin 8. saatinde atakların %97'sinde tespit edildi.

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Sonuç: Asidozu yansıtmada anyon açığının değeri tartışmalı olarak bulunsa da, DKA ataklarının ağır derecede olması ve hastaneye yatışta beyaz kürenin yüksek olması; tedavi sırasında verilen yüksek miktarda klorür ve KCl içeren sıvı ile potasyum replasmanı asidozun daha uzun sürede düzelmesi ile ilişkilendirilmiştir.

Anahtar Sözcükler: Asidoz, Diyabetik ketoasidoz, Hipopotasemi, Pediatri, Tip 1 diyabet

INTRODUCTION

The autoimmune destruction of the pancreatic beta cells that produce insulin is the cause of type 1 diabetes mellitus (1). Diabetic ketoacidosis (DKA) is one of the most life-threatening complications of type 1 diabetes mellitus (T1D). Its frequency at the onset of T1D ranges from 15% to 70% (2).

Insufficient insulin and elevated counter-regulatory hormones result in gluconeogenesis, glycogenolysis, lipolysis, and muscle proteolysis, which leads to hyperglycemia, hyperosmolality, and ketoacidosis. Hyperglycemia causes glycosuria, which leads to osmotic diuresis and significant loss of fluid and electrolytes. The fundamental components of managing DKA involve replacing fluids and electrolytes, administering insulin therapy, and closely monitoring the patient's progress using current laboratory tools (2,3).

Despite a comprehensive randomized controlled trial, it was determined that the rate of administration and sodium chloride (NaCl) content of intravenous (IV) fluids did not have a significant impact on neurological outcomes in children with DKA (4). However, there is still ongoing discussion regarding the ideal volume, infusion rate, and sodium content for IV fluid replacement in these patients (3,5). Normal saline (0.9%) has traditionally been the preferred fluid for treating DKA. However, it can lead to an increase in chloride levels and the development of hyperchloremic metabolic acidosis due to the excessive administration of fluids rich in chloride during DKA treatment (6-9). Hyperchloremia affects the duration of acidosis, making it difficult to monitor the patient (10).

Serum potassium levels are usually normal or slightly elevated at DKA presentation due to the shift of potassium ions from the intracellular to extracellular space. Urinary potassium loss can occur due to osmotic diuresis, increased levels of aldosterone in response to reduced blood volume, and the excretion of ketoacids. Hypokalemia is an expected finding due to the intracellular entry of potassium during DKA treatment (11, 12).

Glycosuria-induced osmotic diuresis also causes phosphate deficiency in children. However, the serum phosphate concentration is usually normal or even slightly elevated initially, as both metabolic acidosis and insulin deficiency result in the movement of phosphate from the extracellular space. The levels of phosphate decrease during the therapy of DKA due to the reversal of this transcellular shift.

We aimed to investigate the effect of treatment with DKA on alterations of pH, HCO_3, anion gap, chloride, and potassium levels, as well as the time to resolution of acidosis in children with DKA. This study will be among the rare studies on this subject, adding data to the literature and providing new ideas about future studies.

MATERIALS and METHODS

This retrospective study was performed at the emergency department of Dr. Sami Ulus Training and Research Hospital between January 1, 2015, and December 31, 2017. Children below 18 years of age diagnosed with DKA due to T1D were included. Patients with comorbidities that could lead to diagnostic confusion, patients who were referred to our institution after initial presentation at another hospital, and children who did not meet the diagnostic criteria for DKA were excluded from the study. Patients who subsequently had another episode of diabetic ketoacidosis during the study period were also enrolled in the study. The analysis of the results was based on the number of episodes of DKA. Ninety-three children were included in the study, with a total of 96 episodes of DKA.

University of Health Sciences, Ankara Pediatrics Hematology Oncology Hospital Clinical Research Ethics Committee approved the study (ID: 2018-058). Written informed consent was obtained from the parents or guardians of all enrolled patients.

Patients' data were obtained from the hospital registration system. Age at diagnosis, gender, clinical findings (nausea, vomiting, abdominal pain, tachypnea, altered consciousness, fever, polyuria, polydipsia, weight loss), degree of dehydration, and severity of DKA were recorded.

The biochemical criteria for diagnosis of DKA were based on hyperglycemia (blood glucose >200 mg/dL [11 mmol/L]), metabolic acidosis (venous pH <7.3 or serum bicarbonate <15 mEq/L [15 mmol/L]) and ketosis (presence of ketones in the blood [>3 mmol/L beta-hydroxybutyrate] or urine ["moderate or large" urine ketones]). Ketoacidosis was categorized into three stages of severity. DKA was classified as: mild (pH: 7.2-7.3, HCO_3: 10-15 mmol/L), moderate (pH 7.1- 7.2, HCO_3: 5-10 mmol/L) and severe (pH < 7.1, HCO_3 <5-10 mmol/L) (9).

All initial laboratory parameters, including pH, serum bicarbonate (HCO^3), blood glucose level, serum sodium (Na) (corrected sodium level not calculated), potassium (K), chloride (Cl), phosphorus (P), creatinine, blood urea nitrogen (BUN), HbA1c, white blood cell (WBC), urine and blood ketone levels, were recorded.

The normal range of potassium levels is between 3.5-5.0 mEq/L. Lower than 3.5 mEq/L was defined as hypokalemia and higher than 5 mEq/L was defined as hyperkalemia (13).

Serial measurements of blood glucose, HCO_3, pH, and electrolytes were taken upon arrival and at certain time intervals (4-8-12-16-20-24 and 36 hours) after the start of treatment. Acidosis was considered resolute if the pH levels were above 7.30 and/or the HCO_3 levels were over 15 mmol/L. The time of first oral intake (based on fluid withdrawal time) and initial insulin dose were recorded.

The total amount of fluid (in milliliters [mL]), sodium, chloride and potassium (as potassium chloride [KCl] or potassium phosphate [KPO_4]) (in milliequivalent [mEq]) administered at the 1st, 8th, 16th, 24th and 36th hours of treatment were calculated. The total amount of fluid and chloride were divided by body weights to find the fluid and chloride levels per kg. The chloride level was also expressed as the amount of chloride contained in 100 mL of fluid. The potassium content per 1000 mL of fluid in the first 8, 16, and 24 hours of treatment was calculated by subtracting the loading fluid given in the first hour.

Anion gap (Na - [Cl+HCO3]) and serum osmolarity (2x [plasma Na] + plasma glucose/18 [mmol/L] + BUN/2.8 [mmol/L]) levels of the patients were calculated with the formula in the SPSS program. A Cl/Na ratio > 0.79 was defined as hyperchloremia (8).

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Armonk, NY, IBM Corp., USA) software version 20.0. Of the continuous variables, those with a normal distribution were expressed as mean and standard deviation (SD). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Categorical variables were expressed as numbers and percentages. The significance of the difference between the median or mean of the two groups was evaluated with the Mann Whitney-U Test for data that were not normally distributed, and the Student t-Test for normal distributions. The significance of the difference between the two groups in categorical variables was evaluated with the Chi-Square test. $p<0.050$ was considered statistically significant.

RESULTS

The study included a cohort of 93 patients diagnosed with DKA. Out of these patients, three experienced a recurrence of DKA during the trial. Hence, a grand total of 96 separate episodes of DKA were examined.

Out of the total number of patients, 50 (53.8%) were male and 43 (46.2%) were female (male-to-female ratio=1.16:1). The mean age was 8.33±4.9 years at the onset of the disease. Of the 96 DKA episodes, 78 (81.3%) were at the time of the initial diagnosis of T1D. The most common symptoms were polyuria (76%) and polydipsia (76%). Forty-five (46.9%) episodes were classified as severe DKA. The demographic and clinical characteristics were shown in Table I.

Table I: Demographic and clinical characteristics of patients presenting with diabetic ketoacidosis

Gender, male* (n=93)	50 (53.8)
Age at diagnosis (year)†	8.33±4.9
New diagnosis* (n=96)	78 (81.3)
Degree of dehydration* (n=96)	
Severe	13 (13.5)
Moderate	83 (86.5)
Clinical Findings*(n=96)	
Polyuria-polydipsia	73 (76)
Nausea-vomiting	47 (49)
Weight loss	43 (44.8)
Tachypnea	39 (40.6)
Consciousness change	24 (25)
Abdominal pain	22 (22.9)
Fever	13 (13.5)
DKA severity* (n=96)	
Mild DKA	19 (19.8)
Moderate DKA	32 (33.3)
Severe DKA	45 (46.9)

:** *n(%),* **†:** *(mean±SD),* ***DKA: *Diabetic ketoacidosis*

The laboratory parameters at the time of admission and the subsequent changes that occurred within a few hours are shown in Table II.

Insulin therapy was started at a dose of 0.05 IU/kg in 4 (4.1%) episodes, 0.1 IU/kg in 90 (93.8%) episodes, and 0.15 IU/kg in 2 (2.1%) episodes.

The mean amount of fluid administered at the first hour was 13.1±5.02 mL/kg. The total fluid administered was calculated as 39.6±10.1 mL/kg at the 8th hour, 71.5±18.9 mL/kg at the 16th hour and 100±28.8 mL/kg at the 24th hour. The mean duration of fluid therapy was 17.9±7.1 hours. The longest transition time to oral intake was 52 hours in one patient.

Potassium level at admission was <3.5 mmol/L in 8 (8.3%) episodes, 3.5-5.5 mmol/L in 77 (80.2%) episodes, and >5.5 mmol/L in 9 (9.4%) episodes. During follow-up, potassium levels decreased to <3.5 mmol/L in 43 (44.8%) episodes. The total amount of potassium given at the 24th hour was 90±53.3 mEq. In patients who were normokalemic at the time of diagnosis, the mean amount of potassium given at 8, 16 and 24 hours was 31.4±10.5, 35.5±10.4 and 38.2±15.2 mEq/L, respectively, while in hyperkalemic patients, the mean amount of potassium in the fluid within 24 hours was 18.4±9.3 mEq/L. KPO_4-containing fluid was given in 60 (62.5%) episodes (only KPO_4 in 3 episodes, KCl+KPO_4 in 57 episodes) and only KCl containing fluid was given in 36 (37.5%) episodes. The initial pH in episodes given KPO_4 for potassium replacement was significantly lower than episodes given KCl ($p<0.001$). In the subgroup analysis of the changes at 8th, 16th and 24th hours according to initial serum pH and HCO_3 values, it was observed that the pH increase was rapid, and the resolution of acidosis took shorter time in KPO_4-treated patients compared to KCl-treated patients ($p<0.001$) (Table III).

Table II: The laboratory parameters of diabetic ketoacidosis patients at admission and their changes according to hours

	At admission	4th hour	8th hour	12th hour	16th hour	20th hour	24th hour
pH*	7.07±0.14	7.19±0.09	7.25±0.07	7.27±0.06	7.30±0.05	7.31±0.06	7.34±0.05
HCO3* (mmol/L)	8.4±3	11±3.2	13.4±3.3	14.1±2.2	15±2.3	15.9±2.5	17.2±3.5
Glucose* (mg/dL)	476±137	263±118	226±93	208±70	214±74	216±76	224±99
Anion gap* (mmol/L)	19.7±5.5	11±4.2	7.9±4.2	6.7±2.7	6.2±3.3	11.4±23	6.7±2.6
Sodium* (mmol/L)	133±6	136±5	136±6	137±5	137±4	137±4	137±4
Potassium* (mmol/L)	4.46±0.8	4.12±0.88	3.81±0.62	3.58±0.57	3.65±0.57	3.38±0.59	3.37±0.47
Chloride* (mmol/L)	105±7	113±6	115±6	115±6	117±5	115±5	112±6
Phosphorus* (mg/dL)	3.8±1.1	2.8±1	2.7±1.1	2.9±1.2	2.9±1.2	3.3±1.2	2.9±1.2
Creatinine* (mg/dL)	0.89±0.31	0.8±0.25	0.73±0.19	0.65±0.2	0.63±0.22	0.61±0.21	0.56±0.11
Osmolality* (mOsm/kg)	305.7±13.6	299±14.6	296.4±11.5	297.8±14.4	299.5±10.2	297.5±9.5	296.5±9.5

***:** *Mean ± SD*

Table III: Acidosis recovery time and pH changes over hours in patients with and without potassium phosphate

	KPO_4	n	mean	SD	p
pH at admission	-	36	7.153	.105	<0.001*
	+	60	7.026	.137	
pH change in the first 4 hours	-	34	.097	.083	0.029*
	+	55	.142	.097	
pH change in the first 8 hours	-	27	.151	.113	0.026†
	+	53	.210	.110	
pH change in the first 16 hours	-	16	.196	.101	0.003†
	+	44	.296	.115	
pH change in the first 24 hours	-	5	.226	.114	0.011†
	+	16	.415	.134	
Acidosis resolution time (hours)	-	59	15.42	6.76	<0.001*
	+	35	10.23	6.61	<0.001*
Oral intake time (hours)	-	36	14.53	6.23	<0.001*
	+	60	20.02	6.99	<0.001*

***:** *Student t Test,* **†:** *Mann Whitney-U Test,* ***KPO_4:** potassium phosphate,* ***SD:** Standard deviation,* ***+ :** Fluid containing with KPO_4,* ***- :** KPO_4 free fluid*

Table IV: The factors affecting the time to resolution of acidosis at 16 hours

	Acidosis at the 16th hour	n	mean	SD	p*
pH	-	68	7.105	.133	<0.001
	+	28	6.998	.127	
HCO3 (mmol/L)	-	67	8.96	3.15	0.003
	+	27	7.01	1.93	
WBC (10^9/L)	-	68	14.8	7.9	<0.001
	+	28	22.9	11.6	
Total amount of chloride given in 100 mL of fluid in 16 hours	-	39	11.86	1.61	0.031
	+	28	12.62	1.00	

***:** Student t Test,* ***SD:** Standard deviation,* ***HCO_3:** sodium bicarbonate,* ***WBC:** white blood cell,* ***+ :** Those who continue to have acidosis at the 16th hour,* ***- :** Those whose acidosis does not persist at 16th hours*

The mean chloride level at the time of admission was 105±7 mmol/L. The mean Cl/Na ratio was 0.78 at the time of diagnosis. It was > 0.79 after 8 hours of treatment in 93 (96.8%) episodes. It increased to a maximum of 145 mmol/L and an average of 116.6 mmol/L at the 16th hour of treatment. The mean total amount of chloride given within 16 hours was 8.64±2.16 mEq/kg and 11.6±3.2 mEq/kg within 24 hours.

The mean anion gap on admission was 19.7±5.5 mmol/L. The anion gap was returned to normal in 68 (70.8%) episodes after 4 hours of therapy, with a mean value of 11±4.2 mmol/L.

The mean correction time for acidosis was 13.4±7.1 hours (6.67±3.6 hours in mild, 11±6 hours in moderate, and 18±5.7 hours in severe DKA cases). A statistically significant difference was observed in the average resolution time of acidosis between the severity levels of ketoacidosis (p<0.001). The acidosis was corrected in 69 (71.9%) episodes at the 16th hour of admission. Acidosis persisted at the 16th hour of treatment in episodes with lower pH, lower HCO_3 and higher WBC values on admission (p<0.001, p=0.003, p<0.001, respectively) (Table IV). Patients with acidosis lasting longer than 16 hours had lower pH on admission (p=0.039).

It was determined that the WBC count at the time of admission was significantly related to the resolution time of acidosis (p<0.001). The mean white blood cell count at admission was 14.8x10^9/L in those whose acidosis resolved at 16 hours and 22.9 x10^9/L in those whose acidosis did not resolve at 16 hours.

DISCUSSION

In this study, the relationship between fluid-electrolyte therapy and the alterations in chloride and potassium levels and the resolution time from acidosis in 96 episodes of diabetic ketoacidosis due to T1D were evaluated.

In this study, acidosis was resolved in 69 (71.9%) episodes at the 16th hour of admission and the mean resolution time of acidosis was below 14 hours. A statistically significant difference was observed in the average resolution time of acidosis between the severity levels of ketoacidosis The duration of acidosis in this study is reasonable, as nearly half of the episodes were severe. These findings correlate with the results of previous studies conducted on children with DKA. In a study by von Oettingen

et al. (14), mean resolution time of acidosis was reported to be 8.4 hours, where it reached 14.5 hours in severe cases. In a study by Mrozik et al. (15), the mean resolution time of acidosis was reported to be 17.1 hours in severe episodes and 10.5 hours in milder episodes. The differences between mean acidosis resolution times in the literature may have been related to the varieties in DKA episode severity, subsets of patients enrolled in the study, fluid infusion rates and proposed DKA protocols (14).

The clinical significance of hyperchloremia in DKA is currently being studied. In the study of Taylor D. et al. (8), the rate of hyperchloremia was 6% at the beginning of treatment and 94% at the 20th hour, and they stated that chloride increased rapidly in the first 4 hours and became the dominant component for acidosis at the end of the 20th hour. In this study, the rate of hyperchloremia (Cl/Na ratio > 0.79) after 8 hours of treatment was nearly 97%. Additionally, episodes with persistent acidosis after 16 hours of treatment received a higher total dose of chloride throughout the first 16 hours of treatment. Also, no significant correlation was found between the amount of chloride given during treatment and the resolution time for acidosis. This may be due to the fact that hyperchloremia was observed in 97% of patients at the 8th hour of treatment and a similar treatment protocol was administered to each patient. More information about the link between chloride and the length of acidosis will be gained from prospective multicenter studies that use different types of fluids that contain chloride as part of the treatment.

The value of the anion gap in reflecting acidosis during DKA treatment was discussed and its role in reflecting acidosis was found controversial because of its correlation with increased chloride levels during DKA treatment (8). Hyperchloremic metabolic acidosis can happen when the kidneys get rid of more ketones than chloride ions in people with DKA or when a lot of NaCl is infused during treatment for DKA (16,17). Von Oettingen JE et al. (14) reported that the dominant component of acidosis after 12 hours was chloride, which caused masking in calculations based on the anion gap level. In the study of Mrozik RN et al. (15), it was reported that secondary hyperchloremic metabolic acidosis occurred in 58% of patients and there was a difference of >6 hours between HCO_3 and anion gap level in the acidosis resolution time calculations. In this study, the anion gap returned to normal in nearly 70% of episodes at 4th hour of treatment, whereas the resolution time of acidosis was above 13 hours. This indicates that the anion gap level did not reflect the resolution time of acidosis as reported in the literature.

In the DKA protocol, it is recommended to add 40 mEq/L potassium to fluid therapy in cases of a potassium level <5.5 mmol/L at the time of diagnosis (9). Peeters E. et al. (18) found that over 25% of the patients had a potassium level below 3.5 mEq/L when they were given a treatment with a potassium amount of 20 mEq/L. In a study by Naeem MA et al. (19), potassium levels were found to be 4.03±0.66 mmol/L and 3.84±0.59 mmol/L, respectively, at the 6th and 12th hours of treatment, in which 40 mEq/L potassium was given according to the ISPAD protocol. In another study, it was found that 8.8% of people who had replacement fluid with 40 mEq/L of potassium still had hypokalemia (20). In our study, the potassium levels gradually declined to values lower than 3 mmol/L after the 4th hour of treatment, resulting in hypokalemia in around 45% of the cases. This may be due to the detection of potassium levels below 40 mEq/L at the 8th and 16th hours. To prevent hypokalemia, it has been proposed to initiate insulin infusion one hour after beginning fluid replacement, as the reduction in serum potassium level is most noticeable within the first two hours of treatment (20). The causes of hypokalemia were demonstrated to be urinary potassium excretion due to insulin infusion and osmotic diuresis. A study found that administering insulin at a rate of 0.05 U/kg/hour reduced the occurrence of hypokalemia, with no significant changes in resolving acidosis and ketosis compared to an insulin infusion rate of 0.1 U/kg/hour (21). The insulin infusion rate was 0.1 U/kg/hour in nearly 95% of episodes, which was thought to be another reason for the high rate of hypokalemia in our study. It is essential to administer a 40 mEq/L dosage of potassium when the potassium level is below 5.5 mmol/L after the diagnosis of DKA. Additionally, considering a lower-dose insulin infusion may be an option to prevent hypokalemia.

The study investigating the relationship between KPO_4 supplementation and pH change was not found in the literature. This study will be a guide for systematic studies that will investigate the relationship between KPO_4 replacement and pH change. It will consider the movement of potassium and phosphate out of the cell during acidosis, their movement into the cell with the effects of rehydration and insulin, and the acidification effect caused by chloride when given with KCl, leading to hyperchloremia (21).

Markers of oxidative stress (WBC, platelets, and MPV) were associated with increased severity of DKA. Sehgal M. et al. (22) reported that both leukocytosis and thrombocytosis were associated with severe metabolic acidosis. Karavanaki K. et al. (23) reported a significantly higher WBC value in patients with moderate or severe DKA compared to those with mild DKA. In this study, it was determined that the number of WBC on admission was associated with the resolution time of acidosis. This condition is thought to be associated with high levels of H^+ can be associated with the production and release of leukocytes, systemic inflammation, oxidative stress response, or the severity of dehydration, as previously stated in the literature (24,25).

One of the limitations of this study was its retrospective nature. The data from a single center did not reflect the universe, so it would have been better if it was a multi-center prospective study. All episodes were managed according to the same treatment protocol, so the relationship between treatment differences could not be clearly demonstrated. Nevertheless, the data of this study is valuable because it is the data of the

busiest third-level emergency department in our country. It is among the rare studies on this subject, adding data to the literature and providing new ideas about future studies.

CONSLUSION

Episodes of DKA characterized by a severe degree and higher WBC upon hospital admission, along with a high administration of chloride during therapy and potassium replacement using fluid containing KCl, were found to be associated with a longer time for the resolution of acidosis. The value of the anion gap in reflecting acidosis was found to be controversial. To explore the association between the length of acidosis and various chloride-containing liquids or the addition of KPO_4 and pH change, it is important to conduct multicenter, thorough prospective research.

REFERENCES

1. Sezer A, Paketçi A, Gören Y, Çatlı G, Ahmet A, Tuhan H, et al. Evaluation of Demographic, Clinical and Laboratory Features of Cases with Type 1 Diabetes Mellitus at Diagnosis. Turkish J Pediatr Dis 2018;12:173-9.
2. Wolfsdorf JI, Glaser N, Agus M, Fritsch M, Hanas R, Rewers A, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. Pediatr Diabetes 2018;19:155-77.
3. Rewers A, Kuppermann N, Stoner MJ, Garro A, Bennett JE, Quayle KS, et al. Effects of fluid rehydration strategy on correction of acidosis and electrolyte abnormalities in children with diabetic ketoacidosis. Diabetes Care 2021;44:2061-8.
4. Kuppermann N, Ghetti S, Schunk JE, Stoner MJ, Rewers A, McManemy JK, et al. Clinical trial of fluid infusion rates for pediatric diabetic ketoacidosis. N Engl J Med 2018;378:2275-87.
5. Maurice L, Julliand S, Polak M, Bismuth E, Storey C, Renolleau S, et al. Management of severe inaugural diabetic ketoacidosis in paediatric intensive care: retrospective comparison of two protocols. Eur J Pediatr 2022;181:1497-506.
6. Adrogué HJ, Wilson H, Boyd III AE, Suki WN, Eknoyan G. Plasma acid-base patterns in diabetic ketoacidosis. N Engl J Med 1982;307:1603-10.
7. 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.
8. Taylor D, Durward A, Tibby SM, Thorburn K, Holton F, Johnstone IC, et al. The influence of hyperchloraemia on acid base interpretation in diabetic ketoacidosis. Intensive Care Med 2006;32:295-301.
9. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N, Jain V, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Diabetic ketoacidosis and hyperglycemic hyperosmolar state. Pediatr Diabetes 2014;15:154-79.
10. Ferreira JP, Hamui M, Torrents M, Carrano R, Ferraro M, Toledo I. The Influence of Chloride for the Interpretation of Plasma Bicarbonate During the Treatment of Diabetic Ketoacidosis. Pediatr Emerg Care 2020;36:e143-e45.
11. Chinoy A, Wright N, Bone M, Padidela R. Severe hypokalaemia in diabetic ketoacidosis: a contributor to central pontine myelinolysis? Endocrinol Diabetes Metab Case Rep 2019;2019:19-0034.
12. Palmer BF, Clegg DJ. Electrolyte and acid–base disturbances in patients with diabetes mellitus. N Engl J Med 2015;373:548-59.
13. Kardalas E, Paschou SA, Anagnostis P, Muscogiuri G, Siasos G, Vryonidou A. Hypokalemia: a clinical update. Endocr Connect 2018;7:R135-R46.
14. 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.
15. Mrozik LT, Yung M. Hyperchloraemic metabolic acidosis slows recovery in children with diabetic ketoacidosis: a retrospective audit. Aust Crit Care 2009;22:172-7.
16. Chua H-R, Venkatesh B, Stachowski E, Schneider AG, Perkins K, Ladanyi S, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care 2012;27:138-45.
17. Ramanan M, Attokaran A, Murray L, Bhadange N, Stewart D, Rajendran G, et al. Sodium chloride or Plasmalyte-148 evaluation in severe diabetic ketoacidosis (SCOPE-DKA): a cluster, crossover, randomized, controlled trial. Intensive Care Med 2021;47:1248-57.
18. Peeters E, Van Ijperen W, Robertson L, Royle P, van IJperen Sr W. Analysis of the safety and efficacy of diabetic ketoacidosis management in a Community General Hospital, 2001–2010: a descriptive study. Scott Med J 2015;60:121-5.
19. Naeem MA, Al-Alem HA, Al-Dubayee MS, Al-Juraibah FN, Omair A, Al-Ruwaili AS, et al. Characteristics of pediatric diabetic ketoacidosis patients in Saudi Arabia. Saudi Med J 2015;36:20-5.
20. Edge J, Nunney I, Dhatariya K. Diabetic ketoacidosis in an adolescent and young adult population in the UK in 2014: a national survey comparison of management in paediatric and adult settings. Diabet Med 2016;33:1352-9.
21. Rameshkumar R, Satheesh P, Jain P, Anbazhagan J, Abraham S, Subramani S, et al. Low-dose (0.05 Unit/kg/hour) vs standard-dose (0.1 Unit/kg/hour) insulin in the management of pediatric diabetic ketoacidosis: a randomized double-blind controlled trial. Indian Pediatr 2021;58:617-23.
22. Sehgal M, Batra M, Jha P, Sanchez O. Risk Factors and Laboratory Findings Associated With Diabetic Ketoacidosis in Hospitalized Pediatric Patients. Cureus 2022;14:e25410.
23. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, Konstantopoulos I, et al. Cytokine response to diabetic ketoacidosis (DKA) in children with type 1 diabetes (T1DM). Endocr J 2011;58:1045-3.
24. Xu W, Wu H-f, Ma S-g, Bai F, Hu W, Jin Y, et al. Correlation between peripheral white blood cell counts and hyperglycemic emergencies. Int J Med Sci 2013;10:758-65.
25. Abdel-Moneim A, Zanaty MI, El-Sayed A, Khalil RG, Rahman HA. Relation between oxidative stress and hematologic abnormalities in children with type 1 diabetes. Can J Diabetes 2020;44:222-8.