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Sodium bicarbonate is safe but not useful in the management of severe diabetic ketoacidosis

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Abstract

Aim: Diabetic ketoacidosis is a cause of high anion gap metabolic acidosis. Sodium bicarbonate treatment is controversial; it should be avoided as much as possible. This study aims to determine the indications of sodium bicarbonate and its effects on the clinical and laboratory findings in diabetic ketoacidosis patients.

Materials and Methods: Patients aged between 1 month and 18 years and hospitalized due to diabetic ketoacidosis between 01.01.2018 and 31.12.2022 were included in the study. The patients received sodium bicarbonate in cases of a pH less than 6.9 and/or partial pressure of carbon dioxide less than 15 mmol/L. Length of stay in the pediatric intensive care unit, the recovery time of acidosis, and the insulin infusion duration; respiratory and heart rates, blood gas analyses, and electrolyte levels of the patients in the first two hours of hospitalization were compared between the patients who received sodium bicarbonate and who did not.

Results: Forty-four (19%) of 232 patients received sodium bicarbonate. Twenty-five patients received this treatment, although the pH was greater than 6.9, but the pCO_2 was less than 15 mm Hg. The length of stay in the PICU, intravenous insulin infusion duration, and acidosis recovery time were significantly higher in the group receiving sodium bicarbonate. Sodium bicarbonate had no significant effect on respiratory and heart rates, pH, partial pressure of carbon dioxide, anion gap, and bicarbonate level. The elevation in the Glasgow coma score was greater in the sodium bicarbonate receiving group. Neurological deterioration or any other side effects were not detected.

Conclusion: Sodium bicarbonate treatment seems to be safe but not useful in the management of diabetic ketoacidosis. However, for determining the indication of this treatment, not only pH, but also partial pressure of carbon dioxide and anion gap should be considered.

Introduction

Diabetic ketoacidosis (DKA) is a cause of high anion gap metabolic acidosis [1]. Biochemical diagnostic criteria consist of hyperglycemia (blood glucose >200mg/dL), metabolic acidosis (venous pH<7.3 or $cHCO_3$<15 mmol/L), and ketosis (ketonemia and ketonuria). Mild DKA can be categorized by a pH between 7.2-7.3 and a bicarbonate level between 10-15 mmol/L, a pH between 7.1-7.2, and a bicarbonate level between 5-10 mmol/L is graded as moderate DKA, pH<7.1 and $cHCO_3$ <5 mmol/L is defined as severe DKA [2]. The treatment aims to correct dehydration, acidosis, and ketosis, achieve a normal or near-normal blood gas analysis, treatment of complications, and detect and treat the triggering causes [2]. In general, sodium bicarbonate is not a part of the treatment. It is thought that sodium bicarbonate administration is not beneficial and even can cause paradoxical central nervous system acidosis and hypokalemia [3]. If sodium bicarbonate administration is considered necessary, it is recommended to administer 1-2 mmol/kg over 1 hour [4]. As in treating other causes of high anion gap metabolic acidosis, sodium bicarbonate is not the first-line

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treatment option. It is used mainly in the acute phase of severe acidosis [4]. DKA, where the pH is less than 6.9, is one of these conditions [5]. Sodium bicarbonate treatment can be considered in case of clinical respiratory distress, hypocapnia, and other problems caused by acidosis in DKA patients with severe acidosis. However, there is no consensus on this issue [4]. Current guidelines recommend sodium bicarbonate treatment in cases where the pH is less than 6.9, life-threatening hyperkalemia, or cardiac dysfunction due to acidosis [6-8]. This study aims to determine the clinical (primarily neurological, cardiac, and respiratory findings) and laboratory (especially pH, pCO_2, lactate, and anion gap) effects of intravenous sodium bicarbonate treatment; to determine whether this treatment affects the recovery time of acidosis, the duration of intravenous insulin infusion, and the length of stay in the PICU and whether it causes any adverse effects. The secondary aim of the study is to determine the indications for the use of intravenous sodium bicarbonate in DKA management.

Materials and Methods

Study design

In this single-center retrospective study, all patients aged between 1 month and 18 years hospitalized in the pediatric intensive care unit (PICU) due to DKA between 01.01.2018 and 31.12.2022 were included. Before the study, ethics approval was obtained from the ethics committee University of Health Sciences Dr. Sami Ulus Gynecology and Obstetrics, Child Health and Diseases Training and Research Hospital (Approval number: E-22/06-345). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Study settings

The study was conducted in the PICU of a tertiary hospital. The PICU has 16 beds, and three pediatric intensivists and six pediatric research assistants run the unit during the day. An intensivist and a pediatric endocrinologist are available for consultation 24/7.

Variables and measurements

Diabetic ketoacidosis definition

Patients with hyperglycemia (blood glucose >200mg/dL), metabolic acidosis (venous pH<7.3 or $cHCO_3$<15mmol/L), and ketosis (ketonemia and ketonuria) were diagnosed with DKA.

Diabetic ketoacidosis management

A pediatric intensivist and a pediatric endocrinologist managed all the patients in the PICU. The indication for sodium bicarbonate treatment was accepted as pH less than 6.9 and/or partial pressure of carbon dioxide (pCO2) less than 15 mm Hg. Sodium bicarbonate treatment was given as a 1-hour intravenous infusion at the dose of 1 mmol/kg. For all patients, in the first two hours, heart and respiratory rates, Glasgow coma score (GCS), venous blood gas parameters (pH, pCO_2, $cHCO_3$, anion gap), duration of insulin infusion and intravenous fluids, length of stay in the PICU, and whether sodium bicarbonate was administered were recorded. In these two hours, sodium bicarbonate infusion was completed in those receiving sodium bicarbonate. It was evaluated whether there was a change in the parameters in the two-hour period and whether the amount of change was different in the bicarbonate and non-bicarbonate groups. Assuming that the vital signs and laboratory parameters of the group receiving sodium bicarbonate would be worse, the same analyzes were performed to evaluate better the effect of sodium bicarbonate in the group receiving sodium bicarbonate and the group whose pH was less than 7.1 (severe DKA) but did not receive sodium bicarbonate.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics (version 22.0.0; IBM Co., Armonk, NY, USA), and p-values <0.05 were considered statistically significant. The normal distribution of variables was analyzed visually (histogram and probability graphs) and statistically (Kolmogorov-Smirnov test). Variables with normal distribution in the descriptive statistics were shown as mean ± standard deviation, those without normal distribution as median (25th-75th percentiles), categorical variables as number of cases, and percentage (%). Chi-square or Fisher's exact test was used to compare differences between frequencies. Student t-test was used to compare numerical variables with normal distribution, and Mann-Whitney U test was used to compare numerical variables without normal distribution. Paired-Sample t-test and Wilcoxon test were used to analyze numerical dependent variables.

Results

Two hundred and thirty-two (126 male, 54.3%) patients were included in the study. 44 (24 male, 54.5%) received intravenous sodium bicarbonate treatment (Table 1). Two patients received two doses of sodium bicarbonate. The median age of the patients who received sodium bicarbonate was 101 (25th-75th percentiles: 52-148) months and the median age of those who did not was 120 (25th-75th percentiles: 75.25-166) months (p=0.972) (Table 1). Both groups had similar body weight, height, and body mass index standard deviation scores. The majority of patients (81.5%) in both groups were diagnosed with diabetes during the ketoacidosis episode included in the study (Table 1).

Twenty-five patients received sodium bicarbonate although the pH was greater than 6.9, but the pCO2 was less than 15 mm Hg. Two of these patients had a pH greater than 7.1.

The length of stay in the PICU, the duration of intravenous insulin infusion, and the recovery time of acidosis were significantly higher in the group receiving sodium bicarbonate (p<0.05) (Table 1). While uric acid, white blood cell, and platelet counts were significantly elevated in the patients who received sodium bicarbonate (p<0.05), there was no significant difference between blood urea nitrogen, creatinine, and hemoglobin levels (Table 1).

Upon physical examination, the GCS was lower, and the respiratory and heart rates were higher in the group receiving sodium bicarbonate (Table 2). Laboratory tests

Table 1. Demographic and basal laboratory features of the patients.

	Received bicarbonate	Did not receive bicarbonate	p value
Gender, male	24/44 (%54.5)	102/188 (%54.3)	0.972
Age, months (median, 25-75p)	101 (52-148)	120 (75.25-166)	**0.047**
Body weight, SDS n1=42, n2=185, (mean ± SD)	-0.37 ± 1.03	-0.20 ± 1.40	0.440
Height, SDS n1=40, n2=179, (mean ± SD)	0.029 ± 1.15	0.19 ± 1.23	0.451
Body mass index, SDS n1=39, n2=179, (mean ± SD)	-0.54 ± 1.47	-0.46 ± 1.56	0.775
Time from diabetes mellitus diagnosis, years (median, 25-75p, min-max)	0 (0-0) (0-10)	0 (0-0.75) (0-11)	0.487
The number of the DKA episodes from the time of diagnosis (median, 25-75p, min-max)	1 (1-1) (1-3)	1 (1-1) (1-10)	0.167
The mean HbA1c value in the last year, (mean ± SD)	12.51 ± 2.12	12.42 ± 2.43	0.822
Length of stay in the PICU, hours (median, 25-75p) n1=43, n2=182	24 (20-34)	19 (14.9-24)	**<0.001**
Duration of insulin infusion, hours (median, 25-75p) n1=42, n2=179	18.5 (16-24)	12 (8-17)	**<0.001**
Duration of acidosis, hours (median, 25-75p)	15 (12-18)	9 (5-14)	**<0.001**
Blood urea nitrogen, mg/dL (median, 25-75p)	12 (10-17)	11 (8-15)	**0.079**
Creatinine, mg/dL (median, 25-75p)	0.79 (0.67-0.99)	0.77 (0.64-0.96)	0.383
Uric acid, mg/dL (median, 25-75p)	7.05 (4.42-8.30)	5.10 (4.00-7.50)	**0.038**
Hemoglobin, gr/dl (median, 25-75p)	14.45 (13.70-15.57)	14.50 (13.70-15.50)	0.969
White blood cells, cells/mm^3 (median, 25-75p)	20.82 (16.53-24.96)	12.52 (9.24-17.78)	**<0.001**
Platelets cells/mm^3 (median, 25-75p)	427 (351-518)	356 (277-421)	**<0.001**

n1= number of the patients received bicarbonate treatment, n2= number of the patients did not receive bicarbonate treatment SD: standard deviation; SDS: standard deviation score, PICU: pediatric intensive care unit.

revealed that the pH, pCO_2, and bicarbonate levels were lower, and the anion gap was higher in the group receiving sodium bicarbonate (Table 2).

When all patients were evaluated together, GCS increased in those who received sodium bicarbonate within two hours after the initiation of treatment, but no change was observed in those who did not (Table 2). Respiratory and heart rates did not change in those who received sodium bicarbonate but decreased in those who did not, while the amount of change in the respiratory rate in these two hours was similar in both groups; heart rate decreased more in those who did not receive sodium bicarbonate (Table 2). In two hours in both groups, pH and $cHCO_3$ increased, pCO_2 did not change, anion gap decreased ($p<0.05$) (Table 2). The increase in pH was higher in those who received sodium bicarbonate than those who did not ($p=0.001$) (Table 2). While the sodium level increased in both groups, the change was greater in those receiving sodium bicarbonate ($p=0.003$) (Table 2). While chloride increased in both groups, the amount of change was similar (Table 2). While potassium decreased in both groups, the amount of change was similar in both groups (Table 2). Phosphorus increased in those who received sodium bicarbonate but decreased in those who did not (Table 2).

When patients who received sodium bicarbonate were compared with patients with severe DKA whose pH was less than 7.1, but did not receive sodium bicarbonate, unlike the results above, it was observed that the change in pH was similar in those who received and did not receive sodium bicarbonate ($p=0.170$) (Table 3). The elevation in GCS was greater in the bicarbonate-receiving group (Table 3).

Discussion

According to current guidelines, sodium bicarbonate, which is controversial for DKA management, is recommended in severe cases where the pH is less than 6.9 [6-8]. In a study evaluating the effectiveness of sodium bicarbonate treatment in DKA, no difference was found in terms of recovery time of acidosis, length of stay in the PICU, and insulin requirement [5]. In another study, it was reported that it did not provide an advantage in terms of ketone clearance, the recovery time of anion gap, lactate, renal function tests, GCS, respiratory rate, and heart rate; however, the threshold pH value determined for sodium bicarbonate treatment in this study was 7.1 [3]. The general opinion for sodium bicarbonate treatment was that it only temporarily improved the acidosis [6].

In the present study, firstly, patients were divided into two groups, those who received sodium bicarbonate and those who did not, to evaluate the effectiveness of sodium bicarbonate treatment. As expected; pH, pCO_2, bicarbonate level, and GCS were lower; the length of stay in the PICU, insulin infusion duration, acidosis recovery time, respiratory and heart rates, and anion gap were higher in the sodium bicarbonate receiving group. In other words, the patients treated with sodium bicarbonate were more severe DKA patients. However, when the clinical and laboratory parameters in the first two hours of the treatment were evaluated, it was seen that only the increase in GCS and pH was higher in those who received sodium bicarbonate. Changes in respiratory rate, pCO_2, and bicarbonate levels were similar in both groups over two hours. Interestingly, heart rate and anion gap decreased more in those who did not receive sodium bicarbonate. When all these findings were examined, it was seen that sodium bicarbon-

Table 2. Change of clinical and laboratory features between 0 and 2nd hours of treatment for all patients.

	Did not receive bicarbonate		Received bicarbonate		p value
	Mean ± SD	Median	Mean ± SD	Median	
Glasgow coma score					
0^{th} hour	14.9 ± 0.4	15.0	14.1 ± 1.3	15.0	**0.000**[m]
2^{nd} hour	14.9 ± 0.3	15.0	14.8 ± 0.6	15.0	**0.005**[m]
0 to 2^{nd} hour difference	0.0 ± 0.3	0.0	0.7 ± 1.2	0.0	**0.000**[m]
0 to 2^{nd} hour difference p value	0.083[w]		**0.000**[w]		
Respiratory rate, /min					
0^{th} hour	26.0 ± 7.1	24.0	34.5 ± 9.3	33.0	**0.000**[m]
2^{nd} hour	23.1 ± 6.3	22.0	32.8 ± 8.8	32.0	**0.000**[m]
0 to 2^{nd} hour difference	-2.8 ± 5.2	-3.0	-1.9 ± 8.7	-4.0	0.569[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		0.071[w]		
Heart rate, /min					
0^{th} hour	123.0 ± 23.8	123.0	136.9 ± 27.4	143.0	**0.000**[m]
2^{nd} hour	116.3 ± 21.1	116.0	139.0 ± 17.0	143.0	**0.000**[m]
0 to 2^{nd} hour difference	-7.1 ± 20.2	-7.0	1.0 ± 18.7	-3.0	**0.009**[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		0.442[w]		
pH					
0^{th} hour	7.14 ± 0.11	7.15	6.94 ± 0.10	6.92	**0.000**[m]
2^{nd} hour	7.21 ± 0.10	7.23	7.05 ± 0.13	7.05	**0.000**[m]
0 to 2^{nd} hour difference	0.07 ± 0.07	0.06	0.12 ± 0.11	0.11	**0.001**[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.000**[w]		
pCO_2					
0^{th} hour	23.5 ± 6.7	23.4	18.2 ± 5.3	18.3	**0.000**[t]
2^{nd} hour	23.6 ± 6.6	23.2	15.8 ± 6.3	15.0	**0.000**[t]
0 to 2^{nd} hour difference	0.1 ± 6.9	0.4	-2.2 ± 7.6	-2.1	0.084[t]
0 to 2^{nd} hour difference p value	0.836[p]		0.108[p]		
Bicarbonate, mmol/L					
0^{th} hour	8.6 ± 3.5	8.2	4.8 ± 4.8	3.9	**0.000**[m]
2^{nd} hour	10.3 ± 4.4	9.7	5.0 ± 3.0	4.6	**0.000**[m]
0 to 2^{nd} hour difference	1.7 ± 3.2	1.5	0.4 ± 5.4	0.7	0.183[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.041**[w]		
Anion gap, mmol/L					
0^{th} hour	21.0 ± 5.5	20.1	24.9 ± 4.2	24.7	**0.002**[t]
2^{nd} hour	16.5 ± 4.7	16.3	23.1 ± 3.3	23.0	**0.000**[t]
0 to 2^{nd} hour difference	-4.3 ± 4.8	-4.0	-1.6 ± 3.1	-2.0	**0.017**[t]
0 to 2^{nd} hour difference p value	**0.000**[p]		**0.026**[p]		
Chloride, mmol/L					
0^{th} hour	106.6 ± 6.4	107.0	107.3 ± 4.9	106.0	0.777[m]
2^{nd} hour	110.9 ± 5.0	111.0	112.1 ± 5.3	110.0	0.461[m]
0 to 2^{nd} hour difference	4.1 ± 5.0	4.0	4.8 ± 3.7	4.0	0.548[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.000**[w]		
Sodium, mmol/L					
0^{th} hour	133.8 ± 4.4	134.0	134.0 ± 6.1	133.0	0.533[m]
2^{nd} hour	135.8 ± 3.5	136.0	137.9 ± 5.9	137.0	0.050[m]
0 to 2^{nd} hour difference	2.1 ± 3.5	2.0	3.9 ± 3.3	4.0	**0.003**[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.000**[w]		
Potassium, mmol/L					
0^{th} hour	4.1 ± 0.8	4.1	4.3 ± 0.7	4.1	0.260[m]
2^{nd} hour	3.9 ± 0.7	3.9	3.9 ± 0.8	3.9	0.864[m]
0 to 2^{nd} hour difference	-0.2 ± 0.6	-0.2	-0.3 ± 0.7	-0.4	0.114[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.001**[w]		
Phosphorus, mg/dL					
0^{th} hour	3.7 ± 1.3	3.6	4.1 ± 1.5	4.0	0.174[m]
2^{nd} hour	3.3 ± 1.1	3.2	3.1 ± 1.5	3.0	0.189[m]
0 to 2^{nd} hour difference	-0.5 ± 1.1	-0.4	-1.1 ± 1.2	-1.1	**0.001**[m]
0 to 2^{nd} hour difference p value	**0.000**[w]		**0.000**[w]		

pCO_2: partial pressure of carbon dioxide, [m]: Mann-Whitney U Test, [w]: Wilcoxon Test, [t] :Independent Sample t-Test, [p]: Paired Sample t-Test.

Table 3. Change of clinical and laboratory features between 0 and 2nd hours of treatment for patients received bicarbonate versus patients with severe diabetic ketoacidosis (pH <7.1) but did not receive bicarbonate.

	Did not receive bicarbonate (pH<7.1)		Received bicarbonate		p value
	Mean ± SD	Median	Mean ± SD	Median	
Glasgow coma score					
0^{th} hour	14.9 ± 0.4	15.0	14.1 ± 1.3	15.0	**0.000**^{m}
2^{nd} hour	14.9 ± 0.3	15.0	14.8 ± 0.6	15.0	**0.033**^{m}
0 to 2^{nd} hour difference	0.0 ± 0.2	0.0	0.7 ± 1.2	0.0	**0.000**^{m}
0 to 2^{nd} hour difference p value	0.564^{w}		**0.000**^{w}		
Respiratory rate, /min					
0^{th} hour	28.1 ± 7.9	26.5	34.5 ± 9.3	33.0	**0.001**^{m}
2^{nd} hour	24.6 ± 6.8	23.0	32.8 ± 8.8	32.0	**0.000**^{m}
0 to 2^{nd} hour difference	-3.8 ± 5.8	-4.0	-1.9 ± 8.7	-4.0	0.853^{m}
0 to 2^{nd} hour difference p value	**0.000**^{w}		0.071^{w}		
Heart rate, /min					
0^{th} hour	129.1 ± 22.3	132.0	136.9 ± 27.4	143.0	**0.028**^{m}
2^{nd} hour	121.5 ± 25.1	124.0	139.0 ± 17.0	143.0	**0.000**^{m}
0 to 2^{nd} hour difference	-9.2 ± 20.5	-7.0	1.0 ± 18.7	-3.0	**0.020**^{m}
0 to 2^{nd} hour difference p value	**0.000**^{w}		0.442^{w}		
pH					
0^{th} hour	7.01 ± 0.06	7.03	6.94 ± 0.10	6.92	**0.000**^{m}
2^{nd} hour	7.11 ± 0.10	7.11	7.05 ± 0.13	7.05	**0.006**^{m}
0 to 2^{nd} hour difference	0.09 ± 0.09	0.07	0.12 ± 0.11	0.11	0.170^{m}
0 to 2^{nd} hour difference p value	**0.000**^{w}		**0.000**^{w}		
pCO_2					
0^{th} hour	22.0 ± 7.8	22.2	18.2 ± 5.3	18.3	**0.012**^{t}
2^{nd} hour	19.5 ± 6.7	18.6	15.8 ± 6.3	15.0	**0.007**^{t}
0 to 2^{nd} hour difference	-2.4 ± 7.9	-3.3	-2.2 ± 7.6	-2.1	0.907^{t}
0 to 2^{nd} hour difference p value	**0.031**^{p}		0.108^{p}		
Bicarbonate, mmol/L					
0^{th} hour	5.6 ± 2.2	5.5	4.8 ± 4.8	3.9	**0.001**^{m}
2^{nd} hour	6.6 ± 3.5	5.7	5.0 ± 3.0	4.6	**0.001**^{m}
0 to 2^{nd} hour difference	1.0 ± 3.1	0.7	0.4 ± 5.4	0.7	0.972^{m}
0 to 2^{nd} hour difference p value	**0.018**^{w}		**0.041**^{w}		
Anion gap, mmol/L					
0^{th} hour	22.7 ± 4.9	22.0	24.9 ± 4.2	24.7	0.093^{t}
2^{nd} hour	18.2 ± 4.0	17.6	23.1 ± 3.3	23.0	**0.000**^{t}
0 to 2^{nd} hour difference	-4.2 ± 5.0	-3.5	-1.6 ± 3.1	-2.0	**0.039**^{t}
0 to 2^{nd} hour difference p value	**0.000**^{p}		**0.026**^{p}		
Chloride, mmol/L					
0^{th} hour	109.2 ± 5.8	110.0	107.3 ± 4.9	106.0	0.239^{m}
2^{nd} hour	112.3 ± 5.1	112.0	112.1 ± 5.3	110.0	0.843^{m}
0 to 2^{nd} hour difference	2.9 ± 4.5	3.0	4.8 ± 3.7	4.0	0.161^{m}
0 to 2^{nd} hour difference p value	**0.002**^{w}		**0.000**^{w}		
Sodium, mmol/L					
0^{th} hour	133.5± 5.0	134.0	134.0 ± 6.1	133.0	0.805^{m}
2^{nd} hour	135.0 ± 3.5	135.0	137.9 ± 5.9	137.0	**0.011**^{m}
0 to 2^{nd} hour difference	1.5 ± 4.0	2.0	3.9 ± 3.3	4.0	**0.007**^{m}
0 to 2^{nd} hour difference p value	**0.001**^{w}		**0.000**^{w}		
Potassium, mmol/L					
0^{th} hour	4.3 ± 0.9	4.1	4.3 ± 0.7	4.1	0.919^{m}
2^{nd} hour	4.0 ± 0.8	3.9	3.9 ± 0.8	3.9	0.688^{m}
0 to 2^{nd} hour difference	-0.3 ± 0.7	-0.3	-0.3 ± 0.7	-0.4	0.414^{m}
0 to 2^{nd} hour difference p value	**0.008**^{w}		**0.000**^{w}		
Phosphorus, mg/dL					
0^{th} hour	4.1 ± 1.5	3.8	4.1 ± 1.5	4.0	0.924^{m}
2^{nd} hour	3.0 ± 1.2	2.8	3.1 ± 1.5	3.0	0.933^{m}
0 to 2^{nd} hour difference	-1.0 ± 1.2	-0.8	-1.1 ± 1.2	-1.1	0.549^{m}
0 to 2^{nd} hour difference p value	**0.001**^{w}		**0.000**^{w}		

pCO_2: partial pressure of carbon dioxide, ^{m}: Mann-Whitney U Test, ^{w}: Wilcoxon Test, ^{t} :Independent Sample t-Test, ^{p}: Paired Sample t-Test.

ate treatment did not provide a significant benefit in both clinical and laboratory findings except pH and GCS. It was also challenging to assess whether the elevation in pH and GCS was related to sodium bicarbonate treatment. Because this treatment was already administered to more severe DKA patients with lower pH and GCS, a comparison between two groups of similar severity would be more appropriate for evaluating the efficacy of sodium bicarbonate. Therefore, the study's analysis was repeated between those receiving sodium bicarbonate and those with severe DKA (pH<7.1) but not receiving sodium bicarbonate. When these two groups were compared, it was seen that the change in pH was similar between the two groups; only the increase in GCS was higher in the sodium bicarbonate receiving group. Sodium bicarbonate treatment can cause paradoxical cerebral acidosis and decrease the GCS [3]. However, sodium bicarbonate did not cause clinical neurological deterioration in any patient in the present study. Sodium bicarbonate seems to be safe in this respect.

Another undesirable effect of sodium bicarbonate treatment is hypokalemia [3]. In the present study, the change in potassium and phosphorus in two hours was similar in those who received sodium bicarbonate and those who did not.

A systematic review of 44 studies found heterogeneity in timing and indications for sodium bicarbonate treatment [9]. In this review, an improvement in acidosis was detected within the first two hours; however, its clinical benefit has not been demonstrated. Risks such as brain edema, paradoxical worsening of ketosis, and hypokalemia have been noted [9].

Sodium bicarbonate is recommended in severe cases where the pH is less than 6.9 [6-8]. There is no recommendation in the literature for sodium bicarbonate treatment based on pCO_2 or anion gap. Making the treatment decision by considering only pH will result in not giving this treatment to patients who respiratorily compensate for metabolic acidosis and who manage to keep the pH greater than 6.9 by reducing the pCO_2 too much. In our study, the pH threshold value for the indication of treatment with sodium bicarbonate was 6.9; and the threshold value of pCO_2 was accepted as 15 mmHg. If the indication were determined only according to pH, sodium bicarbonate would not have been administered to 25 of 44 patients who received this treatment in the present study. If the respiratory compensation amount of two patients with the same degree of metabolic acidosis were different, their pH would not be the same, and sodium bicarbonate would not be administered to those who managed to raise the pH greater than 6.9 by lowering the pCO_2, while those who could not raise the pH greater than 6.9 would be administered. Therefore, we think pCO_2 and anion gap should be considered along with pH when determining the indication for sodium bicarbonate.

Hypocapnia is a poor prognostic factor in DKA [10]. In addition to the distress caused by the increased respiratory effort in the patient trying to compensate for the metabolic acidosis respiratorily, the resulting hypocapnia also has harmful effects. Hypocapnia, cerebral vasospasm, and the related decrease in cerebral oxygen supply may cause brain damage by causing an increase in cerebral oxygen demand [11]. Factors that cause cerebral ischemia should be avoided in cases such as DKA, which carry the risk of cerebral edema, and the need for protection of brain perfusion requires special attention.

Limitations

This study has several limitations. It was a single-center retrospective study. Therefore it has limited generalizability. Because the patients who received sodium bicarbonate were more severe than those who did not, an optimal comparison to evaluate the effect of sodium bicarbonate could not be possible. Given these limitations, we invite readers to interpret these results carefully.

Conclusion

In our study, we predicted that the most important clinical effect of sodium bicarbonate treatment would be on hemodynamic variables. However, sodium bicarbonate treatment had no significant beneficial effect on clinical findings such as respiratory and heart rates, nor on laboratory findings such as pH, pCO_2, anion gap, and bicarbonate level. No neurological deterioration or any other side effects were detected. In this study, we could not see a significant impact on pCO_2 either. However, although its use is controversial, we think that not only pH or bicarbonate level but also other parameters such as pCO_2 and anion gap should be considered when determining an indication for sodium bicarbonate treatment. More extensive studies should be conducted to evaluate clinical efficacy and safety when the indication is determined using these parameters.

Conflicts of interest

The authors declare that they have no conflict of interest.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Zeynelabidin Ozturk, Ayça Kılıç and Göktuğ Özdemir. The first draft of the manuscript was written by Zeynelabidin Ozturk and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethical approval

Ethics approval was obtained from the ethics committee of University of Health Sciences, Dr. Sami Ulus Obstetrics and Gynecology, Pediatric Health and Disease Training and Research Hospital (Approval number: E-22/06-345).

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