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Original Article

The factors affecting resolution of acidosis in children with diabetic ketoacidosis - A retrospective study from a tertiary care center in India

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ABSTRACT

Background: Diabetic ketoacidosis (DKA) is characterized by a spectrum of clinical manifestations due to deficiency of insulin which results in hyperglycemia, ketonemia with ketonuria, and metabolic acidosis. Administration of insulin inhibits the production of keto acids and facilitates their metabolism, thereby helps in correcting the acidosis. However, in some situations, the acidosis takes longer to get corrected. **Objectives:** The aim of this study is to evaluate the factors at admission predicting the duration of acidosis in a child presenting with DKA. **Methods: Study Type:** This was a retrospective case record review. **Inclusion Criterion:** All children <15 years who were admitted under the pediatric intensive care unit of a tertiary care hospital from April 2012 to January 2016 with DKA were included in this study. Their demographic data, investigations, treatment details, and length of hospital stay were noted in a predesigned pro forma. Prolonged acidosis was defined as acidosis taking longer than 24 h to resolve. **Results:** Forty-eight cases met the inclusion criteria; of the 48 cases, 27 (56%) had prolonged acidosis. The median duration of correction of acidosis was 31 h (interquartile range 18.75-48 h/range of 6-192 h). On univariate analysis, children with prolonged acidosis had a low pH (7.1 vs. 7.25), a low serum bicarbonate (4.69 vs. 7.49 mEq/L), base excess (−22.7 vs −17.04), a high total leukocyte count (TLC) (24,275 vs. 13,557 cells/mm^3), and platelet count (450,651 vs. 316,140 cells/mm^3) at admission (t-test, $p<0.05$**).** On stepwise logistic regression analysis, only low pH and a high TLC were associated with prolonged acidosis. The presence of rhabdomyolysis and myocardial impairment and degree of dehydration at admission which could contribute to prolonged acidosis were not measured in this study. **Conclusion:** Prolonged acidosis (lasting more than 24 h) was associated with a high TLC and a low pH at admission.

Key words: *High anion gap, Diabetic ketoacidosis, Metabolic acidosis, Normal anion gap*

Diabetic ketoacidosis (DKA) is characterized by a spectrum of clinical manifestations due to deficiency of insulin which results in hyperglycemia, ketonemia with ketonuria, and metabolic acidosis. It is the most serious complication of pediatric diabetes causing hospitalization and requiring admission in a pediatric intensive care unit (PICU). The incidence of pediatric diabetes presenting as DKA varies from 15% to 67% [1,2]. It is also one of the leading causes of mortality in diabetes. Although the mortality from DKA in developed countries has come down to 0.15-0.31% [3,4], it still ranges between 3.4% and 13.4% in developing countries [5-8].

The accumulation of beta-hydroxybutyrates and acetoacetate leads to a high anion gap metabolic acidosis (HAGMA) in DKA. However, a normal anion gap metabolic acidosis (NAGMA) can be there at presentation or develop during the course of treatment. One of the reasons for developing NAGMA could be the loss of bicarbonate ions during the urinary excretion of ketones. The second reason could be the development of hyperchloremic metabolic acidosis (HMA). A patient can also have other coexistent acid-base disorders such as metabolic alkalosis due to vomiting and metabolic acidosis due to dehydration and shock. The delta ratio can be used to identify these mixed acid-base disorders in the HAGMA group.

During the treatment of DKA, administration of insulin inhibits the production of keto acids and facilitates their metabolism, thereby helps in correcting the acidosis. The presence of NAGMA during admission or the development of HMA during the course of treatment has been shown to delay the recovery of acidosis which in turn can delay the transition from continuous insulin infusion to subcutaneous insulin [9,10]. There are very few studies comparing the factors at admission with the duration of acidosis [9,10]. There is a paucity of data on pediatric DKA from the Indian subcontinent. The aim of our study was to evaluate these factors at admission predicting the duration of acidosis in a child presenting in DKA.

MATERIALS AND METHODS

We did a retrospective analysis of case notes of children <15 years presenting to the PICU of a tertiary care hospital

in from April 2012 to January 2016 with a diagnosis of DKA. A child was diagnosed to be in DKA if there was hyperglycemia (blood glucose>200 mg/dl) along with a blood pH of <7.3 and/or a serum bicarbonate of <15 mEq/L along with ketonuria. DKA severity was further classified into mild, moderate, and severe according to the International Society for Pediatric and Adolescent Diabetes consensus of 2014 [2]. Each admission was taken as a separate case. Children who received intravenous sodium bicarbonate before admission or during the hospital stay and children with a history of chronic kidney disease were excluded from the study.

The demographic data, history, and investigations (serial arterial blood gases, electrolytes, renal function tests, and glycosylated hemoglobin) were noted in a predesigned pro forma. The anion gap AG was calculated as Na-(CL+HCO3). The delta gap (DG) was calculated as AG-12-(24-HCO3). The true Na was calculated as Na + (1.6 mEq/L Na for every 100 mg/dl excess RBS above 100 mg/dl). The total leukocyte count (TLC) was taken to be elevated if it was higher than the age-specific normal values. The duration of PICU and hospital stay was also noted. The time taken for resolution of acidosis (defined as serum bicarbonate >15 mEq/L) was recorded from the retrospective records. A child was taken to have prolonged acidosis if the serum bicarbonate took longer than 24 h to reach a value of >15 mEq/L. The fluid resuscitation and treatment were carried out as per the Milwaukee protocol. Several factors such as age, pH, serum bicarbonate, partial pressure of carbon dioxide (PCO_2), base excess (BE), AG, DG, random blood sugar (RBS), sodium, corrected sodium, TLC, platelet count, creatinine, antibiotics used, and history of diabetes were analyzed. The study was approved by the Institutional Ethics Committee.

Statistical Analysis

A pilot study carried out by the investigator revealed that 50% of the patients had prolonged acidosis. Based on the above findings, with an absolute precision of 15 and desired confidence level of 95%, it was estimated that 43 patients of DKA need to be recruited. A study carried out by Kimura et al. observed that patients who tend to have prolonged acidosis tend to have lower admitting mean bicarbonate values at admission (4.7±1.9) mEq/L as compared to patients with quicker resolution (9.5±3) mEq/L [9].

Statistical analysis of data: Continuous variables such as electrolytes (Na, K) were expressed as mean and standard deviation (SD). Categorical variables were expressed as a percentage with 95% confidence interval (CI). Student's t-test or appropriate non-parametric tests were employed to test for differences in the mean values between the 2 groups, namely, patients with or without prolonged acidosis. Similarly, association factors of categorical variables were studied through chi-square test of significance. In case of non-normality, median with interquartile range was estimated. To evaluate the independent risk factors associated with prolonged acidosis, stepwise logistic regression methodology was employed.

RESULTS

We had a total of 58 admissions of DKA with a mean±SD age of presentation being 10±4 years (range: 0.75-15 years). Out of these, 10 admissions were excluded as they had received intravenous sodium bicarbonate. Females formed 52% (n=30) and males 48% (n=28) of the patient cohort. Polyuria and polydipsia (n=30/58, 52%) and vomiting (n=28/48, 48%) were the most common presenting symptoms. Majority of the children presented in severe DKA at admission (n=28/48, 48%), whereas moderate and mild DKA formed 36% and 15.5% of the sample population, respectively. Newly diagnosed diabetes was seen in 67% (n=39) of cases.

Of the 48 cases, 27 cases (56%) had prolonged acidosis. The distribution of cases in the two groups with respect to age and gender was not statistically significant. The median duration of correction of acidosis was 31 h with an interquartile range of 18.75-48 h. Of the 27 cases with prolonged acidosis, 63% (n=17) had a NAGMA at 24 h of admission.

As shown in Table 1, children with prolonged acidosis had a lower mean pH (7.1 vs. 7.25), bicarbonate (4.69 vs. 7.49 mEq/L), base excess (−22.7 vs. −17.04), and higher total TLC (24,275 vs. 13,557 cells/mm^3) and platelet count (450,651 vs. 316,140 cells/mm^3) at admission. These differences were found to be statistically significant ($p<0.05$). The differences in the two groups with respect to AG, random blood sugar, total and corrected sodium, and serum creatinine at admission were not significant. An elevated TLC (based on age appropriate values) was present in 74% (n=20/27) of cases in the prolonged acidosis group as against 29% (n=6/21) in the acidosis corrected group. Of the total 26 cases with an elevated total count, only 5 had a culture proven sepsis all of which were in the prolonged acidosis group. 58 % (n=15/26) of these with an elevated total count presented in severe DKA.

Out of the 48 cases, 22.9% (n=11/48) had a positive DG (>+6) and 8.3% (n=4) had a negative DG (<−6) indicating that they had a coexistent metabolic alkalosis and non-gap metabolic acidosis, respectively. The median DG in the prolonged acidosis group was 1.2 as compared to 4 in the acidosis corrected group. However, this difference was not statistically significant (p=0.142).

On univariate analysis, as shown in Table 2, children with severe acidosis pH <7.1 and serum bicarbonate <5 mEq/L were more likely to develop prolonged acidosis (OR=17, 95% CI=2.83-102, p=0.002) (OR=7.29, 95% CI=1.17-45.25, p=0.03), respectively. It was also found that patients with a high TLC (OR=8.3, 95% CI=2.23-31, p=0.002) and platelet count (OR= 14.6, 95% CI=1.7-126.3, p=0.015) were likely to take longer time to correct the acidosis. After logistic regression analysis, all factors were eliminated except a low pH (<7.1) (adjusted OR=24, 95% CI=3.36-171.5, p=0.002) and a high TLC (adjusted OR=7.87, 95% CI=1.6-38.6, p=0.011).

DISCUSSION

The mean±SD age of our study population was 10±4 years (range of 0.75-15 years). This was slightly higher compared to other

Table 1: Mean and standard deviation of factors affecting duration of acidosis

Factors	Total cases (n=48)	Acidosis <24 h mean±SD (n=24)	Acidosis >24 h mean±SD (n=27)	p-value
Age in years	10.2 (4.1)	9.52±4.17	10.78±4.04	0.296
pH	7.17 (0.13)	7.25±0.12	7.10±0.11	0.00
HCO_3 (mEq/L)	5.9 (3.4)	7.49±3.8	4.69±2.52	0.04
PCO_2 (mm Hg)	15 (5.3)	16.19±5.73	14.16±4.82	0.19
BE (mEq/L)	−20 (5.6)	−17.04±5.55	−22.7±4.35	0.00
AG	26.5 (5.8)	26.6±4.5	26.4±6.7	0.91
DG[1]	2.6 (−9,2.6,6.6)	4±(−0.25,4,7.95)	1.2±(−2.2,1.2,5)	0.142
RBS (mg/dl)	472 (132)	456±118	484±144	0.376
Na (mEq/L)	133.2 (6.2)	133±6.2	133.3±6.2	0.826
Corrected Na (mEq/L)	139 (6.2)	139.1±6.59	139.4±6.0	0.664
Creatinine (mg/dl)	0.77 (0.26)	0.72±0.22	0.81±0.28	0.266
Total leukocyte count (cells/mm^3)	19,486 (12,314)	13,557±5879	24,275±14071	0.00
Platelet count (cells/mm^3)	3,90,551 (232000)	3,16,140±79255	4,50,651±293,265	0.047
PICU stay (d)	3.632.4)	2.86±1.56	4.22±2.8	0.038
Hospital stay (d)	9.04 (3.8)	8.1±3.44	9.88±4.0	0.489

SD: Standard deviation, PICU: Pediatric intensive care unit, DG: Delta gap, AG: Anion gap

Table 2: Univariate and multivariate stepwise forward logistic regression analysis of the factors associated with prolonged acidosis

Variable	Levels	Univariate analysis OR	95% CI	p-value	Multivariate analysis OR	95% CI	p-value
pH	>7.25	1.0					
	7.15-7.25	2.33	0.454-12.0	0.311	3.5	0.56-21.66	0.178
	<7.15	17.0	2.83-102.0	0.002	24.00	3.36-171.5	0.002
HCO_3	>10	1.0					
	5-10	3.0	0.46-19.59	0.25			
	<5	7.29	1.17-45.25	0.033			
Total WBCs	<15000	1.0					
	>15000	8.33	2.23-31.0	0.002	7.87	1.6-38.6	0.011
Platelet count	<450000	1.0					
	>450000	14.66	1.7-126.3	0.015			

studies, where the mean was 6.9±3.5 and 7.5±3.6 [5,11]. The main symptoms at admission were vomiting, polyuria, and polydipsia which are comparable to another study [7]. Respiratory distress (87.1%) and vomiting (77.7%) were the most common presenting complaints in another study from a developing country [11]. 58% (n=28) of our patients presented in severe DKA, whereas another study from India had nearly two-thirds of the cases coming with severe DKA [7]. This could reflect the lack of awareness and late presentation in the clinical course of the disease in our study group. The mean duration of correction of acidosis was 37 h in our study as against 11.6±6.2 h in another study [12]. This may be because most of our patients presented in severe DKA.

The increase in the AG should be equal to the decrease in serum bicarbonate in a setting of high-AG acidosis. The DG which measures the difference between the two, if found to be positive DG (>+6), suggests the presence of coexistent metabolic alkalosis which can result due to persistent vomiting. A negative DG (<−6) suggests a non-AG acidosis which can result from excess chloride load administered during the treatment. Persistent HMA in one study and low base excess and DG in another were shown to slow recovery from acidosis [9,10]. In our study, we found that the presence of leukocytosis and a low pH was associated with a longer time taken for correction of acidosis. Leukocytosis may be present in 50-60% of children with DKA and it may be due to stress response. Studies have shown that there is a non-infectious systemic inflammation response in DKA patients as evidenced by leukocytosis and pro-inflammatory cytokines [13,14]. A high TLC has also been correlated with both acute as well as chronic complications in diabetes. Microvascular and macrovascular complications such as peripheral arterial disease, albuminuria, and retinopathy have been associated with an elevated TLC in type 2 diabetes [15-18]. The presence of a high total leukocyte and platelet count could probably indicate that our children were presenting with more severe dehydration. A major limitation of our study was that the degree of dehydration at admission was not studied which could be an important confounding factor.

Severe DKA at admission was associated with a longer time to correction of acidosis. A low pH rather than a low serum bicarbonate had a more significant association with prolonged acidosis in our study. Serum bicarbonate can also be affected by the metabolic alkalosis that results from the vomiting that causes loss of H^+ as well as from bicarbonate loss from diarrhea

and coexistent renal dysfunction. Studies have shown that serum bicarbonate has a good correlation with the pH in DKA and that it can be used to diagnose as well as classify the severity [19,20].

In our study, we documented culture positive sepsis in 10% of cases. 12% of children with DKA were found to have culture-positive sepsis in another study [21]. Intravenous sodium bicarbonate correction was given in 10 admissions in our study, the reasons being persistent acidosis after rehydration, extremely low pH, and cardiorespiratory compromise. There were 2 deaths in our study and the reasons were sino-orbital mucormycosis and septicemia. The predominant cause of mortality in DKA in developing countries is cerebral edema, sepsis, shock, and renal failure [4]. No child in our study population had cerebral edema. The incidence of cerebral edema in developing countries is reported to vary from 24% to 26% [5].

One of the limitations of this study was that certain blood investigations such as albumin and triglycerides were not done in all patients as this was a retrospective review which can impact the AG among other investigations. Another limitation was that myocardial impairment and rhabdomyolysis were not ruled out and they too could contribute to the prolongation of acidosis. The degree of dehydration at admission was not studied which could also influence the correction of acidosis. A small sample size was another limitation. A prospective study with a larger sample size in this field taking into account the above investigations could give a more meaningful insight into the factors contributing to prolonged acidosis.

CONCLUSIONS

A low pH and a high TLC in children with DKA at admission were observed to be associated with prolonged acidosis in our retrospective review. However, further prospective studies are needed to determine if they can predict that a child in DKA at admission takes longer to normalize their acidosis.

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REFERENCES

1. Dunger DB, Sperling MA, Acerini CL, Bohn DJ, Daneman D, et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child. 2004;89(2):188-94.
2. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, et al. Diabetic ketoacidosis in children and adolescents with diabetes. Pediatr Diabetes. 2009;10 Suppl 12:118-33.
3. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in Ontario children. Diabetes care. 2002;25(9):1591-6.
4. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. J Pediatr. 2005;146(5):688-92.
5. Jayashree M, Singhi S. Diabetic ketoacidosis predictors of outcome in a pediatric intensive care unit of a developing country. Pediatr Crit Care Med. 2004;5(5):427-33.
6. Tiwari LK, Muralindharan J, Singhi S. Risk factors for cerebral edema in diabetic ketoacidosis in a developing country: Role of fluid refractory shock. Pediatr Crit Care Med. 2012 Mar;13(2):e91-6.
7. Kanwal SK, Bando A, Kumar V. Clinical profile of diabetic ketoacidosis in Indian children. Indian J Pediatr. 2012;79(7):901-4.
8. Jahagirdar RR, Khadilkar VV, Khadilkar AV, Lalwani SK. Management of diabetic ketoacidosis in PICU. Indian J Pediatr. 2007;74(6):551-4.
9. Kimura D, Raszynski A, Balagangadhar RT. Admission and treatment factors associated with the duration of acidosis in children with diabetic ketoacidosis. Pediatr Emerg Care. 2012;28:1302-6.
10. Mrozik LT, Yung M. Hyperchloraemic metabolic acidosis slows recovery in children with diabetic ketoacidosis: A retrospective audit. Aust Crit Care. 2009;22(4):172-7.
11. Syed M, Khawaja FB, Saleem T, Khalid U, Rashid A, Humayun KN. Clinical profile and outcomes of paediatric patients with diabetic ketoacidosis at a tertiary care hospital in Pakistan. J Pak Med Assoc. 2011;61(11):1082.
12. Fiordalisi I, Novotny WE, Holbert D, Finberg L, Harris GD. An 18 yr prospective study of pediatric diabetic ketoacidosis: An approach to minimizing the risk of brain herniation during treatment. Pediatr Diabetes. 2007;8(3):142-9.
13. Stentz FB, Umpierrez GE, Cuervo R, Kitabchi AE. Proinflammatory cytokines, markers of cardiovascular risks, oxidative stress, and lipid peroxidation in patients with hyperglycemic crises. Diabetes. 2004;53:2079-86.
14. Karavanaki K, Karanika E, Georga S, Bartzeliotou A, Tsouvalas M, et al. Cytokine response to diabetic ketoacidosis (DKA) in children with Type 1 diabetes (T1DM). Endocr J. 2011;58:1045-53.
15. Tong PC, Lee KF, So WY, Ng MH, Chan WB, et al. White blood cell count is associated with macro-and microvascular complications in Chinese patients with Type 2 diabetes. Diabetes Care. 2004;27:216-22.
16. Moradi S, Kerman SR, Rohani F, Salari F. Association between diabetes complications and leukocyte counts in Iranian patients. J Inflamm Res. 2012;5:7-11.
17. Woo SJ, Ahn SJ, Ahn J, Park KH, Lcc K. Elevated systemic neutrophil count in diabetic retinopathy and diabetes: A hospital-based cross-sectional study of 30,793 Korean subjects. Invest Ophthalmol Vis Sci. 2011;52:7697-03.
18. Papazafiropoulou A, Kardara M, Sotiropoulos A, Bousboulas S, Stamataki P, et al. Plasma glucose levels and white blood cell count are related with ankle brachial index in Type 2 diabetic subjects. Hellenic J Cardiol. 2010;51:402-6.
19. Von Oettingen J, Wolfsdorf J, Feldman HA, Rhodes ET. Use of serum bicarbonate to substitute for venous pH in new-onset diabetes. Pediatrics. 2015;136(2):e371-7.
20. Nadler OA, Finkelstein MJ, Reid SR. How well does serum bicarbonate concentration predict the venous pH in children being evaluated for diabetic ketoacidosis? Pediatr Emerg Care. 2011;27(10):907-10.
21. Varadarajan P, Suresh S. Delayed diagnosis of diabetic ketoacidosis in children—a cause for concern. Int J Diabetes Dev Ctries. 2015;35(2):66-70.

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