Hyperchloremic Metabolic Acidosis in Diabetic Ketoacidosis – Boon or Bane in Paediatrics? Prospective Cohort Study

Anusha K Patil and Vishwanath B

Department of Paediatrics, Shri B.M. Patil Medical College, Vijayapur, Karnataka, India
Department of Paediatrics, Vijayanagar Institute of Medical Sciences, Ballari, Karnataka, India

ABSTRACT

Introduction: Patients with DKA generally present with a high anion gap metabolic acidosis (AG > 16) due to the presence of ketones but may also develop a narrow anion gap metabolic acidosis related to hyperchloremia. This study attempts to determine the incidence of hyperchloremic metabolic acidosis (before starting IV fluids) in children with DKA and to evaluate the impact of hyperchloremic metabolic acidosis on acute kidney injury and cerebral edema and in turn on mortality and duration of PICU stay.

Methods: This was a prospective study conducted in the Department of Paediatrics, VIMS, Bellary between May 2016 to December 2017 and a total of 32 patients with DKA were enrolled in the study. Along with routine investigations, ABG and serum chloride levels were measured at the time of admission for categorization into normochloremic (high anion-gap) metabolic acidosis and hyperchloremic (normal anion-gap) metabolic acidosis. Incidence of hyperchloremic metabolic acidosis and its impact on the development of acute kidney injury and cerebral edema was taken as the primary outcome of the study. Mortality rate and duration of PICU stay were taken as a secondary outcome.

Results: Hyperchloremic metabolic acidosis was observed in 18.8% of the study group. Acute kidney injury was seen in 38.4% of children who had normochloremic metabolic acidosis and in 83.3% of children with hyperchloremia. About 50% patients developed cerebral edema in the hyperchloremia group and only 3.8% developed cerebral edema in normochloremic group. These differences were statistically significant. Mortality rate in normochloremic and hyperchloremic metabolic acidosis was 3.8% and 50% respectively.

Conclusions: Hyperchloremia at presentation in DKA is a risk factor for increased mortality. This fact should be born in mind while treating patients aggressively with chloride-containing fluids. Simple investigations like ABG and serum chloride levels can direct careful management of DKA and appropriate selection of IV fluids.

Key Words: acute kidney injury; cerebral edema; Hyperchloremia; metabolic acidosis; PICU stay
INTRODUCTION
The incidence of type 1 diabetes mellitus (DM) has increased worldwide. On average, 78,000 children are diagnosed with diabetes every year. One among every five children with newly diagnosed type 1 DM is found to be an Indian, and Diabetic ketoacidosis (DKA) is a dreaded complication of DM. On average, around 30-50% of children with type 1 DM present with DKA at diagnosis and many develop DKA during the course of the disease. It is a life-threatening complication of DM with reported frequency ranging from 15 - 70% across different study population. Mortality in DKA is mainly due to cerebral edema, other causes being venous thrombosis, dyselectrolytemia, sepsis and AKI. Cerebral edema complicating DKA is solely a paediatric problem and is almost unknown in adults. The reason for the predisposition of children to cerebral edema as well as pathogenetic mechanisms of this complication are unclear even 70 years after its initial description. DKA is characterized by metabolic acidosis with high anion gap (with normal chloride levels), but it can also present with normal anion gap (hyperchloremic) metabolic acidosis. The anion gap (sodium + potassium – chloride – bicarbonate) classifies metabolic acidosis into high anion gap (HMA) (indicating the presence of routinely unmeasured anions like ketones and lactate) or normal anion gap (NMA) disorders (where the acidosis is not related to unmeasured anions and it is associated with high chloride levels). Patients with DKA generally present with a wide AG acidosis (AG > 16) indicating the presence of ketones but may develop a narrow anion gap acidosis related to hyperchloremia. Hyperchloremia is attributed to both the urinary excretion of ketones (as HCO3 precursors) with chloride retention and also treatment with NS. Once the serum concentration of the anionic ketones exceeds the kidneys' normal threshold, the ketones are excreted in the urine and the anion chloride is reabsorbed to maintain electroneutrality. The term hyperchloraemic acidosis in DKA has been documented in the literature for over 70 years however, only recently has the incidence of this phenomenon been investigated.

Hyperchloraemic acidosis due to prolonged ketonuria may coexist with DKA at the time of presentation or may develop during the management of DKA from an excess chloride load administered in intravenous fluid containing equal concentrations of sodium and chloride. The present study is undertaken to determine the prevalence of the hyperchloraemic component in metabolic acidosis at presentation (before starting iv fluids) and its impact on development of complications like cerebral edema and AKI. We also evaluated the impact of hyperchloremic metabolic acidosis on mortality and duration of PICU stay.

METHODS
The present study was a prospective cohort study conducted in the Department of Paediatrics, VIMS, Bellary, India after obtaining clearance from the institutional ethical committee. The study was conducted for one and half years, i.e., between May 2016 to December 2017. Any child <18 years with clinical and lab confirmed diagnosis of DKA was included in the study. Diagnostic criteria of DKA was as per International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines.

Children with sepsis or multiorgan failure along with DKA, those with known previous kidney diseases, those who received IV fluid therapy before admission and those who had symptoms for more than 24 hours before admission were excluded from the study. Informed written consent was taken from the parents / guardians. The study population’s relevant information was collected by interviewing the parents or guardians of the child using a pre-designed proforma. Each patient was subjected to thorough clinical assessment including history, review of past medical records, general physical examination with special emphasis on clinical features suggestive of acidosis and cerebral edema, blood pressure measurement, anthropometry, quantification of acidosis using ABG, serum electrolytes including chloride levels, RFT, CBC and CRP and other relevant investigations as indicated were done.

DKA was diagnosed and managed according to the guidelines of ISPAD. Isotonic saline was
continued until the blood glucose fell to 250 mg/dL, after which fluid was changed to N/2 saline with 5% Dextrose. Insulin was started after first hour at a rate of 0.05 - 0.1 U/kg/hour. DKA was categorized using ABG parameters as per Nelson textbook of Paediatrics. Mild DKA was treated using 0.05 U/kg/hr, Moderate to severe DKA was treated using 0.1 U/kg/hr. AKI was defined by pRIFLE classification using estimated creatinine clearance (eCCl), as urine output criterion is not reliable in the setting of osmotic diuresis.

Cerebral edema associated with DKA is primarily a clinical diagnosis. Early warning signs include drowsiness after initial improvement, headache, vomiting, relative bradycardia and relative hypertension. Management of cerebral edema included mannitol (20% 5 mL/kg single IV dose followed by 2.5 mL/kg six hourly), head-end elevation, and fluid restriction. All details including length of PICU stay, hydration status, type of fluid given, dose, type and duration of insulin given was documented. Correcting the dehydration by appropriate IV fluid, arresting the ketogenesis by insulin therapy and treating the precipitating causes form the basis of treatment in DKA. After thorough analysis and depending on ABG and chloride levels

at admission, two groups, i.e., normochloremic metabolic acidosis and the other with hyperchloremic metabolic acidosis, were categorized. However serial trends in chloride levels were not monitored. Time to normalization of pH, HCO3, anion gap were recorded in both groups and compared. The spectrum of complications like AKI, cerebral edema was compared between both groups. The duration of PICU stay and mortality were also analysed. All the parameters were statistically analysed and chi-square tests were applied to the results.

**RESULTS**

During the study period, 45 patients were admitted with DKA, out of which 13 patients were excluded as they IV fluid therapy before reaching our hospital. Total 32 patients who satisfied inclusion criteria were included in the study (20 females and 12 males) with mean age of presentation being 10.2 ± 1.6 years. Of 32 children enrolled, 26 (81%) were new onset diabetes presenting as DKA. Hyperchloremic metabolic acidosis (before starting IV fluids) was observed in six patients accounting for 18.8% and the remaining 26 patients had normochloremic metabolic acidosis (81.2%). The incidence of AKI and cerebral edema were compared between both groups. The duration of PICU stay and mortality were also analysed. All the parameters were statistically analysed and chi-square tests were applied to the results.

### Table 1. Comparison of AKI in hyperchloremic and normochloremic metabolic acidosis

| Condition                              | AKI present | AKI absent |
|----------------------------------------|-------------|------------|
| Hyperchloremic metabolic acidosis      | 05 (83.3%)  | 01 (16.7%) |
| Normochloremic metabolic acidosis      | 10 (38.4%)  | 16 (61.6%) |

Chi-square: 3.941
p value: 0.04 (<0.05) (Significant)

### Table 2. Comparison of cerebral edema in hyperchloremic and normochloremic metabolic acidosis

| Condition                              | Cerebral edema present | Cerebral edema absent |
|----------------------------------------|------------------------|----------------------|
| Hyperchloremic metabolic acidosis      | 3(50%)                 | 3(50%)               |
| Normochloremic metabolic acidosis      | 1(3.8%)                | 25(96.2%)            |

chi square: 9.495 p value = 0.02 (< 0.05) (Significant)

### Table 3. Comparison of duration of PICU stay in hyperchloremic and normochloremic metabolic acidosis

| Duration of PICU stay | <48 hours | >48 hours |
|------------------------|-----------|-----------|
| Hyperchloremic metabolic acidosis | 2         | 1         |
| Normochloremic metabolic acidosis    | 20       | 5         |

Chi-square=0.2828 p value=0.59(>0.05) (Not significant)

### Table 4. Mortality pattern in hyperchloremic and normochloremic metabolic acidosis

| Outcome                              | Survival | Death |
|--------------------------------------|----------|-------|
| Normochloremic metabolic acidosis     | 25(96.2%)| 01(3.8%)|
| Hyperchloremic metabolic acidosis    | 03(50%)  | 03(50%)|

Chi-square=9.49 P-value=0.002(<0.05) (Significant)
patients) children who had normochloremic metabolic acidosis developed AKI. Meanwhile, 83.3% (Five) patients who had hyperchloremic metabolic acidosis developed AKI, which was significant statistically (Table 1). Among six with hyperchloremia, 50% (Three) patients developed cerebral edema and only 3.8% (One) patient among 26 with normochloremia developed cerebral edema. The rate of development of cerebral edema was also more in hyperchloremia group (Table 2).

Time to normalization of pH, HCO₃⁻, anion gap was recorded in both groups and compared. The duration of PICU stay and mortality were also analyzed. The categorization of duration of PICU stay as < 48 hrs and > 48 hrs, based on fluid deficit correction time as per ISPAD guidelines. However all 22 cases who were shifted out from PICU had an average correction of acidosis within 30 hours. Six cases who took more than 48 hrs stay were complicated with AKI (Table 3). Out of six patients with hyperchloremia, 50% (three) patients succumbed to the illness. Mortality rate in normochloremic metabolic acidosis was 3.8% and this difference was significant statistically (Table 4).

### DISCUSSION

The incidence of DM is increasing worldwide. The prevalence of DM has been rising more rapidly in low and middle-income countries than in high-income countries. DKA is one of the acute metabolic complication of DM. DKA presents with a broad spectrum of acid-base disturbances complicated by metabolic alkalosis from emesis, respiratory alkalosis, metabolic acidosis from poor perfusion, and metabolic acidosis from excess chloride administration. The interaction of multiple factors during the development and recovery from DKA is responsible for this wide variation in the acid-base and electrolyte pattern. In DKA, AG increases primarily due to an increase in the concentration of major ketone bodies in serum. Hyperchloremic acidosis due to prolonged ketonuria may coexist with DKA at the time of presentation (before starting IV fluids) or may develop during the management of DKA from an excess chloride load administered in IV fluid containing equal concentrations of sodium and chloride. Although recovery from acidosis is known to be slower in patients admitted with pure hyperchloremic acidosis; the exact prevalence and impact of hyperchloremia on DKA treatment remains unknown. The present study was conceptualized to determine the prevalence of the hyperchloremic component in metabolic acidosis at presentation and to assess whether it is associated with cerebral edema and AKI.

Chloride is the most prominent anion in the extracellular fluid and forms nearly one-third of the extracellular fluid tonicity. Chloride plays a prominent role in many body functions including acid-base balance, muscular activity, osmosis, and immunomodulation. Despite its physiological importance, chloride has captured little attention by the scientific community until recently when chloride-rich solutions were associated with hyperchloremic metabolic acidosis. Our study adds to the growing body of evidence showing that elevated chloride levels may be harmful in certain inpatient populations of DKA. Hyperchloremia, in many clinical settings, has been hypothesised to cause renal hypoperfusion and AKI by virtue of its renal vascular smooth muscle constrictor effect.

In a prospective cohort study done in Brazil by Boniatti and his team on chloride levels in ICU in adult patients, it was found that hyperchloremia in any sick patient was associated with increased risk of mortality. This study had emphasized careful use of fluids containing chloride for resuscitation and shock management in ICU. In a retrospective analysis done in Kansas Hospital, US by Shaw et al, a significant association was found between greater amounts of chloride received during crystalloid resuscitation and increased in-hospital mortality, even after controlling the total fluid volume received. In a study done by Tani and team in Okayama University, Japan, on chloride levels in
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critically ill patients with systemic inflammatory response syndrome, it was found that even hypochloremia was associated with increased mortality. These studies showed conflicting results and included only a small number of patients with severe sepsis or septic shock. Small experimental studies in animals and humans have shown reductions in renal blood flow, GFR, and renal cortical tissue perfusion when exposed to high intravenous chloride loads.

Although our study is single centric, small sized, and the diagnosis of cerebral edema was clinical alone and not confirmed radiologically, we presume that this study is going to shed more light on the complicated topic of DKA complications in children. However, our study requires further substantiation from more larger, multi centric and comprehensive studies in the future.

CONCLUSIONS
Although the incidence of hyperchloremic metabolic acidosis in DKA was only 18.8%, we found statistically significant increased occurrence of AKI and cerebral edema in them as compared to normochloremic metabolic acidosis patients of DKA. This in turn was associated with higher rate of mortality in the hyperchloremia cohort. This study adds a quote on caution in treating DKA patients using a simple investigations i.e., serum chloride levels and ABG. There is, thus, a need for future large prospectivestudies on the potential causal relationship between hyperchloremia and mortality so that we can take more steps in this regard.

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