Original Article

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Chloride as a Prognostic Factor in Children with Diabetic Ketoacidosis: A Retrospective Cohort Study

Paediatrics Section

PREETHI SURESH[1], SURESH RANGARAJ[2], PRASANNA RAJU[3], SUBASH SUNDAR[4]

ABSTRACT

Introduction: In the management of Diabetic Ketoacidosis (DKA), importance is given to electrolytes such as sodium and potassium, but not chloride. There is evidence that high chloride levels can lead to Acute Kidney Injury (AKI). However, chloride as a prognostic factor has not been thoroughly investigated.

Aim: To evaluate the role of chloride as a prognostic factor in the treatment of children with DKA.

Materials and Methods: This retrospective cohort study collected data from 22 children with severe DKA, aged under 14 years, admitted to the Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India, between January 2016 and October 2020. Data included demographic details, blood glucose, arterial blood gas, renal function tests, serum electrolytes at admission and at 24 hours, and outcome parameters. All children received regular monitoring and standard treatment as per the International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines. The children were divided into two groups: Recovery within 48 hours (Group-A) and more than 48 hours (Group-B). Electrolyte and renal parameters after 24 hours of treatment were compared. Univariate analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0. Student's t-test, Chi-square test, and odds ratio were used for statistical analysis. A p-value of <0.05 was considered significant.

Results: Among the 22 children, 50% recovered within 48 hours, while the remaining half took more than 48 hours. A total of 13 had hyperchloraemia at 24 hours (59%). The mean serum chloride at 24 hours was 115.91 mmol/L in Group-B compared to 106.09 mmol/L in Group-A (p=0.0079*). Two developed AKI, requiring renal replacement therapy and ventilatory support, and eventually died.

Conclusion: In the present study, children with severe DKA who developed hyperchloraemia after 24 hours of admission, following fluid resuscitation with 0.9% normal saline and subsequent standard treatment, took a longer time to recover.

Keywords: Acute kidney injury, Hyperchloraemia, Hyperchloraemic acidosis, Prognosis

INTRODUCTION

The DKA is a metabolic manifestation of diabetes mellitus, comprising a triad of hyperglycaemia, high Anion Gap (AG) metabolic acidosis, and ketonaemia [1]. DKA in children carries the risk of both morbidity and mortality [2]. Cerebral edema and AKI are known complications seen in children with DKA [3]. Children usually present with nausea, vomiting, excessive thirst, and frequent urination [2]. The subsequent dehydration necessitates initial fluid resuscitation aimed at replenishing interstitial, intravascular, and intracellular volumes [4]. Current guidelines recommend normal saline as the fluid of choice [2].

Rehydration and insulin therapy with frequent monitoring of vitals and titration of serum electrolytes form the mainstay of treatment [2,4]. There has been growing evidence that high chloride levels, as an independent risk factor, can lead to AKI and thereby increase the morbidity and mortality of children with DKA [5]. There are a few known poor prognostic factors in DKA, such as severe hypocapnea and high blood nitrogen at presentation, but chloride as such has not been investigated as a prognostic factor [6].

As there is a paucity of literature in the evaluation of chloride as an independent risk factor in children with DKA [7,8], there is a crucial need to evaluate its role as a prognostic factor, which in turn can guide fluid management, as normal saline plays a major role in the rehydration of these children.

Therefore, the aim of the present study was to evaluate the role of chloride as a prognostic factor in the treatment of children with DKA.

MATERIALS AND METHODS

The present study was a retrospective cohort study in which the data of all children with severe DKA (pH of <7.15), aged less than 14 years, admitted to the Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India, between January 2016 and October 2020 were collected. The collected data was compiled, studied, and analysed in 2021.

Inclusion criteria: All children with severe DKA (pH <7.15), aged below 14 years, directly admitted to the study institute, with no prior treatment outside, and no other co-morbidities were included in the study.

Exclusion criteria: Children with DKA who were initially managed outside with rehydration and/or insulin therapy, those with non availability of baseline blood investigation values, those with mild to moderate DKA (pH >7.15), children aged more than 14 years, and those presenting with sepsis were excluded from the study.

Study Procedure

The collected data included demographic details such as age, sex, and locality; baseline parameters that included new onset or already known case of diabetes; values of blood glucose, pH, Blood Urea Nitrogen (BUN), serum creatinine, serum sodium, potassium, chloride, and bicarbonate at admission; values of BUN, serum creatinine, serum sodium, potassium, chloride, and bicarbonate after 24 hours of treatment; outcome parameters such as recovery time, development of AKI, requirement of renal replacement therapy, inotrope support, mechanical ventilation, and mortality. All these children had received regular monitoring and standard treatment as per the International Society for Paediatric and Adolescent Diabetes (ISPAD) guidelines [2]. The fluid of choice used for initial resuscitation was isotonic saline (normal saline), and once the Capillary Blood Gas (CBG) values were below 300 mg/dL,

the choice of fluid was either 0.45% NS or 0.9% NS along with dextrose, depending upon the clinical status, osmolality, and the serum sodium levels.

Based on the data collected from the hospital records, the children fulfilling the inclusion criteria were divided into two groups, Group-A (severe DKA children with recovery within 48 hours) and Group-B (severe DKA children with recovery after 48 hours). Recovery was defined as the time taken for the switching over of insulin infusion to subcutaneous insulin and correction of acidosis; the 48-hour cut-off point for recovery was taken because the standard deficit correction is between 24-48 hours as per treatment guidelines [2] Severe DKA was diagnosed as pH (venous) <7.15 [9].

The electrolyte parameters - serum sodium, potassium, chloride, and bicarbonate before and after 24 hours of treatment between the two groups were compared. The AKI was defined by Kidney Disease Improving Global Outcome (KDIGO) classification using serum creatinine levels [10]. The requirement of inotrope, respiratory support, and mortality were all taken into consideration for the data analysis.

STATISTICAL ANALYSIS

The univariate analysis was conducted using SPSS version 21.0. A Student's t-test was utilised to compare the baseline characteristics such as age, blood glucose, blood pH, blood bicarbonate, serum creatinine, BUN. The outcome parameters - serum sodium, potassium, chloride, bicarbonate, creatinine, and BUN - were analysed using Odds ratio with a 95% Confidence Interval (CI). A Chi-square test was employed to compare the presence or absence of hyperchloraemia at 24 hours across the recovery groups. A p-value of <0.05 was considered significant.

RESULTS

During the study period, a total of 24 children were diagnosed with severe DKA. Two of them were excluded based on the aforementioned exclusion criteria. Data from the medical records of the 22 children who met the inclusion criteria were collected. Among these 22 children, 17 (77%) had new onset DKA, and the majority were female.

A total of 11 children recovered within 48 hours of treatment initiation, while the remaining 11 took more than 48 hours to recover. The maximum recovery time was 88 hours. Baseline parameters such as age, blood glucose, arterial blood gas, bicarbonate, serum creatinine, and BUN were compared between the two groups. The mean age was 9.86 years in Group A, compared to 8.63 years in Group B [Table/Fig-1].

Baseline parameters	Group-A (n=11) (Recovery within 48 hours) (Mean±SD)	Group-B (n=11) (Recovery after 48 hours) (Mean±SD)	p-value
Age (years)	9.86±3.59	8.63±3.50	0.4266
Sex n (%)			
Male	3 (27)	2 (18)	
Female	8 (73)	9 (82)	
Blood glucose (mg/dL)	569.27±147.36	570.91±127.30	0.9776
Blood pH	6.91±0.02	6.89±0.03	0.0802
Blood bicarbonate (mmoL/L)	4.91±2.88	4.45±1.13	0.6312
Serum creatinine(mg/dL)	0.800±0.23	0.827±0.54	0.8794
Blood Urea Nitrogen (BUN) (mg/dL)	14.09±3.56	17.82±9.30	0.2290

[Table/Fig-1]: Baseline characteristics between recovery within 48 hours and recovery after 48 hours groups.
SD: Standard deviation

Prognostic factors such as serum sodium, serum chloride, and serum potassium, both admission values and 24-hour values, were compared between the two groups, along with the pH at admission. The mean serum chloride at 24 hours was 115.91 mmol/L in children who took a longer time to recover, compared to 106.09 mmol/L in children who had an early recovery, and this difference was found to be significant (p-value=0.0079*) [Table/Fig-2].

Prognostic parameters	Group-A (n=11) (Mean±SD)	Group-B (n=11) (Mean±SD)	p-value
Corrected serum sodium (mmol/L) at admission	138.91±5.54	137.64 (7.65)	0.6596
Serum chloride (mmol/L) at admission	100.73±5.66	102.82±7.93	0.4850
Serum potassium (mmol/L) at admission	4.38±1.07	4.34±0.87	0.9304
Corrected serum sodium (mmol/L) at 24 hours	133.73±3.38	135.64±6.39	0.3916
Serum chloride (mmol/L) at 24 hours	106.09±5.77	115.91±9.40	0.0079*
Serum potassium (mmol/L) at 24 hours	3.58±0.67	3.93±1.14	0.3857

[Table/Fig-2]: Prognostic factor comparison between Group-A (Recovery within 48 hours) and Group-B (Recovery after 48 hours).

The presence of hyperchloraemia at 24 hours was compared between the recovery groups (recovery within 48 hours and recovery more than 48 hours) using a Chi-square test, and the observed p-value was statistically significant (p-value=0.0126*) [Table/Fig-3].

Recovery group	Presence of hyperchloraemia at 24 hours	Absence of hyperchloraemia at 24 hours
Group-A (Recovery within 48 hours)	2	9
Group-B (Recovery more than 48 hours)	11	0

[Table/Fig-3]: Presence vs absence of hyperchloraemia at 24 hours across the recovery groups.
p-value equals to 0.0126* (Chi-square test)

Out of the 22 children, 13 had hyperchloraemia at 24 hours. Two children required ventilator support, and both of them had AKI requiring renal replacement therapy. Eventually, both of them died, but the odds ratio with a 95% CI was not significant (0.38-213). Inotrope support was given to five children, four of whom had hyperchloraemia, and the odds ratio with a 95% CI was not statistically significant (0.84-108) [Table/Fig-4].

Outcome parameters	Severe DKA children with hyperchloraemia at 24 hours (n=13)	Severe DKA children without hyperchloraemia at 24 hours (n=9)	Odds ratio	95% CI
Inotrope requirement	4	1	9.60	0.84-108
Mechanical ventilation requirement	2	0	9.00	0.38-213
AKI	2	0	9.00	0.38-213
Mortality	2	0	9.00	0.38-213

[Table/Fig-4]: Association between the outcome of children with severe DKA and with and without hyperchloraemia at 24 hours.

DISCUSSION

In the present study, out of 22 children, 11 took a longer time to recover (more than 48 hours) and were found to have hyperchloraemia at 24 hours, which was statistically significant (p=0.0079*). In total, 13 children had hyperchloraemia at 24 hours, and among them, 11 had a longer recovery time, while two recovered within 48 hours. Out of these 13 children with hyperchloraemia, five required inotrope

support (4 in the hyperchloraemia group and 1 in the group without hyperchloraemia). Two children in the hyperchloraemia group required ventilatory support and also developed AKI requiring renal replacement therapy, eventually leading to death, but the odds ratio with 95% CI was not significant.

Among the various prognostic factors, chloride measured at 24 hours was higher in the slow recovery group, although the chloride measured at admission was similar in both groups. One possible explanation for this high chloride at 24 hours could be iatrogenic. Thus, it was observed that 11 out of 13 children with severe DKA, who developed hyperchloraemia after 24 hours of admission following initial fluid resuscitation with 0.9% normal saline, along with subsequent standard treatment resulting in a subsequent normal AG acidosis, took a longer time for recovery (more than 48 hours).

In 2020, Goad NT et al., studied the association of hyperchloraemia with unfavourable clinical outcomes in patients with DKA. The study included 102 adult patients [11]. Among them, 52 developed hyperchloraemia and took a longer time for final DKA resolution - 16.3 hours versus 10.9 hours (p=0.024). Patients with hyperchloraemia also developed AKI (26.9% vs 8.0%; p=0.01). The study inferred that the presence of hyperchloraemia in patients with DKA was associated with increased time to DKA resolution and a higher risk of in-hospital AKI.

In 2004, Taylor D et al., conducted a study on 18 children with severe DKA. After the initiation of therapy, the children were followed for 20 hours [12]. There was a steady increase in pH over this time. However, at 20 hours, a significant base deficit (mean 10.1 mmoL/l) persisted despite the AG having normalised. The base deficit at this time was mostly attributed to hyperchloraemia (98%) [12].

A similar finding has also been reported in a study by Mrozik LT and Yung M on 59 paediatric DKA cases, which concluded that the AG normalised earlier than bicarbonate in children with DKA treated with normal saline. Children with persisting hyperchloraemic metabolic acidosis recovered from acidosis more slowly [13]. This was also affirmed by Basnet S et al., who analysed 33 children with severe DKA and stated that hyperchloraemia resulting in normal AG acidosis could occur and prolong the duration of insulin infusion and the length of Paediatric Intensive Care Unit (PICU) stay in patients receiving normal saline as a post-bolus rehydration fluid [14].

A study by Baalaaji M et al., published in 2018, also states that hyperchloraemia at 24 hours had an independent association with AKI, although a cause-effect relation could not be ascertained [7]. Among the various prognostic factors, chloride measured at 24 hours was higher in the slow recovery group, although the chloride measured at admission was similar in both groups. One possible explanation for this high chloride at 24 hours could be iatrogenic.

In a study by Toledo I et al., on children with DKA, a prevalence of metabolic acidosis with a hyperchloraemic component of 55% was noted, and it was not associated with a better hydration status nor with a faster recovery from the metabolic decompensation [8]. In India, Patil AK and Vishwanath B also reported a statistically significant association (p-value- 0.04) between the incidence of hyperchloraemic metabolic acidosis in DKA and increased occurrence of AKI and cerebral edema compared to DKA patients with normochloraemic metabolic acidosis. This, in turn, was associated with a higher rate of delayed recovery and higher mortality in the hyperchloraemia cohort [15].

According to ISPAD guidelines [2], isotonic fluid (normal saline) was used for resuscitation followed by hypotonic fluid (half normal saline) or normal saline, depending upon the clinical condition and the serum sodium levels, to manage cerebral edema, which could be a major and frequent complication of DKA. Normal saline has considerable shortcomings, including a pH of 5.5 and high chloride content that could worsen the pre-existing metabolic acidosis in DKA, delay recovery, and subsequent AKI requiring renal replacement therapy. The administration of hypotonic fluids is associated with lesser chances of hyperchloraemia but increased incidence of cerebral edema, as its protective role in the latter has not been established [16].

Considering the benefits and detriments of isotonic normal saline and hypotonic low chloride solutions, a balanced electrolyte solution could be the need of the globe. Although the use of balanced electrolyte solution might confer certain advantages over normal saline, there is a paucity of literature to support the theory. Thus, a large randomised controlled trial is needed to further assess differences in the choice of resuscitation fluid in the management of DKA.

Limitation(s)

The study sample was small in size, and the study was retrospective in nature.

CONCLUSION(S)

In the present study, 11 out of 13 children with severe DKA developed hyperchloraemia after 24 hours of admission following initial fluid resuscitation with 0.9% normal saline, along with standard treatment. This resulted in subsequent normal AG acidosis, leading to a longer recovery time (more than 48 hours) for the resolution of metabolic acidosis. However, randomised controlled trials comparing normal saline with balanced fluids for initial resuscitation in DKA are needed to determine the fluid choice in DKA.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate, Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
2. Associate Professor, Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
3. Professor, Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.
4. Professor and Head, Department of Paediatrics, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Preethi Suresh,
106 K/4, Chinnamani Nagar, Millerpuram, Thoothukudi-628008, Tamil Nadu, India.
E-mail: preethisuresh2700@gmail.com

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