RESEARCH PAPER

Predictors and Outcome of Acute Kidney Injury in Children with Diabetic Ketoacidosis

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Objective: To identify predictors and outcome of acute kidney injury (AKI) in children with diabetic ketoacidosis (DKA) admitted to a Pediatric Intensive Care Unit (PICU). **Methods:** Retrospective case review of 79 children with DKA admitted between 2011-2014. **Results:** 28 children developed AKI during the hospital stay; 20 (71.4%) recovered with hydration alone. Serum chloride at 24 hours was independently associated with AKI. Children with AKI had prolonged acidosis, longer PICU stay, and higher mortality. **Conclusions:** Majority of children with AKI and DKA recover with hydration. Hyperchloremia at 24 hours had independent association with AKI, although cause-effect relation could not be ascertained.

Keywords: *Diabetes, Hyperchloremia, Outcome, Renal failure.*

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Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes with a reported frequency ranging from 15-70% across different study populations. Mortality from DKA in developing countries is still high (3.4%-13%), due to putative reasons like cerebral edema, sepsis, venous thrombosis and dyselectrolytemias [1-3]. Although renal injury is frequently encountered in hyperglycemic hyperosmolar state, it is not so well reported in DKA [4]. Furthermore, renal injury can be masked in children with DKA, due to osmotic diuresis and spurious elevations in creatinine secondary to ketonemia. We undertook this study to evaluate the predictors and outcome of AKI in children with DKA admitted to a Pediatric Intensive Care Unit (PICU).

METHODS

Electronic medical records of children with DKA admitted consecutively to our PICU from 2011-2014 were accessed retrospectively after seeking ethical clearance. DKA was diagnosed using standard definitions [5]. Rehydration was based on sum of 6.5% deficit and maintenance over 36 hours. Additional bolus of 20 mL/kg isotonic saline was administered in first hour to children with hypoperfusion or hypotension. Isotonic saline was continued until the blood glucose fell to ≤13.9 mmol/L (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 [6]. AKI was defined by pRIFLE classification using estimated creatinine clearance (eCCl), as urine output criterion is unreliable in the setting of osmotic diuresis [7]. The patients were classified into one of the three pRIFLE categories at three time points *viz*, admission, 12 hours and 24 hours. Children with pRIFLE category 0-1 were labelled as 'No AKI' and those with pRIFLE category 2-3 at admission were labelled as 'AKI at admission'. Children who progressed from 'No AKI' at admission to pRIFLE 2-3 during hospital stay were labelled as 'AKI progression'.

Univariate and multivariate analyses was done to compare demographic and biochemical characteristics between 'No AKI' and 'AKI progression' groups. *P* value <0.05 was considered significant.

RESULTS

Of 79 children enrolled, 56 (71%) were new onset diabetes presenting as DKA. In children with documented healthcare contacts prior to referral (*n*=51), DKA was diagnosed only in 18 (35.3%), of which just 8 (44.4%) received appropriate fluids and insulin prior to referral. Majority of the children (*n*=59, 75%) had presented as severe DKA.

Twenty eight (35%) children were diagnosed with AKI; 13 (46.4%) at admission and rest within 24 hours of hospital stay. The number (proportion) of children categorized into pRIFLE-0,1,2,3 at admission and end of 24 hours were 35 (44.3%), 31 (39.2%), 11 (13.9%), 2

(2.5%) and 54 (68.4%), 10 (12.6%), 9 (11.4%) and 6 (7.6%), respectively. Twenty (71.4%) children recovered with hydration alone while 8 (28.6%) required renal replacement therapy (RRT).

None of the admission variables could predict AKI. However on multivariable analysis, elevated chloride levels at 24 hours had an independent association with AKI progression [Adjusted OR 1.14 (95% CI 1.04-1.27), *P*=0.007] (***Table* I** and **II**). Serum chloride >112 mmol/L at 24 hours had a sensitivity, specificity and area under ROC curve of 73.3%, 82.4% and 0.835, respectively for development of AKI (*P*<0.001).

Time to resolution of acidosis was significantly longer in those with AKI than those without [Median (IQR) 31 (24, 77) *vs* 26 (20, 35) hours, *P*=0.006]. Children with AKI had higher odds for needing vasoactive drugs and ventilation, and developing cerebral edema. Those with AKI had prolonged PICU stay [Median (IQR) 3 (2, 5) *vs* 2 (1, 2) days, *P*<0.001] and lesser likelihood to survive to hospital discharge (***Table* III**).

TABLE II COMPARISON OF 'NO AKI' AND 'AKI PROGRESSION' – MULTIVARIATE ANALYSIS

Characteristics	*Adjusted OR (95% CI)*	*P value*
PRISM III Score	1.07 (0.96, 1.2)	0.20
24 hours serum corrected sodium (mmol/L)	0.70 (0.39, 1.26)	0.24
24 hours serum effective osmolality (mmol/kg)	1.19 (0.89, 1.57)	0.23
24 hours serum chloride (mmol/L)	1.20 (1.05, 1.37)	0.008

AKI: acute kidney injury.

DISCUSSION

One-third of our patients with DKA had AKI at some point during their PICU stay, with nearly half of them having AKI at presentation. Majority of the children were new-onset DKA, who remained undiagnosed prior to referral and tended to present as severe DKA . This trend was similar to our previous observations [1,2] and in sharp contrast to the data from the developed world [8]. Those with missed diagnosis had more likelihood of

TABLE I COMPARISON OF 'NO AKI' AND 'AKI PROGRESSION' – UNIVARIATE ANALYSIS

Variable	*No AKI (n=51) Mean (SD)*	*AKI progression (n=15) Mean (SD)*	*P value*
Age (years)	7.3 (3.6)	8.2 (3.6)	0.37
PRISM III Score	23 (7)	27 (8)	0.07
At admission			
- Blood glucose (mmol/L)	25.3 (6.8)	23.7 (9.2)	0.44
- Blood urea nitrogen (mmol/L)	2.6 (1.2)	3 (1)	0.19
- Serum creatinine (µmol/L)	53 (26.5)	75 (26.5)	0.01
- Corrected serum sodium (mmol/L)	139 (6)	142 (12)	0.53
- Serum Chloride (mmol/L)	101 (8)	107 (13)	0.09
- Blood bicarbonate (mmol/L)	6 (3)	5 (2)	0.18
- Blood pH	7.05 (0.12)	6.99 (0.13)	0.14
- Serum effective osmolality (mmol/kg)	293.3 (12.4)	296.3 (23.5)	0.64
At 24 hours			
- Blood glucose (mmol/L)	11.3 (4.4)	13.8 (4.4)	0.01
- Blood urea nitrogen (mmol/L)*	3.5 (2.1)	8.1 (5.2)	<0.001
- Serum creatinine (µmol/L)#	41 (18)	124 (86)	<0.001
- Corrected serum sodium (mmol/L)	138.7 (5.9)	145.7 (10.5)	0.001
- Serum chloride (mmol/L)	106.6 (7.2)	118.6 (10.3)	0.001
- Blood bicarbonate (mmol/L)	15.8 (3.4)	10.9 (4.8)	<0.001
- Blood pH	7.25 (0.14)	7.13 (0.13)	0.003
- Serum effective osmolality (mmol/kg)	285.5 (12.5)	301 (21.1)	0.001

**24 hours Blood urea nitrogen (mmol/L) expressed as Median (IQR) among No AKI vs. AKI progression: 2.8 (2,4.8) vs. 6 (5,9.3); P<0.001; #Median (IQR) 24 hours creatinine (µmol/L) No AKI vs AKI progression: 35 (27,49) vs. 97 (57,124); P<0.001.*

WHAT THIS STUDY ADDS?

- 24-hour serum chloride was an independent predictor of acute kidney injury in children with diabetic ketoacidosis.

TABLE III PICU NEEDS, COMPLICATIONS AND OUTCOME OF CHILDREN WITH DKA AND AKI

Characteristics	*Odds ratio (95% CI)*	*P value*
Vasoactive requirement	5.1 (1.5-17)	0.005
Mechanical ventilation requirement	7.6 (1.8-31)	0.002
Cerebral edema	7.6 (1.8-31)	0.002
Mortality in PICU	13.6 (1.5-120)	0.004
Survival to hospital	0.07 (0.01-0.6)	0.004

complications like cerebral edema (CE) and AKI, possibly related to uncorrected hypovolemia [2]. The small proportion in whom AKI did not revert with fluids, needed RRT, indicating that factors other than hypovolemia could have contributed to AKI.

Although children with 'AKI progression' had higher PRISM III and admission chloride levels, only the 24 hours serum chloride was independently associated with 'AKI progression'. Independent association of 24 hour serum chloride rather than admission value leads one to believe that hyperchloremia could have been an iatrogenic element caused by the type of intravenous fluids received. Though the current guidelines favour isotonic saline as the initial fluid in DKA, the recommended duration of infusion is not clear. Since half normal saline without dextrose was not easily available in our setup, children continued to receive isotonic saline till blood glucose fell to 250 mg/dL.

Hyperchloremia, in many clinical settings has been hypothesised to cause renal hypoperfusion and AKI by virtue of its renal vascular smooth muscle constrictor effect [9,10]. Hursh, *et al*. [1] reported AKI in a high proportion of children with DKA (64.2%) using Kidney Disease/Improving Global Outcomes criteria, but none in association with hyperchloremia. Although studies from developing world have reported about 4-11% incidence of renal injury in children with DKA [12,13] neither standard definitions were used nor association with hyperchloremia was reported. The disparity in incidence of AKI between studies is largely related to use of different definitions. Though we demonstrated a significant association between hyperchloremia at 24 hrs and AKI in our study, a causal link cannot be ascertained due to the retrospective nature of our data. Use of balanced crystalloids with lower chloride content have been studied in adults with DKA [14,15], but mostly in relation to hyperchloremia induced normal anion gap acidosis.

There is, thus, a need for for future prospective studies on risk factors of AKI, cause-effect relationship between AKI and type of fluid, and role of balanced salt solutions in preventing AKI in children with DKA.

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