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Determinants and Outcome of Metabolic Acidosis in Diarrheal Children Under 5 Years of Age in an Urban Critical Care Ward in Bangladesh

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Abstract

We evaluated the independent determinants and outcome of metabolic acidosis in diarrheal children. Children under 5 years of age admitted with diarrhea and severe respiratory distress in the critical care ward at Dhaka Hospital of icddr,b (International Centre for Diarrhoeal Disease Research, Bangladesh) from April 2010 to April 2014 who had their reports of arterial blood gas analyses were enrolled in the study. We compared clinical and laboratory characteristics between the study children with (cases = 74) and without metabolic acidosis (controls = 65). Metabolic acidosis was defined if pH < 7.35 and HCO_3 < 22 mmol/L in ABG. Cases had higher mortality (53% vs 29%, $P = .01$) compared to controls. After adjustment of potential confounders, for instance, hypokalemia and dehydration, the cases were independently associated with severe sepsis and raised serum creatinine (for both $P < .05$). Thus, early identification of these features of metabolic acidosis in diarrheal children may help clinicians to have prompt management that may further help reduce mortality in such children especially in resource-limited settings.

Keywords

dehydration, malnutrition, metabolic acidosis, severe sepsis

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Introduction

In developing countries, Diarrhea still plays key role in both morbidity and death among under-5 children and accounts for 9% of 5.9 million global under-5 deaths in 2015.[1] Children with diarrhea often present with respiratory difficulties with or without dehydration, and this is mainly due to the presence of metabolic acidosis,[2,3] resulting mainly from a loss of bicarbonate in feces.[4] Dehydration is the most frequent and dangerous complication responsible for morbidity and mortality in childhood diarrhea and is the main reason for metabolic acidosis in such children.[5] The classical features of metabolic acidosis among under-5 children with dehydration is fast and deep breathing, which dramatically disappears within a few hours of adequate rehydration.[6] However, a number of diarrheal children with metabolic acidosis may not present with dehydration, only present with features of severe sepsis and/or pneumonia, and they often require aggressive treatment with antibiotics and fluid resuscitation.[7] The clinical and biochemical parameters provide very rich and crucial information required for the management of such children.[5] However, we have little knowledge about the various presentations of diarrheal children having metabolic acidosis.

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Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b), treats a good number of diarrheal children with metabolic acidosis with or without dehydration and often associated with fatal outcome.[6] However, data are limited on the determinants of metabolic acidosis and their outcome in such children. The aim of our study was to address the knowledge gap in such children.

Material and Methods

Ethical Statement

This study was approved by the ethical review committee of icddr,b. As this was a retrospective chart analysis, data were analyzed anonymously; thus, no parental consent was required.

Study Sites

The retrospective chart analysis was carried on data of children who were treated in the intensive care unit of Dhaka Hospital of icddr,b. The description of the Dhaka Hospital of icddr,b has been provided extensively elsewhere.[8]

Study Design

This was a retrospective chart analysis where we collected data from children under 5 years of age of both sexes, who were admitted to the intensive care unit between April 2010 and April 2014 and had their arterial blood gas (ABG) analysis done. Comparison was made between diarrheal children with and without metabolic acidosis. Metabolic acidosis was defined as pH < 7.35 with HCO_3 < 22 mmol/L in blood gas analysis. Diarrhea was considered as passage of abnormally loose or watery stool, 3 or more times in the previous 24 hours.[9]

Patient Management

Standard hospital guidelines were applied in the clinical management of the admitted patients, which comprised correction of dehydration using oral rehydration salt solution (for those with some dehydration) and/or intravenous fluids (for those with severe dehydration and also those who were unable to drink due to any reason like frequent vomiting, ileus, etc), as appropriate; antibiotic therapy; feeding; and administration of micronutrients (vitamins and minerals) when indicated. In addition, intravenous fluid resuscitation to combat severe sepsis was also arranged when required. Management of hypoxemia was done using bubble continuous positive airway pressure.[8] Management of severe acute malnutrition was according to the hospital's protocol.[10]

Measurements

Case report forms were developed and finalized for acquisition of study-relevant data. Data collected on the children included their sociodemographic information (age, sex, residence, history of breastfeeding); immunization status; anthropometric information such as weight for age *Z* score of the World Health Organization median and weight for length/height *Z* score of the World Health Organization median; clinical characteristics such as duration and type of diarrhea, dehydration status, presence of fever and its duration; laboratory test results such as severe anemia (hematocrit <15%), bacteremia (isolation of bacterial pathogen from blood sample culture performed only once), hypokalemia (serum potassium < 3.5 mmol/L), hyperkalemia (serum potassium > 5.3 mmol/L), hyponatremia (serum sodium < 130.0 mmol/L), hypernatremia (serum sodium > 146 mmol/L), hypocalcemia (serum calcium < 2.12 mmol/L), hypomagnesemia (serum magnesium < 0.65 mmol/L), and raised creatinine (serum creatinine > 35 mmol/L in infants and >65 mmol/L in children >12 months) on admission; severe sepsis; and outcomes such as deaths during hospitalization. All these information, with the exception of treatment failure and deaths, represent admission characteristics of the enrolled children.

Statistical Methods

All data were entered into a personal computer and edited before analysis using SPSS for Windows (version 20.0; SPSS Inc, Chicago, IL) and Epi Info (version 7.0, USD, Stone Mountain, GA). Differences in proportions were compared by the χ^2 test. In normally distributed data, differences in means were compared by Student's *t* test, and the Mann-Whitney test was used for comparing data that were not normally distributed. A probability of less than .05 was considered statistically significant. Strength of association was determined by a calculating odds ratio and its 95% confidence interval. We have these statistics both in our univariate analyses and logistic regression. In identifying independent determinants of metabolic acidosis in diarrheal children, variables were initially analyzed in a univariate model, and then independently associated factors with metabolic acidosis were identified using logistic regression analysis after controlling for the covariates.

Table 1. Clinical Characteristic of Children Under 5 Years of Age Having Diarrhea With and Without Metabolic Acidosis[a].

Variables	Metabolic Acidosis (n = 74)	Without Metabolic Acidosis (n = 65)	OR	95% CI	*P*
Male	39 (53)	34 (52)	1.02	0.5-2.0	.90
Breastfeeding	17 (28.8)	12 (22.6)	1.38	0.6-3.3	.59
SAM	24 (46)	23 (39.7)	1.3	0.6-2.8	.62
Watery diarrhea	71 (96)	59 (91)	2.41	0.6-10	.37
Vomiting	14 (18.9)	9 (13.9)	1.5	0.6-3.6	.57
Dehydration	30 (40.5)	16 (24.6)	2.1	1.01-4.3	.046
Hct (mean ± SD)	31 ± 7.62	30.79 ± 5.5	—	—	.83
Convulsion	25 (33.8)	23 (35.4)	0.93	0.5-1.9	.98
Fever	42 (56.8)	45 (69.2)	0.6	0.3-1.2	.20
Duration of fever (median, IQR)	2 (1, 4)	3 (2, 5)	—	—	.44
Age (months) (median, IQR)	7 (3.9, 12.3)	7 (4, 12)	—	—	.82
Duration of diarrhea (median, IQR)	3 (1, 5)	3 (2, 5)	—	—	.93
Pneumonia	58 (78.4)	56 (86.2)	0.6	0.2-1.4	.33
Severe sepsis	46 (62.2)	22 (33.85)	3.2	1.6-6.4	.002
Ventilator support	33 (44.6)	20 (30.8)	1.8	0.9-3.6	.13
Hypokalemia	33 (44.6)	14 (21.9)	2.9	1.4-6.1	<.01
Hyperkalemia	12 (16.2)	7 (10.9)	1.6	0.6-4.3	.52
Hyponatremia	30 (40.5)	20 (31.3)	1.5	0.7-3.0	.34
Hypernatremia	25 (33.8)	23 (35.9)	0.91	0.45-1.8	.9
Hypomagnesemia	3 (4.3)	2 (3.3)	1.32	0.2-8.2	1.0
Hypocalcemia	35 (48.6)	32 (51.6)	0.9	0.4-1.7	.9
Raised creatinine	56 (76.7)	19 (30.2)	7.6	3.6-16.4	<.01
Death	38 (52.8)	19 (29.2)	2.7	1.3-5.5	.01

Abbreviations: OR, odds ratio; CI, confidence interval; SAM, severe acute malnutrition; Hct, hematocrit; SD, standard deviation; IQR, interquartile range.
[a]Data are presented as n (%) unless otherwise stated.

Table 2. Results of Logistic Regression to Explore Independent Predictors for Metabolic Acidosis in Diarrheal Children.

Variables	OR	95% CI	*P*
Severe sepsis	2.72	1.2-6.3	.02
Raised creatinine	6.12	2.6-14.6	<.01
Hypokalemia	2.4	0.94-6.02	.07
Dehydration	0.76	0.3-2.0	.57

Abbreviations: OR, odds ratio; CI, confidence interval.

Results

A total 139 children under-5 fulfilled the study criteria of whom 74 had metabolic acidosis. Diarrheal children with metabolic acidosis had higher case-fatality rate compared with those without metabolic acidosis (Table 1). Those having metabolic acidosis more often presented with dehydration and hypokalemia compared with their counterparts (Table 1). After the logistic regression analysis with adjustment of potential confounders, for instance, hypokalemia and dehydration, diarrheal children with metabolic acidosis were independently associated with severe sepsis and raised serum creatinine (Table 2).

Discussion

The main observation of this study is the independent association of severe sepsis and raised creatinine with metabolic acidosis. The next important observation is the higher deaths in diarrheal children having metabolic acidosis compared with those without metabolic acidosis. Severe sepsis is usually responsible for vasodilatation and capillary leakage due to release of cytokines or other inflammatory mediators.[11,12] Such mediators cause microcirculation derangement and as a by-product of anaerobic cellular respiration lactate is produced, which leads to metabolic acidosis.[12-15]

Observation of independent association of raised creatinine with metabolic acidosis is also understandable. Diarrheal children with metabolic acidosis more often had dehydration compared with those without metabolic acidosis, and dehydrating diarrhea was found

to be associated with acute kidney injury whereas raised serum creatinine was one of the markers of acute kidney injury in such children.[16] Moreover, we already observed that diarrheal children with metabolic acidosis more often had severe sepsis and raised serum creatinine and it is one of the intriguing consequences of severe sepsis in children.[16]

Although hypokalemia was associated with metabolic acidosis in 2/2 table analysis, it did not remain significant after logistic regression and this might be due to confounding effect of other covariates in the logistic model.

The observation of higher deaths in diarrheal children with metabolic acidosis compared with those without metabolic acidosis is not surprising. A number of previous studies revealed that severe sepsis,[8] acute kidney injury,[17,18] hypokalemia,[19,20] and dehydration[21] in diarrheal children were independently associated with fatal outcome. Thus, the observation of higher deaths in our study children having metabolic acidosis compared with those without acidosis is understandable.

The main limitation of the study was the retrospective nature as well as small sample size of the study, which might have an impact in preventing some of our variables of interest to be significantly associated with metabolic acidosis. Potential misclassification bias in enrolling our study population during chart analysis was another limitation of the study.

In conclusion, children under 5 years of age with diarrhea encompassing metabolic acidosis had higher case-fatality rate compared with those without metabolic acidosis. They were independently associated with severe sepsis and acute kidney injury. The results underscore the importance of early identification of these simple parameters of metabolic acidosis to have prompt management of these children in order to reduce potential deaths in such children. However, prospective research with a larger sample may consolidate our observation.

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Author Contributions

S: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
MS: Contributed to conception and design; contributed to acquisition and analysis; drafted manuscript; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
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Declaration of Conflicting Interests

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