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Nephrology

OBSERVATIONAL STUDY OF ACUTE DIARRHEAL DISEASES IN RELATION TO ACID BASE CHANGES AND ACUTE KIDNEY INJURY

Dr Bh.V.K. Praveen Varma	Assistant professor, Department of General Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Andhra Pradesh
Dr K L Behera	Professor, Department of General Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Andhra Pradesh;
Dr Siva Krishna Sirasapalli*	Postgraduate Student, Department of General Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Andhra Pradesh *Corresponding Author
Dr S. C. Mahapatra	Head of Department, Department of General Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Andhra Pradesh
Dr Vineesha Kamini	Postgraduate Student, Department of General Medicine, Maharajahs Institute of Medical Sciences, Nellimarla, Andhra Pradesh

ABSTRACT

BACKGROUND : Disorders of acid-base homeostasis complicate a variety of disease conditions and contribute to morbidity and mortality. These disorders disrupt normal functioning of various organ systems and ultimately prove fatal. Diseases of the lungs and kidneys (the two important organs involved in acid-base homeostasis) contribute to an important proportion of such acid-base disturbances.

MATERIALS AND METHODS : In all patients, history regarding duration of diarrhea, presence of vomiting and oliguria was recorded. Clinical examination was focused on identifying the degree of dehydration, acidotic breathing, vital signs and systemic examination to rule out coexisting diseases that might confound the acid-base picture. In all patients, routine urinalysis for albumin, sugar, acetone and deposits was done. In all patients, hemoglobin estimation was routinely done. If any patient was found to have renal failure (defined as serum creatinine)>2 mg%) serial measurements were made as appropriate and after treatment.

RESULTS : 28 out of 104 patients with acute diarrhea had ARF. All 28 patients had increased anion gap metabolic acidosis. 14 out of 104 patients with acute diarrhea had severe metabolic acidosis (pH <7.2). Out of these 14 patients, 10 had renal failure and 4 patients had normal renal parameters.

CONCLUSION : The most common acid-base disturbance observed in patients with acute diarrheal disease is normal anion gap metabolic acidosis. A normal ABG must be interpreted in the clinical context because mixed acid-base disorders may produce normal values in ABG analysis. The acid-base abnormality observed in post diarrheal ARF is increased anion gap metabolic acidosis. Metabolic acidosis is a prognostic factor and early recognition and prompt correction of metabolic acidosis improves the outcome in acute diarrheal disease and post diarrheal ARF.

KEYWORDS : Acute Diarrheal Disease, Acid-Base Changes, acute kidney injury.

BACKGROUND

Disorders of acid-base homeostasis complicate a variety of disease conditions and contribute to morbidity and mortality. Unless promptly recognized, these disorders disrupt normal functioning of various organ systems and ultimately prove fatal. The clinical settings in which such acid-base disorders occur are numerous that attempting to list out all the causes of acid-base disturbances will be unwarranted. Nevertheless, to make some generalisation, it can be said, diseases of the lungs and kidneys (the two important organs involved in acid-base homeostasis) contribute to an important proportion of such acid-base disturbances. Acute Diarrheal Disease (ADD) is yet another cause of acid-base disturbance and the present study aims to explore the various changes that take place in the acid-base milieu of patients who suffer an acute diarrheal disease. The study tries to validate a prognostic role for such acid-base changes in acute diarrheal disease and calls for an early recognition and prompt correction of acid-base changes.

Aim of the Study:

- To find out the acid-base disturbances resulting from ADI and
- ADI in relation to

1. AKI
2. Severe metabolic acidosis (pH < 7.2)
3. Prognosis with early correction

MATERIALS AND METHODS:

STUDY DESIGN: prospective observational study
PLACE OF STUDY: maharajahs Institute of Medical Sciences
STUDY PERIOD: September 2015 to september 2017.
SAMPLE SIZE: 104

Inclusion Criteria:

- Age more than 12 years.
- Acute diarrhea was defined as passage of 3 or more loose stools per day for a duration of less than 14 days.
- Both sexes were included in the study.

Exclusion Criteria:

Patients who had coexisting diseases like

- COPD or other lung diseases
- diabetes mellitus patients (who might have type IV RTA-hyporeninaemic, hypoaldosteronism)
- liver disease
- chronic kidney diseases were excluded.
- Patients who were on drugs likely to produce acid-base disturbances were also excluded. Eg. Metformin (for PCOD), cholestyramine, calcium or magnesium chloride, lysine or arginine hydrochloride, acetazolamide, drugs causing RTA (renal tubular acidosis); e.g. cotrimoxazole, spironolactone and triamterene.

Study Protocol and Laboratory Investigations:

- History regarding duration of diarrhea, presence of vomiting and oliguria was recorded.
- Clinical examination was focused on identifying the degree of dehydration, acidotic breathing if any, vital signs and systemic examination to rule out coexisting diseases that might confound the acid-base picture.
- Routine urinalysis for albumin, sugar and deposits was done. Also, urine was analyzed for acetone, since patients with diarrhea could starve resulting in starvation ketoacidosis.
- Hemoglobin estimation was routinely done. It is mandatory to know the hemoglobin level for determining oxygen content of blood in ABG analysis.

- If any patient was found to have renal failure (defined as serum creatinine >2 mg/dl), serial measurements were made as appropriate and after treatment.

Interpreting ABG Results and Further Actions:
The various parameters obtained like pH, pO2, pCO2, HCO3 and Base Excess (BE) were analyzed and ABG values interpreted in a systematic way as previously described. Anion gap was to be calculated separately using the formula, AG (Anion Gap) = Na+ - (Cl- + HCO3-). Value used as reference was 12-14 mEq/L. An anion gap of more than 14 was interpreted as high anion gap.

In case, a high anion gap acidosis was encountered, serum albumin was measured, since perturbation in albumin level might itself alter anion gap. Further evaluation of increased anion gap acidosis mandated test for ketones, which was routinely done in the study and measurement of serum lactate levels, which could not be done.

All patients were under continuous observation and repeat investigations like renal parameters and ABG were done (even if not mentioned) as the clinical condition would dictate. For instance, administration of bicarbonate intravenously was carefully monitored with serum electrolytes and ABG. Other investigations like stool analysis for evaluating diarrhea were routinely done.

Treatment Protocol Followed:
All patients were rehydrated with oral fluids, ORS and with IV Fluids (2:1 saline, lactate cycle) as required (34). If any patient had severe acidosis (pH <7.2) bicarbonate was administered intravenously. About 50-75 mL of 7.5% sodium bicarbonate was infused IV slowly over a period of one hour. If the patient presented with elevated renal parameters fluid challenge with 1.0 to 1.5 liters of IVF was given. If the patient showed improvement in urine output and clinical picture, rehydration therapy was continued. If the patient had persistent oliguria despite rehydration and other uremic manifestations mandating dialysis, peritoneal or haemodialysis was undertaken. Periodic monitoring of renal functions was also undertaken. Antibiotics were given as appropriate. Patients were discharged once diarrhea stopped and renal functions returned to normal, if they initially had renal failure.

OBSERVATIONS AND RESULTS:
Fifty two patients with acute diarrhea were included in the study. The following observations were made.

Acid-Base Disturbances Observed:
In descending order of frequency-
i. Normal anion gap metabolic acidosis.
ii. Increased anion gap metabolic acidosis.
iii. Normal ABG study.

Figure 1: sex distribution

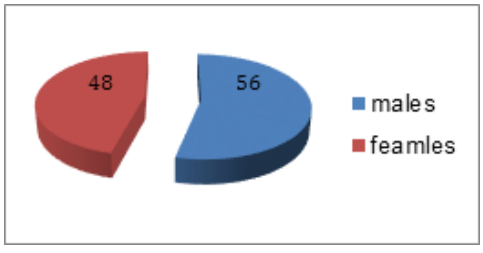

Table: 1

Total no patients studied	Number of patients with normal anion gap acidosis	Number of patients with increased anion gap acidosis	Number of patients with normal abg
104	64	28	12

The relative contribution of each type of ABG study can be pictorially represented as shown in the pie chart in the next page.

Acid-base disturbances in patients with ARF due to acute diarrhea- 28 out of 104 patients with acute diarrhea had ARF. All 28 patients had increased anion gap metabolic acidosis.

Incidence of Severe Metabolic Acidosis (PH <7.2):
14 out of 104 patients with acute diarrhea had severe metabolic acidosis (pH <7.2). Out of these 14 patients, 10 had renal failure and 4 patients had normal renal parameters.

Table 2. Renal Function in Patients with Severe Acidosis

Total number of patients with severe metabolic acidosis	Number of patients with renal failure	Number of patients with normal renal function
14	10	4

Table 3. Incidence of Severe Metabolic Acidosis

Category	Total no of patients	No of patients with severe acidosis	Incidence of metabolic acidosis
Patients with acute diarrhea	104	14	13.46%
Patients with acute renal failure due to acute diarrhea	28	10	35.71%
Patients with normal renal function	76	4	5.26%

Mortality rate: 4 out 104 with acute diarrhea died and both patients had renal failure and severe acidosis.

Table 4: mortality in metabolic acidosis according to ph

pH	Total number of patients	Number of patients death	Mortality rate
Ph <7.2	14	4	28.57%
Ph >7.2	90	0	0%

Table 5: mortality in post diarrheal ARF

Total number of patients	Number of patients died	Mortality rate
28	4	14.2%

DISCUSSION:
This study aims at identifying the various acid-base disturbances that occur in patients with acute diarrhea, the acid-base abnormalities that occur in post diarrheal ARF, and to find out, if there is a prognostic significance for metabolic acidosis.

To accomplish the above tasks, 104 patients with acute diarrhea were included in the study. Among the 104 patients, 56 were males and 48 were females. The mean duration of diarrhea at presentation was 2.01 days.

Among the 104 patients studied, 28 patients (18 men and 10 women) had renal failure (serum creatinine more than 2 mg/dl) at initial presentation to hospital (50). The mean duration of diarrhea on admission in this population was 2.85 days. None of the patients developed renal failure after admission to hospital.

The ABG values of all 104 patients were interpreted in a systematic way as previously described.

Acid-base changes occurring in acute diarrhea- The following 3 types of acid-base changes were observed on analyzing the ABG values of all 104 patients.

1. Normal anion gap metabolic acidosis.
2. Increased anion gap metabolic acidosis.
3. Normal ABG study.

Out of the 104 patients studied, 64 patients had a normal anion gap metabolic acidosis, 28 patients had an increased anion gap metabolic acidosis and 12 patients had normal ABG values. Hence, it is inferred that.

Normal anion gap metabolic acidosis is the most common acid-base abnormality in acute diarrheal illness.

The reason for a normal anion gap metabolic acidosis as described previously is loss of bicarbonate in diarrheic stools.
The other findings noted in this population of patients included-

i. Hyperchloraemia findings (Sr. chloride >105 mEq/L).
ii. Normal Na+ and K+ values.
iii. Less severe acidosis (i.e., pH >7.20) in most (30 out of 32) patients.
iv. Expected range of respiratory compensation.

Hyperchloraemia occurring in this population was a compensatory response to loss of bicarbonate in stools, so as to maintain the electro neutrality of Extra Cellular Fluid (ECF) (Hence, referred to as hyperchloremic acidosis).

Even though, serum sodium and potassium levels were normal, hypokalaemia can also be anticipated, because patients with acute diarrhea disease lose potassium through GIT. Likewise, dysnatraemia can also be anticipated.

60 out 64 patients had a pH above 7.20 and all had respiratory compensation in the expected range.

The next common acid-base disturbance observed was an increased anion gap metabolic acidosis (28 patients).

A patient with acute diarrheal illness can develop increased anion gap metabolic acidosis for the following reasons.

i. Development of renal failure with retention of acidic anions like sulfate, phosphate, etc.
ii. Lactic acidosis occurring as a result of tissue hypo perfusion.
iii. Ketoacidosis due to starvation.

All patients in this group were evaluated with the above possibilities in mind.

It was observed that all 28 patients had renal failure (Sr. creatinine >2.0 mg/dl) and their urine tested negative for ketones. Serum albumin was measured in this population of patients (because albumin is a normal anionic constituent of plasma and perturbations in albumin level may alter AG) and found to be within the normal reference range. Serum lactate could not be measured.

Hence, one explanation that could be offered for the increased anion gap metabolic acidosis in this setting was renal failure.

Serum chloride level was found to be normal in all patients (an expected finding in increased anion gap acidosis). Na+ and K+ levels were found to be normal.

The least common acid-base status in acute diarrheal illness was normal ABG study (12 patients).

The following 3 possibilities must be considered when one encounters a normal ABG analysis in acute diarrhea-

i. A patient might have a mild diarrheal illness, so that there is only a minimal bicarbonate loss, which is of no biochemical significance.
ii. A combination of metabolic acidosis (due to bicarbonate loss in stools) and metabolic alkalosis (due to loss of acid in vomits) may occur in patients with acute diarrheal diseases. So, a normal ABG study in the clinical context of severe vomiting and diarrhea should suggest a combination of metabolic acidosis and metabolic alkalosis. In this clinical situation, pH, pCO2, HCO3 and AG all will be normal.
iii. A combination of high anion gap acidosis (e.g., renal failure, lactic acidosis) and metabolic alkalosis (due to vomiting) may coexist. Here pH, pO2, pCO2 and HCO3 will be normal, but anion gap will be high.

All 6 patients who had normal ABG study were clinically suffering from a milder degree of diarrhea and dehydration and vomiting was not a prominent manifestation.

So, a milder diarrhea illness maybe postulated as the reason behind the normal ABG study than a mixed acid-base disorder. No significant difference in the clinical presentation of each of the 3 groups of patients could be noted.

These 3 patterns of acid-base disturbances are well-recognized manifestation of acute diarrhea described in textbooks in Internal Medicine and arterial blood gas analysis. But, this study gives the relative proportion of each of the 3 patterns observed in acute diarrhea (61.5%, 27% and 11.5%).

A similar study conducted in children with gastroenteritis in February 1993 in Soroka Medical Centre, Beersheba, Israel (Weizman-Z, Houri S et al) inferred that 70% of children with acute gastroenteritis had a normal anion gap metabolic acidosis and the remaining 30% had increased anion gap metabolic acidosis.1

Studies on 'Acidosis in Cholera' - Zalunardo et al, October 2004.2

'The Acidosis of Cholera - contributing factors' - Wang F Butler, et al, NEJM December 1986 is comparable studies.3

Acid-Base Changes in ARF Due to Acute Diarrhea:
The next aim of this study is to analyze the acid-base changes that occur in patients developing renal failure due to acute diarrhea.

Among the 104 patients studied, 28 patients had renal failure at presentation to hospital. All 28 patients demonstrated a high anion gap metabolic acidosis - 10 out of 28 patients had severe metabolic acidosis (pH <7.2). In all 28 patients, urine tested negative for acetone and serum albumin was normal. All 28 patients had normal Na+ and K+ levels. This observation is comparable with pre-existing literature. 4,5,6

Incidence of Severe Metabolic Acidosis:
It was found that 14 out of 104 patients with acute diarrhea had a severe metabolic acidosis, i.e. pH <7.2 in ABG study. Hence, the incidence of severe metabolic acidosis in patients with acute diarrhea was 13.46%.

Among these 14 patients, 10 patients had renal failure and 4 patients had normal renal function. So, the incidence of severe acidosis in patients with renal failure due to diarrhea was 10 out of 28 patients, i.e. 35.71% and the incidence of severe acidosis in patients with normal renal function was 4 out of 76 patients, i.e. 5.26%.

So, severe metabolic acidosis occurred in both groups of patients with acute diarrhea (i.e., patients with renal failure and patients with normal renal function).

The higher incidence of severe acidosis in patients with renal failure than in those without renal failure only exemplifies the pivotal role of kidneys in maintaining a normal acid-base milieu. M.A. Muthusethupathi et al, Zalunardo N et al.7

Is Metabolic Acidosis a Prognostic Marker?
To find out the prognostic significance of metabolic acidosis, patients were stratified into 2 groups, one having a pH <7.2 (severe metabolic acidosis) and the other having a pH >7.2. A pH of 7.2 is used as the demarcation between the 2 groups for the following reasons-

a. Patients with severe metabolic acidosis are at a higher risk of developing adverse manifestations like CNS depression, cardiovascular dysfunction and pulmonary edema.
b. Because of the threat posed by severe metabolic acidosis on various organ systems, patients with pH <7.2 must be promptly recognized and treated with bicarbonate infusion.
c. Previous studies could identify a poor prognosis for patients with pH <7.2 (M.A - Muthusethupathi et al, 1990 MMC, Chennai).7

When such a pH demarcation was used, it was observed that 7 out of 52 patients with acute diarrhea had severe acidosis and the remaining 45 patients had a pH >7.2. All patients with pH <7.2 were treated with IV bicarbonate (7.5%) in a way described previously.

The prognosis in each group was assessed by calculating the mortality rate.

It was found that two out of 14 patients with severe acidosis died, while no death occurred in the remaining 90 patients. So, the incidence of mortality in those with severe acidosis was 28.57%, while no death

occurred in those with a pH >7.2. Hence, it is evident that prognosis in terms of mortality is worse in those with severe acidosis. This calls for early recognition and prompt correction of metabolic acidosis. Among the 14 patients with severe acidosis, both deaths occurred in those with ARF. So, it can be inferred that the mortality rate is still high (4 out of 10), i.e. 40% if both renal failure and severe acidosis operate in the same patient.

A study conducted on post-diarrhea ARF by M.A. Muthusethupathi, S. Sivakumar et al in MMC, Chennai in 1990 aimed at assessing the prognostic significance of metabolic acidosis in post-diarrhea ARF.7 The study concluded that early identification and prompt correction of metabolic acidosis with bicarbonate could reduce the mortality from the previous figures of 53% in post-diarrhea ARF (before the wide spread availability of ABG) to 26%.8,9 In the current study of 104 patients with acute diarrhea, 28 had renal failure and 4 patients died due to ARF and its consequences (including acidosis). So, the mortality rate for post-diarrhea ARF in this study is 4 out of 28 or 14.2%.10 So, this reduction in mortality can be attributed to early identification and prompt correction of metabolic acidosis.

Thus, metabolic acidosis has prognostic significance and early correction of acidosis improves outcome.

CONCLUSION:

The most common acid-base disturbance observed in patients with acute diarrhea disease is normal anion gap metabolic acidosis. Other acid-base patterns observed includes increased anion gap metabolic acidosis and a normal ABG study. A normal ABG must be interpreted in the clinical context because mixed acid-base disorders may produce normal values in ABG analysis. The acid-base abnormality observed in post-diarrhea ARF is increased anion gap metabolic acidosis. Metabolic acidosis is a prognostic factor and early recognition and prompt correction of metabolic acidosis improves the outcome in acute diarrhea disease and post-diarrhea ARF.

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