A PROSPECTIVE CLINICAL STUDY OF ACID-BASE CHANGES IN ACUTE DIARRHOEAL DISEASE

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ABSTRACT

BACKGROUND

Disorders of acid-base homeostasis complicate a variety of disease conditions and contribute to morbidity and mortality. Unless promptly recognised, 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 exhaustive and 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.

MATERIALS AND METHODS

In all patients, preliminary history regarding duration of diarrhoea, presence of vomiting and oliguria was recorded. Clinical examination was focussed 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. In all patients, routine urinalysis for albumin, sugar and deposits was done. Also, urine was analysed for acetone, since patients with diarrhoea could starve resulting in starvation ketoacidosis. In all patients, haemoglobin estimation was routinely done. It is mandatory to know the haemoglobin 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%). Serial measurements were made as appropriate and after treatment.

RESULTS

14 out of 52 patients with acute diarrhoea had ARF. All 14 patients had increased anion gap metabolic acidosis. 7 out of 52 patients with acute diarrhoea had severe metabolic acidosis (pH <7.2). Out of these 7 patients, 5 had renal failure and 2 patients had normal renal parameters.

CONCLUSION

The most common acid-base disturbance observed in patients with acute diarrhoeal disease is normal anion gap metabolic acidosis. Other acid-base patterns observed include 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 diarrhoeal 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 diarrhoeal disease and post diarrhoeal ARF.

KEYWORDS

Acute Diarrhoeal Disease, Acid-Base Changes.

HOW TO CITE THIS ARTICLE: Nagarjuna B, Siva GP. A prospective clinical study of acid-base changes in acute diarrhoeal disease. J. Evid. Based Med. Healthc. 2018; 5(1), 18-22. DOI: 10.18410/jebmh/2018/4

BACKGROUND

Disorders of acid-base homeostasis complicate a variety of disease conditions and contribute to morbidity and mortality. Unless promptly recognised, 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 austive and 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 Diarrhoeal 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 diarrhoeal disease. The study tries to validate a prognostic role for such acid-base changes in acute diarrhoeal disease and calls for an early recognition and prompt correction of acid-base changes.

Financial or Other, Competing Interest: None.
Submission 12-12-2017, Peer Review 19-12-2017,
Acceptance 26-12-2017, Published 01-01-2018.
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DOI: 10.18410/jebmh/2018/4

Aims of the Study- To find out the acid-base disturbances resulting from acute diarrhoeal disease. To analyse the changes in acid-base status in patients with acute renal failure due to acute diarrhoeal disease. To find out the incidence of severe metabolic acidosis (pH <7.2) in acute diarrhoeal disease. To find out whether metabolic acidosis has prognostic significance in acute diarrhoeal disease and whether early detection and correction of metabolic acidosis can improve the outcome.

MATERIALS AND METHODS

Study Design- This study is a prospective study conducted in Konaseema Institute of Medical Sciences, Department of General Medicine. In this study, patients admitted for acute diarrhoeal disease in medical ward and infectious disease ward were included.

Inclusion Criteria

Patients older than 12 years of age who presented with acute diarrhoeal were included. Acute diarrhoea 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

Since this study aims at identifying the acid-base changes occurring as a result of acute diarrhoea, the following patients were excluded.

Patients who had coexisting diseases like COPD or other lung diseases likely to produce respiratory acidosis in ABG diabetes mellitus patients (who might have type IV RTA-hyporeninaemic, hypoaldosteronism), liver disease and chronic kidney diseases were excluded, because these pathologies might themselves produce abnormalities in ABG.

Patients who were on drugs likely to produce acid-base disturbances were also excluded. E.g. Metformin (for PCOD), cholestyramine calcium or magnesium chloride, lysine or arginine hydrochloride, acetazolamide drugs causing RTA (renal tubular acidosis); e.g. co-trimoxazole, spironolactone and triamterene.

Study Period- This study was conducted between September 2015 and August 2018.

Study Population- The study included 52 patients, 28 males and 24 females. The youngest patient in the study was 17 years of age and the oldest patient was 78 years of age. All satisfied the inclusion and exclusion criteria.

Study Protocol and Laboratory Investigations- In all patients, preliminary history regarding duration of diarrhoea, presence of vomiting and oliguria was recorded. Clinical examination was focussed 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. In all patients, routine urinalysis for albumin, sugar deposits was done. Also, urine was analysed for acetone, since patients with diarrhoea could starve resulting in starvation ketoacidosis. In all patients, haemoglobin estimation was routinely done. It is mandatory to know the haemoglobin 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%), 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 analysed 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^- + HCO_3^-). 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 diarrhoea 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 litres 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 uraemic 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 diarrhoea stopped and renal functions returned to normal, if they initially had renal failure.

OBSERVATIONS AND RESULTS

Fifty two patients with acute diarrhoea 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.

Total Number of Patients Studied	Number of Patients with Normal Anion Gap Acidosis	Number of Patients with Increased Anion Gap Acidosis	Number of Patients with Normal ABG
52	32	14	6

Table 1

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 diarrhoea- 14 out of 52 patients with acute diarrhoea had ARF. All 14 patients had increased anion gap metabolic acidosis.

Incidence of Severe Metabolic Acidosis (PH <7.2)

7 out of 52 patients with acute diarrhoea had severe metabolic acidosis (pH <7.2).

Out of these 7 patients, 5 had renal failure and 2 patients had normal renal parameters.

Total Number of Patients With Severe Metabolic Acidosis	Number of Patients with Renal Failure	Number of Patients with Normal Renal Function
7	5	2

Table 2. Renal Function in Patients with Severe Acidosis

Category	Total Number of Patients	Number of Patients with Severe Acidosis	Incidence of Severe Metabolic Acidosis
Patients with acute diarrhoea	52	7	13.46%
Patients with acute renal failure due to acute diarrhoea	14	5	35.71%
Patients with normal renal function	38	2	5.26%

Table 3. Incidence of Severe Metabolic Acidosis

Mortality Rate- Two out of 52 patients with acute diarrhoea died. Both patients had renal failure and severe acidosis.

pH	Total Number of Patients	Number of Patients' Deaths	Mortality Rate
pH <7.2	7	2	28.57%
pH >7.2	45	0	0%

Table 4. Mortality in Metabolic Acidosis According to PH

Total Number of Patients	Number of Patients Who Died	Mortality Rate
14	2	14.2%

Table 5. Mortality in Post-Diarrhoeal ARF

DISCUSSION

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

To accomplish the above tasks, 52 patients with acute diarrhoea were included in the study. Among the 52 patients, 28 were males and 24 were females. The mean duration of diarrhoea at presentation was 2.01 days.

Among the 52 patients studied, 14 patients (9 men and 5 women) had renal failure (serum creatinine more than 2 mg%) at initial presentation to hospital (25). The mean duration of diarrhoea 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 52 patients were interpreted in a systematic way as previously described.

Acid-base changes occurring in acute diarrhoea- The following 3 types of acid-base changes were observed on analysing the ABG values of all 52 patients.

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

Out of the 52 patients studied, 32 patients had a normal anion gap metabolic acidosis, 14 patients had an increased anion gap metabolic acidosis and 6 patients had normal ABG values. Hence, it is inferred that.

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

The reason for a normal anion gap metabolic acidosis as described previously is loss of bicarbonate in diarrhoeic 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 electroneutrality 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 diarrhoeal disease lose potassium through GIT. Likewise, dysnatraemia can also be anticipated.

30 out 32 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 (14 patients).

A patient with acute diarrhoeal 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 hypoperfusion.
iii. Ketoacidosis due to starvation.

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

It was observed that all 14 patients had renal failure (Sr. creatinine >2.0 mg%) 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 diarrhoeal illness was normal ABG study (6 patients).

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

i. A patient might have a mild diarrhoeal 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 diarrhoeal diseases. So, a normal ABG study in the clinical context of severe vomiting and diarrhoea 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 diarrhoea and dehydration and vomiting was not a prominent manifestation.

So, a milder diarrhoeal 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-recognised manifestation of acute diarrhoea 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 diarrhoea (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 are comparable studies.[3]

Acid-Base Changes in ARF Due to Acute Diarrhoea-

The next aim of this study is to analyse the acid-base changes that occur in patients developing renal failure due to acute diarrhoea.

Among the 52 patients studied, 14 patients had renal failure at presentation to hospital. All 14 patients demonstrated a high anion gap metabolic acidosis - 5 out of 14 patients had severe metabolic acidosis (pH <7.2). In all 14 patients, urine tested negative for acetone and serum albumin was normal. All 14 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 7 out of 52 patients with acute diarrhoea had a severe metabolic acidosis, i.e. pH <7.2 in ABG study. Hence, the incidence of severe metabolic acidosis in patients with acute diarrhoea was 13.46%.

Among these 7 patients, 5 patients had renal failure and 2 patients had normal renal function. So, the incidence of severe acidosis in patients with renal failure due to diarrhoea was 5 out of 14 patients, i.e. 35.71% and the incidence of severe acidosis in patients with normal renal function was 2 out of 38 patients, i.e. 5.26%.

So, severe metabolic acidosis occurred in both groups of patients with acute diarrhoea (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 oedema.
b. Because of the threat posed by severe metabolic acidosis on various organ systems, patients with pH <7.2 must be promptly recognised 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 diarrhoea 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 7 patients with severe acidosis died, while no death occurred in the remaining 45 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 7 patients with severe acidosis, both deaths occurred in those with ARF. So, it can be inferred that the mortality rate is still high (2 out of 5), i.e. 40% if both renal failure and severe acidosis operate in the same patient.

A study conducted on post-diarrhoeal 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-diarrhoeal 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-diarrhoeal ARF (before the wide spread availability of ABG) to 26%.[8,9] In the current study of 52 patients with acute diarrhoea, 14 had renal failure and 2 patients died due to ARF and its consequences (including acidosis). So, the mortality rate for post-diarrhoeal ARF in this study is 2 out of 14 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 diarrhoeal disease is normal anion gap metabolic acidosis. Other acid-base patterns observed include 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-diarrhoeal 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 diarrhoeal disease and post-diarrhoeal ARF.

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