

Bicarbonate Therapy in Renally Compromised Critically Ill Patients with Metabolic Acidosis: Study of Clinical Outcomes and Mortality Rate

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Background: Metabolic acidosis is the most frequent medical condition occurring in critically ill renally compromised patients. This study was aimed to determine clinical outcomes of bicarbonate therapy in renally compromised critically ill patients having metabolic acidosis.

Methods: A prospective longitudinal cohort study was undertaken in three military hospitals in Rawalpindi, Pakistan. All patients fulfilling the inclusion criteria who were admitted to the ICU of any of the three study hospitals from July 2019 to March 2020 were studied for clinical outcomes of bicarbonate therapy using an evidence-based clinical checklist. Outcome measures include changes in blood pH, serum potassium, and sodium levels, blood pressure and weight, along with other clinically significant laboratory parameters.

Results: Eighty-one patients fulfilling the inclusion criteria were evaluated. The mean age of the patients was 55.61±19.5 years, while the mean weight was 63.43±14.19 Kg. A mortality rate of 45.7% was observed. Disease-related complications including hypoxia, cardiac failure, multiple organ failure, elevated blood pressure, and ischemic heart disease (IHD) were found to be associated with a higher mortality rate ($P<0.005$). Whereas using Fisher's exact test, concomitant administration of sodium chloride, along with bicarbonate therapy was associated with a low mortality rate and had no significant impact on sodium loading or weight gain. Moreover, various drug-drug interactions were found to be associated with a higher mortality rate ($P<0.05$).

Conclusion: Bicarbonate therapy was not found to affect the mortality rate in critically ill renally compromised patients with metabolic acidosis.

Keywords: metabolic acidosis, chronic kidney disease, bicarbonate therapy, clinical outcomes, mortality rate

Introduction

Metabolic acidosis has become a significant ailment that is represented as inequity within the body's acid-base equilibrium. It frequently occurs in critically ill patients with an overall prevalence of 8–64% where about 14–42% is due to acute acidemia.^{1–3} The significantly higher mortality rate of up to 57% has been reported among patients with persistent acidemia with poor prognosis.⁴ It affects 15% of Chronic Kidney Disease (CKD) patients with serum HCO₃ level below 22 mEq/L and the percentage increases with the worsening of kidney function. As studied, acidosis has been observed in 7% of subjects in CKD stage 2, 13% in stage 3, and 37% in stage 4.^{5,6}

Acidemia is defined as depletion in blood pH from 7.02 leading to low bicarbonate (-HCO_3) ions concentration in the blood accompanied by reduced arterial pressure of CO_2 production.⁷ Metabolic acidosis refers to bicarbonate loss through the kidneys (during impaired renal function) or sometimes during diarrhea. Forms of acidosis other than metabolic encompass lactic acidosis, respiratory and diabetic ketoacidosis.^{8,9} Sodium bicarbonate is the treatment of choice for metabolic acidosis in critically ill patients, which has been practiced in ICU patients for better clinical outcomes.⁷ Due to the lack of evidence based clinical studies, the use of bicarbonate therapy in acidosis patients is still controversial with little evidence to support its use. Furthermore, the therapy is proved to be insignificant in patients with lactic acidosis, hemodynamic and septic shocks.¹⁰

Some noticeable adverse effects of this therapeutic strategy include a decline in levels of calcium and potassium, but a surge in lactate production and sodium levels, prolonged QT interval, calcium accumulation in the vessels, and carbon dioxide generation.¹¹ Among all, production of carbon dioxide is one of the harmful effects which leads to hypocalcaemia and becomes fatal to patients with decreased cardiac output and respiratory failure.^{11,12} However, use of this therapy may act as supportive therapy; for example, it may reduce the need for the renal transplant in most of the CKD patients, detrimental effects of acidosis on cardiac muscles and the supply of oxygen.^{13,14}

Notably, in CKD patients, this treatment is found to be heterogeneous in some studies while many guidelines support its use in CKD and AKI patients.¹⁵ According to NICE guidelines, Bicarbonate therapy should be prescribed in patients with GFR less than 30 mL/min/1.73 (GFR category 4 or 5) and a serum bicarbonate concentration of 20 mmol/L.¹⁶ Similarly, KDIGO 2012 guidelines recommend the use of oral base therapy in CKD and AKI patients having serum Bicarb levels <22 mmol/L.¹⁷ However, lack of scientific data in this area of interest leaves physicians in the ICU in uncertainty whether to use this therapy in such patients or not.

This study was aimed to evaluate clinical outcomes in terms of safety and efficacy of the use of bicarbonate therapy in renally compromised critically ill patients with metabolic acidosis.

Methods

Ethical Approval

Ethical approval was obtained from the hospitals Ethics Review Board (ERB). Before taking part in the study all

the participants were requested to sign a consent form, after the purpose and method of study was explained. In case the patient was unable to give informed consent, his guardians gave the permission on behalf of the patient. Confidentiality of patients' data was in obedience with the Declaration of Helsinki as guaranteed by the institutional Review Boards of the hospitals.

Study Design

This prospective cohort longitudinal research has been conducted at three military hospitals in Rawalpindi Pakistan, ie, Combined Military Hospital (CMH), Pak Emirate Military Hospital (PEMH), and Armed Forces Institute of Urology (AFIU), Rawalpindi, Pakistan.

Study Sample and Sampling Technique

All patients fulfilling inclusion criteria which were admitted in CMH, PEMH, and AFIU from July 2019 to March 2020 were studied. A non-probability convenience sampling technique was used for sampling.

Inclusion and Exclusion Criteria

Adult patients of both genders, age ≥ 12 years admitted in the ICU either because of CKD or Acute Kidney Injury (AKI) having metabolic acidosis and already prescribed with IV Sodium Bicarbonate therapy along with normal saline and other IV fluids by the attending physician, were included. Both renal functions and acidemia were determined using KDIGO 2012 guidelines, where metabolic acidosis is defined as $\text{pH} \leq 7.20$, and serum sodium bicarbonate concentration ≤ 22 mm (KDIGO) while renal failure is explained using the Glomerular filtration rate (GFR) < 60 mL/min/1.73 and comorbidities like hypertension and diabetes has also been included in the factors. Exclusion criteria includes patients having respiratory and lactic acidosis because larger data may hinder the primary outcomes of the study and also the studied treatment has been found to be insignificant in the treatment of these diseases.⁸ Similarly, cancer patients having complex therapeutic intervention will also alter the calculations, therefore were excluded.

Data Collection

After explaining the study rationale and objectives to the subjects and getting the approved and signed consent form data from the patient's medical record file is collected in the clinical checklist.

Clinical Evaluations and Study Tool

An evidence-based clinical checklist was developed from a similar preexisting checklist available in the published literature.¹⁸ This preexisting form was amended after the literature review, focus group discussion pursuant to the aims of this research and used as a data collection tool. The study covered the daily evaluation of clinical outcomes in each patient using standard management guidelines by an experienced clinical pharmacist in consultation with ICU consultants and physicians. The clinical assessment included evaluation of degree and severity of the disease, determination of rationality of the prescribed drugs and administered dose, interactions, risks, evaluation of various laboratory parameters by the severity of disease and in relation to administered drugs with specific doses. The clinical evaluation was based on the recommendations of KDIGO guidelines. The difference in values of all variables analyzed was assessed before and after the therapy commenced. The study followed clinical evaluation of these patients since the day they were admitted to their “discharge” or “death” after treatment. Drug–drug interactions were also observed by Stockley’s drug interaction. The clinical evaluation data was entered in SPSS version 23.0 for further statistical analysis.

Statistical Analyses

All data were analyzed by means of IBM SPSS (Statistical Package for Social Sciences) statistical software Version 23.0. The analyzed data was subjected to statistical analysis using both descriptive as well as inferential statistics. The descriptive statistics involved measure of frequencies, percentage, central tendencies like mean and cross-tabulation. Inferential analysis includes Pearson’s Chi-square test, one-way analysis of variance (ANOVA) tests, and Fischer’s exact test depending on the type of variable. Statistically significant association was considered with a *P*-value <0.05.

Results

Demographics

A total of 81 patients including 51 (63%) males and 30 (37%) females were recruited having a mean age of 55.6 ±19.5 and weight of 63.4±14.1. These demographic and clinical characteristics of all patients are summarized in Table 1.

The serum creatinine levels were measured before the start and at the end of the study. During the study mean

reduction of 1.65 mg/dL of the serum creatinine values were observed. The mean serum creatinine values before and at the end of study and the average difference in creatinine levels are summarized in Table 2.

The end clinical outcomes of the patient in terms of mortality or recovery was also determined and an overall mortality rate of 45.7% was observed. The results of end clinical outcomes are provided in Table 3.

Factors Affecting the Clinical Outcomes

The association of progression of kidney disease and the clinical outcomes were determined and it was found that the mortality rate was not affected by the progression of kidney disease in acidemia patients. The results of the association of progression of kidney disease and clinical outcomes is provided in Table 4.

The association of various laboratory parameters and the clinical outcomes was determined, and it was found that the mortality rate has a statistically significant association with hyperkalemia and hypertension. The results of association of laboratory parameters and clinical outcomes is provided in Table 5.

The association of various co-morbid conditions and the clinical outcomes was determined, and it was found that the co-morbid conditions has no statistically significant association with the clinical outcomes. The results of association of various co-morbid conditions and clinical outcomes is provided in Table 6.

Metabolic acidosis leads to certain complications including imbalance in serum concentrations and progression to secondary medical problems like hypertension, bone mineral disease, and multiple organ disorders.^{19,20} It was observed that disease complications including hypoxia, heart failure, and multiple organ failure has a statistically significant association with the overall mortality rate. The results of association of disease complications with clinical outcomes are provided in Table 7.

Effect of Sodium Bicarbonate Therapy

Sodium bicarbonate therapy was being administered in all the study population for treatment of metabolic acidosis. The majority of the study population were receiving sodium bicarbonate therapy with sodium chloride (normal saline) which has shown a greater recovery rate. However, a statistically significant difference in mortality rate was not observed. The results of mortality rate with sodium bicarbonate and sodium chloride therapy is provided in Table 8.

Table 1 Characteristics of Study Patients

Demographic Variables		Frequency (%)
Age	<40 years	18 (22.2)
	40–60 years	24 (29.6)
	>60 years	39 (48.1)
Gender	Male	51 (63)
	Female	30 (37)
Weight	<70 kg	50.1 (61.9)
	>70 kg	49.9 (38.1)
CKD Stage	G1	4 (5.1)
	G2	9 (11.4)
	G3a	1 (1.3)
	G3b	6 (7.6)
	G4	9 (11.4)
	G5	50 (66.3)
Comorbidities	Hypertension	48 (59.3)
	Diabetes	45 (55.6)
	Ischemic Heart Disease	19 (23.5)
	Liver disease	5 (6.2)
	Renal Disease	57 (70.3)
	Recent Infection disease	2 (2.5)
	Surgery	9 (11.1)
Dialysis Status	Non-dialysis	34 (42)
	Pre-dialysis	27 (33.3)
	Post-dialysis (1st time)	20 (24.7)
Edema	Yes	44 (62.9)
	No	37 (37.1)
Blood Glucose (Random)	Normal	23 (35.4)
	High	40 (61.5)
Blood Glucose (Fasting)	Normal	20 (38.5)
	High	32 (61.5)
Number of Comorbidities	<3 comorbidities	53 (65.4)
	>3 comorbidities	18 (22.2)
	No comorbidities	10 (12.3)
Stay in ICU	<3 days	14 (17.3)
	4–10 days	54 (66.6)
	>10 days	13 (16.1)
Stay in Hospital	<3 days	6 (7.4)
	4–10 days	53 (65.4)
	>10 days	22 (27.2)

Table 2 Serum Creatinine Values for the Study Patients

	Initial Value (mg/dL)	Final Value (mg/dL)	Difference (mg/dL)
Mean±SD	6.27±6.35	4.70±3.24	-1.65±5.78
Minimum	0.28	0.79	-32.64
Maximum	45.44	22.25	17.69

Table 3 Clinical Outcomes of the Disease

Outcomes	Frequency (%)
Discharge	44 (54.3)
Death	37 (45.7)

Effect of Medications

The total number of medicines prescribed per patient is 18.75 ± 6.244 , of which 2.96 ± 1.76 are antibiotics, 1.37 ± 1.34 are antihypertensives, 0.7 ± 0.68 are antidiabetics, 0.28 ± 0.5 are immunosuppressants, 2.25 ± 1.09 are IV fluids, and 13.69 ± 5.42 are injectable medications. The brief description of medication prescribed among the study patient is provided in [Table 9](#).

Several medications were prescribed and observed to determine their effect on mortality rate, of which some antihypertensive medications were found to play a role in mortality rate. The impact of various drug therapies on the end clinical outcomes are described in [Table 10](#).

Furthermore, drug interactions were also recorded in this study as 49 (60.5%) of the study population were receiving contraindicated medications having serious side-effects, 19 (23.5%) had significant interactions that needed monitoring, six (7.4%) had minor interactions, and 17 (8.6) received no such medications. The results of interactions among the prescribed medicine and their association with the mortality rate is described in [Table 11](#).

Discussion

Metabolic acidosis is a serious medical condition characterized by low serum pH levels due to the reduction in HCO_3 ions followed by compensatory decrease in pCO_2 .⁷ This condition is very common in ICU patients having

complex medical conditions and receiving a multifaceted clinical interventions. This complexity interferes with the mortality rate and other end outcomes in critically ill patients. Renal diseases leading to metabolic acidosis are a common phenomenon as identified by Landmark studies that the reduction in the renal ammonia substantially leads to acidosis.^{19,20} Therefore, progression in stages of CKD should have been a complication in metabolic acidosis patients, but it has been observed conversely that CKD and AKI were both found to be non-significant with the mortality rate.

Impact of Co-Morbid Conditions on the Clinical Outcomes

The current study highlights medical complications caused by acidemia like multiple organ failure, hypoxia, risk of heart failure, and elevated heart rate affecting the end outcomes. Cardiovascular complications may be caused due to an increase in sodium levels of some patients. Several patients went into multiple organ failure during the study. One of the reasons of this complication is increased levels of lactate in the blood. Serum lactate is involved in tissue perfusion and oxygenation, therefore an increase in serum lactate indicates that the organ failure has started which corresponds with the results of hyperlactemia and multiple organ failure reported in this study. This phenomenon is supported by another study conducted in 2016, according to which hyperlactemia is associated with high mortality rate among acidemia patients.²¹ The relationship between kidney and cardiovascular diseases is well established, acidosis on top of it creates a definite cardiovascular risk.²² Acidosis causes sodium accumulation in blood serum, ultimately resulting in increased

Table 4 Association of Progression of Kidney Diseases and Clinical Outcomes

CKD Stages	Deaths	Recovered	P-value
	N (%)	N (%)	
G1	2 (50)	2 (50)	0.817
G2	4 (44.4)	5 (55.6)	
G3a	1 (100)	0 (0)	
G3b	3 (50)	3 (50)	
G4	5 (55.6)	4 (44.4)	
G5	20 (40)	30 (60)	
AKI stages	0.714		
AKI Stage 1		5 (50)	5 (50)
AKI Stage 2		6 (66.7)	3 (33.3)
AKI Stage 3		4 (50)	4 (50)

Table 5 Association of Laboratory Parameters with Clinical Outcomes

Test	Effect	Count	Deaths	Recovered	P-value
		N (%)	N (%)	N (%)	
Sodium	Hyponatremia	24 (30.8)	8 (10.3)	16 (20.5)	0.113*
	Hypernatremia	22 (28.2)	14 (17.9)	8 (10.3)	0.097**
	Normal	32 (41)	18 (23.1)	14 (17.9)	
Calcium	Hypocalcemia	56 (77.8)	30 (41.7)	26 (36.1)	0.105*
	Hypercalcemia	1 (1.4)	1 (1.4)	0 (0)	0.545**
	Normal	15 (20.8)	4 (5.6)	11 (15.3)	
Magnesium	Hypomagnesemia	21 (35)	14 (23.3)	7 (11.7)	0.117*
	Hypermagnesemia	9 (15)	6 (10)	3 (5)	0.911**
	Normal	30 (50)	12 (20)	18 (30)	
Urea	High	76 (95)	32 (94.1)	42 (95.5)	0.791*
	Normal	4 (5)	2 (5.9)	2 (4.5)	
Serum Creatinine	Normal	5 (6.3)	2 (5.7)	3 (6.8)	0.841*
	High	75 (93.8)	33 (97.3)	41 (93.2)	
Potassium	Normal	26 (32.9)	13 (16.5)	13 (16.5)	0.144*
	Hyperkalemia	33 (41.8)	11 (13.9)	22 (27.8)	0.044**
	Hypokalemia	26 (32.9)	12 (15.2)	8 (10.1)	
Blood Pressure	Baseline	24 (29.6)	3 (3.7)	17 (21.0)	<0.001*
	Increase in BP from Baseline	27 (33.3)	10 (12.3)	6 (7.4)	
	Decrease in BP from Baseline	30 (37)	24 (29.6)	21 (25.9)	0.116**

Notes: *Chi Square **ANOVA.

Table 6 Association of Various Co-Morbid Conditions with Clinical Outcomes

Test	Effect	Deaths	Recovered	P-value
		N (%)	N (%)	
Hypertension	Yes	21 (43.8)	27 (56.3)	0.423
	No	16 (48.5)	17 (51.5)	
Diabetes	Yes	21 (46.7)	24 (53.3)	0.510
	No	16 (44.4)	20 (55.6)	
Ischemic Heart Disease	Yes	12 (63.2)	7 (36.8)	0.069
	No	25 (40.3)	37 (59.7)	
Liver Disease	Yes	4 (80)	1 (20)	0.130
	No	33 (43.4)	43 (56.6)	
Renal Disease	Yes	23 (40.4)	34 (59.6)	0.108
	No	14 (58.3)	10 (41.7)	
Recent infectious disease	Yes	0 (0)	2 (100)	0.292
	No	37 (46.8)	42 (53.2)	
Surgery	Yes	4 (44.4)	5 (55.6)	0.611
	No	33 (45.8)	39 (54.2)	

Table 7 Association of Various Complications of CKD with Clinical Outcomes

Test	Effect	Deaths	Recovered	P-value
		N (%)	N (%)	
Edema	Yes	18 (46.2)	21 (53.8)	0.541
	No	17 (44.7)	21 (55.3)	
Hypoxia	Yes	17 (60.7)	11 (39.3)	0.029
	No	17 (35.4)	31 (64.6)	
Anemia	Yes	31 (44.9)	38 (55.1)	0.612
	No	5 (45.5)	6 (54.5)	
Hyperlactemia	Yes	26 (86.7)	4 (13.3)	0.000
	No	10 (23.3)	33 (76.7)	
Heart Failure	Yes	31 (88.6)	4 (11.4)	0.000
	No	5 (11.6)	38 (88.4)	
Multiple organ failure	Yes	24 (75)	8 (25)	0.000
	No	11 (24.4)	34 (75.6)	
	No	33 (45.8)	39 (54.2)	

Table 8 Mortality Rate with Various Treatment Therapies

Treatment	Total N (%)	Death	Recovered	P-value
Sodium bicarbonate alone	8 (9.87)	3 (37.5)	5 (62.5)	0.498*
Sodium bicarbonate + Sodium chloride	73 (90.12)	39 (53.4)	34 (46.5)	

Notes: *P-value through Fisher's exact test.

Table 9 Number of Medicines of Various Categories Prescribed

Total Medication	Mean±SD
Total medicines prescribed	18.75±6.244
Total antibiotics prescribed	2.96±1.76
No of antihypertensive drugs prescribed	1.37±1.346
No of antidiabetic drugs	0.73±0.689
No of immune suppressant drugs prescribed	0.28±0.506
No of IV fluids prescribed	2.25±1.090
No of injectable drugs prescribed	13.69±5.426
No of interacting drugs	4.91±2.599
No of drug interactions	3.22±1.830

urinary excretion of sodium as well as an imbalance of other ions like sodium bicarbonate, hypercalcemia, etc., which eventually leads to cardiovascular problems.²³

Impact of Biochemical Parameters on the Clinical Outcomes

One of the most significant outcomes reported in this study is the relationship between metabolic acidosis and biochemical parameters leading to an increased mortality rate. Although hypernatremia was not statistically significant in this study, a higher mortality rate was observed among hypernatremia patients. Other blood levels like urea, serum creatinine, magnesium, and calcium were also found to be high among those with higher mortality rate. These findings correspond with a similar study related to biochemical imbalance in critically ill patients with acidosis.²⁵ However, factors like hypernatremia and hyperkalemia were found to influence mortality as both play a vital role in the regulation of heart rhythms.²⁴

Table 10 Effect of Medications on Mortality Rate

Treatments	Died	Recovered	P-value
Drugs interfering with the excretion of creatinine	5 (13.5)	2 (4.5)	0.152
Drugs used for management of BP	27 (73.0)	30 (68.2)	0.638
Drugs used for managing anemia	33 (89.2)	33 (75.0)	0.102
Drugs used for prevention of AKI	36 (97.3)	43 (97.7)	0.901
Drugs for MBD	27 (73.0)	36 (81.8)	0.340
Drugs for management of lipid disorder	10 (27.0)	6 (13.6)	0.132
Antibiotics	37 (100.0)	40 (90.9)	0.060
Anti-ulcer drugs	33 (89.2)	41 (93.2)	0.524
Drugs for nausea and vomiting	14 (37.8)	24 (54.5)	0.133
Drugs for pain and fever	31 (83.8)	30 (68.2)	0.105

Table 11 Impact of Drug–Drug Interactions on Clinical Outcomes

Type of Drug–Drug Interaction	Total N (%)	Death	Recovered	P-value
No interaction	7 (8.6)	2 (5.4)	5 (11.4)	0.044
Minor interaction	6 (7.4)	3 (8.1)	3 (6.8)	
Significant (needs monitoring)	19 (23.5)	4 (10.8)	15 (34.1)	
Serious (contraindicated)	49 (60.5)	28 (75.7)	21 (47.7)	

Impact of Drug Therapy on the Clinical Outcomes

Complexity in medical conditions of ICU patients allowed us to further expand these findings and determine which clinical interventions are being used to treat acidosis as well as the risk factor and complications. Sodium bicarbonate therapy was determined to be insignificant with mortality rate either with or without sodium chloride, although recovery has been shown in comparison to death, but this difference is not substantial. Furthermore, as hypothesized in the objective, the effect of sodium chloride when administered with sodium bicarbonate may increase the mortality rate, but it was observed that it promotes recovery, although these significant results are not quite pronounced. Similarly, various published studies have raised concerns over the concomitant administration of sodium chloride and sodium bicarbonate since they may cause hypernatremia and weight gain. On the contrary, this study has observed that a higher mortality rate was not observed, hence it is safe to administer sodium chloride and sodium bicarbonate together among the academic patients.

Several contraindicated drugs were prescribed to the study patients, especially antibiotics, which have been found to increase the mortality rate in patients with metabolic acidosis. Antibiotics not only worsen the acidosis they also reduce the

ability of the kidneys to function properly.²⁶ Some of the IV fluids were also interfering with the outcomes of the disease. Several drugs that were being prescribed were contraindicating, while fewer needed monitoring. The drug interactions were found to have a statistically significant relationship with the mortality rate. The incidence of such significant drug-interactions highlights the need for clinical pharmacists to review the drug therapy for critically ill patients in ICU settings, since none of the hospitals under study had a dedicated clinical pharmacist. It can be observed that drug-interactions were among the most significant factors which were affecting the mortality rate ($P < 0.05$), hence the clinical pharmacy services should be introduced in the ICU settings to improve the clinical outcomes and reduce the higher mortality rate.

Study Limitations

The study limitations included small sample size and patient diversity. The study patients included patients with different stages of CKD as well as AKI which may create difficulties in developing and discussing the results.

Conclusion

Multiple factors including primary disease, complications, and biochemical parameters like serum lactate affect the mortality rate in renally compromised critically ill metabolic acidosis patients. Patients having cardiovascular

complications due to acidosis and those having higher serum lactate levels were found to be at higher risk. Sodium bicarbonate therapy alone or in combination with sodium chloride was not found to affect the mortality rate in acidosis patients. Drug–drug interactions were found to be associated with higher mortality rate. The study has opened new ways to put forward research in this area.

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