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The Effect of Sodium Bicarbonate Versus Tris-Hydroxymethyl Aminomethane on Improvement of Metabolic Acidosis in Patients Post Coronary Artery Bypass Graft Surgery

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Abstract: Metabolic acidosis or reduction of serum bicarbonate (HCO_3^-) concentration is a common disorder in patient with serious illness which causes morbidity and mortality in them. Buffer therapy is a major treatment to correct metabolic acidosis. In this study, the buffering effect of sodium bicarbonate and Tris Hydroxymethylaminomethane (THAM) on patients with metabolic acidosis post elective Coronary Artery Bypass Graft Surgery (CABG) was compared. Patients diagnosed with metabolic acidosis (pH<7.25, BE<5) after elective coronary artery bypass grafting were enterd into the study. In situations in which HCO_3 administration is used, the total dose required to correct the base deficit can be calculated using the equation: dose (mEq) = 0.3×weight (kg)×base deficit (mEq/L) from $NaHCO_3$ (8/5%) solution which half this dose is usually given.In cardiac bypass surgery with metabolic acidosis, when THAM solution (ml from 0.3 M) is used the total dose can be calculated using the equation: dose: 9 mL/kg IV, maximum 500 mg/kg. Our results demonstrated that THAM reduced serum lactate, $PaCO_2$, length of Intensive Care Unit (ICU) stay, additional dose of administration and inotrope need, compared with sodium bicarbonate. Also, THAM significantly enhanced patient's cardiac output in comparison with sodium bicarbonate. In conclusion, our results indicated that THAM is more suitable than sodium bicarbonate in buffering metabolic acidosis post CABG.

Key words: Metabolic acidosis, sodium bicarbonate, THAM, intensive care unit, Coronary Artery Bypass Graft Surgery (CABG)

INTRODUCTION

Metabolic acidosis has been defined as an acid base disorder which initiated by reduction in serum bicarbonate (HCO_3^-) concentration lasts for a few minutes to a few days (acute), or weeks to years (chronic) (Kraut and Madias, 2010). Metabolic acidosis is common phenomenon in seriously ill patients, especially those in Intensive Care Unit (ICU) and it can be associated with a poor clinical outcome (Khosravani *et al*., 2009; Gunnerson *et al*., 2006). Metabolic acidosis, based on severity has been divided into three forms according to the level of systemic arterial blood pH: mild (pH 7.30-7.36), moderate (pH 7.20-7.29) and severe (pH<7.20) (Kraut and Madias, 2012). Lactic acidosis or ketoacidosis are the major causes of severe cases of metabolic acidosis (Gabow, 1985). Also, non-anion gap (hyper-chloraemic) acidosis occurs as a result of administration of large quantities of sodium chloride during treatment of hypotension (Kellum, 2002). However, its mortality is lower than that associated with high anion gap acidosis. The evaluation of severity of metabolic acidosis has been done by examination of acid-base parameters, usually measured in arterial blood (Treger *et al*., 2010) and less frequently in peripheral venous or arterialized venous blood (Toftegaard *et al*., 2008). As observed with circulatory shock, under conditions of markedly impaired tissue perfusion, acid-base parameters obtained from central venous blood might more accurately reflect the acid-base milieu of poorly perfused tissues with pH being substantially lower and partial Pressure of CO_2 (PCO_2) being substantially higher than in simultaneously obtained arterial blood (Sato *et al*., 1998; Planta *et al*., 1989; Androgue *et al*., 1989). In addition, serum Na, Cl and HCO_3^- levels should be measured to assess the serum anion gap. Also, determination of serum K^+ is essential, because its level can change variably with metabolic acidosis (Kraut and Madias, 2012).

In many cases, metabolic acidosis can be treated with therapy tailored to the specific disorder, otherwise, treatment with base or other general therapies are often required. Since, reductions in pH can cause cellular dysfunction, it seems that base therapy would be beneficial. Sodium bicarbonate is the most conventional form of base recommended by physicians (Sabatini and Kurtzman, 2009; Kraut and Kurtz, 2001, 2006). Up to

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now, conflicting data related to the effect of sodium bicarbonate administration on mortality and cardiovascular function has been reported (Halperin *et al*., 1996; Arieff *et al*., 1982). Due to the concerns about sodium bicarbonate therapy and further reducing pH, Tris Hydroxymethylaminomethane (THAM) was introduced into clinical practice as an alternative buffer (Nahas *et al*., 1998; Mohmmadi *et al*., 2014). Because 30% of THAM exists in non-ionized form, a portion can penetrate into cells and thereby raise pH. THAM is a small molecule that can be removed by dialysis and can therefore be used in patients with severe renal failure on dialysis. THAM has caused improvement in extracellular acid-base parameters in patients with lactate and respiratory acidosis (Weber *et al*., 2000; Wildenthal *et al*., 1968).

The aim of the present study is to compare the buffering effect of sodium bicarbonate versus THAM on improvement of metabolic acidosis post Coronary Artery Bypass Graft surgery (CABG).

MATERIALS AND METHODS

Patients: In this case-control study, 60 patients (age: 56±5.3 years) who underwent elective coronary artery bypass surgery admitted in open heart ICU Department of Kermanshah hospital and diagnosed with metabolic acidosis (pH<7.25, BE<-5).

Exclusion criteria: Patients with emergency surgery, electrolyte disorders like hypernatremia, ejection fraction lower than 40% and Cardio Pulmonary Bypass (CPB) time >90 min were excluded from this study.

Performance: Patients (n = 60) were randomly assigned to receive 0.3×weight (kg)×base deficit (mEq/L) sodium bicarbonate (n = 30, average age = 55.96±5.46 years) or 9 mL/kg THAM (n = 30, average age = 56.13±5.27 years). Arterial Blood Gas (ABG) sampling was done before and 0, 30 and 60 min after buffering. Cardiac Output (CO) was measured using Swan Ganz catheter, Inotrope need and mean Blood Pressure (BP) were recorded at each time point (0, 30, 60 min). Moreover, the length of ICU and hospital stay was recorded and compared in all patients.

Ethical consideration: This study was carried out in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of our institution.

Data analysis: Qualitative and quantitative data were analyzed and reported as frequency % and mean± standard deviation, respectively. The p<0.05 were considered statistically significant. All data were analyzed with IBM SPSS Statistics for Windows, Version 21.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS AND DISCUSSION

There were no significant differences between groups with respect to the days of hospital stay, however ICU stay time was significantly (p<0.0001) lowered in THAM group compared with bicarbonate group. Cardio Pulmonary Bypass (CPB) time was significantly (p<0.04) higher (about 8 min) in THAM group compared with bicarbonate group. Number of patients who needed additional dose of buffer was lower in THAM group compared with sodium bicarbonate group (Table 1).

Table 2 shows pH, $PaCO_2$, base excess, Na, K, lactate, cardiac output, inotrope need and mean blood pressure at the different measuring points (0, 30 and 60 min) for both groups. At the 0 time point, no significant differences between groups were detected.

The pH value was significantly (p = 0.042) increased from 7.21-7.35 at 60 min in THAM group compared to bicarbonate. Also, THAM decreased the value of $PaCO_2$ and blood sodium concentration while sodium bicarbonate increased it. Both of sodium bicarbonate and THAM decreased the lactate concentration, however this effect was significantly higher in patients treated with THAM. Cardiac Output (CO) significantly increased for patients treated with THAM and sodium bicarbonate increased cardiac output significantly (p<0.02). In addition, inotrope need, among patients treated with THAM, decreased after 60 min compared with patients treated with sodium bicarbonate. There was no significant difference between effect of THAM and sodium bicarbonate on base excess, potassium concentration and mean blood pressure. Previous studies have shown that sodium bicarbonate administration inevitably exacerbate intracellular. A few animal studies on acidosis have

Table 1: Demography of patients distributed in two different groups treated with sodium bicarbonate and THAM

Variables	Na bicarbonate	THAM	p-values
Age (years)	55.96±5.46	56.13±5.27	0.9000
Gender			
Male	16 (53)	17 (57)	
Female	14 (47)	13 (43)	
CPB time* (min)	61.35±20.46	70±6.48	0.0400
Additional dose			
Yes	6 (20)	2 (7)	
No	24 (80)	28 (93)	
ICU stay (days)	3.53±0.56	2.1±0.3	0.0001
Hospital stay (days)	7.8±1.22	7.8±0.9	1.0000

[a]Data are presented as Mean±SD and frequency %. *Cardiopulmonary Bypass (CPB) time

Table 2: Metabolic acidosis at different time of treatment with sodium bicarbonate or THAM

Variables	Na bicarbonate			THAM			
Recording time relative to treatment	Before 0 min or baseline	30 min after	60 min after	Before 0 min or baseline	30 min after	60 min after	p-values
pH	7.21±0.01	7.33±0.05	7.33±0.058	7.21±0.01	7.34±0.02	7.35±0.02	0.042
$PaCO_2$ (mmHg)	39.73±1.89	47.7±1.46	47.43±1.52	40.13±1.56	39.3±1.29	39.3±1.26	0.000
Base excess (L/min)	-7.56±1.05	-4.46±1.52	-4.26±1.98	-7.63±1.015	-4.6±0.75	-4.26±0.81	1.000
Na	140.06±1.78	148±1.29	147.8±1.64	140.06±1.78	139.26±1.56	139.26±1.61	0.000
K	4.65±0.34	4.39±0.34	4.46±0.37	4.65±0.34	4.59±0.33	4.59±0.33	0.262
Lactate (L/min)	2.86±0.30	2.50±0.38	2.44±0.39	2.87±0.30	2.01±0.42	1.92±0.43	0.000
CO* (L/min)	3.14±0.37	3.39±0.42	3.43±0.45	3.15±0.33	3.62±0.36	3.71±0.37	0.020
Inotrope need (μg/kg/min)	0.08±0.03	0.07±0.02	0.06±0.03	0.08±0.02	0.054±0.02	0.046±0.02	0.011
Mean blood pressure	61.6±8.86	67.7±9.5	68.33±9.83	60.96±8.03	70.23±8.15	71.16±8.16	0.230

[a]Data are presented as Mean±SD. *Cardiopulmonary Bypass (CPB) time

demonstrated that bicarbonate administration can actually raise pHi (interacellular pH) (Forsythe and Schmidt, 2000). Also, administration of sodium bicarbonate or THAM was reported successfully restore blood acid-base parameters without inducing either a fall in blood pressure or a significant increase in $PaCO_2$ (Rehm and Finsterer, 2003). In the present study, administration of bicarbonate and or THAM, increased blood pH of patients; however, the effect of THAM was remarkably higher on pH improvement than that of bicarbonate. Kallet *et al.* (2000) study, showed that administration of THAM to six patients with acute metabolic acidosis and acute lung injury improved acid-base parameters while reduced blood $PaCO_2$; on the other hand, bicarbonate administration failed to improve acid-base parameters while it improved $PaCO_2$ concentration. The result of our study is consistently demonstrated that bicarbonate administration caused an increase in $PaCO_2$ from 39.73-47.43 mmHg while THAM decreased this value from 40.13-39.3 mmHg. Additionally, administration of THAM did not make any significant increase in serum potassium compared with bicarbonate group which is consistent with the previously reported data in both animals and humans (Kallet *et al*., 2000; Hoste *et al*., 2005). Serum sodium increased in patients treated with sodium bicarbonate while itdecreased in patients treated with THAM. These results can be due to non-ionized composition of THAM and ionization of sodium bicarbonate in serum.

Post-operative serum lactate and base deficit are considered as predictors of mortality from organ failure. Hyperlactatemia occurs frequently after normothermic cardiac surgery and is an indication of patients with higher risk of mortality (Maillet *et al*., 2003). Epinephrine and β_2-Agonists are well known to induce severe lactic acidosis (Boldt *et al*., 1999; Manthous, 2001) as a result of disorder in glycogenolysis, gluconeogenesis and lipolysis and inhibition of pyruvate conversion to acetyl-coenzyme a (Rizza *et al*., 1980; Greene, 1961). There is a strong correlations between lactate and perioperative blood pressure, blood transfusion requirements and postoperative Hemoglobin (H_b) and elevated serum lactate has been attributed to severe and irreversible whole body hypo-perfusion (Singhal *et al*., 2005). However, higher lactate levels with no significant difference in base deficit and no correlation between the two markers has been observed in non-survivors compared with survivors admission to the ICU (Husain *et al*., 2003). In the present study, higher level of lactate and base deficit were observed in patients post elective coronary artery bypass grafting. Both of THAM and sodium bicarbonate compensated these deficiency by lowering lactate level and increasing base excess. Although, there was no difference between capability of THAM and sodium bicarbonate in increasing base excess, THAM was stronger than sodium bicarbonate to decrease the concentration of lactate. As a result, it is suggested that THAM will be more suitable than sodium bicarbonate in buffering metabolic acidosis after coronary artery bypass graft surgery.

It has been demonstrated that administration of sodium bicarbonate to patients with heart disease but normal acid-base parameters resulted in reduction of myocardial oxygen consumption, enhancement of glycolysis and decrease cardiac output (Bersin *et al*., 1989). However, in our study, sodium bicarbonate treatment did not decrease cardiac output. The effect of THAM buffer on improvement of cardiac output was significantly higher than sodium bicarbonate. Moreover, patients treated with THAM required less inotrope than those treated with sodium bicarbonate which indicated to an improvement in muscle contraction after THAM administration. Many studies have shown that sodium bicarbonate did not have any on improvement on blood pressure, the rate of recovery from ketoacidosis and reduction of hospitalization stay time (Kraut and Kurtz, 2001; Green *et al*., 1998; Gamba *et al*., 1992; Hale *et al*., 1984; Gabow, 1985). Our present study, show that THAM administration did not reduce hospital stay time but it significantly reduced length of ICU stay from 3.50-2.1

days. In addition, the number of patients who needed additional dose of buffer decreased in THAM group.

CONCLUSION

In conclusion, sodium bicarbonate or THAM, each has its own advantages and disadvantages. Sodium bicarbonate is inexpensive and simple to use while it may exacerbate intracellular acidosis and increase sodium load. THAM penetrates cells without generating CO_2 but hyperkalaemia, hypercapnia and liver necrosis in newborns have been reported (4). Our results demonstrated that THAM reduce length of ICU stay, $PaCO_2$ and lactate concentration and inotrope need. It also increased blood pH and cardiac output more efficient than sodium bicarbonate.

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