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ORIGINAL ARTICLE

SODIUM BICARBONATE INFUSION: TO PREVENT CARDIAC SURGERY-ASSOCIATED ACUTE KIDNEY INJURY

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ABSTRACT: OBJECTIVES: The incidence of cardiac surgery–associated acute kidney injury is 50% of patients and is associated with increased mortality and morbidity. This study aimed to determine if perioperative urinary and plasma alkalization with sodium bicarbonate infusion reduces the incidence of cardiac surgery–associated acute kidney injury. **SETTING AND DESIGN:** This study is double blind randomized control trial conducted at U N Mehta Institute of Cardiology and Research Center, India. **METHODS AND RESULT:** A total of 140 patients scheduled to undergo elective cardiac surgery, who were at increased risk of development of cardiac surgery–associated acute kidney injury using recognized risk factors. Patients were randomly allocated to receive either sodium bicarbonate (n = 70) or sodium chloride (n = 70) infusion, commencing at the start of anesthesia, in a dose of 4 mmol/kg over 24 hour. The primary outcome measure was the number of patients with development of CSA-AKI, defined as an increase in creatinine greater than 25% from baseline to peak value within the first three postoperative days. Significant differences among the groups in both plasma and urinary pH were achieved 6 hours after commencement of the infusion, and these changes persisted for more than 24 hours. A total of 7 out of 70(10%) patients in the sodium bicarbonate group and 16 out of 70(22.85%) patients in the sodium chloride group developed acute kidney injury within the first three postoperative days with p value of 0.06 which is statistically not significant. There were also no significant differences in ventilation hours, ICU or hospital length of stay, or mortality. **CONCLUSIONS:** Perioperative alkalization of blood and urine using an infusion of sodium bicarbonate did not result in a decrease in the incidence of acute kidney injury in patients undergoing cardiac surgery.

KEYWORDS: Acute kidney injury; Cardiac surgery; Cardiopulmonary bypass; Creatinine; outcome; Urinary output.

INTRODUCTION: Cardiac surgery using cardio-pulmonary bypass is one of the most common and major surgical procedures worldwide. The likelihood of cardiac surgery associated with acute kidney injury (CSA-AKI) requiring dialysis following cardiac surgery varies greatly. Acute kidney injury is a global health problem with more than 10 million people affected annually and estimated 4 million people die of acute kidney injury each year. Acute renal dysfunction is a common and serious post-operative complication of cardiopulmonary bypass and may affect 25-40% of patients.[1,2,3]

Evidence suggests that even minimal increase in serum creatinine is associated with poorer outcomes.[4,5] AKI induces injury to distant organs such as lungs, heart and brain. Many causes of cardio pulmonary bypass associated acute renal dysfunction have been proposed such as ischemia-reperfusion, generation of reactive oxygen species, hemolysis and activation of inflammatory pathways.[6,7,8,9] Till date no safe, simple and effective intervention for prevention of cardiopulmonary bypass- associated acute renal dysfunction has been found.[10,11,12,13]

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Urinary acidity may enhance the generation and toxicity of reactive oxygen species induced by cardio pulmonary bypass and may also participated in renal injury. Urinary alkalization by using sodium bicarbonate may protect from renal injury induced by oxidant substances, iron mediated free radical pathways, and compliment activation and tubular hemoglobin cast formation.[8,9]

The mechanism behind these observed protective effects is thought to relate to the ability of bicarbonate to alkalinize the urine and to slow the Haber-weiss reaction that generate reactive oxygen species via iron-dependent pathways.[14,15] Mechanism of action for sodium bicarbonate are supported by the findings from a large meta-analysis in contrast nephropathy (Another form of acute kidney injury), demonstrating a positive outcome.[16]

Accordingly we hypothesized that urinary alkalization might protect kidney function in patients at increased risk of acute renal dysfunction undergoing cardiopulmonary bypass and conducted a randomized controlled trial with perioperative sodium bicarbonate infusion.

MATERIAL METHODS: Study was approved by our institutional ethics committee and informed and written consent was obtained from all the patients. Study was done in the period of August 2013 to November 2014 at U.N. Mehta institute of cardiology and research center, Ahmedabad. This study was a double-blind, randomized controlled trial designed to assess if the administration of sodium bicarbonate as a continuous infusion commenced prior to cardiopulmonary bypass would result in less postoperative acute renal dysfunction in patients undergoing cardiac surgery. This prospective study enrolled 140 consecutive patients who underwent on pump cardiac surgery. A Microsoft Excel–based (Microsoft Corp., Redmond, WA) random-number generator was used to create the randomization list.

Allocation concealment to patients, anesthesiologists, cardiac surgeons, intensive care specialists, bedside nurses, and investigators was ensured. Treatment allocation was only revealed after the study had been completed, the database locked, and statistical analysis completed. Research Randomizer online random number generator was used to create the randomization. All the patients were randomly divided in to two group. One was study group in all the patients were given NaHCO3 and another group is control group in all the patients were given NaCL. NaHCO3 group of Patients received a dose of 4 mmol/kg body weight over 24 hour. And NaCL group of patients received same amount of NaCl.

Inclusion criteria	Exclusion criteria:
Age >40 year	End-stage renal disease (plasma creatinine concentration > 3.4 mg/dL)
New York Heart Association class III/IV or impaired left ventricular function (left ventricular ejection fraction < 40%)	Emergency cardiac surgery
Valvular surgery or concomitant valvular and coronary artery bypass graft surgery	Known blood-borne infectious disease
Redo cardiac surgery	Planned off-pump cardiac surgery
Insulin-dependent diabetes mellitus	Chronic inflammatory disease on immunosuppression
	Age < 18 year

Inclusion and exclusion criteria shown in this table

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Despite of this addition of the infusion of the study drug, there were no change to normal clinical practice i.e. anesthesia technique, including pre-operative and post-operative medication given by the attending anesthetist. Surgical approach and cardiopulmonary bypass was conducted on bases of standard technique of our institute. And post-operative care like hemodynamic monitoring, analgesic medication, and fluid all were carried out by intensivist and nursing staff as per institute protocol.

Data Collection: The primary outcome measure was the number of patients who had postoperative AKI development. This was defined as an increase in plasma creatinine concentration greater than 25% from baseline to peak value at any time within the first 3 days after cardiopulmonary bypass.

Data collected included age (Days), weight (kilograms), sex, height, preoperative creatinine postoperative creatinine on day 1 day 2 and day 3 and its creatinine clearance. As well as mean arterial pressure, pH, urea and bicarbonate. CPB time, cross clamp time, mechanical ventilation time (hours), intensive care unit (ICU) stay (hours), and hospital stay also collected. Postoperative morbidity and mortality data were also collected.

The occurrence of specific adverse events including the prevalence of hypernatremia ([Na+] >150 mmol/L), hypokalemia ([K+] < 3.5 mmol/L), alkalemia (pH > 7.50), postoperative atrial fibrillation, and other postoperative arrhythmias (supraventricular arrhythmias, ventricular tachycardia and ventricular fibrillation) during the first 3 postoperative days were recorded.

STATISTICS: The statistical analysis was performed using SPSS v20.0. The values were expressed as Mean±sd. To compare the data between two groups one sample t test were used. Independent-sample t test were used to compare the categorical variables. 'p' <0.05 was considered statistically significant.

RESULT: The patients were distributed into two groups on the basis of either they received sodium bicarbonate or sodium chloride.

No statistical difference between the groups was detected in terms of age (41.84 ± 13.762 vs 46.77 ± 13.249) days, P=0.331; age range, 16 year -80 years), weight (49.17 ± 10.413vs 56.17 ± 17.666 kg, P =0.183, and duration of CPB (93.2857 ± 33.79913 vs 105.8429 ± 41.68955 minutes, P=0.270) and in cross clamp time (67.1143 ± 27.20110 vs 75.9143 ± 37.93539 minutes, P=0.079) which is shown in Table.1, 3.

Significant differences in urinary pH and plasma pH from baseline to 48 hours were found between the two groups. Sodium bicarbonate infusion induced urinary alkalization 6 and 24 hours after commencement of study drug infusion which is shown in Figure (1, 2). And 3 patients from each group needed renal replacement therapy but they died during hospital stay due to multi organ dysfunction.

There was a no significant differences found in preoperative and postoperative metabolic profile such as, serum creatinine and creatinine clearance, urea, mean arterial pressure (Table.2, 3).

A total of 7 out of 70(10%) patients in the sodium bicarbonate group and 16 out of 70(22.85%) patients in the sodium chloride group developed acute kidney injury within the first three postoperative days with p value of 0.06 which is statistically not significant. Overall, 16.42 % of patients had an increase of creatinine greater than 0.5 mg/dl. Urine output was comparable for the two groups.

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There was no significance difference found in mechanical ventilator stay (8.47 ± 5.296 vs8.14 ± 5.787 hours, P=0.317), duration of ICU stay (3.67 ± 1.271 vs 3.83 ± 2.085 days, P=0.341) and in duration of hospital stay (19.71 ± 7.410 vs 18.47 ± 5.115 days, P=0.124). (Table.3).We did not find any adverse events or safety concerns during this study.

DISCUSSION: AKI is not only a frequent complication in cardiac surgical patients[17] but has also been associated with morbidity and mortality independently.[18,19] Unfortunately, there is not much progress within the last years in the development of strategies to reduce the incidence and improve the prognosis of this complication. Recently, Haase and coworkers have elegantly delineated a pathophysiological line of evidence that the severity of the renal insult induced by on-pump cardiac surgery may, at least in part, be related to the degree of hemoglobinuria: the histological features of CSA-AKI resemble the pigment nephropathy typically observed during rhabdomyolysis.[20] Since alkalization of the urine is among the best treatment option available to treat rhabdomyolysis[21] they used this concept successfully as a strategy for the prevention of CSA-AKI in a small pilot trial.[22]

And the fact that urine alkalization for the treatment of rhabdomyolysis has a longstanding tradition in clinical medicine.[21] As per their promising findings and the relatively high incidence of CSA-AKI at our institution with the lack of other available measures for preventing renal dysfunction during cardiac surgery,[23] we chose to implement this concept into our clinical study. It is of note that an interdisciplinary working group on this topic also gave a positive recommendation to use hydration and bicarbonate to reduce the nephrotoxic effects of myo- and hemoglobinuria.[24]

We conducted a double-blind, randomized controlled trial to investigate whether perioperative sodium bicarbonate infusion to achieve urinary alkalization could attenuate the creatinine rise associated with cardiopulmonary bypass in cardiac surgical patients. In this randomized controlled trial, we found that the infusion of sodium bicarbonate commencing before cardiopulmonary bypass and continuing postoperatively for a total of 24 hours achieved serum and urinary alkalization but did not reduce kidney damage, defined as a rise in serum creatinine during the first three postoperative days.

Previous single-center double-blind controlled study demonstrated that sodium bicarbonate administration may reduce CSA-AKI, However this was not confirmed in our study. It is interesting to note that the use of sodium bicarbonate to prevent CIN has shown positive results in several small single-centre studies, but these also have not been replicated consistently in larger studies.

We did not used any scoring systems to define AKI but we used the same risk factors that were used in other studies.[25] The administration of sodium bicarbonate by continuous infusion did produce alkalization of both blood and urine. This was clinically relevant and statistically significant at all-time points beyond baseline. The degree of these physiological effects was similar to that observed in the other study. In our study, patients with increased risk of CSA-AKI development was identified, a biochemical effect consistent with the proposed mechanism of action was produced, and excellent separation between the two groups for the biochemical endpoints was maintained.

A similar pattern of risk factors for postoperative acute kidney dysfunction as described in the largest randomized controlled trial in the prevention of this postoperative complication was found.[11] This observation confirms that the selected patient population was at increased risk of acute kidney dysfunction.

This study demonstrates that there is no reduction of CSA-AKI in patients who are administered sodium bicarbonate despite achieving adequate plasma and urinary alkalization. Therefore, we cannot recommend the routine prophylactic use of this therapy in patients undergoing cardiac surgery.

CONCLUSION: In patients at high risk of CSA-AKI, bicarbonate infusion alkalinized both blood and urine but did not result in a decrease in the prevalence of CSA-AKI. On this basis of these results, we have concluded that, the use of perioperative infusions of sodium bicarbonate may not reduce the CSA-AKI in this patient group.

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	With NaHCO3	Without NaHCO3	
	Mean ± SD	Mean ± SD	p value
Age (year)	41.84 ± 13.762	46.77 ± 13.249	0.331
sex	M=34, F = 36	M=39, F = 31	
Height (cm)	161.09 ± 8.686	160.00 ± 14.022	0.428
Weight (kg)	49.17 ± 10.413	56.17 ± 17.666	0.183

Table 1:Demographic data

	With NaHCO3 Mean ± SD	Without NaHCO3 Mean ± SD	P VALUE
Creatinine baseline (mg/dl)	0.9099 ± 0.34010	0.9001 ± 0.25229	P=0.24
Creatinine day1(mg/dl)	0.9671 ± 0.34453	1.0470 ± 0.42861	P=0.101
Creatinine day 2 (mg/dl)	0.8683 ± 0.34365	0.9474 ± 0.38440	P=0.159
Creatinine day 3 (mg/dl)	0.8304 ± 0.35251	0.8746 ± 0.43745	P=0.735
Creatinine clear baseline (ml/min)	76.2126 ± 33.70187	77.3189 ± 22.47714	P=0.076
Creatinine clear day1 (ml/min)	70.7376 ± 28.48894	71.4380 ± 26.64827	P=0.773
Creatinine clear day 2 (ml/min)	79.6992 ± 31.35400	78.5197 ± 30.29545	P=0.327
Creatinine clear day 3 (ml/min)	83.7348 ± 34.87537	83.5094 ± 26.86457	P=0.299
Urea baseline (mg/dl)	31.7303 ± 16.35761	29.5560 ± 13.34579	P=0.209
Urea day1 (mg/dl)	37.0034 ± 16.92377	38.8937 ± 18.63299	P=0.741
Urea day 2 (mg/dl)	35.7780 ± 19.32018	41.6833 ± 21.28555	P=0.158
Urea day 3 (mg/dl)	35.8784 ± 23.88313	38.0890 ± 23.18158	P=0.786
Urine output day1 (mg/dl)	1.7132 ±.74410	1.6648 ±.71119	P=0.789
Urine output day2 (mg/dl)	1.9475 ±.60983	1.7550 ±.62096	P=0.460
Urine output day 3 (mg/dl)	1.7618 ±.61321	1.7153 ±.57512	P=0.279

Table 2: Primary variables

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	With NaHCO3 Mean ± SD	Without NaHCO3 Mean ± SD	P VALUE
MAP preop (mmHg)	81.4000 ± 11.16724	80.5429 ± 15.94982	P=0.158
MAP at ICU admission (mmHg)	80.7429 ± 13.28035	82.1286 ± 14.72641	P=0.590
MAP 12 hr ICU admission (mmHg)	78.9429 ± 10.11798	78.7571 ± 13.17159	P=0.054
MAP 24 hr ICU admission (mmHg)	75.4571 ± 13.18397	78.9857 ± 10.22003	P=0.998
CPB duration (min)	93.2857 ± 33.79913	105.8429 ± 41.68955	P=0.270
X clamp duration (min)	67.1143 ± 27.20110	75.9143 ± 37.93539	P=0.079
Duration of mechanical ventilation (hr)	8.47 ± 5.296	8.14 ± 5.787	P=0.317
Duration of ICU stay (days)	3.67 ± 1.271	3.83 ± 2.085	P=0.341
Duration of hospital stay (days)	19.71 ± 7.410	18.47 ± 5.115	P=0.124

Table 3: Secondary variables

Figure 1: Biochemical outcome of patients receiving sodium bicarbonate compared with sodium chloride.

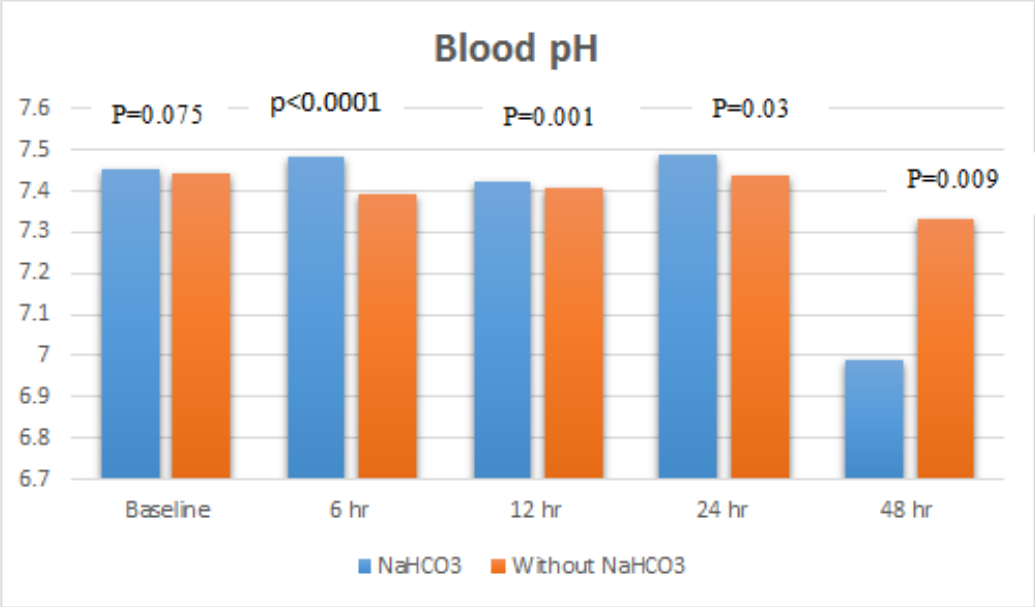

Fig. 1

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Figure 2: Biochemical outcome of patients receiving sodium bicarbonate compared with sodium chloride.

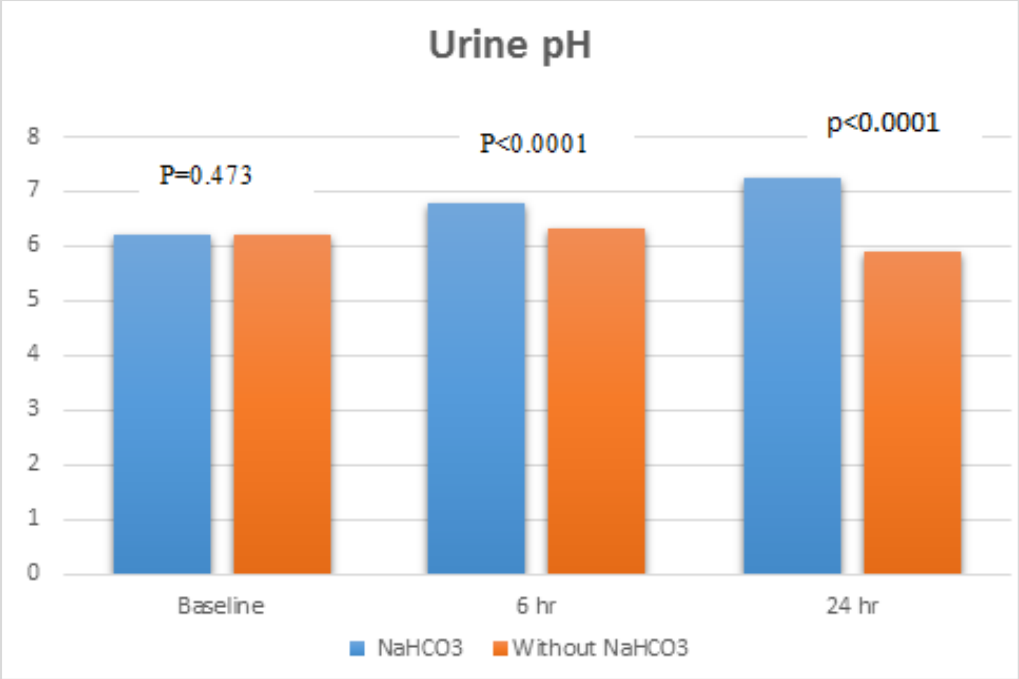

Fig. 2

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