Effect of sodium bicarbonate infusion in off-pump coronary artery bypass grafting in patients with renal dysfunction

Muralidhar Kanchi, Rudresh Manjunath, Jos Maessen¹, Lloyd Vincent², Kumar Belani³

Department of Anesthesia and Intensive Care, Narayana Institute of Cardiac Sciences, Narayana Health, ²Department of Nephrology, Mazumdar Shaw Medical Center, Narayana Health, Bengaluru, Karnataka, India, ³Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands, ⁴Department of Anesthesiology, Medicine and Pediatrics, University of Minnesota, Minnesota, USA

Introduction

Acute kidney injury (AKI) after cardiac surgery continues to be a major devastating complication because it may result in multi-organ dysfunction, death, increased resource utilization and high cost. Globally, 800,000 patients undergo coronary revascularization annually with the use of cardiopulmonary bypass (CPB). Approximately 77,000 patients in a year develop postoperative AKI, among which 14,000 require dialysis for the first time. Up to 30% of patients undergoing coronary artery bypass grafting (CABG) sustain sufficient renal injury to meet the threshold criteria, i.e., a creatinine increase of >0.3 mg% or 50% of their baseline within 48 h of surgery. The reported incidence of AKI after cardiac surgery varies according to the definition of kidney injury as well as the institution reporting the results. Additionally, the current models poorly predict the likelihood of AKI. About 3% of

Access this article online

How to cite this article: Kanchi M, Manjunath R, Maessen J, Vincent L, Belani K. Effect of sodium bicarbonate infusion in off-pump coronary artery bypass grafting in patients with renal dysfunction. J Anaesthesiol Clin Pharmacol 2018;34:301-6.
patients sustain AKI following CABG of sufficient severity requiring dialysis. As many as 60% of patients requiring dialysis after CABG die before hospital discharge and the survivors continue with chronic renal disease with or without the need for dialysis.

Serum creatinine reflects the balance between the synthesis of creatinine and its excretion by the kidney. Creatinine production in the body varies with muscle mass, physical activity, protein intake and catabolism while creatinine excretion is dependent on the glomerular filtration rate (GFR). The serum creatinine and GFR are inversely and exponentially related. Halving of GFR implies that there will be doubling of creatinine concentration.[3] Maintenance of volume status along with pretreatment with sodium bicarbonate (NaHCO₃) has been shown to be effective for prophylaxis for contrast-induced nephropathy.[4] Alkalization reduces free radicals responsible for renal injury[5–8] and pretreatment with NaHCO₃ has been demonstrated to be more protective than sodium chloride (NaCl) in both doxorubicin and ischemia-induced animal models of acute renal failure.[9–11] In a small, randomized, double-blind trial of 100 patients undergoing cardiac surgery who were at increased risk of AKI, a 24 h infusion of NaHCO₃ decreased the incidence of acute renal dysfunction.[12] The effects of NaHCO₃ infusion in patients with coronary artery disease (CAD) with preexisting renal dysfunction (non-dialysis dependent) has not been studied in patients undergoing OP-CABG to the best of our knowledge.

Present study was designed to determine the effect of urinary alkalization with systemically administered NaHCO₃ in those patients who have preexisting renal dysfunction but not on maintenance dialysis and scheduled for OP-CABG.

Material and Methods

We prospectively studied 60 adult (aged 18 years or above) consecutive stable chronic kidney disease (CKD) patients not on dialysis who were scheduled for elective off-pump CABG (OP-CABG) at a tertiary care cardiac center. This study was approved by the ethics committee and institutional review board. All these patients were identified by eGFR ≤60 ml/min/1.73 m² or creatinine ≥1.4 mg/dl prior to OP-CABG. Preoperative eGFR was estimated by using modification of diet in renal disease (MDRD) formula.

We excluded patients scheduled for on-pump CABG, emergency surgery or redo operations, and those who had end-stage renal disease, chronic inflammatory disease or immune-suppression, those enrolled in a conflicting research study, and patients on corticosteroid therapy, renal replacement therapy (RRT) and renal-transplanted patients. All patients received a standard anesthetic consisting of midazolam, isoflurane, fentanyl, vecuronium or atracurium, endotracheal intubation and mechanical ventilation adjusted to achieve normocarbia. Following median sternotomy and heparinization, distal coronary anastomosis was done on the beating-heart using “octopus” (Medtronic Inc, Minneapolis, MA, USA) suction device tissue stabilizer for immobilization of the local heart muscle. Those requiring conversion to “on-pump” (CPB) were excluded from the study.

Surgical procedure

Hemodynamic management included a targeted mean arterial pressure of at least 70 mmHg, central venous pressure of 8–12 mmHg, pulse pressure variation (PPV) of ≤12% using either Flotrac (Vigileo, I PX 1, Edward Lifesciences, Irvine, USA) or Lidco rapid (model POC-125, ADVANTECH, Taiwan) when not on intra-aortic balloon plasty (IABP) and cardiac index of ≥2.5 L/min/m². Infusion of epinephrine at a rate of 0.01–0.05 μg/kg/min and nitroglycerine at a rate of 0.05–0.1 μg/kg/min were used as inotrope/vasodilator at the discretion of the anesthesia care team. All patients were electively ventilated postoperatively until the criteria for separation from ventilator and tracheal extubation were met. Postoperative analgesia was provided with fentanyl infusion at 0.5–1.0 μg/kg/h until removal of chest tube/s and then only paracetamol. No nephrotoxic agents were used and non-steroidal anti-inflammatory drugs were avoided in all patients.

Patients were randomly allocated to one of the two groups to receive NaHCO₃ at a rate of 0.5 mmol/kg/h during the first hour of surgery followed by 0.2 mmol/kg/h[13,14] till the end of surgery and standard care or 0.9% NaCl infusion instead of NaHCO₃ and standard care. In addition, simultaneously we included age-matched control group of 30 patients who did not have any renal dysfunction and were undergoing OP-CABG with a preoperative serum creatinine of ≤1.4 mg/dL and eGFR ≥60 ml/min/1.73 m². Anesthesia and surgery were similar in all the three groups, mean arterial pressure and intravascular volume status was maintained with appropriate clinical measures during the course of surgery in all patients. Blood samples were drawn at specified intervals namely, at the beginning of surgery after anesthetic induction, at the end of surgery and 24 h after surgery, for measurement of serum creatinine, troponin-I, and prior to, at the end of surgery and at 24 h after surgery. The diagnosis of postoperative AKI was made using “kidney
disease; improving global outcomes” (KDIGO) criteria\(^{15}\) in terms of increase in serum creatinine on any of the first five postoperative days. RRT was instituted based on the criteria listed in Table 1.

CABG-related myocardial infarction (MI) was defined as elevation of cardiac biomarker, i.e., troponin-C values (≤10 × 99\(^{th}\) percentile URL) in patients with normal baseline cTn values along with either (i) new pathological Q waves or new left bundle branch block (LBBB) or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

### Statistical analysis

The data were analyzed by the SPPS (Version 15, SPSS Inc., Chicago, USA) and Microsoft excel. Standard statistical methods for assessment on proportions, percentages and measures of central tendencies (mean, SD) were used. One-way analysis of variance (ANOVA) was used to determine the significance of variables between the groups.

### Results

Basic demographics and clinical data of each group are described in Table 2. By design, the preoperative serum creatinine was significantly higher and eGFR significantly lower in the NaCl and NaHCO\(_3\) groups compared to the normal group. The numerical Euroscore was higher in the NaCl and NaHCO\(_3\) groups compared to the normal group. Prevalence of diabetes mellitus and hypertension was similar in all the three groups. Two patients, one in normal group and one in NaHCO\(_3\) were converted to on-pump due to surgical reasons. One patient in each NaCl group and normal group needed IABP for cardiac support. The incidence of further deterioration in renal function postoperatively is described in Table 3. None of the patients required re-exploration for bleeding or prolonged ventilation. All patients were discharged from intensive care unit and hospital in a hemodynamically stable condition. Six patients (20%) in normal control group, 10 (33.3%) patients in NaCl group and 6 (20%) patients in NaHCO\(_3\) developed Stage-1 AKI. However, there was no incidence of Stage-2 and Stage-3 AKI in any of the group. The elevation of serum creatinine in each group is shown in Table 3. There was no significant difference in other variables with infusion of NaHCO\(_3\) as compared to NaCl group [Table 3].

### Discussion

AKI after cardiac surgery is not an uncommon complication. AKI is associated with increased in morbidity, mortality and hospital costs. Even when RRT (dialysis) is avoided, milder forms of AKI are associated with adverse outcomes and degree of AKI correlates negatively with long-term survival despite successful hospital discharge. Renal dysfunction after cardiac surgery is multifactorial in origin and there are multiple risk factors that contribute to the development of AKI.

Both the study groups (placebo and sodium bicarbonate) had preexisting renal dysfunction. But none required RRT, and none demonstrated Stage-2 or Stage-3 AKI following the surgery. There was a 40% reduction in incidence of Stage-1 AKI in patients who received NaHCO\(_3\) compared to NaCl group in patients who suffered from preexisting renal dysfunction. However, the incidence of Stage-1 AKI

| Condition                  | Description                                      |
|----------------------------|--------------------------------------------------|
| Oliguria                   | ≤200 ml/12 h                                     |
| Anuria                     | Urine output 0-50 ml/12 h                        |
| Blood urea                 | ≥35 mmol/L or ≥98 mg/dL                          |
| Serum creatinine           | ≥400 mmol/L or ≥4.5 mg/dL                        |
| Uncompensated metabolic acidosis | pH ≤7.1                                    |
| Serum potassium            | ≥6.5 mmol/L or rapidly rising values             |
| Serum sodium               | ≤110 and ≥160 mmol/L                             |
| Pulmonary edema            | Unresponsive to diuretics                        |
| Uremic manifestations      | Encephalopathy                                   |

### Table 2: Demographic and clinical data of patients undergoing off-pump coronary artery bypass grafting in the study

| Variable                  | Normal control\(^1\) (n=30) | NaCl group\(^2\) (n=30) | NaHCO\(_3\) group\(^2\) (n=30) | P (one-way ANOVA) |
|---------------------------|-----------------------------|--------------------------|-----------------------------|-------------------|
| Age (years)               | 57.11±9.5                   | 60.87±7.1                | 60.81±9.2                   | NS                |
| Male/female               | 28/2                        | 27/3                     | 29/1                        | NS                |
| Diabetes mellitus (%)     | 17 (56)                     | 15 (50)                  | 14 (46)                     | NS                |
| Hypertension (%)          | 17 (56)                     | 18 (60)                  | 15 (50)                     | NS                |
| Euro score                | 2.30±1.97                   | 4.48±2.39**              | 4.67±2.22**                 | <0.001            |
| Preoperative eGFR (ml/min/1.73 m\(^2\)) | 84.65±16.63 | 49.05±10.89**            | 50.44±7.17**                | <0.001            |
| Preoperative creatinine (mg%) | 0.99±0.15                 | 1.43±0.15**              | 1.54±0.33**                 | 0.001             |

\(^1\) Patients with normal renal function; \(^2\) patients with preexisting renal dysfunction and received sodium chloride; \(^*\)patients with preexisting renal dysfunction and received sodium bicarbonate; One-way ANOVA test, \(^{**}\)P<0.001 for between group comparison; NS=Not significant; eGFR=Estimated glomerular filtration rate.
was similar in patients received NaHCO₃ and patients with normal renal function. This is suggestive of possible renal protective effect of NaHCO₃ infusion in patients undergoing OP-CABG with preexisting renal dysfunction.

In a meta-analysis with total of 1092 patients, the influence of alkalinization of urine with NaHCO₃ was studied in patients undergoing cardiac surgery.[16] The incidence of AKI, requirement for RRT, duration of postoperative mechanical ventilation, length of ICU/hospital stay and death was determined using accepted methods. Though the treatment methodology varied a little in each of the studies, NaHCO₃ was infused at a dose 0.5 mmol/kg/h for the first hour followed by 0.2 mmol/kg/h infusion.[13,14]

Table 3: Creatinine, urine output and troponin data of study patients

| Variable                      | Normal control group* (n=30) | NaCl group* (n=30) | NaHCO₃ group* (n=30) | P*  |
|-------------------------------|-------------------------------|--------------------|----------------------|-----|
| Creatinine (mg%) mean±SD      |                               |                    |                      |     |
| Immediate preoperative        | 0.99±0.16                     | 1.56±0.43**        | 1.48±0.41**          | <0.001 |
| Immediate postoperative       | 1.01±0.27                     | 1.60±0.47**        | 1.49±0.42**          | <0.001 |
| Postoperative 24 h            | 1.04±0.16                     | 1.62±0.52**        | 1.45±0.48*           | <0.05 |
| Postoperative 48 h            | 1.03±0.17                     | 1.64±0.52**        | 1.45±0.59*           | <0.05 |
| Postoperative 72 h            | 0.96±0.15                     | 1.53±0.35*         | 1.42±0.53            | <0.05 |
| Postoperative 96 h            | 0.97±0.14                     | 1.52±0.35*         | 1.43±0.49            | <0.05 |
| Troponin-1 (ng/ml) (mean±SD)  |                               |                    |                      |     |
| Preoperative                  | 0.04±0.1                      | 0.18±0.4           | 0.07±0.1             | NS   |
| Immediate postoperative       | 2.15±6.2                      | 5.69±12.5          | 8.57±16.6            | <0.01 |
| Postoperative 24 h            | 6.71±15.2                     | 3.69±5.6           | 20.74±44.4           | <0.05 |
| Stage-1 AKI (N)**            | 6                             | 10                 | 6                    |     |
| Urine output (ml/24 h)        |                               |                    |                      |     |
| Day 1 postoperative           | 2183.86±658.94                | 2066.57±629.78     | 2479.28±581.81       |      |
| Day 2 postoperative           | 3184.77±786.57                | 3299.47±405.31     | 2820.85±897.78       |      |
| Day 3 postoperative           | 3101.25±627.91                | 2664.41±792.13     | 2881.25±928.06       |      |

1Patients with normal renal function; *patients with preexisting renal dysfunction and received sodium chloride; †patients with preexisting renal dysfunction and received sodium bicarbonate; ‡serum creatinine elevation by 0.3 mg%; *one-way ANOVA test, *P<0.05; **P<0.001 for between group comparison; NS=Not significant; SD=Standard deviation; AKI=Acute kidney injury

Our study findings disagree with the results of another study reported recently by Kristeller et al. However, this prospective randomized study was done in patients undergoing cardiac surgery under cardiopulmonary bypass.[17] On the other hand, in a prospectively planned double-blind randomized controlled trial looking at NaHCO₃ and renal function after cardiac surgery with individual patient data meta-analysis (IPDMA) on 877 patients, urinary alkalinization using NaHCO₃ did not decrease the overall incidence of AKI, but it reduced severe AKI and need for RRT in low-risk elective CABG.[18] Our study produced similar results showing a trend towards a reduction in Stage-1 AKI with NaHCO₃ infusion. The avoidance of CPB may have also played a role in influencing renal outcomes but is unlikely as shown by a recent report by Hynes and associates.[19]

One recent study demonstrated that periprocedural intravenous isotonic NaHCO₃ showed no benefit over intravenous isotonic
A double-blind randomized control study by Soh et al., reported that perioperative administration of NaHCO₃ does not prevent the postoperative AKI in after off-pump coronary revascularization. The study showed similar incidences of AKI in NaHCO₃ group and control group who received same amount of 0.9% NaCl (21% vs 26%; \( P = 0.458 \)), and there were no differences in proportions of AKI stages.\(^{[21]}\) However, in contrast to this study, we found that perioperative administration of NaHCO₃ reduced the incidence of postoperative AKI in patients with preexisting renal dysfunction and underwent OP-CABG. This may be attributed to the methodological differences between the two studies, e.g., patients with an estimated GFR of 30–89 ml/min/1.73 m² were grouped as preexisting chronic renal disease in Soh’s study where as our study considered eGFR of <60 ml/min/m². Secondly balanced hydroxyethyl starch (HES) 130/0.4 solution was used to compensate for blood loss in Soh’s study but no HES was used in our study.

**Conclusion**

Our current study findings show that the perioperative administration of NaHCO₃ infusion in OP-CABG reduces the incidence of Stage-1 AKI in patients with preexisting renal dysfunction. However, a study on larger group of patients required to strengthen our findings.

**Limitations of the study**

One of the important limitations of our study is small number of patients (n = 90) tested.

**Acknowledgment**

The authors would acknowledge Karthik for statistical input, Esai Malar and Hilda for support in data collection and V.M. Annapandian for help in editing this document.

**Financial support and sponsorship**

Partial funding received from Maastricht University, The Netherlands.

**Conflicts of interest**

There are no conflicts of interest.

**References**

1. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT, et al. Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. The Multicenter Study of Perioperative Ischemia Research Group. Ann Intern Med 1998;128:194-203.
2. Liu K, Stafford-Smith M, Shaw A. Renal function monitoring. In: Miller RD, editor. Miller’s Anesthesia. 8th ed. Saunders, Amsterdam: Elsevier Inc.; 2015. p. 1580-603.
3. McIlroy D, Robert N. Renal physiology, pathophysiology, and pharmacology. In: Miller RD, editor. Miller’s Anesthesia. 8th ed. Saunders, Amsterdam: Elsevier Inc.; 2015. p. 545-88.
4. Huber W, Huber T, Baum S, Franzen M, Schmidt C, Stadlbauer T, et al. Sodium bicarbonate prevents contrast-induced nephropathy in addition to theophylline: A randomized controlled trial. Medicine (Baltimore) 2016;95:e3720.
5. Bakris GL, Gaber AO, Jones JD. Oxygen free radical involvement in urinary Tamm-Horsfall protein excretion after intrarenal injection of contrast medium. Radiology 1990;175:57-60.
6. Bakris GL, Lass N, Gaber AO, Jones JD, Burnett JC Jr. Radiocontrast medium-induced declines in renal function: A role for oxygen free radicals. Am J Physiol 1990;258:F115-20.
7. Katholi RE, Woods WT Jr., Taylor GJ, Deitrick CL, Womack KA, Katholi CR, et al. Oxygen free radicals and contrast nephropathy. Am J Kidney Dis 1998;32:64-71.
8. Lindinger MI, Franklin TW, Lands LC, Pedersen PK, Welsh DG, Heigenhauser GJ. NaHCO₃(3) and KHCO₃(3) ingestion rapidly increases renal electrolyte excretion in humans. J Appl Physiol (1985) 2000;88:540-50.
9. Atkins JL. Effect of sodium bicarbonate preloading on ischemic renal failure. Nephron 1986;44:70-4.
10. Sporer H, Lang F, Oberleithner H, Greger R, Deetjen P. Inefficacy of bicarbonate infusions on the course of postischaemic acute renal failure in the rat. Eur J Clin Invest 1981;11:311-5.
11. Baroni EA, Costa RS, Volpini R, Coimbra TM. Sodium bicarbonate treatment reduces renal injury, renal production of transforming growth factor-beta, and urinary transforming growth factor-beta excretion in rats with doxorubicin-induced nephropathy. Am J Kidney Dis 1999;34:328-37.
12. Haase M, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, et al. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: A pilot double-blind, randomized controlled trial. Crit Care Med 2009;37:39-47.
13. Haase M, Haase-Fielitz A, Lass N, Kuppe H, Hetzer R, Hannon C, et al. Prophylactic perioperative sodium bicarbonate to prevent acute kidney injury following open heart surgery: A multicenter double-blind randomized controlled trial. PLoS Med 2013;10:e1001426.
14. McGuinness SP, Parke RL, Bellomo R, Van Haren FM, Bailey M. Sodium bicarbonate infusion to reduce cardiac surgery-associated acute kidney injury: A phase II multicenter double-blind randomized controlled trial. Crit Care Med 2013;41:1599-607.
15. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2012;81:1-268.
16. Kim JH, Kim HJ, Kim JY, Ahn HS, Ahn IM, Choe WJ, et al. Meta-analysis of sodium bicarbonate therapy for prevention of cardiac surgery-associated acute kidney injury. J Cardiothorac Vasc Anesth 2015;29:1248-56.
17. Kristeller JL, Zavorsky GS, Prior JE, Keating DA, Brady MA, Romaldini TA, et al. Lack of effectiveness of sodium bicarbonate in preventing kidney injury in patients undergoing cardiac surgery: A randomized controlled trial. Pharmacotherapy 2013;33:710-7.
18. Bailey M, McGuinness S, Haase M, Haase-Fielitz A, Parke R, Hodgson CL, et al. Sodium bicarbonate and renal function after cardiac surgery: A prospectively planned individual patient meta-analysis. Anaesthesia 2015;122:294-306.
19. Hynes CF, Colo S, Amdur RL, Chawla LS, Greenberg MD,
Kanchi, et al.: Renal protective effect of NaHCO$_3$ in OP-CABG

Trachiotis GD. Long-term effects of off-pump coronary bypass versus conventional coronary bypass grafting on renal function. Innovations (Phila) 2016;11:54-8.

20. Weisbord SD, Gallagher M, Jneid H, Garcia S, Cass A, Thwin SS, et al. Outcomes after angiography with sodium bicarbonate and acetylcysteine. N Engl J Med 2018;378:603-14.

21. Soh S, Song JW, Shim JK, Kim JH, Kwak YL. Sodium bicarbonate does not prevent postoperative acute kidney injury after off-pump coronary revascularization: A double-blinded randomized controlled trial. Br J Anaesth 2016;117:450-7.

---

**CONFERENCE CALENDAR July-Sepetember 2018**

| Name of conference | Dates | Venue | Name of organising Secretary with contact details |
|--------------------|-------|-------|--------------------------------------------------|
| IAPA 2019 | 8th-10th February 2019 | AIIMS, new Delhi | Prof Rajeshwari<br>Prof & Head Dept of Anesthesiology & Critical care<br>Conference Secretariat Address : Room no. 5014 A, 5th floor Teaching Block, Ansari Nagar, AIIMS New Delhi – 110029<br>Dr. Manpreet : +91 9868595487<br>Dr. Anjolie Chhabra : +91 9810104383<br>Email : iapaaiims2019@gmail.com |
| ISNACC 2019 | 15th-17th February 2019 | Gurugram India | www.isnacc2019.com |
| 22nd IACTACON 2019 | 22nd-24th February 2019 | Swabhumi The Heritage, Kolkata, West Bengal, India | Dr. Rahul Guhabiswas<br>CIMGlobal India Pvt. Ltd<br>BB – 31, Ground Floor, Salt Lake City, Sector – I Near Punjab National Bank, Kolkata – 700064<br>Mr. Gaurav Sinha<br>Email: gaurav@cimglobal.in<br>iacta2019@gmail.com |
| 29th Annual National Conference of the Research Society of Anaesthesiology Clinical Pharmacology | 29th-31st March 2019 | PGIMS, Rohtak | Prof Dr Savita Saini<br>Prof & Head, Deptt of Anesthesiology & Critical Care, PGIMS, Rohtak<br>Email: www.rsacpcon2019@gmail.com<br>Website: www.rsacpcon2019.com |