

Neutrophil Gelatinase-associated Lipocalin as a Biomarker for Predicting Acute Kidney Injury during Off-pump Coronary Artery Bypass Grafting

Abstract

Background: Acute kidney injury (AKI) following cardiac surgery is a major complication resulting in increased morbidity, mortality, and economic burden. In this study, we assessed the usefulness of estimating serum neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker in predicting AKI in patients with stable chronic kidney disease (CKD) and undergoing off-pump coronary artery bypass grafting (OP-CABG). **Patients and Methods:** We prospectively studied sixty nondialysis-dependent CKD patients with estimated glomerular filtration rate <60 ml/min/1.73 m² who required elective OP-CABG. Patients were randomized into two groups, Group D received dopamine infusion at 2 µg/kg/min following anesthesia induction till the end of the surgery and Group P did not receive any intervention. Serum creatinine, NGAL, brain natriuretic peptide, and troponin-I were estimated at specified intervals before, during, and after surgery. The results of the study patients were also compared to a simultaneous matched cohort control of thirty patients (Group A) without renal dysfunction who underwent OP-CABG. **Results:** No patient required renal replacement therapy, and no mortality was observed during perioperative and hospitalization period. Six patients from control group ($n = 30$), ten patients from placebo group ($n = 30$), and 12 patients from dopamine group ($n = 30$) developed stage 1 AKI. However, we did not observe any stage 2 and stage 3 AKI among all the groups. There was a significant increase in serum NGAL levels at the end of surgery and 24 h postoperatively in placebo and dopamine groups as compared to the control. **Conclusion:** The measurement of NGAL appears to predict the occurrence of AKI after OP-CAB surgery. However, large multicentric studies may be required to confirm the findings of this study.

Keywords: Acute kidney injury, cardiac surgery, coronary artery bypass grafting, creatinine, dopamine, neutrophil gelatinase-associated lipocalin

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Introduction

Acute kidney injury (AKI) after cardiac surgery continues to be a major devastating complication because it can result in multiorgan dysfunction, death, increased resource utilization, and high cost.^[1] 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.^[2] Up to 30% of patients undergoing coronary artery bypass grafting (CABG) sustain a sufficient renal injury to meet the threshold criteria, i.e., a creatinine increase of >0.3 mg% or by 50% of the baseline value 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. In addition, the current models poorly predict the likelihood of AKI. As many as 3% of patients sustaining AKI following CABG require dialysis and as many as 60% of these patients 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] There are several limitations for creatinine as a marker of kidney injury in acute

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perioperative situations. However, it has a poor, predictive accuracy for kidney injury, particularly in the early stages of AKI.^[4]

Neutrophil gelatinase-associated lipocalin (NGAL) is an iron-transporting glycoprotein which accumulates in the kidney tubules and urine after nephrotoxic and ischemic insults.^[5] This glycoprotein increases 3–4-fold within 2–3 h and up to 10,000-fold by 24 h of renal insult. NGAL has been proposed as an early, sensitive, noninvasive biomarker for AKI. NGAL measured in the immediate postoperative period is an excellent predictor of AKI following pediatric cardiac surgery^[6] and adult cardiac surgery.^[7] To the best of our knowledge, there is scant literature looking at NGAL as a biomarker for predicting AKI in off-pump coronary artery bypass grafting (OP-CABG) receiving dopamine infusion. In this study, we measured both NGAL and serum creatinine to predict renal adverse outcomes in patients with stable chronic kidney disease (CKD) and not on dialysis undergoing elective OP-CABG. In addition, we also studied whether dopamine infusion during OP-CABG is beneficial in reducing renal injury in this group of patients.

Patients and Methods

After an approval from the Institutional Ethical Committee and Review Board, we prospectively enrolled sixty patients who underwent an elective OP-CABG at Narayana Institute of Cardiac Sciences, Bengaluru, between January 2012 and October 2016. The eligibility criteria included the presence of stable CKD (not on dialysis) and estimated GFR (eGFR) ≤ 60 ml/min/1.73 m² or creatinine ≥ 1.4 mg% before the surgery. Preoperative eGFR was estimated using modification of diet in renal disease formula, and eGFR of < 60 ml/min/1.73 m² was taken as indicative of renal impairment. Patients scheduled for OP-CABG were examined a day before the surgery, and all the baseline investigations were noted. Demographic data (age, sex, height, and weight), preoperative risk factors, and preoperative surgical and anesthetic management were recorded for all the patients.

Patients scheduled for on-pump CABG, emergency surgery, redo operations, end-stage renal disease, chronic inflammatory disease/immunosuppression, corticosteroid therapy, age < 18 years, enrolled in a conflicting research study, patients on renal replacement therapy (RRT) and renal transplanted patients were excluded from the study. All patients received a standard anesthetic which consisted of midazolam, propofol, isoflurane, fentanyl, vecuronium or atracurium, endotracheal intubation, and mechanical ventilation to achieve normocarbida. Following median sternotomy and heparinization, the surgeons conducted distal coronary anastomosis on the beating heart using “octopus” (Medtronic Inc., Minneapolis, MA, USA) suction device tissue stabilizer for immobilization of the local heart muscle.

Hemodynamic care included a targeted mean arterial pressure of at least 70 mmHg, central venous pressure of 8–12 mmHg, stroke volume variation of $\leq 12\%$ using either Flotrac (Vigileo, I PX 1, Edwards Lifesciences, Irvine, USA) or Lidcorapid (model POC-125, ADVANTECH, Taiwan), and cardiac index of ≥ 2.5 L/min/m². Epinephrine at 0.01–0.05 $\mu\text{g/kg/min}$ and nitroglycerine at 0.05–0.1 $\mu\text{g/kg/min}$ were used as an 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 $\mu\text{g/kg/h}$ until the removal of chest tubes and then a combination of oral tramadol and paracetamol. No nephrotoxic agents were used and nonsteroidal anti-inflammatory drugs were avoided in all patients.

The identified sixty patients with impaired renal function not requiring dialysis were scheduled for elective OP-CABG. We randomly allotted the patients to two groups. Group D received dopamine 2 $\mu\text{g/kg/min}$ following anesthesia induction till the end of the surgery and standard care. Group P, this was the placebo group that received 0.9% sodium chloride infusion and standard care. In addition, there was an age-matched control group of thirty patients (Group A) who had no renal dysfunction (preoperative serum creatinine of ≤ 1.4 mg/dl and eGFR ≥ 60 ml/min/1.73 m²). Anesthesia and surgery were similar in all groups; mean arterial pressure and intravascular volume status was maintained with appropriate clinical measures during the course of surgery in all patients. Serum creatinine, NGAL, brain natriuretic peptide (BNP), and troponin-I were measured at specified intervals, i.e., at the beginning of surgery after anesthetic induction, at the end of surgery, and 24 h after surgery. Thereafter, serum creatinine was estimated at 24 h intervals until 96 h. The rationale for inclusion of estimation of BNP was based on the GALLANT trial which looked into prognostic utility of plasma NGAL in patients with acute heart failure assessed utility of NGAL alone and in combination with BNP as an aid to risk assessment of heart failure-related adverse outcomes.^[8] The study demonstrated that NGAL is a powerful predictor of outcomes and this was stronger than BNP. In addition, combination of high BNP/high NGAL had the worst outcomes. While risk in low BNP/high NGAL was significant, high BNP/low NGAL group had outcomes similar to when both markers were low. This was explained by the fact that even though BNP was high, it represented “dry” but not the “wet” BNP.

The diagnosis of AKI postoperatively was made using “kidney disease improving global outcomes” criteria in terms of increase in serum creatinine on any of the first 3 postoperative days. Stage 1 AKI was defined as rise in serum creatinine by 0.3 mg/dL or by an increase ≥ 1.5 -fold from the reference value, stage 2 AKI classified by a

2–2.9-fold increase in serum creatinine, and stage 3 AKI by ≥ 3.0 -fold increase in serum creatinine.

CABG-related myocardial infarction was defined by elevation of cardiac biomarker troponin-I values ($\geq 10 \times 99^{\text{th}}$ percentile URL) in patients with normal baseline cardiac troponin values along with either (i) new pathological Q-waves or new left bundle branch block, (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.

Results

In a total of ninety patients who underwent OP-CABG, sixty patients suffered from stable CKD before surgery and thirty patients had normal renal function. Basic demographics and baseline clinical details of patients are shown in Table 1. The numerical Euroscore was higher in the Group D and Group P compared to the control Group A. One patient in Group A was converted to OP-CABG due to surgical reasons; this patient's data were excluded in the final analysis. There was a significant increase in serum NGAL and BNP levels at the end of surgery and at 24 h after surgery in placebo and dopamine groups compared to normal group. One patient from each group needed intra-aortic balloon pump for cardiac support. The details of renal function postoperatively are shown in Table 2 and Figure 1. Neither stage 3 nor stage 2 AKI was

observed from this study groups. However, six patients from control group had an elevation of serum creatinine by 0.3 mg\% from pre- to post-operative ($1.0 \pm 0.12 \text{ mg\%}$ vs. $1.44 \pm 2.4 \text{ mg\%}$) with corresponding increase in the NGAL from $108 \pm 46 \text{ ng/ml}$ to $212 \pm 95 \text{ ng/ml}$. Ten out of thirty patients in placebo group had an elevation of serum creatinine from $1.45 \pm 0.15 \text{ mg\%}$ to $2.16 \pm 0.49 \text{ mg\%}$ with a corresponding increase in NGAL 141.7 ± 55 – $349 \pm 350 \text{ ng/ml}$. Twelve patients in dopamine group (out of thirty patients) showed an elevation of serum creatinine from $1.7 \pm 0.61 \text{ mg\%}$ to $2.4 \pm 0.65 \text{ mg\%}$ pre- and post-operative, respectively, with corresponding NGAL value of 179 ± 116 – $390 \pm 291 \text{ ng/ml}$. There was no difference in other variables with infusion of dopamine as compared to nonintervention group (ANOVA $P > 0.05$ for all variables) [Table 3]. There was no requirement for RRT and no mortality in any of the groups.

Discussion

The present study was designed to evaluate the usefulness of NGAL measurement during OP-CABG for predicting AKI in patients with stable CKD. In addition, we examined the possible beneficial effects of dopamine infusion during OP-CABG in the same group of patients.

AKI after cardiac surgery is not an uncommon complication, and AKI is associated with increased morbidity, mortality, and hospital costs. Even when RRT is avoided, milder forms of AKI are associated with adverse

Table 1: Basic demographics and clinical data of patients undergoing off-pump coronary artery bypass grafting

| Variable | Group A Control (n=29), n (%) | Group P Placebo (n=30), n (%) | Group D Dopamine (n=30), n (%) |
|---|-------------------------------|-------------------------------|--------------------------------|
| Age (years), mean \pm SD | 57.1 \pm 9.5 | 61.1 \pm 7.6 | 60.7 \pm 5.9 |
| Male/female | 27/3 | 27/3 | 30/0 |
| Diabetes mellitus | 17 (56) | 20 (66) | 24 (80) |
| Hypertension | 17 (56) | 22 (73) | 26 (87) |
| Euroscore | 2.30 \pm 1.9 | 4.48 \pm 2.4** | 6.27 \pm 1.8** |
| Preoperative eGFR (ml/min/1.73 m ²) | 84.65 \pm 16.6 | 49.05 \pm 10.9** | 43.20 \pm 10.4** |
| Preoperative creatinine (mg%) | 0.99 \pm 0.2 | 1.32 \pm 0.2** | 1.81 \pm 0.5** |

* $P < 0.05$; ** $P < 0.001$ comparison between groups. eGFR: Estimated glomerular filtration rate, SD: Standard deviation

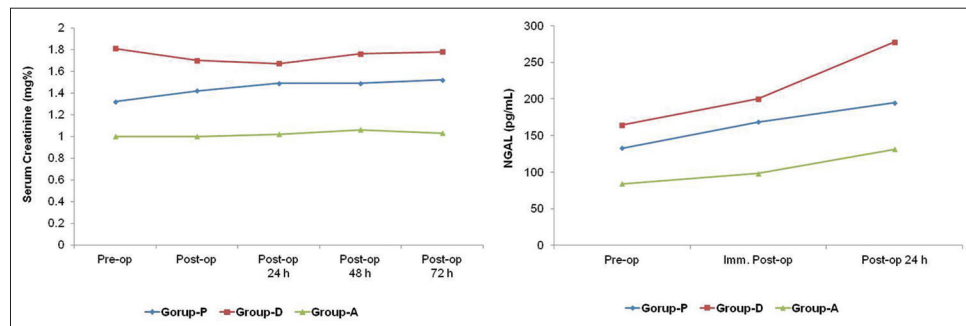


Figure 1: Comparison of serum creatinine and neutrophil gelatinase-associated lipocalin between study groups

Table 2: Serum creatinine, neutrophil gelatinase-associated lipocalin, troponin, and brain natriuretic peptide levels

| | Group A Control (n=29) | Group P Placebo (n=30) | Group D Dopamine (n=30) | ANOVA (P) |
|---------------------------------|-------------------------|---------------------------|---------------------------|-----------|
| Serum creatinine (mg%), mean±SD | | | | |
| Immediate preoperative | 0.99±0.16 | 1.56±0.43** | 1.69±0.61** | <0.001 |
| Immediate postoperative | 1.01±0.27 | 1.60±0.47** | 1.67±0.58** | <0.001 |
| Postoperative 24 h | 1.04±0.16 | 1.62±0.52** | 1.76±0.51** | <0.001 |
| Postoperative 48 h | 1.03±0.17 | 1.64±0.52** | 1.78±0.54** | <0.001 |
| Postoperative 72 h | 0.96±0.15 | 1.53±0.35* | 1.89±0.64** | <0.001 |
| NGAL (ng/ml), mean±SD | | | | |
| Preoperative | 84.41±35 | 183.52±250** | 156.34±99* | 0.011 |
| Immediate postoperative | 91.19±52 | 168.43±132** | 203.41±148* | <0.001 |
| Postoperative 24 h | 135.2±90 | 249.95±262** [‡] | 274.72±223** [‡] | 0.002 |
| Troponin (ng/ml), mean±SD | | | | |
| Preoperative | 0.04±0.1 | 0.18±0.4 | 0.03±0.1 | 0.605 |
| Immediate postoperative | 2.15±6.2 | 5.69±12.5 | 29.65±74.2 | 0.006 |
| Postoperative 24 h | 6.71±15.2 | 3.69±5.6 | 12.08±17.2 | 0.017 |
| BNP (pg/ml), mean±SD | | | | |
| Preoperative | 89.77±85 | 121.00±137 | 91.43±88 | 0.875 |
| Immediate postoperative | 105.26±166 | 202.71±243** | 85.42±67 | 0.226 |
| Postoperative 24 h | 349.87±483 [‡] | 250.85±234 [‡] | 547.51±466** [‡] | 0.062 |

* $P<0.05$; ** $P<0.001$ comparison between groups, [‡] $P<0.05$; [§] $P<0.001$ comparison within groups. NGAL: Neutrophil gelatinase-associated lipocalin, BNP: Brain natriuretic peptide, SD: Standard deviation

Table 3: Renal function following off-pump coronary artery bypass grafting

| Group | Group P Placebo (n=30) | Group D Dopamine (n=30) | Group A Normal (n=29) |
|---------------------|------------------------|-------------------------|-----------------------|
| Need for RRT | 0 | 0 | 0 |
| Stage 3 AKI*** | 0 | 0 | 0 |
| Stage 2 AKI** | 0 | 0 | 0 |
| Stage 1 AKI* | 10 | 12 | 6 |
| Urine output (ml) | | | |
| Day 1 postoperative | 2510±569 | 2183.86±659 | 2069.76±679 |
| Day 2 postoperative | 2845.70±904 | 3184.77±787 | 3350±466 |
| Day 3 postoperative | 2881.25±928 | 3101.25±673 | 2720.78±812 |

$P\geq 0.05$ by ANOVA between groups. *Serum creatinine elevation by 0.3 mg%, **Serum creatinine increase by >2-2.9-fold,

***Serum creatinine elevation of >3.0-fold. RRT: Renal replacement therapy, AKI: Acute kidney injury

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. Serum creatinine was used as a marker of renal function; despite the fact that it is not completely reliable and delayed indicator of renal injury in acute setting. Biomarkers such as NGAL are detectable in urine and blood within 2–4 h of injury and proven to be better indicator of renal insult in acute settings. Initial studies reported a strong relationship between NGAL and renal outcomes.^[6,7,9] However, recent studies found a variable relationship between NGAL and renal outcomes.^[10-14] Recent insights into the molecular nature of NGAL suggest that it might be released not only by tubular renal cells but also by neutrophils activated by systemic inflammatory triggers, such as CPB.^[15-19] These studies were performed on patients who underwent OP-CABG to determine if NGAL is a marker of renal injury in this form of cardiac surgery.

In this study, there was no incidence of stage 2 and stage 3 AKI in all the three groups. However, stage 1 AKI was seen in all the three groups. Six (20%) patients in the normal group, ten (33%) patients in placebo group, and 12 (40%) patients in dopamine group had elevation of serum creatinine postoperatively compared to preoperative values. Correspondingly, NGAL values also increased in all these patients.

In a study published on 2004, there was a significant reduction in postoperative renal failure (17% vs. 9%; $P = 0.022$) and need for new dialysis (10% vs. 3%; $P = 0.022$) when CPB was eliminated for coronary revascularization strategy (OP-CABG) in patients with preexisting renal dysfunction. Avoidance of CPB results in (i) a reduction in the incidence of postoperative renal failure, (ii) a reduction in the need for new dialysis, and (iii) improved inhospital and midterm survival.^[20]

In a meta-analysis of 22 randomized controlled trials (4819 patients), the weighted incidence of AKI in the

OP-CABG group was 4.0% (95% confidence interval [CI]: 1.8%, 8.5%), dialysis requirement 2.4% (95% CI: 1.6%, 3.7%), and mortality 2.6% (95% CI: 1.6%, 4.0%). However, OP-CABG was associated with a 40% lower odds of postoperative AKI (odds ratio [OR]: 0.60; 95% CI: 0.43, 0.84; $P = 0.003$) and a nonsignificant 33% lower odds for dialysis requirement (OR: 0.67; 95% CI: 0.40, 1.12; $P = 0.12$). Within the selected trials, OP-CABG was not associated with a significant decrease in mortality. The authors concluded that OP-CABG may be associated with a lower incidence of postoperative AKI but may not affect dialysis requirement, a serious complication of cardiac surgery.^[21] This meta-analysis did not evaluate the usefulness of NGAL measurement in predicting AKI after OP-CABG.

NGAL has good sensitivity and specificity for diagnosis of AKI, with a significantly earlier rise following injury when compared to creatinine. NGAL began to rise within 2 h after renal insult while creatinine rise occurred over 1–3 days.^[22] Our study also demonstrated the similar findings. NGAL values rose before the creatinine climb up. Hence, NGAL can be used as an early biomarker for detection of postoperative AKI.

NGAL value at 4 h in patients who developed AKI was significantly higher than in those patients who did not develop AKI ($P < 0.05$). It was not clear whether the degree of rise in NGAL levels was associated with more severe form of AKI or not. Furthermore, the rise in urine NGAL levels at 4 h in these patients was not uniform. One patient who developed AKI had 100-fold rise in urine NGAL levels at 4 h while the other six had a lesser degree of elevation of urine NGAL at 4 h. Six patients who developed AKI had a normal serum creatinine value at 4 h postoperatively. Serum creatinine levels rose only at 24 h or more in all these six patients. However, urine NGAL levels at 4 h were significantly high in the patients who developed AKI. They concluded that urine NGAL as an early biomarker of AKI in patients undergoing OP-CABG surgeries.^[5] In this study, we have noted a significant increase ($P < 0.05$) in NGAL values immediately after surgery in dopamine and placebo groups [Table 4].

A meta-analysis of 58 studies including 17 randomized clinical trials showed that dopamine did not prevent

mortality (relative risk, 0.90 [0.44–1.83]; $P = 0.92$), onset of acute renal failure (relative risk, 0.81 [0.55–1.19]; $P = 0.34$), or need for dialysis (relative risk, 0.83 [0.55–1.24]; $P = 0.42$). There was a sufficient statistical power to exclude any large (>50%) effect of dopamine on the risk of acute renal failure or need for dialysis. They concluded that the use of low-dose dopamine for the treatment or prevention of acute renal failure cannot be justified on the basis of available evidence and should be eliminated from routine clinical use.^[23] Our findings were also similar to that of existing study. We did not find any improved outcome with the use of dopamine in the patients with underlying renal dysfunction undergoing OP-CABG. Both the study groups (placebo and dopamine) had preexisting renal dysfunction. None of the patients required RRT, and none demonstrated stage 2 or stage 3 AKI following surgery. There was an increase in serum creatinine from 1.45 ± 0.15 to 21.6 ± 0.49 and 1.77 ± 0.61 to 2.45 ± 0.65 in placebo and dopamine groups, respectively, in the occurrence of stage 1 AKI, which was statistically not significant, and the group without preexisting renal dysfunction had a lesser incidence of stage 1 AKI. The use of dopamine at $2 \mu\text{g/kg}$ did not decrease the incidence of stage 1 AKI in patient with stable CKD undergoing OP-CABG.

Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic than norepinephrine.^[24] It may also influence the endocrine response through the hypothalamic–pituitary axis and has immunosuppressive effects. However, information from five randomized trials ($n = 1993$; patients with septic shock) comparing norepinephrine to dopamine does not support the routine use of dopamine in the management of septic shock.^[25–27]

A large randomized trial and meta-analysis comparing low-dose dopamine to placebo found no difference in either primary outcomes (peak serum creatinine, need for renal replacement, urine output, and time to recovery of normal renal function) or secondary outcomes (survival to either intensive care unit [ICU] or hospital discharge, ICU stay, hospital stay, and arrhythmias).^[23,28] Thus, the available data do not support administration of low doses of dopamine solely for the purpose of maintaining renal function.

Table 4: Highest serum creatinine (mean±standard deviation) and highest neutrophil gelatinase-associated lipocalin (mean±standard deviation) values of patients who developed stage 1 acute kidney injury in three groups

| Group | Creatinine (mg%) | | NGAL (ng/ml) | |
|----------------------------|------------------|-----------------------------|--------------|-----------------------------|
| | Baseline | Maximum postoperative value | Baseline | Maximum postoperative value |
| Group A | 1.0±0.12 | 1.35±0.24* | 108.5±46.5 | 202±95.32* |
| Six patients ($n=29$) | | | | |
| Group P | 1.45±0.15 | 2.16±0.49* | 141.7±55.18 | 340.2±350.3* |
| Ten patients ($n=30$) | | | | |
| Group D | 1.77±0.61 | 2.41±0.65* | 179.36±116.4 | 390±291.07* |
| Twelve patients ($n=30$) | | | | |

* $P > 0.05$. Figures in parenthesis represent the total number in that group. NGAL: Neutrophil gelatinase-associated lipocalin

Conclusion

Our study findings suggest that the monitoring of NGAL values could be beneficial for predicting AKI in patients with stable CKD and undergoing OP-CABG. The use of dopamine during OP-CABG is controversial since our study did not show any reduction in the risk of AKI in patients with preexisting renal dysfunction. We do not support administration of low doses of dopamine solely for renal preservation on OP-CABG. However, large multicentric studies may be needed to strengthen our findings.

Limitations of the study

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

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