Original Article

A Comparison of Sevoflurane versus Sevoflurane-Propofol Combination on Renal Function in Patients Undergoing Valvular Heart Surgery—A Prospective Randomized Controlled Pilot Study

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ABSTRACT

Aim: The objective of the present study was to compare the effect of sevoflurane with the sevoflurane-propofol combination on renal function in patients undergoing valvular heart surgery. The renal protective effect was assessed using a novel marker called neutrophil gelatinase-associated lipocalin (NGAL).

Materials and Methods: This was a prospective randomized controlled pilot study conducted at a tertiary care center in India. The study enrolled 36 patients undergoing elective valvular heart surgery, but only 31 were included. All the patients were randomized into two groups, that is, 15 in the sevoflurane group (S-group) and 16 in the sevoflurane–propofol group (SP-group). The baseline NGAL level and test NGAL level at 4 h after cardiopulmonary bypass were measured.

Results: There was a significant rise in the test NGAL levels compared to baseline in both the groups. The test NGAL level in the S-group was significantly high compared to that of the SP-group ($P = 0.034$). The number of patients with acute kidney injury was less in the SP-group without reaching statistical significance ($P = 0.210$).

Conclusion: Renal function was better preserved in patients anesthetized with a combination of sevoflurane and propofol. This could be due to the enhanced protective effect on renal function by both sevoflurane and propofol.

Keywords: Acute kidney injury, propofol, sevoflurane, valvular heart surgery

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INTRODUCTION

Acute kidney injury (AKI) is a highly prevalent (40%) and prognostically significant complication of cardiac surgery.[1,2] Cardiac surgery contributes to AKI by inciting a strong systemic inflammatory response. The contact of blood components with nonphysiological surfaces of cardiopulmonary bypass (CPB) circuits, duration of CPB, ischemia-reperfusion injury (I-R injury) due to aortic cross-clamping (ACC), operative trauma, preexisting left ventricular dysfunction, diabetes mellitus, and endotoxemia stimulates the systemic inflammatory response leading

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to AKI.[3,4] Despite the various pharmacological and non-pharmacological interventions available to prevent AKI, it is still one of the leading causes of morbidity and mortality after cardiac surgery.

Volatile anesthetic agents offer multi-organ protection through preconditioning against I-R injury after CPB.[5,6] Propofol exerts both anti-inflammatory and free-radical scavenging activity.[4,7-9] Some studies have demonstrated a comparable effect for sevoflurane and propofol on renal function.[10] However, as sevoflurane and propofol exert their beneficial effects by diverse mechanisms, we hypothesized that the combination of both the drugs may offer a beneficial effect on renal function in patients undergoing valvular heart surgery compared to sevoflurane alone.

Thus, the present study was aimed to determine whether the combination of sevoflurane and propofol, for induction and maintenance of anesthesia, offered any benefit over sevoflurane alone with regard to renal function by analyzing the neutrophil gelatinase-associated lipocalin (NGAL) levels before and after valvular heart surgery. The secondary objective was to study the requirement of inotropic support and to compare the duration of intensive care unit (ICU) and hospital stay between both the groups.

MATERIALS AND METHODS

Study design and patient selection

This was a prospective randomized controlled pilot study conducted at a tertiary care center in India from 2013 to 2015. A total of 36 patients who were undergoing valve surgery were enrolled for the study. The study was approved by the institutional ethics committee and funded by the institute. From 36 patients, five were excluded from the study as their blood samples were hemolyzed. All the patients were randomly allocated into two groups, that is, S-group (sevoflurane) and SP-group (sevoflurane + propofol). Written informed consent was obtained from all the patients for participation and the use of data in the study. The study followed standard ethical guidelines as per the Declaration of Helsinki (2008).

Patients undergoing emergency surgery, patients with infective endocarditis, serum creatinine more than 2 mg/dL, hepatic dysfunction, on nephrotoxic drugs, and those undergoing concomitant coronary artery bypass surgery (CABG) were excluded from the study.

Anesthesia protocol

All preoperative cardiac medications were continued on the day of surgery except for angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. All patients were premedicated with oral diazepam-10 mg, the night before and on the day of surgery. During the procedure, electrocardiogram, pulse oximetry, bi-spectral index (BIS), capnography, arterial blood pressure, central venous pressure, body temperature, and urine output were continuously monitored.

Midazolam (0.025 mg/kg) and fentanyl (3–5 μg/kg) were administered in both groups approximately 3 min prior to the administration of induction agents. Anesthesia was induced with 6–8% of sevoflurane with 6 L/min of oxygen in the S group and with sleep dose of propofol and sevoflurane at 1–2 v% in the SP group. BIS levels were monitored and pancuronium/vecuronium (0.2 mg/kg) was administered once BIS levels dropped below 50. After endotracheal intubation, anesthesia was maintained using sevoflurane at 2–3 v% (1–1.5 minimum alveolar concentration) in S-group. Propofol at 50–150 μg/kg/min and sevoflurane at 0.5–1.5 v% were used to maintain anesthesia in SP-group. Morphine at 0.2–0.3 mg/kg was administered as a bolus dose prior to sternotomy. Approximately 10 mcg/kg of fentanyl was used during the entire surgery. Anesthetic agents were titrated to maintain a BIS value of 35–60 throughout the surgery.

CPB was carried out using a Sarns 9000 CPB machine (Terumo Corporation, Tokyo, Japan) and affinity adult oxygenator (Medtronics, United States). Datex Ohmeda Tec-7 vaporizer was used for sevoflurane delivery. During CPB, sevoflurane was administered at 1–2 v% in the S group and sevoflurane at 0.5–1 v% with propofol at 25–100 mcg/kg/min in the SP group. Depending upon the type of valvular surgery, blood cardioplegia was administered at 30 min interval either through the aortic root or coronary ostium with or without retrograde cardioplegia. At the end of the surgery, all patients were transferred to the ICU.

Analgesia, sedation, weaning of artificial ventilation, and extubation followed normal institutional practice. Morphine infusion was continued for analgesia in the postoperative period. Patients were weaned off the ventilator and extubated within 6–8 h when they were fully warm and the drains were settled.

Parameters measured and sample collection

The variables that were measured during CPB included CPB time, ACC time, the amount of phenylephrine used to maintain mean arterial pressure above 60 mmHg, and minimal core temperature on CPB. The requirements of inotropic support, duration of ICU, and hospital stay were also measured.

NGAL, a novel biomarker of renal function, was measured for the diagnosis of AKI. Blood samples for baseline NGAL estimation were drawn from the inserted arterial cannula before anesthetic induction and for test NGAL estimation after 4 h of CPB. The blood samples were collected in ethylene-diamine-tetra-acetate tubes. In the biochemistry laboratory, plasma was separated using standard techniques. The prepared clinical specimen was stored at −20°C. The NGAL rapid enzyme-linked immunosorbent assay kit (Kit-036, Bioporto diagnostics) was used to test the specimens.

Statistical analysis

All the statistical analysis was performed with SPSS version 15.0 (Chicago, IL, USA). Continuous variables were presented as mean and standard deviation, while categorical variables were presented as the frequency with percentages. Independent student *t*-test and Chi-square tests were used for statistical analysis of continuous and categorical study variables, respectively, with a 5% level of significance. The mean of baseline NGAL levels in the study population was calculated and the value of two standard deviations above the baseline value was considered as significant. The cutoff NGAL level was calculated to be 200 ng/mL, above which the patients were classified as having AKI. Experimental event rate (EER), control event rate (CER), absolute risk reduction (ARR), and relative risk reduction (RRR) were also calculated. EER and CER are the ratios of the number of patients with renal injury to the total number of patients in the study group and control group, respectively. ARR is the absolute amount by which the intervention reduces the risk of renal injury (CER-AER). Relative risk reduction is the amount by which the risk of renal injury is reduced in the SP group compared to the S group (ARR/CER).

RESULTS

The mean age of all the patients was 44.0 ± 11.5 years with no statistically significant difference in both the groups. Among all the patients, two (6.5%) were hypertensive, two (6.5%) were diabetic, and six (19.4%) were smokers. The baseline demographic details of both groups are outlined in Table 1.

The mean ejection fraction of S-group and SP-group was 62.3 ± 10.2% and 64.8 ± 11.2%, respectively, with no statistical difference between the groups. The mean CPB duration was 106.1 ± 33.5 min and mean ACC time was 76.5 ± 28.8 min (P = 0.653 and 0.867, respectively). The amount of phenylephrine used and the vasoactive inotropic score were comparable between the two groups. No statistically significant difference was found for ICU stay (P = 0.307) as well as for hospital stay (P = 0.945) between both the groups [Table 2].

The baseline NGAL levels were comparable between the two groups (S-group = 123.4 ± 45.2 ng/mL and SP-group = 107.7 ± 31.9 ng/mL, P = 0.270). There was a significant rise in the post-CPB NGAL levels compared to baseline in both the groups. The test NGAL level in the S-group was significantly high compared to that of the SP-group (P = 0.034). The number of patients with AKI was 9 (60%) in the S-group and 6 (37.5%) in the SP-group. Although the number of patients with AKI was lower in the SP-group, it was not statistically significant (P = 0.210) [Table 3].

Our study failed to reveal any significant difference in serum creatinine levels (S. Cr) between the groups on the 1st, 2nd, and 5th postoperative days. Although not statistically significant, fewer patients developed AKI (increase in S. Cr > 0.3 mg% from baseline) in SP group (2 out of 16, 12.5%) as compared to S group (5 out of 15 patients, 33.3%) on the 1st postoperative day [Table 3].

EER and CER were 37.5% and 60%, respectively. The SP-group achieved an absolute risk reduction of 22.5%. The relative risk of AKI occurrence in the SP group compared with the S group was 0.38.

DISCUSSION

The present study investigated the effect of propofol coadministered with sevoflurane to attenuate renal injury in patients undergoing valvular heart surgery. AKI is one of the leading causes of morbidity and mortality after cardiac surgery. NGAL, a renal stress marker, was used to identify patients at risk of AKI. NGAL is a small covalently bound polypeptide from neutrophils that is readily detected in urine and blood. NGAL is a sensitive, early predictor of AKI as it is elevated in urine and blood within 2 h of renal injury.[11,12] Felitz *et al*.[13] identified strong supportive pieces of evidence for the use of NGAL as a biomarker for the prediction of AKI from various studies. The investigators proposed a grey zone of plasma NGAL concentration between 97 ng/mL and 133 ng/mL which was associated with a moderate risk of AKI.[13] Several studies describe serum NGAL value more than 150 ng/mL as a cutoff to predict AKI after cardiac surgery.[14]

Although we recruited patients with normal renal function based on S. Cr, the mean and median values of baseline NGAL in the S and SP group (123.4 ± 45.2 and 111.4 in the S group and 107.7 ± 31.9 and 107.4 in the SP group)

Table 1: Baseline demographic details of patients in both the groups

Variables	Sevoflurane + propofol group	Sevoflurane group	Total	*P*
Age (mean±SD, years)	45.1±12.8	42.7±10.1	44.0±11.5	0.570
Gender				
Male, *n* (%)	7 (43.8)	7 (46.7)	14 (45.2)	0.870
Female, *n* (%)	9 (56.3)	8 (53.3)	17 (54.8)	
Weight (mean±SD, kg)	61.3±12.3	59.4±9.2	60.4±10.8	0.635
Height (mean±SD, cm)	160.8±9.00	162.3±10.4	161.5±9.5	0.679
BSA (mean±SD, kg/m^2)	1.6±0.2	1.6±0.2	1.6±0.2	0.841
Hypertension, *n* (%)	1 (6.3)	1 (6.7)	2 (6.5)	0.962
Diabetes, *n* (%)	2 (12.5)	0	2 (6.5)	0.157
Smokers, *n* (%)	2 (12.5)	4 (26.7)	6 (19.4)	0.406
Asthma, *n* (%)	1 (6.3)	0	1 (3.2)	0.406
AF, *n* (%)	8 (50)	5 (33.3)`	13 (41.9)	0.347
NYHA, *n* (%)				
Class-II	7 (43.8)	5 (33.3)	12 (38.7)	0.552
Class-III	9 (56.3)	10 (66.7)	19 (61.3)	0.552

BSA: Body surface area; AF: Atrial fibrillation; NYHA: New York heart association functional classification; CPB: Cardiopulmonary bypass and ACC: Aortic cross-clamp

Table 2: Diagnostic and procedural parameters in both the groups

Parameters (mean±SD)	Sevoflurane + propofol group	Sevoflurane group	*P*
Ejection fraction (%)	62.3±10.2	64.8±11.2	0.523
CPB time (minutes)	108.8±29.9	103.2±37.8	0.653
ACC time (minutes)	77.4±26.8	75.6±31.6	0.867
Temperature (°C)	28.7±1.3	29.7±1.9	0.080
Phenylephrine use (μg/mL)	412.5±206.2	313.3±285.0	0.274
ICU stay (days)	3.8±0.8	3.5±0.7	0.307
Hospital stay (days)	8.6±1.1	8.5±1.2	0.945

CPB: Cardiopulmonary bypass; ACC: Aortic cross-clamp and ICU: Intensive care unit

were found to lie in the grey zone. The decreased cardiac output and/or the congestive symptoms caused by the left-sided valvular disease might have resulted in subclinical renal injury. Assuming a normal distribution for the baseline NGAL values, 95% of observations will fall in the mean ± 2 standard deviation range. Hence, any value beyond this range of normal distribution (more than 200 ng/mL) was considered to have a renal injury. Therefore, patients with test NGAL values above 200 ng/mL (the samples collected after cardiac surgery) were considered to have a renal injury caused as a result of cardiac surgery.

Volatile anesthetics precondition endothelial and smooth muscle cells with a protective effect on myocardium, brain, spinal cord, liver, and kidneys. Sevoflurane also reduces necrotic and inflammatory cell death by attenuation of inflammatory cytokines, chemokines, and nuclear transcription factor kappa-B.[15,16] Propofol limits cellular oxidative injury by acting as a scavenger of oxygen free radicals and reduces inducible nitric oxide activity. It also suppresses neutrophil chemotaxis and phagocytosis.[8,10]

In our study, anesthetic agents were titrated to maintain a BIS value of 35–60 in all patients during surgery. Studies have shown that propofol exerts its antioxidant and anti-inflammatory effects even at lower doses.[8,11] We used propofol at a dose of 50–150 mcg/kg/min. Luccinetti *et al.* have shown that sevoflurane inhalation at a sedative concentration less than 1 v% can provide endothelial protection against I-R injury.[6]

The baseline NGAL levels were comparable in both groups. The rise in postoperative NGAL levels was significantly lower in the combination group (195.1 ± 63.4 ng/mL) compared to the sevoflurane group (280.5 ± 138.7 ng/mL) with a *P* value of 0.034. This could be explained by the enhanced protective effect on renal function during CPB offered by both sevoflurane and propofol through their distinct organ protective mechanisms.

Earlier, Julier *et al.*[5] studied the effect of sevoflurane preconditioning in decreasing the biochemical markers for myocardial and renal dysfunction in CABG patients. Anesthesia was induced with propofol/etomidate and maintained with propofol infusion. Sevoflurane was administered during the initiation of CPB in the study group. They concluded that sevoflurane preconditioning preserved renal function compared to the placebo group as assessed by changes in cystatin-C levels. Furthermore, Yoo *et al.*[17] demonstrated a reduced incidence and severity of AKI in patients receiving propofol anesthesia compared with sevoflurane anesthesia following valvular heart surgery. This was attributed to propofol's better ability to attenuate perioperative increases in pro-inflammatory mediators.[17] Fernando *et al.*[10] studied the effect of sevoflurane and propofol on renal injury during the perioperative period in laparoscopic bariatric surgery. They observed that the choice of anesthetic agents did not affect the serum levels of NGAL.[18]

Table 3: NGAL level, renal injury, and inotrope requirements between the two groups

	Sevoflurane + propofol group	Sevoflurane group	*P* (between-group)
NGAL level (ng/ml)			
Baseline	107.7±31.9	123.4±45.2	0.270
Test	195.1±63.4	280±138.7	0.034
P (within group)	0.001	0.001	-
Renal injury based on NGAL level, *n* (%)			
Baseline	0	1 (6.7%)	0.294
Test	6 (37.5%)	9 (60%)	0.210
No Renal injury	10 (62.5%)	6 (40%)	-
Renal injury based on S. creatinine (S. Cr >0.3 mg/dL over baseline)			
1st Postoperative day	2 (12.5%)	5 (33.33%)	0.170
2nd Postoperative day	4 (25%)	5 (33.33%)	0.454
Vasoactive inotropic score			
Inotropic score	2.31±3.13	2.87±2.75	0.375

NGAL: Neutrophil gelatinase-associated lipocalin

The difference observed in the two above mentioned studies may be related to the difference in the mechanism of AKI in valvular heart surgery and bariatric laparoscopic surgeries. The production of bioactive substances by adipose tissue, rhabdomyolysis during surgery, and increased intra-abdominal pressure are the factors contributing to AKI in bariatric laparoscopic surgeries.

Although the number of patients with renal risk were lower in the combination group (37.5% in the SP-group vs. 60% in the S-group), it was not statistically significant. There was an ARR of 22.5% in the SP-group and RRR of 0.38. This shows that sevoflurane and propofol combination is better in reducing renal injury than sevoflurane alone.

The use of phenylephrine and the inotropic requirement were also comparable in both groups. It was found that the duration of ICU stay and hospital stay were not influenced by the choice of anesthetic agents.

The positive strength of the current study includes the recruitment of a homogenous cohort of adults in whom renal I-R injury occurred during valvular heart surgery. These patients did not have any difference in terms of comorbid variables such as atherosclerotic disease, diabetes, and nephrotoxins use, as all of these can confound and hinder the identification of early biomarkers for ischemic AKI.

Limitations

An important limitation of the present study includes the enrollment of patients who were at a comparatively lower risk of postoperative renal dysfunction, as patients with preoperative serum creatinine greater than 2 mg/dL were excluded. Consequently, this was not an outcome study, as the incidence of hemodialysis was zero. This was a pilot study for which no exact power analysis concerning the main variable (serum NGAL) was possible. Moreover, the post-CPB NGAL level was measured only at a single time point (4 h) in order to determine the incidence of AKI.

Although the results elicit a significant decrease in renal dysfunction in the postoperative period in the SP-group, the number of patients with renal injury was not significantly different between the two groups. It could be because of the small sample size that we were not able to obtain a significant reduction in the number of patients with renal injury in the SP-group. Thus, larger studies may be required to delineate the difference between the groups.

A comparable effect of sevoflurane and propofol on renal function in previous studies was observed. However, in this study, we compared the renal protective effect of sevoflurane-propofol combination with that of sevoflurane alone. There was no control group for propofol. So, it was not proved that whether the protective effect of the combination was additive or synergistic.

CONCLUSION

Renal function was better preserved in patients anesthetized with the sevoflurane-propofol combination compared to sevoflurane alone. This was reflected by the lesser rise in NGAL level after surgery in the combination group. This can be attributed to the organ protective effect offered by both the agents. Since there was no control group for propofol, we were not able to elicit whether the protective effect of the combination was additive. However, further studies with a larger sample size may be needed to validate or refute the findings of the present study.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mariscalco G, Lorusso R, Dominici C, Renzulli A, Sala A. Acute kidney injury: A relevant complication after cardiac surgery. Ann Thorac Surg 2011;92:1539-47.
2. Rosner MH, Okusa MD. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 2006;1:19-32.
3. Paparella D, Yau T, Young E. Cardiopulmonary bypass induced inflammation: Pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002;21:232-44.
4. Laffey JG, Boylan JF, Cheng DC. The systemic inflammatory response to cardiac surgery implications for the anesthesiologist. Anesthesiology 2002;97:215-52.
5. Julier K, da Silva R, Garcia C, Bestmann L, Frascarolo P, Zollinger A, *et al*. Preconditioning by sevoflurane decreases biochemical markers for myocardial and renal dysfunction in coronary artery bypass graft surgery: A double-blinded, placebo-controlled, multicenter study. Anesthesiology 2003;98:1315-27.
6. Lucchinetti E, Ambrosio S, Aguirre J, Herrmann P, Härter L, Keel M, *et al*. Sevoflurane inhalation at sedative concentrations provides endothelial protection against ischemia–reperfusion injury in humans. Anesthesiology 2007;106:262-8.
7. Xia Z, Godin DV, Chang TK, Ansley DM. Dose-dependent protection of cardiac function by propofol during ischemia and early reperfusion in rats: Effects on 15-F2t-isoprostane formation. Can J Physiol Pharmacol 2003;81:14-21.
8. Corcoran TB, Engel A, Sakamoto H, O'Callaghan-Enright S, O'Donnell A, Heffron JA, *et al*. The effects of propofol on lipid peroxidation and inflammatory response in elective coronary artery bypass grafting. J Cardiothorac Vasc Anesth 2004;18:592-604.
9. Rodríguez-López JM, Sánchez-Conde P, Lozano FS, Nicolás JL, García-Criado FJ, Cascajo C, *et al*. Effects of propofol on the systemic inflammatory response during aortic surgery. Can J Anaesth 2006;53:701-10.
10. Fernandes A, Ettinger J, Amaral F, Ramalho MJ, Alves R, Módolo NS. General anesthesia type does not influence serum levels of neutrophil gelatinase-associated lipocalin during the perioperative period in video laparoscopic bariatric surgery. Clinics 2014;69:655-9.
11. Lorsomradee S, Cromheecke S, Lorsomradee S, De Hert SG. Effects of sevoflurane on biomechanical markers of hepatic and renal dysfunction after coronary artery surgery. J Cardiothorac Vasc Anesth 2006;20:684-90.
12. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, *et al*. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-8.
13. Haase-Fielitz A, Haase M, Devarajan P. Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury: A critical evaluation of current status. Ann Clin Biochem 2014;51:335-1.
14. Haase M, Bellomo R, Devarajan P, Ma Q, Bennett MR, Möckel M, *et al*. Novel biomarkers early predict the severity of acute kidney injury after cardiac surgery in adults. Ann Thorac Surg 2009;88:124-30.
15. Lee HT, Ota-Setlik A, Fu Y, Nasr SH, Emala CW. Differential protective effects of volatile anesthetics against renal ischemia–reperfusion injury *in vivo*. Anesthesiology 2004;101:1313-24.
16. Zhong C, Zhou Y, Liu H. Nuclear factor κB and anesthetic preconditioning during myocardial ischemia-reperfusion. Anesthesiology 2004;100:540-6.
17. Yoo YC, Shim JK, Song Y, Yang SY, Kwak YL. Anesthetics influence the incidence of acute kidney injury following valvular heart surgery. Kidney Int 2014;86:414-22
18. Sánchez-Conde P, Rodríguez-López JM, Nicolás JL, Lozano FS, García-Criado FJ, Cascajo C, *et al*. The comparative abilities of propofol and sevoflurane to modulate inflammation and oxidative stress in the kidney after aortic cross-clamping. Anesth Analg 2008;106:371-78.