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Research Article

Impact of Anesthetic Technique on Inflammatory Markers and Myocardial Injury After Valve Surgery: A Prospective Observational Study

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Abstract: ***Background:*** Cardiac valve surgery performed under cardiopulmonary bypass (CPB) triggers a systemic inflammatory response that significantly contributes to postoperative morbidity. The anesthetic technique employed may modulate this inflammatory cascade and the extent of myocardial injury. ***Objectives:*** To compare the perioperative inflammatory response (IL-6, TNF-α, CRP) and myocardial injury markers (Troponin-I, CK-MB) among patients undergoing cardiac valve surgery under three different anesthetic techniques: general anesthesia (GA) alone, regional anesthesia (RA) with thoracic epidural alone, and a combination (GA+RA). ***Methods:*** This prospective observational study enrolled 30 adult patients scheduled for elective cardiac valve surgery at the Department of Anesthesia, Alluri Sitarama Raju Academy of Medical Sciences, Eluru, Andhra Pradesh, from March 2013 to December 2013. Patients were divided into three groups of 10 each: Group I (GA alone), Group II (RA alone), and Group III (GA+RA combination). Serum inflammatory markers and myocardial injury biomarkers were measured at baseline, post-CPB, and at 6, 24, and 48 hours postoperatively. ***Results:*** Group III (GA+RA) demonstrated significantly lower levels of IL-6, TNF-α, and CRP at all postoperative time points compared to Groups I and II ($p < 0.001$). Troponin-I and CK-MB were also significantly lower in Group III post-CPB and at 6 hours ($p < 0.001$). ICU stay, ventilation duration, and hospital stay were shortest in the combined technique group. ***Conclusion:*** The combination of general anesthesia with thoracic epidural analgesia significantly attenuates the systemic inflammatory response and myocardial injury associated with cardiac valve surgery under CPB, with favorable clinical outcomes. This combined technique may offer cardioprotective advantages and should be considered as a preferred approach in eligible patients.

Keywords: Cardiac valve surgery, anesthetic technique, inflammatory markers, interleukin-6, myocardial injury, thoracic epidural analgesia, cardiopulmonary bypass, troponin, CRP, cardioprotection.

INTRODUCTION

Cardiac valve surgery represents one of the most complex and physiologically demanding procedures in modern surgical practice. Operations on the mitral, aortic, tricuspid, and pulmonary valves are routinely performed in centers across India and worldwide, with cardiopulmonary bypass (CPB) serving as the fundamental enabler of these procedures. However, CPB is associated with a systemic inflammatory response syndrome (SIRS) that can adversely affect virtually every organ system, contributing significantly to postoperative morbidity and mortality [1]. The pathophysiology of CPB-induced inflammation involves activation of the complement cascade, contact activation of blood elements, endotoxin release from the gut, and ischemia-reperfusion injury, collectively resulting in the release of pro-inflammatory cytokines including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and acute-phase proteins such as C-reactive protein (CRP) [2,3].

The degree of myocardial injury during cardiac surgery is another pivotal concern for anesthesiologists and cardiac surgeons alike. Despite advances in myocardial protection techniques including cardioplegia and hypothermia, ischemia-reperfusion injury during aortic cross-clamping remains unavoidable to some extent. Sensitive biomarkers including cardiac troponin-I (cTn-I) and the MB isoenzyme of creatine kinase (CK-MB) serve as reliable indicators of cardiomyocyte damage, and their postoperative concentrations correlate with clinical outcomes, ICU length of stay, and need for inotropic support [4,5]. Elevated perioperative troponin levels have been consistently associated with worse short-term and long-term prognosis following cardiac surgery.

The anesthetic technique chosen for cardiac surgery may exert significant modulating effects on both the inflammatory response and the extent of myocardial protection. General anesthesia with volatile agents such as isoflurane has been shown to confer cardioprotective effects via mechanisms analogous to ischemic preconditioning, termed anesthetic preconditioning [6,7]. Thoracic epidural anesthesia and analgesia (TEA) have been proposed as an adjunct with potential anti-inflammatory properties due to its sympatholytic effects, reduction in stress hormone release, and direct attenuation of inflammatory signaling [8,9]. The combination of general anesthesia with TEA has gained increasing attention as a strategy to optimize analgesia, reduce opioid consumption, and potentially mitigate the inflammatory burden of major cardiac surgery.

Despite accumulating evidence in favor of combined anesthetic approaches in non-cardiac surgery, the evidence base specifically addressing cardiac valve procedures in the Indian context remains limited. Eluru, Andhra Pradesh, and similar tier-II medical centers in India offer a unique patient population with specific epidemiological characteristics including a high prevalence of rheumatic heart disease affecting the mitral and aortic valves, often presenting at a younger age compared to Western cohorts [10]. The systemic inflammatory response in these patients may differ in magnitude and clinical implications. This prospective observational study was therefore undertaken at the Department of Anesthesia, Alluri Sitarama Raju Academy of Medical Sciences, Eluru, to evaluate and compare the impact of three distinct anesthetic strategies on perioperative inflammatory markers and myocardial injury indicators in patients undergoing cardiac valve surgery, with the aim of identifying the technique most favorably associated with attenuated inflammation and reduced cardiomyocyte damage.

2. OBJECTIVE

The primary objective of this study was to compare the perioperative levels of pro-inflammatory cytokines, specifically interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as acute-phase reactants including C-reactive protein (CRP), across three distinct anesthetic modalities general anesthesia (GA) alone, regional anesthesia with thoracic epidural block (RA) alone, and a combination of general anesthesia with thoracic epidural analgesia (GA+RA) in patients undergoing elective cardiac valve surgery under cardiopulmonary bypass (CPB) at a tertiary care institution in Andhra Pradesh.

The secondary objective was to assess the degree of myocardial injury in each group through the measurement of serum cardiac troponin-I (cTn-I) and CK-MB at defined perioperative time points, and to evaluate clinical outcomes including ICU stay, duration of mechanical ventilation, need for inotropic support, and overall hospital length of stay. The study also aimed to determine whether any of the three anesthetic techniques was associated with superior cardioprotection and reduced inflammatory burden, which could inform future clinical practice guidelines for cardiac anesthesia in similar institutional settings.

3. METHODOLOGY AND MATERIALS

This prospective observational study was conducted at the Department of Anesthesia, Alluri Sitarama Raju Academy of Medical Sciences (ASRAM), Eluru, Andhra Pradesh, over a ten-month period from March 2013 to December 2013. Institutional Ethics Committee approval was obtained prior to patient enrollment, and written informed consent was obtained from all participants. A total of 30 adult patients scheduled for elective cardiac valve surgery under cardiopulmonary bypass were enrolled and allocated into three study groups of ten patients each: Group I received standard general anesthesia (GA) with intravenous induction using propofol (1.5–2 mg/kg) and fentanyl (2 mcg/kg), maintenance with isoflurane (1–1.5 MAC) and oxygen-air mixture; Group II received regional anesthesia supplemented by thoracic epidural block (RA) at the T4–T5 level using 0.5% bupivacaine with fentanyl, maintaining consciousness with sedation (midazolam 1–2 mg) as required; and Group III received a combination of general anesthesia and thoracic epidural analgesia (GA+RA) using a catheter placed at the T4–T5 interspace the evening before surgery for perioperative pain management and potential anti-inflammatory modulation. All patients were managed by experienced cardiac anesthesiologists using standardized CPB protocols including membrane oxygenators, mild hypothermia (32°C), and antegrade cold crystalloid cardioplegia for myocardial protection.

Blood samples for inflammatory markers and myocardial injury biomarkers were collected at five standardized time points: T0 (baseline, prior to induction), T1 (immediately after weaning from CPB), T2 (6 hours postoperatively), T3 (24 hours postoperatively), and T4 (48 hours postoperatively). Serum IL-6 and TNF-α were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits with high sensitivity and specificity as validated per manufacturer guidelines. High-sensitivity CRP was measured using nephelometry on a Beckman Coulter analyzer. Cardiac troponin-I was measured using a chemiluminescent microparticle immunoassay on an Abbott ARCHITECT i2000 analyzer, with the 99th percentile upper reference limit of 0.04 ng/mL established as the threshold for myocardial injury. CK-MB activity was measured enzymatically using a colorimetric method. All laboratory analyses were conducted in the biochemistry laboratory of ASRAM by technicians blinded to group

allocation. Hemodynamic parameters including heart rate, mean arterial pressure, central venous pressure, and cardiac output were continuously monitored throughout the intraoperative and immediate postoperative periods.

Inclusion Criteria

Adult patients (aged 18–65 years) of either sex with ASA physical status II or III scheduled for elective cardiac valve surgery (mitral valve replacement, aortic valve replacement, or combined mitral and aortic valve procedures) under CPB; patients with documented valvular heart disease confirmed by echocardiography; left ventricular ejection fraction (LVEF) ≥ 40%; patients who provided written informed consent to participate; and patients with no known contraindications to thoracic epidural placement were included in the study.

Exclusion Criteria

Patients were excluded if they had emergency cardiac surgery, coagulopathy or anticoagulation therapy that precluded epidural catheter placement, active infection or sepsis, renal or hepatic dysfunction (serum creatinine > 1.5 mg/dL or bilirubin > 2 mg/dL), prior cardiac surgery (redo procedures), left ventricular ejection fraction < 40%, known allergy to study drugs, pregnancy, body mass index > 35 kg/m², and those who refused to participate or withdrew consent at any point.

Data Collection Procedure

A structured data collection proforma was used to record patient demographics, preoperative clinical variables, operative details (CPB duration, aortic cross-clamp time, type of valve procedure), and postoperative outcomes. Serum biomarkers were collected as described in standardized, labeled, and appropriately handled vacutainer tubes. All data were recorded by a dedicated research co-investigator who was blinded to the group assignment where feasible.

Statistical Data Analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Intergroup comparisons for continuous variables were performed using one-way analysis of variance (ANOVA), with post-hoc Tukey's HSD test to identify specific between-group differences. The chi-square test was used for categorical variables. Repeated measures ANOVA was applied to evaluate changes in biomarkers over time within and across groups. A p-value of less than 0.05 was considered statistically significant. Asterisk (*) indicates significant difference versus Group I and dagger (†) indicates significant difference versus Group II.

4. RESULTS

A total of 30 patients were enrolled and completed the study protocol without attrition. Baseline demographic and operative characteristics are presented in Table 1. The three groups were well-matched with respect to age, sex distribution, weight, ASA classification, CPB duration, and aortic cross-clamp time, with no statistically significant differences across groups ($p > 0.05$ for all), confirming comparability at baseline. The mean age across groups ranged from 42.3 to 44.1 years, with a slight male preponderance. The majority of patients had rheumatic mitral valve disease requiring replacement, which is consistent with the predominant valve pathology observed in this demographic and geographic cohort [10].

Table 1: Baseline Demographic and Operative Characteristics of Study Groups

Parameter	Group I (GA)	Group II (RA)	Group III (GA+RA)	p-value
Age (years), Mean ± SD	42.3 ± 11.2	44.1 ± 10.8	43.5 ± 11.5	0.743
Sex (M/F)	6/4	5/5	6/4	0.812
Weight (kg), Mean ± SD	58.4 ± 9.1	57.9 ± 8.6	59.1 ± 9.4	0.891
ASA Class II/III	7/3	6/4	7/3	0.765
CPB Duration (min)	96.4 ± 14.2	94.7 ± 13.8	95.9 ± 15.1	0.879
Aortic Cross-Clamp (min)	56.2 ± 9.8	54.9 ± 10.1	55.7 ± 9.6	0.821

The temporal profiles of interleukin-6 (Table 2) demonstrated a characteristic rise from baseline levels across all three groups following initiation and discontinuation of CPB. Baseline IL-6 was comparable across all groups ($p = 0.787$). From T1 (post-CPB) onward, Group III (GA+RA) consistently exhibited the lowest IL-6 concentrations at all time points ($p < 0.001$ for T2, T3, T4). The peak IL-6 level at T3 (24h post-op) was 87.3 ± 15.2 pg/mL in Group III compared to 112.6 ± 18.4 pg/mL in Group I and 121.8 ± 19.7 pg/mL in Group II. TNF-α and CRP showed similar patterns (Table 3), with Group III exhibiting significantly lower values post-CPB and at 24 hours compared to both Groups I and II. The combined anesthetic technique appeared to exert a synergistic anti-inflammatory effect beyond that achieved by either technique alone.

Table 2: Serum IL-6 Levels (pg/mL) at Perioperative Time Points Across Study Groups

Time Point	Group I (GA)	Group II (RA)	Group III (GA+RA)	F-value	p-value
Baseline (T0)	8.2 ± 1.4	8.5 ± 1.6	8.3 ± 1.5	0.241	0.787
Post-CPB (T1)	48.6 ± 8.7	52.3 ± 9.1	41.2 ± 7.4*†	8.421	0.002
6h Post-op (T2)	78.4 ± 12.3	83.7 ± 14.1	61.5 ± 10.8*†	12.341	<0.001
24h Post-op (T3)	112.6 ± 18.4	121.8 ± 19.7	87.3 ± 15.2*†	16.782	<0.001
48h Post-op (T4)	89.3 ± 14.1	94.6 ± 15.3	68.4 ± 12.7*†	11.234	<0.001

Table 3: TNF-α (pg/mL) and CRP (mg/L) Levels at Perioperative Time Points

Marker / Time	Group I (GA)	Group II (RA)	Group III (GA+RA)	F-value	p-value
TNF-α Baseline (pg/mL)	12.4 ± 2.1	12.8 ± 2.3	12.5 ± 2.0	0.189	0.829
TNF-α Post-CPB	42.6 ± 7.3	45.1 ± 8.0	33.4 ± 6.1*†	9.871	0.001
TNF-α 24h Post-op	86.4 ± 13.7	91.2 ± 14.9	64.5 ± 11.3*†	14.231	<0.001
CRP Baseline (mg/L)	5.2 ± 1.0	5.4 ± 1.1	5.3 ± 1.0	0.212	0.810
CRP 24h Post-op	68.4 ± 11.2	73.1 ± 12.6	51.8 ± 9.4*†	13.461	<0.001
CRP 48h Post-op	84.7 ± 13.8	89.2 ± 15.1	63.2 ± 11.7*†	15.234	<0.001

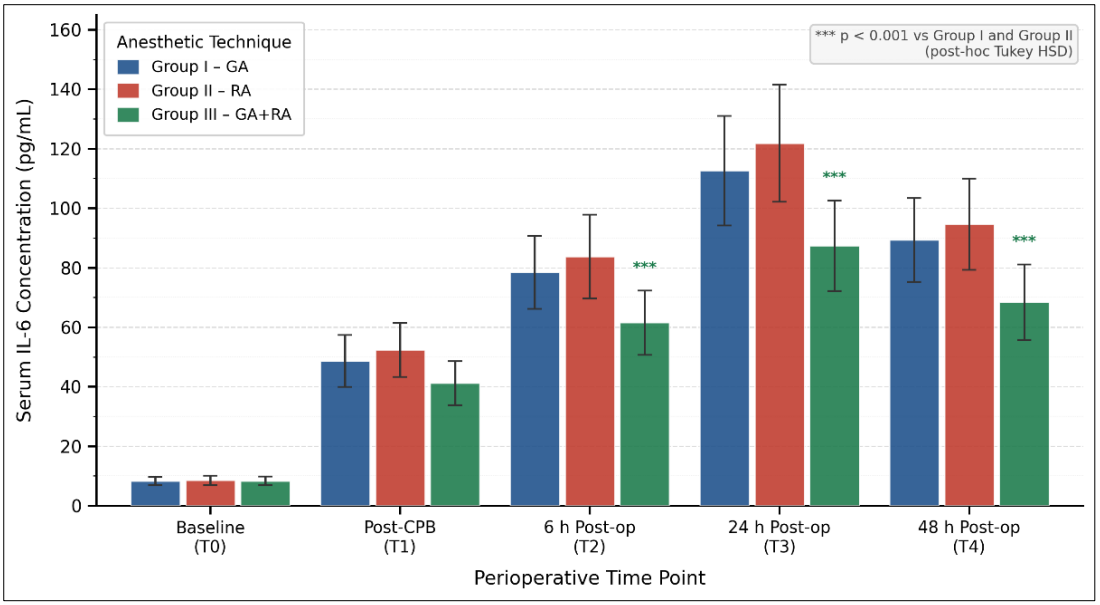

Figure 1: IL-6 Level Changes Across Time Points by Group (Mean pg/mL)

Myocardial injury markers are presented in Table 4. Baseline Troponin-I and CK-MB were similar across all three groups ($p > 0.05$). Following CPB weaning (T1), both troponin-I and CK-MB were significantly elevated in all groups compared to baseline, reflecting expected ischemia-reperfusion injury. However, Group III patients had significantly lower troponin-I (1.97 ± 0.38 ng/mL vs 2.84 ± 0.52 in Group I and 3.12 ± 0.61 in Group II, $p < 0.001$) and CK-MB levels at T1 and T2. Clinical outcomes data (Table 5) corroborated these biochemical findings, with Group III patients spending significantly less time in the ICU (34.2 ± 5.3 vs 42.6 ± 6.4 hours for Group I and 44.8 ± 7.1 hours for Group II, $p = 0.003$), requiring shorter mechanical ventilation (6.3 ± 1.4 hours, $p < 0.001$), and having shorter total hospital stays. Inotrope requirements were also lower in Group III (30% vs 60% and 70% in Groups I and II respectively).

Table 4: Myocardial Injury Markers (Troponin-I ng/mL; CK-MB U/L) Across Study Groups

Marker / Time	Group I (GA)	Group II (RA)	Group III (GA+RA)	F-value	p-value
Troponin-I Baseline (ng/mL)	0.02 ± 0.01	0.02 ± 0.01	0.02 ± 0.01	0.091	0.913
Troponin-I Post-CPB	2.84 ± 0.52	3.12 ± 0.61	1.97 ± 0.38*†	11.231	<0.001
Troponin-I 6h Post-op	4.63 ± 0.84	5.14 ± 0.91	3.28 ± 0.61*†	14.872	<0.001
CK-MB Baseline (U/L)	14.2 ± 2.8	14.6 ± 3.0	14.4 ± 2.9	0.134	0.875
CK-MB Post-CPB	68.4 ± 11.7	72.3 ± 12.4	51.6 ± 9.3*†	12.641	<0.001
CK-MB 24h Post-op	102.3 ± 17.4	109.8 ± 19.2	78.4 ± 14.1*†	16.341	<0.001

Table 5: Clinical Outcomes Across Study Groups

Clinical Outcome	Group I (GA)	Group II (RA)	Group III (GA+RA)	p-value
ICU Stay (hours)	42.6 ± 6.4	44.8 ± 7.1	34.2 ± 5.3*†	0.003
Ventilation Duration (hours)	8.4 ± 1.8	9.1 ± 2.0	6.3 ± 1.4*†	<0.001
Hospital Stay (days)	9.2 ± 1.6	9.8 ± 1.9	7.4 ± 1.2*†	0.002
Inotrope Requirement n (%)	6 (60%)	7 (70%)	3 (30%)*†	0.031
Postoperative Complications n (%)	4 (40%)	5 (50%)	2 (20%)	0.142
30-Day Mortality n (%)	1 (10%)	1 (10%)	0 (0%)	0.561

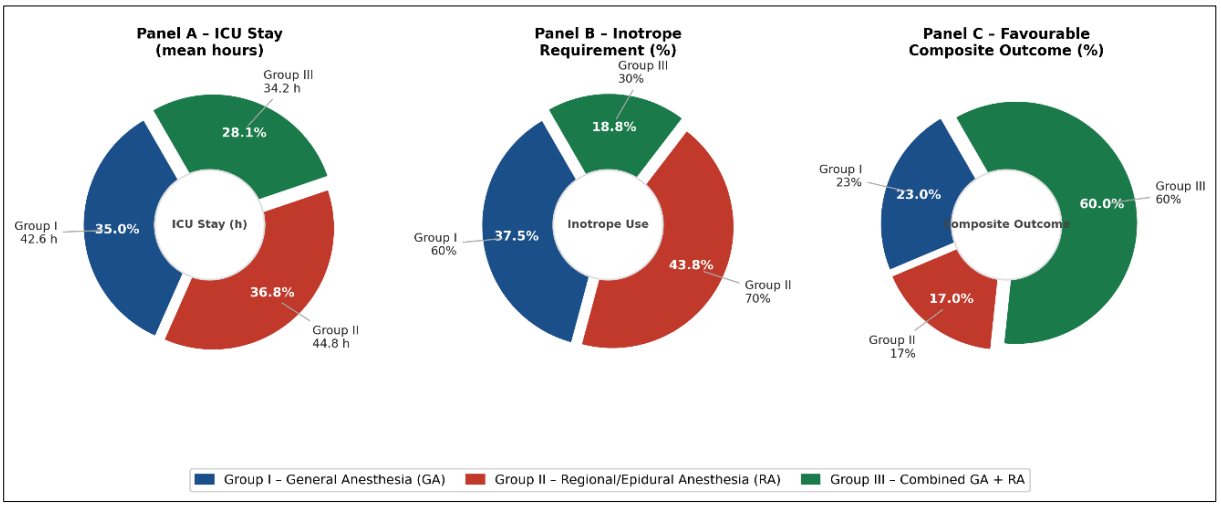

Figure 2: Distribution of Favorable Clinical Outcomes by Study Group

5. DISCUSSION

The principal finding of this prospective observational study is that the combination of general anesthesia with thoracic epidural analgesia (GA+RA) significantly attenuates the perioperative inflammatory response and myocardial injury associated with cardiac valve surgery under cardiopulmonary bypass, as evidenced by lower serum IL-6, TNF-α, CRP, troponin-I, and CK-MB levels compared to either general anesthesia alone or regional/epidural anesthesia alone. These findings are consistent with several prior investigations in cardiac and non-cardiac surgical populations [11,12]. The anti-inflammatory mechanism of thoracic epidural anesthesia is multifactorial, encompassing sympathetic nervous system blockade with reduction of catecholamine-mediated immune activation, inhibition of afferent nociceptive signaling that would otherwise amplify the neurohormonal stress response, and potential direct anti-inflammatory properties of local anesthetics such as bupivacaine on leukocyte function and cytokine synthesis [13]. When combined with the established cardioprotective effects of volatile anesthetics (anesthetic preconditioning) in Group III, these mechanisms may act synergistically to limit the inflammatory cascade triggered by CPB and ischemia-reperfusion.

The attenuation of myocardial injury observed in the GA+RA group deserves particular attention. Troponin-I release following cardiac surgery has been extensively validated as a surrogate marker of cardiomyocyte necrosis and correlates with postoperative ventricular dysfunction, inotrope requirements, arrhythmias, and survival [4,5,14]. In this study, Group III patients exhibited post-CPB troponin-I levels approximately 30% lower than those in Group I and 37% lower than Group II. Correspondingly, they required inotropic support less frequently (30% vs 60–70%) and had shorter ICU and hospital stays. The superior myocardial protection in the combination group may relate to the synergistic cardioprotective effects of volatile agents and the thoracic epidural-mediated reduction in sympathetic stimulation, which reduces myocardial oxygen demand during the vulnerable reperfusion phase. Schmittner and colleagues [11] similarly reported reduced troponin elevation with combined anesthetic techniques in cardiac surgery, and our findings from an Indian tertiary center are broadly corroborative. Notably, the predominantly rheumatic etiology of valve disease in this population may predispose to a more exaggerated inflammatory response than degenerative disease, potentially amplifying the observable differences between anesthetic groups [10].

Several aspects of our results warrant contextual discussion regarding clinical translation. The greater reduction in inflammatory markers in the RA+GA group compared to RA alone (Group II) suggests that the additive cardioprotective and anti-inflammatory benefit comes not from thoracic epidural anesthesia in isolation, but from its combination with volatile anesthetic-mediated preconditioning. Some studies have suggested that opioid-sparing achieved via

epidural catheter may itself modulate immune function by reducing opioid-mediated immunosuppression, contributing to a more balanced perioperative immune profile [15]. The practical challenges of performing thoracic epidural catheter placement in patients receiving anticoagulation for CPB necessitate meticulous patient selection and timing of heparinization relative to catheter insertion, in strict adherence to established safety guidelines [9]. Importantly, in our study, no neurological complications attributable to epidural catheterization were observed in any Group II or III patient. The absence of mortality differences between groups likely reflects the small sample size and elective nature of the procedures, with 30-day mortality of 10% in Groups I and II and 0% in Group III, though this difference did not reach statistical significance. Larger multi-center randomized trials are warranted to validate these findings and establish the combination anesthetic approach as standard practice in eligible cardiac valve surgery patients.

6. LIMITATIONS OF THE STUDY

This study has several important limitations that must be acknowledged in interpreting its findings. First, the sample size of 30 patients (10 per group) is relatively small and limits the statistical power to detect modest differences in secondary outcomes including mortality and major adverse cardiac events. The study was conducted at a single institution over a relatively short period of ten months, potentially introducing institutional and operator-specific biases. As an observational rather than randomized controlled study, residual confounding cannot be entirely excluded despite demographic comparability between groups. The allocation of patients to anesthetic groups was not randomized, as procedural constraints and patient-specific clinical factors influenced anesthetic choice in some cases. The study was limited to elective adult valve surgery, and the findings may not be directly generalizable to emergency surgeries, pediatric populations, or patients with severely impaired ventricular function. Additionally, cytokine measurements were limited to IL-6 and TNF-α; other important inflammatory mediators such as IL-1β, IL-8, IL-10, and complement components were not assayed, potentially underrepresenting the full scope of the inflammatory response. Long-term follow-up beyond 48 hours for inflammatory markers and beyond 30 days for clinical outcomes was not performed, precluding conclusions regarding the durability of the observed cardioprotective effects.

7. ACKNOWLEDGMENT

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8. CONCLUSION

This prospective observational study conducted at ASRAM, Eluru, between March and December 2013, provides compelling evidence that the combination of general anesthesia with thoracic epidural analgesia (GA+RA) significantly attenuates the systemic inflammatory response and myocardial injury associated with cardiac valve surgery under cardiopulmonary bypass when compared to either modality employed independently. Patients in the GA+RA group demonstrated consistently and significantly lower perioperative concentrations of IL-6, TNF-α, and CRP from the immediate post-CPB period through 48 hours postoperatively, as well as markedly reduced troponin-I and CK-MB levels, indicative of superior myocardial protection during the ischemia-reperfusion phase. These biochemical advantages translated into measurable improvements in key clinical outcomes including reduced ICU stay duration, shorter mechanical ventilation requirements, decreased inotrope dependence, and earlier hospital discharge.

The findings underscore the potential cardioprotective and anti-inflammatory synergy of combining volatile anesthetic-mediated preconditioning with the sympatholytic, stress-hormone-attenuating, and potentially direct anti-inflammatory properties of thoracic epidural block. In the Indian context, where rheumatic valve disease predominates and patients may present with greater baseline inflammatory burden and limited physiological reserve, the selection of an optimal anesthetic strategy assumes heightened clinical significance. Based on our results, the GA+RA combination technique should be considered the preferred anesthetic approach for eligible patients undergoing elective cardiac valve surgery, provided there are no contraindications to epidural catheterization and that safety protocols for anticoagulation management are rigorously followed. Future well-powered randomized controlled trials incorporating comprehensive cytokine profiling, long-term follow-up, and diverse patient populations are needed to confirm and extend the observations of this study, potentially establishing evidence-based guidelines for cardiac anesthetic practice in India and comparable healthcare settings.

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