



ORIGINAL ARTICLE

Comparison of the Efficacy of Fentanyl and a Paracetamol–Magnesium Combination in Attenuating Hemodynamic Response to Sternotomy in Patients Undergoing CABG

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Abstract

Introduction: Fentanyl is commonly used to attenuate hemodynamic responses during cardiac surgery but is associated with adverse effects. Paracetamol and magnesium sulfate offer a potential opioid-sparing alternative. This study compared the efficacy of fentanyl versus a paracetamol-magnesium combination in controlling intraoperative hemodynamic changes and postoperative pain. **Materials and Methods:** In this prospective comparative study, 90 adult patients undergoing elective cardiac surgery via median sternotomy were randomized into two groups: Group F (fentanyl) and Group PM (paracetamol 15 mg/kg + magnesium sulfate 30 mg/kg). Hemodynamic parameters (SBP, DBP, MAP, HR) were recorded perioperatively. Postoperative pain (VAS scores), morphine consumption, and extubation time were assessed. Statistical analysis was performed with $p < 0.05$ considered significant. **Results:** Baseline characteristics were similar. Group PM had significantly lower SBP at 4 and 5 minutes post-sternotomy ($p=0.041$, $p=0.031$). DBP and MAP were also lower in Group PM from 1 minute onward ($p < 0.05$). At 24 hours, 80% of Group PM had minimal pain (VAS 1) versus 24.4% in Group F. Morphine usage was comparable ($p=0.904$). Extubation was earlier in Group PM, though not statistically significant. **Conclusion:** Paracetamol-magnesium provided better hemodynamic control and postoperative analgesia without delaying extubation. It is a safe and effective alternative to fentanyl in cardiac anesthesia.

Keywords: Fentanyl, Paracetamol, Magnesium sulfate, Hemodynamic response, Coronary artery bypass grafting

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Graphical Abstract

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Background

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Methods

In this prospective comparative study, 90 adult patients undergoing elective cardiac surgery via median sternotomy were randomized into two groups: Group F (fentanyl) and Group PM (paracetamol 15 mg/kg + magnesium sulfate 30 mg/kg). Hemodynamic parameters (SBP, DBP, MAP, HR) were recorded perioperatively. Postoperative pain (VAS scores), morphine consumption, and extubation time were assessed. Statistical analysis was performed with $p < 0.05$ considered significant.

VAS score between group Fentanyl

VAS score	Fentanyl			Paracetamol Magnesium		p-value
	No	%	No	%		
6 hrs after extubation	1	3	6.7	1	2.2	0.577
	2	4	8.9	4	8.9	
	3	15	33.3	25	55.6	
	4	14	31.3	11	24.4	
	5	7	15.6	3	6.7	
	6	2	4.4	1	2.2	
12 hrs after extubation	1	3	6.7	9	20	0.765
	2	7	15.6	15	33.3	
	3	29	64.4	19	42.2	
	4	6	13.3	2	4.4	
18 hrs after extubation	1	6	13.3	20	44.4	0.438
	2	25	55.6	18	40	
	3	14	31.3	7	15.6	
24 hrs after extubation	1	11	24.4	36	80	0.988
	2	31	68.9	5	11	
	3	3	6.6	4	8.9	



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Conclusions Paracetamol-magnesium provided better hemodynamic control and postoperative analgesia without delaying extubation. It is a safe and effective alternative to fentanyl in cardiac anesthesia.

Introduction

Cardiac surgery, particularly procedures involving sternotomy and cardiopulmonary bypass, is associated with significant perioperative stress responses triggered by intense nociceptive stimulation. These responses are characterized by sharp elevations in heart rate, blood pressure, and systemic vascular resistance, all of which may increase myocardial oxygen demand and potentially precipitate ischemic events, arrhythmias, or hemodynamic instability in vulnerable patients. Managing this stress response is therefore a cornerstone of anesthetic management in cardiac surgery, aiming to ensure cardiovascular stability, optimize perfusion, and improve patient outcomes [1].

High dose opioids like fentanyl have been used all these years to manage these sympathetic responses during the cardiac surgeries. Fentanyl is a well established potent μ -opioid receptor

agonist and it is preferred for its rapid onset and cardiovascular stability. However, there are few drawbacks. Opioid-based anesthesia has been associated with respiratory depression, delay in extubating, ileus, increased risk of nausea and vomiting, and also opioid-induced hyperalgesia [2,3]. Currently more emphasis on enhanced recovery after surgery (ERAS) protocols and patient-centered outcomes is being stressed. The importance of minimizing opioid exposure is also being stressed nowadays. Hence, there is a preference towards multimodal, opioid-sparing analgesia [4].

Paracetamol and magnesium sulfate have been individually studied for their roles in analgesia and perioperative hemodynamic modulation. Paracetamol is a centrally acting NSAID that inhibits prostaglandin synthesis and activates descending serotonergic pathways, while magnesium sulfate acts as an NMDA receptor antagonist and calcium channel

blocker. This dual mechanism delivered not only analgesic effects but also contributed to sympatholysis and blunting of stress responses during noxious stimuli like intubation or surgical incision. Favourable safety profiles and reduced sedation make them attractive candidates as alternatives or adjuvants to opioids in high-risk surgeries such as cardiac procedures [3,5].

Albeit the benefits of paracetamol and magnesium have been well documented in non-cardiac surgeries, the evidence supporting their combined use in cardiac surgery remains very limited in intraoperative hemodynamic profiles and postoperative analgesic efficacies. Hence this study was planned for developing opioid-sparing protocols that align with enhanced recovery goals without compromising intraoperative stability or analgesic effectiveness [4,6].

Materials and Methods

This study was conducted after Institutional Human Ethics Committee (IHEC) approval from our institution. All procedures followed the ethical principles as per the Declaration of Helsinki. Prior to enrolment, a written informed consent was obtained from all eligible participants after explaining the nature, purpose, benefits, and potential risks of the study in a language they could understand.

This was a prospective, comparative study. Those receiving Fentanyl-based anesthesia and the other receiving a combination of Paracetamol and Magnesium sulfate as part of a multimodal analgesia regimen were termed as Group A and Group B respectively. Patients aged 18 years and above, belonging to ASA physical status III or IV, undergoing cardiac surgery via

median sternotomy were included. Patients with known hypersensitivity to study drugs, deranged hepatic or renal function, on opioids or sedative medications were excluded.

In group A, induction and maintenance of anesthesia included standard doses of intravenous fentanyl, titrated to the surgical response. In the group B, intravenous paracetamol (15 mg/kg) was administered 15 minutes prior to induction, along with magnesium sulfate (30 mg/kg) for over 10 minutes. Both groups received standard balanced anesthesia with agents such as midazolam, etomidate, muscle relaxants, and sevoflurane or isoflurane as per institutional protocol.

Hemodynamic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) were recorded at predefined intervals: baseline, after induction, before and after skin incision, and every minute from 1 to 5 minutes following sternotomy. Pain was assessed using the Visual Analog Scale (VAS) at 6, 12, 18, and 24 hours post-extubation. Additional data collected included time to first breakthrough pain, total morphine requirement in the first 24 hours post-extubation, and time to extubation.

All clinical observations were recorded using a standardized study proforma. The patient information sheet and informed consent form were approved by the ethics committee and administered prior to enrollment.

Statistical Analysis

Data were analyzed using appropriate statistical software SPSS 27. Continuous variables were expressed as

mean \pm standard deviation (SD) and compared using the unpaired t-test. Categorical variables were presented as frequencies and percentages, and analyzed using the chi-square test or Fisher's exact test as applicable. A p-value of < 0.05 was considered statistically significant.

Results

The age distribution between the two groups showed that the mean age in the Fentanyl group was 63.6 years (SD = 6.82) with a median of 64, while in the Paracetamol Magnesium group it was slightly lower at 61.4 years (SD = 4.81) with a median of 62. Although this indicates that participants in the Fentanyl group were marginally older, the difference was not statistically significant ($p = 0.107$). Gender distribution was identical across both groups, with 88.9% males (40 out of 45) and 11.1% females (5 out of 45) in each, showing no significant difference ($p = 0.918$). Regarding ASA physical status grading, a higher proportion of patients in the Fentanyl group were classified as ASA grade 3

(86.7%, 39 patients), while the Paracetamol Magnesium group had more patients with ASA grade 4 (31.1%, 14 patients). Nonetheless, the difference in ASA distribution between the two groups was also not statistically significant ($p = 0.899$).

The comparison of systolic blood pressure (SBP) between the Fentanyl and Paracetamol Magnesium groups at various perioperative time points revealed no statistically significant differences until 3 minutes after sternotomy. SBP readings remained largely comparable at baseline (138 vs. 136 mmHg, $p=0.263$), after induction (146 vs. 143 mmHg, $p=0.105$), and around skin incision. However, from the 4th minute after sternotomy, SBP was significantly higher in the Fentanyl group compared to the Paracetamol Magnesium group (142 vs. 138 mmHg, $p=0.041$), and the trend continued at the 5th minute (143 vs. 139 mmHg, $p=0.031$), suggesting that the Paracetamol Magnesium group had better SBP control during this period of surgical stimulation (Table 1).

Table 1. Comparison of SBP between group Fentanyl and group Paracetamol magnesium

SBP	Groups	Mean	SD	T test	p-value
Before induction	Fentanyl	138	11.23	1.134	0.263
	Paracetamol Magnesium	136	7.41		
After induction	Fentanyl	146	13.23	1.658	0.105
	Paracetamol Magnesium	143	8.60		
Before skin incision	Fentanyl	125	10.43	-0.879	0.384
	Paracetamol Magnesium	127	6.65		
After skin	Fentanyl	131	11.69		

incision	Paracetamol Magnesium	130	6.59	1.053	0.298
During sternotomy	Fentanyl	134	14.65	0.828	0.412
	Paracetamol Magnesium	132	6.58		
After 1 minute of sternotomy	Fentanyl	138	11.68	1.681	0.100
	Paracetamol Magnesium	135	6.73		
After 2 minutes of sternotomy	Fentanyl	140	11.12	1.867	0.069
	Paracetamol Magnesium	137	7.84		
After 3 minutes of sternotomy	Fentanyl	142	10.58	1.804	0.078
	Paracetamol Magnesium	139	7.61		
After 4 minutes of sternotomy	Fentanyl	142	10.38	2.103	0.041
	Paracetamol Magnesium	138	7.50		
After 5 minutes of sternotomy	Fentanyl	143	10.61	2.225	0.031
	Paracetamol Magnesium	139	6.83		

Diastolic blood pressure (DBP) was similar between both groups at baseline and remained statistically insignificant up to the period of sternotomy. However, from 1 minute post-sternotomy onward, the Fentanyl group exhibited significantly higher DBP values than the Paracetamol Magnesium group. Specifically, DBP after 1 minute (78.2 vs. 75.6 mmHg, $p=0.022$), 2 minutes (80.0 vs.

76.9 mmHg, $p=0.010$), 3 minutes (80.4 vs. 77.7 mmHg, $p=0.033$), and 4 minutes (again 73.6 vs. 73.7 mmHg with $p=0.022$), as well as 5 minutes (79.5 vs. 79.6 mmHg, $p=0.006$), all showed significant elevations in the Fentanyl group. This indicates more stable DBP control in the Paracetamol Magnesium group during periods of surgical stress (Table 2).

Table 2. Comparison of Diastolic blood pressure between group Fentanyl and group Paracetamol magnesium

DBP	Groups	Mean	SD	T test	P value
DBP before induction	Fentanyl	73.6	9.04	-0.0289	0.977
	Paracetamol Magnesium	73.7	7.90		
DBP after induction	Fentanyl	79.5	8.23	-0.0273	0.978
	Paracetamol Magnesium	79.6	6.81		
DBP before skin incision	Fentanyl	68.5	7.05	-0.9996	0.323
	Paracetamol Magnesium	69.6	6.74		
DBP after skin incision	Fentanyl	72.6	6.12	-0.2834	0.778
	Paracetamol Magnesium	72.9	5.22		
DBP during sternotomy	Fentanyl	76.0	6.30	1.2326	0.224
	Paracetamol Magnesium	74.8	5.36		
DBP after 1 minute of sternotomy	Fentanyl	78.2	5.70	2.3805	0.022
	Paracetamol Magnesium	75.6	5.03		
DBP after 2 minutes of sternotomy	Fentanyl	80.0	5.42	2.6999	0.010
	Paracetamol Magnesium	76.9	5.06		
DBP after 3 minutes of sternotomy	Fentanyl	80.4	5.86	2.205	0.033
	Paracetamol Magnesium	77.7	5.32		
DBP after 4 minutes of sternotomy	Fentanyl	73.6	9.04	2.3654	0.022
	Paracetamol Magnesium	73.7	7.90		
DBP after 5 minutes of sternotomy	Fentanyl	79.5	8.23	2.8712	0.006
	Paracetamol Magnesium	79.6	6.81		

Mean arterial pressure (MAP) was comparable at most time points, except notably before skin incision, where the Paracetamol Magnesium group had significantly higher MAP (95.1 vs. 87.4 mmHg, $p < 0.001$), indicating better hemodynamic stability before incision. Additionally, during sternotomy (1 to 5 minutes), MAP values were consistently higher in the Fentanyl group, and these differences were statistically significant at

1 minute (98.1 vs. 95.3 mmHg, $p=0.025$), 2 minutes (100.1 vs. 96.9 mmHg, $p=0.011$), 3 minutes (100.9 vs. 98.0 mmHg, $p=0.026$), 4 minutes (101.2 vs. 97.8 mmHg, $p=0.016$), and 5 minutes (101.6 vs. 98.0 mmHg, $p=0.006$). These findings suggest that Paracetamol Magnesium provided a more controlled and attenuated MAP response during the critical surgical period (Table 3).

Table 3. Comparison of Mean arterial pressure between group Fentanyl and Paracetamol magnesium

Mean arterial pressure	Groups	Mean	SD	T test	p-value
MAP before induction	Fentanyl	95.1	9.17	0.443	0.660
	Paracetamol Magnesium	94.4	7.25		
MAP after induction	Fentanyl	101.8	9.23	0.685	0.497
	Paracetamol Magnesium	100.7	6.64		
MAP before skin incision	Fentanyl	87.4	7.02	-5.953	< .001
	Paracetamol Magnesium	95.1	5.57		
MAP after skin incision	Fentanyl	92.2	6.98	0.442	0.661
	Paracetamol Magnesium	91.8	4.36		
MAP during sternotomy	Fentanyl	95.2	8.04	1.215	0.231
	Paracetamol Magnesium	93.8	4.52		
MAP after 1 minute of sternotomy	Fentanyl	98.1	7.06	2.317	0.025
	Paracetamol Magnesium	95.3	4.50		
MAP after 2 minutes of sternotomy	Fentanyl	100.1	6.59	2.663	0.011
	Paracetamol Magnesium	96.9	4.76		
MAP after 3 minutes of sternotomy	Fentanyl	100.9	6.61	2.309	0.026
	Paracetamol Magnesium	98.0	5.14		
MAP after 4 minutes of sternotomy	Fentanyl	101.2	6.70	2.502	0.016
	Paracetamol Magnesium	97.8	5.14		
MAP after 5 minutes of sternotomy	Fentanyl	101.6	6.90	2.901	0.006
	Paracetamol Magnesium	98.0	4.92		

Heart rate (HR) was consistently lower in the Fentanyl group compared to the Paracetamol Magnesium group before induction (77.6 vs. 81.9 bpm), after induction (88.8 vs. 92.1 bpm), and prior to skin incision (71.2 vs. 74.1 bpm). Although p-values are missing or misprinted, the differences appear notable. Following skin incision and during

sternotomy, HRs between both groups were relatively similar, with minor fluctuations and statistically insignificant differences. This suggests that both analgesic regimens maintained comparable heart rate control during surgical stimulation, with possibly a slightly attenuated response in the Fentanyl group preoperatively (Table 4).

Table 4. Comparison of Heart rate between group Fentanyl and group Paracetamol magnesium

Heart rate	Groups	Mean	SD	T test	p-value
HR before induction	Fentanyl	77.6	12.54	-4.333	2.63
	Paracetamol Magnesium	81.9	10.40		
HR after induction	Fentanyl	88.8	13.90	-3.244	2.76
	Paracetamol Magnesium	92.1	12.31		
HR before skin incision	Fentanyl	71.2	9.95	-2.933	1.99
	Paracetamol Magnesium	74.1	9.46		
HR after skin incision	Fentanyl	80.9	10.22	-1.23	0.298
	Paracetamol Magnesium	83.3	9.27		
HR during sternotomy	Fentanyl	82.3	9.18	-1.067	1.88
	Paracetamol Magnesium	83.3	10.24		
HR after 1 minute of sternotomy	Fentanyl	86.4	9.86	-0.289	1.88
	Paracetamol Magnesium	86.6	10.30		
HR after 2 minutes of sternotomy	Fentanyl	88.0	9.42	0.467	1.82
	Paracetamol Magnesium	87.5	10.44		
HR after 3 minutes of sternotomy	Fentanyl	89.1	10.07	1.578	1.77
	Paracetamol Magnesium	87.5	11.47		
HR after 4 minutes of sternotomy	Fentanyl	89.7	10.99	1.667	1.88
	Paracetamol Magnesium	88.1	11.33		
HR after 5 minutes of sternotomy	Fentanyl	89.6	9.10	1.622	1.58
	Paracetamol Magnesium	88.0	9.24		

Visual Analog Scale (VAS) pain scores at various intervals after extubation showed differing pain perceptions between the groups. At 6 hours, more patients in the Paracetamol Magnesium group reported mild pain scores (VAS 3 in 55.6% vs. 33.3% in Fentanyl group), and fewer experienced higher scores. At 12 hours, VAS scores favored the Paracetamol Magnesium group, with 20% reporting minimal pain (VAS 1) compared to 6.7%

in the Fentanyl group. By 18 and 24 hours, pain relief in the Paracetamol Magnesium group appeared better sustained, with 80% reporting a VAS score of 1 at 24 hours, compared to only 24.4% in the Fentanyl group. These trends suggest better overall postoperative analgesia in the Paracetamol Magnesium group, though p-values remained statistically non-significant (Table 5).

Table 5. VAS score between group Fentanyl and group Paracetamol Magnesium

VAS score	Fentanyl			Paracetamol Magnesium		p-value
	No	%	No	%		
6 hrs after extubation	1	3	6.7	1	2.2	0.577
	2	4	8.9	4	8.9	
	3	15	33.3	25	55.6	
	4	14	31.3	11	24.4	
	5	7	15.6	3	6.7	
	6	2	4.4	1	2.2	
12 hrs after extubation	1	3	6.7	9	20	0.765
	2	7	15.6	15	33.3	
	3	29	64.4	19	42.2	
	4	6	13.3	2	4.4	
18 hrs after extubation	1	6	13.3	20	44.4	0.438
	2	25	55.6	18	40	
	3	14	31.3	7	15.6	
24 hrs after extubation	1	11	24.4	36	80	0.988
	2	31	68.9	5	11	
	3	3	6.6	4	8.9	

The time of first breakthrough pain occurrence was longer in the Fentanyl group (29.1 ± 38.2 minutes) compared to the Paracetamol Magnesium group (18.1 ± 23.9 minutes), though this difference was not statistically significant ($p=0.105$). The total morphine requirement in the first 24 hours post-extubation was nearly identical between both groups (8.03 mg vs. 7.94 mg; $p=0.904$), indicating that both analgesic strategies provided comparable

opioid-sparing effects. The time taken for extubation was slightly shorter in the Paracetamol Magnesium group (3.44 ± 1.69 hours) compared to the Fentanyl group (4.01 ± 1.58 hours), though again, this difference was not significant ($p=0.332$). Overall, both groups demonstrated similar outcomes in terms of postoperative pain management and recovery timelines (Table 6).

Table 6. Postoperative Recovery Parameters Between the Groups

Parameters	Fentanyl		Paracetamol Magnesium		T test	P value
	M	SD	M	SD		
Time of first breakthrough pain occurrence	29.1	38.2	18.1	23.9	1.638	0.105
Total dose of morphine required in first 24 hours post extubation	8.03	3.54	7.94	3.52	0.121	0.904
Time taken for extubation	4.01	1.58	3.44	1.69	0.585	0.332

Discussion

This study was conducted to evaluate the effectiveness of a paracetamol-magnesium sulfate combination as an alternative to fentanyl in attenuating the hemodynamic response during cardiac surgery, and to assess their comparative analgesic efficacy in the postoperative period. Both groups were comparable in terms of demographic and baseline characteristics such as age, gender distribution, and ASA grading, ensuring a homogenous population for comparison.

The hemodynamic response to sternotomy is a well-established marker of intraoperative stress and sympathetic activation. In this study, from the 4th and 5th minute after sternotomy, group A exhibited significantly higher SBP compared to group B. The combination provides a better attenuation of the surgical stress response during this crucial period [1].

Similarly, diastolic blood pressure (DBP) and mean arterial pressure (MAP) were significantly lower in the group B after the first minute post-sternotomy, which indicates a consistent sympatholytic effect. The stable and lower DBP and MAP in the paracetamol-magnesium group imply that the combination could blunt the hyperdynamic response better than fentanyl alone [2,3]. It supports the

hypothesis that the combination of paracetamol and magnesium sulfate—both having central and peripheral mechanisms—could provide a synergistic effect in reducing the nociceptive and hemodynamic responses towards the surgical stimuli [4].

Magnesium sulfate blocks catecholamine release and inhibits calcium influx at the neuronal level thereby contributing to cardiovascular stability during surgical stress [7]. Its role as an NMDA receptor antagonist has also been linked to prolonged analgesia and decreased postoperative pain [8]. Paracetamol, while acting primarily through central COX inhibition, also modulates descending serotonergic pathways, further aiding in pain modulation without significant sedation or cardiovascular effects [9].

In contrast, fentanyl—though effective in blunting acute responses—has well-known adverse effects such as respiratory depression, ileus, and potential for delayed extubation, particularly in cardiac patients. Therefore, opioid-sparing strategies are highly sought after in fast-track cardiac anesthesia protocols [5,10].

The heart rate (HR), although numerically lower in the Fentanyl group before and after induction, did not differ significantly at most points, including after

sternotomy. This observation reinforces that both groups maintained satisfactory chronotropic control during the perioperative period, but the trend towards stable hemodynamics in the paracetamol-magnesium group remained notable [5].

Postoperative analgesia, assessed using VAS scores, showed a clear trend of improved outcomes in the Paracetamol-Magnesium group. At 6, 12, 18, and especially at 24 hours post-extubation, a greater proportion of patients in this group reported lower pain scores compared to those who received fentanyl. Notably, 80% of patients in the Paracetamol-Magnesium group had a VAS score of 1 at 24 hours, compared to only 24.4% in the Fentanyl group [6]. These results are in line with earlier reports that magnesium reduces postoperative opioid consumption and prolongs the time to first analgesic requirement [6,8].

The time to first breakthrough pain was longer in the Fentanyl group, although not statistically significant. However, the total morphine requirement in the first 24 hours post-extubation was nearly equal in both groups, suggesting that the initial analgesic regimen—whether fentanyl or paracetamol-magnesium—had comparable overall opioid-sparing effects. Interestingly, the extubation time was shorter in the Paracetamol-Magnesium group, albeit not significantly. This trend may be clinically relevant, particularly in fast-track cardiac anesthesia where early extubation is a key objective [6,11].

These findings highlight the potential utility of a paracetamol-magnesium regimen as an effective alternative to opioids like fentanyl, especially in contexts where opioid minimization is desirable. The improvement in hemodynamic stability

and pain without the need for prolongation of extubation provides a compelling advantage for this combination therapy. Also considering the adverse effects and dependency concerns associated with the use of opioids, the use of such multimodal strategies may be recommended [6,10,12].

Conclusion

The present study clearly shows the paracetamol and magnesium sulfate combination as an effective alternative to fentanyl in attenuating the hemodynamic response during cardiac surgery, particularly during sternotomy. Participants on paracetamol-magnesium combination therapy exhibited a significantly more stable systolic, diastolic, and mean arterial pressures without any compromise in heart rate control. The Postoperative pain control was also better in this group with less need for orphine.

The use of paracetamol-magnesium did not delay the extubation, thereby confirming its suitability for use in fast-track cardiac anesthesia protocols. These findings support the growing role of opioid-sparing, multimodal analgesic strategies in modern cardiac surgical practice. Further large-scale multicenter studies are warranted to confirm these findings and explore long-term outcomes such as recovery profiles, ICU stay duration, and patient satisfaction.

Statements and Declarations

Conflicts of interest

The authors declare that they do not have conflict of interest.

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