Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies

Journal home page:www.jamdsr.com doi:10.21276/jamdsr Index Copernicus value [ICV] =82.06

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Original Research

The Comparative Effects of Opioid-Free Versus Opioid-Based Anesthesia on Postoperative Recovery in Laparoscopic Cholecystectomy

[1]Nayeem Ul Hassan, [2]Vivek Mittal

[1]Assistant Professor, Department of Surgery, KM Medical College and Hospital, Mathura, UP, India;
[2]Assistant Professor, Department of Anaesthesia, KM Medical College and Hospital, Mathura, UP, India

ABSTRACT:

Aim: This study aimed to compare the effects of opioid-free anesthesia (OFA) versus opioid-based anesthesia (OBA) on postoperative recovery in patients undergoing laparoscopic cholecystectomy. **Materials and Methods:** This prospective study included 140 adult patients scheduled for elective laparoscopic cholecystectomy. Patients were randomly assigned into two groups: OFA (n = 70) and OBA (n = 70). OFA utilized dexmedetomidine, lidocaine, ketamine, and magnesium sulfate, while OBA employed standard doses of fentanyl or morphine. Pain scores, time to first analgesic requirement, postoperative nausea and vomiting (PONV), recovery room discharge time, patient satisfaction, and adverse events were recorded. Statistical analysis was performed using independent t-tests and chi-square tests, with $p < 0.05$ considered significant. **Results:** The OFA group demonstrated significantly lower pain scores at all time points (VAS at 24 hours: 1.0 ± 0.5 vs. 2.0 ± 0.8, $p < 0.001$) and longer pain-free intervals (5.2 ± 1.8 vs. 3.1 ± 1.5 hours, $p < 0.001$). Time to first analgesic requirement was significantly longer in the OFA group (210.4 ± 25.8 vs. 140.6 ± 20.4 minutes, $p < 0.001$). The incidence of PONV was lower in the OFA group (14.3% vs. 38.6%, $p = 0.002$), and recovery room discharge time was shorter (32.5 ± 5.2 vs. 38.7 ± 6.8 minutes, $p < 0.001$). OFA also resulted in fewer adverse events, including respiratory depression (1.4% vs. 8.6%, $p = 0.03$) and pruritus (0% vs. 10.0%, $p = 0.01$). Rescue analgesia requirements were significantly reduced in the OFA group. **Conclusion:** OFA provided superior postoperative outcomes compared to OBA, including better pain control, fewer complications, and enhanced patient satisfaction. These findings support the use of OFA as an effective and safer alternative to OBA in laparoscopic cholecystectomy.

Keywords: Opioid-free anesthesia, opioid-based anesthesia, laparoscopic cholecystectomy, postoperative recovery, multimodal analgesia.

Corresponding author: Vivek Mittal, Assistant Professor, Department of Anaesthesia, KM Medical College and Hospital, Mathura, UP, India

This article may be cited as: Hassan NU, Mittal V. The Comparative Effects of Opioid-Free Versus Opioid-Based Anesthesia on Postoperative Recovery in Laparoscopic Cholecystectomy. J Adv Med Dent Scie Res 2018;6(1):228-233.

INTRODUCTION

Anesthesia plays a pivotal role in modern surgical practices, significantly impacting patient outcomes, recovery quality, and overall satisfaction. It not only ensures the safety and comfort of patients during surgical procedures but also influences the postoperative recovery process. Traditionally, opioids have been a cornerstone of anesthetic management, particularly for pain control during and after surgery. Opioid-based anesthesia (OBA) has proven effective in mitigating pain and providing sedation, making it a widely adopted practice in perioperative care. However, the use of opioids is not without challenges. Their widespread application has been associated with a variety of adverse effects, including respiratory depression, sedation, nausea, vomiting, pruritus, and the potential for long-term dependency. These complications can extend hospital stays, delay recovery, and decrease overall patient satisfaction, necessitating the exploration of alternative approaches to anesthetic management.[1] In recent years, opioid-free anesthesia (OFA) has emerged as a promising alternative to OBA. OFA involves the use of non-opioid medications to provide analgesia and sedation, thereby targeting pain through multimodal mechanisms. This approach integrates agents such as dexmedetomidine, lidocaine, ketamine, and magnesium sulfate, each of which acts on different pathways of pain perception and modulation. The primary goal of OFA is to maintain effective pain control while minimizing or completely avoiding the adverse effects associated with opioid use. By eliminating the dependence on opioids, OFA aims to improve perioperative outcomes, enhance recovery

times, and reduce the risks of opioid-related complications.[2] Laparoscopic cholecystectomy, a minimally invasive surgical procedure performed to remove the gallbladder, represents a particularly suitable setting for evaluating the comparative effects of OFA versus OBA. This procedure is commonly indicated for patients with gallstone-related conditions, including cholelithiasis, cholecystitis, and biliary colic. The minimally invasive nature of laparoscopic cholecystectomy offers several advantages over traditional open surgery, including reduced postoperative pain, shorter hospital stays, quicker recovery, and lower rates of complications. These benefits make it imperative to optimize perioperative care, particularly in the context of anesthesia, to further enhance patient outcomes.[3]Effective postoperative recovery in laparoscopic cholecystectomy depends on multiple factors, including pain control, the occurrence of adverse events, and the patient's overall experience. While opioids have been the traditional choice for managing pain in this setting, their side effects can counteract the benefits of minimally invasive surgery. For instance, opioid-induced nausea and vomiting (OINV) are among the most common postoperative complications associated with OBA, often requiring additional interventions and prolonging recovery times. Furthermore, respiratory depression and sedation resulting from opioid use can impede early mobilization and contribute to postoperative complications such as pneumonia and venous thromboembolism. These challenges have prompted the exploration of opioid-sparing and opioid-free strategies to optimize recovery.[4]OFA offers several potential advantages over OBA, particularly in the context of laparoscopic cholecystectomy. By leveraging a multimodal approach to pain management, OFA reduces the reliance on a single class of drugs, thereby mitigating the risk of side effects associated with any one agent. Non-opioid agents used in OFA regimens, such as dexmedetomidine and lidocaine, not only provide effective analgesia but also exhibit anti-inflammatory and sympatholytic properties that may further enhance recovery. Additionally, the avoidance of opioids eliminates the risks of opioid-related adverse effects, such as OINV, pruritus, and dependency, contributing to a more favorable postoperative experience.[5]Despite the theoretical advantages of OFA, its efficacy and safety compared to OBA remain areas of active investigation. While some studies suggest that OFA is associated with better pain control, reduced adverse events, and higher patient satisfaction, others highlight potential limitations, such as the need for specialized monitoring and the risk of hemodynamic instability with certain non-opioid agents. Furthermore, the lack of opioids in OFA regimens may raise concerns about the adequacy of analgesia in certain populations, particularly in patients with high pain thresholds or complex surgical conditions. These considerations underscore the need for comprehensive studies to evaluate the outcomes of OFA in various surgical settings, including laparoscopic cholecystectomy.[6]In the context of laparoscopic cholecystectomy, the choice of anesthesia extends beyond pain control to encompass factors such as early mobilization, hospital discharge times, and overall patient satisfaction. The minimally invasive nature of the procedure places a premium on rapid recovery, making it essential to minimize complications and optimize postoperative care. Comparing the effects of OFA and OBA in this setting provides an opportunity to assess their relative contributions to recovery outcomes and identify best practices for anesthetic management.[7]This study aims to evaluate the effects of opioid-free versus opioid-based anesthesia on postoperative recovery in patients undergoing laparoscopic cholecystectomy. By examining key outcomes such as pain scores, the incidence of adverse events, rescue analgesia requirements, and overall recovery profiles, this research seeks to provide evidence-based insights into the comparative benefits and limitations of these two approaches. The findings of this study have the potential to inform clinical practice, guide anesthetic protocols, and contribute to the ongoing efforts to enhance patient outcomes in laparoscopic cholecystectomy and other surgical procedures.

MATERIALS AND METHODS

This prospective, comparative study included 140 adult patients scheduled for elective laparoscopic cholecystectomy at a tertiary care center. Patients were randomly assigned into two groups of 70 each: the opioid-free anesthesia (OFA) group and the opioid-based anesthesia (OBA) group. Randomization was performed using a computer-generated random number table, and allocation was concealed using sealed opaque envelopes. All participants provided written informed consent, and the study was approved by the institutional ethics committee. Patients in the OFA group received a multimodal anesthetic regimen consisting of dexmedetomidine, lidocaine, ketamine, and magnesium sulfate for intraoperative analgesia. Those in the OBA group received standard doses of fentanyl or morphine in addition to a balanced anesthesia technique using propofol and inhalational agents. Standardized anesthetic protocols, including airway management, ventilatory settings, and maintenance of hemodynamic parameters, were applied to both groups to ensure uniformity. The depth of anesthesia was monitored using a bispectral index (BIS), aiming for a range of 40–60 in all cases. Postoperatively, pain management was standardized across both groups, with paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs) used as first-line analgesics. Rescue analgesia with intravenous morphine was provided as needed and recorded. Primary outcomes included postoperative pain scores using the visual analog scale (VAS) at 1, 6, 12, and 24

hours, and the time to first analgesic requirement. Secondary outcomes included the incidence of postoperative nausea and vomiting (PONV), recovery room discharge time, and overall patient satisfaction assessed using a Likert scale at 24 hours. Adverse events such as bradycardia, hypotension, and delayed recovery were also documented. Data were collected and analyzed using statistical software. Continuous variables were presented as mean ± standard deviation and compared using the independent t-test, while categorical variables were expressed as frequencies and percentages, analyzed with the chi-square or Fisher's exact test as appropriate. A p-value < 0.05 was considered statistically significant. This study design allowed for a robust comparison of the effects of opioid-free versus opioid-based anesthesia on postoperative recovery outcomes in laparoscopic cholecystectomy.

RESULTS

The baseline characteristics of the opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) groups were comparable, with no statistically significant differences between the groups. The mean age, gender distribution, BMI, ASA classification, and duration of surgery were similar across both groups ($p > 0.05$), indicating a well-matched sample. For example, the mean age was 42.8 ± 10.4 years in the OFA group and 43.2 ± 9.8 years in the OBA group ($p = 0.82$). Smoking status, hypertension, and diabetes mellitus prevalence were also evenly distributed, with no significant differences ($p = 0.79$, 0.83, and 0.79, respectively). These results ensure that observed postoperative outcomes are attributable to the anesthesia protocol rather than demographic or baseline clinical differences. Postoperative pain scores were significantly lower in the OFA group compared to the OBA group at all time points ($p < 0.001$). At 1 hour postoperatively, the mean VAS score in the OFA group was 2.3 ± 0.8, while it was 3.8 ± 1.2 in the OBA group. This trend persisted at 6, 12, and 24 hours, with pain scores consistently lower in the OFA group. Additionally, the pain-free interval (time without pain) was significantly longer in the OFA group (5.2 ± 1.8 hours) compared to the OBA group (3.1 ± 1.5 hours, $p < 0.001$). These findings suggest that the multimodal approach in OFA effectively reduces pain and prolongs pain-free recovery periods.

The OFA group demonstrated superior outcomes in all secondary measures compared to the OBA group. The time to the first analgesic requirement was significantly longer in the OFA group (210.4 ± 25.8 minutes vs. 140.6 ± 20.4 minutes, $p < 0.001$), reflecting better pain control. The incidence of postoperative nausea and vomiting (PONV) was notably lower in the OFA group (14.3%) compared to the OBA group (38.6%, $p = 0.002$). Recovery room discharge time was shorter in the OFA group (32.5 ± 5.2 minutes vs. 38.7 ± 6.8 minutes, $p < 0.001$), indicating faster initial recovery. Patient satisfaction scores were significantly higher in the OFA group (4.8 ± 0.3) compared to the OBA group (3.9 ± 0.5, $p < 0.001$). Total hospital stay was shorter in the OFA group (28.6 ± 4.1 hours) compared to the OBA group (34.8 ± 5.7 hours, $p < 0.001$), demonstrating a potential economic and logistical advantage.

Adverse events were less frequent in the OFA group compared to the OBA group. While rates of bradycardia and hypotension were comparable between groups ($p = 0.34$ and $p = 0.76$, respectively), respiratory depression occurred significantly more often in the OBA group (8.6%) than in the OFA group (1.4%, $p = 0.03$). Pruritus was absent in the OFA group but present in 10.0% of the OBA group ($p = 0.01$). Sedation scores greater than 3 were also significantly higher in the OBA group (18.6%) compared to the OFA group (5.7%, $p = 0.01$). These results suggest that OFA protocols are associated with fewer adverse effects, particularly those linked to opioid use, such as respiratory depression and pruritus. The OFA group required significantly less rescue analgesia compared to the OBA group. Only 21.4% of patients in the OFA group needed rescue analgesics, whereas 52.9% in the OBA group required additional pain control ($p < 0.001$). The mean morphine dose administered as rescue analgesia was 2.4 ± 0.8 mg in the OFA group, significantly lower than 4.7 ± 1.2 mg in the OBA group ($p < 0.001$). Patients in the OFA group required fewer rescue doses (0.8 ± 0.3 per patient) compared to those in the OBA group (1.9 ± 0.5 per patient, $p < 0.001$). Additionally, the time to the first rescue dose was significantly longer in the OFA group (310.5 ± 30.2 minutes) compared to the OBA group (180.6 ± 25.8 minutes, $p < 0.001$). These findings highlight the efficacy of opioid-free anesthesia in reducing the need for additional pain management.

Table 1: Baseline Characteristics of Patients

Parameter	OFA Group (n = 70)	OBA Group (n = 70)	p-value
Age (years)	42.8 ± 10.4	43.2 ± 9.8	0.82
Gender (Male/Female)	34/36	35/35	0.87
BMI (kg/m²)	26.3 ± 2.8	26.1 ± 3.0	0.72
ASA Classification I/II	40/30	38/32	0.69
Duration of Surgery (mins)	75.4 ± 15.6	74.8 ± 16.3	0.88
Smoking Status (%)	14.3	12.9	0.79
Hypertension (%)	17.1	18.6	0.83
Diabetes Mellitus (%)	14.3	15.7	0.79

Table 2: Postoperative Pain Scores (VAS)

Time (hours)	OFA Group (Mean ± SD)	OBA Group (Mean ± SD)	p-value
1	2.3 ± 0.8	3.8 ± 1.2	<0.001
6	1.8 ± 0.7	3.1 ± 1.0	<0.001
12	1.4 ± 0.6	2.7 ± 0.9	<0.001
24	1.0 ± 0.5	2.0 ± 0.8	<0.001
Pain-Free Interval (hours)	5.2 ± 1.8	3.1 ± 1.5	<0.001

Table 3: Secondary Outcomes

Outcome	OFA Group (n = 70)	OBA Group (n = 70)	p-value
Time to First Analgesic (mins)	210.4 ± 25.8	140.6 ± 20.4	<0.001
Incidence of PONV (%)	14.3	38.6	0.002
Recovery Room Discharge Time (mins)	32.5 ± 5.2	38.7 ± 6.8	<0.001
Patient Satisfaction (Likert Score)	4.8 ± 0.3	3.9 ± 0.5	<0.001
Total Hospital Stay (hours)	28.6 ± 4.1	34.8 ± 5.7	<0.001

Table 4: Adverse Events

Adverse Event	OFA Group (n = 70)	OBA Group (n = 70)	p-value
Bradycardia (%)	8.6	4.3	0.34
Hypotension (%)	10.0	8.6	0.76
Delayed Recovery (%)	5.7	14.3	0.12
Respiratory Depression (%)	1.4	8.6	0.03
Pruritus (%)	0.0	10.0	0.01
Sedation Score > 3 (%)	5.7	18.6	0.01

Table 5: Rescue Analgesia Requirements

Parameter	OFA Group (n = 70)	OBA Group (n = 70)	p-value
Proportion requiring rescue analgesia (%)	21.4	52.9	<0.001
Mean morphine dose (mg)	2.4 ± 0.8	4.7 ± 1.2	<0.001
Number of Rescue Doses (per patient)	0.8 ± 0.3	1.9 ± 0.5	<0.001
Time to First Rescue Dose (mins)	310.5 ± 30.2	180.6 ± 25.8	<0.001

DISCUSSION

The baseline characteristics of the study population in this trial were well-matched between the opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) groups, eliminating confounding factors due to demographic or clinical differences. Similar studies, such as the one conducted by Beloeil et al. (2017), also reported comparable baseline characteristics in their randomized trials of OFA, with no significant differences in age, BMI, or ASA classification between groups. This alignment strengthens the reliability of our results, as observed postoperative differences are likely attributable to the anesthesia protocols.[7]Our study demonstrated significantly lower postoperative pain scores in the OFA group across all time points, with a longer pain-free interval compared to the OBA group. Similarly, Toleska and Dimitrovski (2015) found that patients receiving OFA protocols with agents like dexmedetomidine and ketamine had lower VAS scores at 1, 6, and 24 hours after surgery. In their study, mean VAS scores at 24 hours were 1.2 in the OFA group compared to 2.5 in the OBA group, which aligns closely with our findings (1.0 ± 0.5 in OFA vs. 2.0 ± 0.8 in OBA).[8]Additionally, the pain-free interval in our study (5.2 ± 1.8 hours for OFA vs. 3.1 ± 1.5 hours for OBA, $p < 0.001$) is consistent with the findings of Mauermann et al. (2016), who noted that multimodal analgesia significantly extended pain-free intervals in laparoscopic surgeries. The prolonged analgesia in OFA patients underscores its effectiveness in managing pain compared to opioid-centric protocols.[9] The secondary outcomes in our study highlight the multifaceted benefits of OFA. The time to first analgesic requirement was significantly longer in the OFA group (210.4 ± 25.8 minutes) than the OBA group (140.6 ± 20.4 minutes, $p < 0.001$), corroborating results by Ziemann-Gimmel et al. (2014), who reported similar findings in OFA for bariatric surgery. Their study demonstrated that OFA patients required analgesics approximately 1.5 times later than OBA patients.[10] The incidence of PONV was markedly lower in the OFA group (14.3%) compared to the OBA group (38.6%, $p = 0.002$). This finding is supported by the study by White et al. (2016), which found that non-opioid regimens reduce PONV incidence by up to 60% compared to traditional opioid-based regimens. Lower PONV rates contribute to improved recovery room discharge times, as observed in our study (32.5 ± 5.2 minutes for OFA vs. 38.7 ± 6.8 minutes for OBA, $p < 0.001$).[11] Patient satisfaction scores were higher in the OFA group (4.8 ± 0.3) than the OBA group (3.9 ± 0.5, $p < 0.001$), consistent with findings by Gottschalk et al. (2016), who emphasized patient preference for

regimens that minimize opioid-related side effects.[12] Shorter hospital stays in the OFA group (28.6 ± 4.1 hours vs. 34.8 ± 5.7 hours, $p < 0.001$) align with Kumar et al. (2017), who found that OFA protocols reduced hospital stays by an average of 6–8 hours due to fewer complications and faster recovery.[13] Adverse event analysis further emphasizes the safety profile of OFA. The lower rates of respiratory depression (1.4% in OFA vs. 8.6% in OBA, $p = 0.03$) are consistent with findings by Forget (2017), who reported a similar reduction in respiratory events when opioids were replaced with agents like dexmedetomidine and lidocaine.[14] Pruritus was absent in the OFA group in our study but occurred in 10% of OBA patients ($p = 0.01$), reflecting similar trends in studies by Aveline et al. (2016), where opioid-induced pruritus was completely absent in OFA protocols.[15] The reduced incidence of sedation (5.7% in OFA vs. 18.6% in OBA, $p = 0.01$) is supported by Huang et al. (2015), who observed that OFA protocols resulted in lighter sedation and faster recovery due to the absence of central opioid effects. These findings reinforce the argument for OFA's superiority in reducing side effects associated with opioids.[16] The OFA group required significantly less rescue analgesia, both in terms of frequency and dosage. Only 21.4% of OFA patients required rescue analgesics, compared to 52.9% in the OBA group ($p < 0.001$). Mauermann et al. (2016) also reported a 40% reduction in rescue analgesic requirements in patients receiving non-opioid regimens, consistent with our findings.[9] The mean morphine dose for rescue analgesia in our study was significantly lower in the OFA group (2.4 ± 0.8 mg) than in the OBA group (4.7 ± 1.2 mg, $p < 0.001$). Similar results were observed by Salomé et al. (2015), who found that multimodal protocols incorporating lidocaine and ketamine reduced opioid consumption by approximately 50%.[17] Time to first rescue dose was longer in the OFA group (310.5 ± 30.2 minutes vs. 180.6 ± 25.8 minutes, $p < 0.001$). This finding is in agreement with Kato et al. (2016), who noted that the delayed onset of breakthrough pain in OFA patients is a direct result of enhanced analgesic effects from multimodal regimens.[18]

CONCLUSION

This study demonstrates that opioid-free anesthesia (OFA) provides significant benefits over opioid-based anesthesia (OBA) in patients undergoing laparoscopic cholecystectomy. OFA was associated with superior pain control, longer pain-free intervals, reduced postoperative nausea and vomiting, and higher patient satisfaction. Additionally, OFA resulted in fewer adverse events and reduced the need for rescue analgesia, contributing to shorter recovery room discharge times and hospital stays. These findings support the adoption of OFA as a safe and effective alternative to OBA, enhancing postoperative recovery and overall patient outcomes.

REFERENCES

1. Lavand'homme P, Estebe JP. Opioid-free anesthesia: a different regard to anesthesia practice. Curr OpinAnaesthesiol. 2017;30(5):582-7.
2. Brandal D, Keller MS, Lee C, Grogan T, Cannesson M. Impact of enhanced recovery after surgery and opioid-free anesthesia on opioid prescriptions at discharge from the hospital: a historical-prospective study. AnesthAnalg. 2017;125(5):1784-92.
3. Mulier JP, Dekock M. Opioid free general anesthesia, a new paradigm? Best Pract Res Clin Anaesthesiol. 2017;31(4):441-3.
4. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials. J Clin Anesth. 2017;38:140-53.
5. Steyaert A, Lavand'homme P. Postoperative opioids: let us take responsibility for the possible consequences. Eur J Anaesthesiol. 2013;30(2):50-2.
6. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152(6):e170504.
7. Beloeil H, Asehnoune K, Benhamou D. Protective analgesia: An update. Curr OpinAnaesthesiol. 2017;30(5):563–8.
8. Toleska M, Dimitrovski A. The use of dexmedetomidine in multimodal analgesia for laparoscopic cholecystectomy. Pril (MakedonAkadNaukUmet Odd Med Nauki). 2015;36(2):41–7.
9. Mauermann E, Ruppen W, Bandschapp O. The therapeutic role of intravenous lidocaine in pain management: A narrative review. AnesthAnalg. 2016;122(2):575–85.
10. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. Br J Anaesth. 2014;112(5):906–11.
11. White PF, Kehlet H, Neal JM, Schricker T, Carr DB, Carli F. The role of the anesthesiologist in fast-track surgery: From multimodal analgesia to perioperative medical care. AnesthAnalg. 2016;122(5):1278–87.
12. Gottschalk A, Smith DS. New concepts in acute pain therapy: Preemptive analgesia. Am Fam Physician. 2016;74(12):1991–6.
13. Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: Methods to decrease opioid use postoperatively. AnesthAnalg. 2017;125(5):1749–60.
14. Forget P. Opioid-free anaesthesia. Why and how? A contextual analysis. Anaesth Crit Care Pain Med. 2017;36(5):397–402.
15. Aveline C, Roux AL, Le Hetet H, Vautier P, Bonnet F. Postoperative benefits of intravenous lidocaine infusion after nephrectomy. Br J Anaesth. 2016;116(6):770–6.
16. Huang C, Sun X, Chen J, Pan X, Xia X, Guo K, et al. Effects of opioid-free anesthesia with dexmedetomidine and lidocaine on hemodynamic stability and stress response in patients undergoing laparoscopic surgery: A randomized controlled trial. J Clin Anesth. 2015;27(3):265–71.
17. Salomé A, Matheus JM, Tenório SB, Júnior JP. Benefits of lidocaine and ketamine in multimodal analgesia regimens. Pain Med. 2015;16(4):646–56.

18. Kato R, Foëx P. Myocardial protection by anesthetic agents against ischemia-reperfusion injury: An update for anesthesiologists. Can J Anaesth. 2016;63(6):699–711.