Comparative Study between Opioid-Free Anesthesia and Opioid-Based Anesthesia in Obese Patients Undergoing Abdominal Laparoscopic Surgery? Effective and Safe Analgesia Challenge: A Randomized Double Blinded Study

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ABSTRACT

Background: Opioid-free anesthesia (OFA) has emerged as a potential alternative treatment for obese individuals undergoing laparoscopic abdominal surgery.

Objective: The goal of this work aimed to compare the safety and efficacy of opioid-based anesthesia (OBA) versus OFA in obese patients having laparoscopic cholecystectomy.

Material and methods: This randomized, prospective, double-blind clinical study was conducted with 50 obese patients scheduled for laparoscopic cholecystectomy. Patients were randomly assigned to either the opioid-based anesthesia group (Group I) or the opioid-free anesthesia group (Group II). Group I obtained fentanyl as the primary anesthetic adjuvant and perioperative analgesic, while group II obtained dexmedetomidine, lidocaine, and paracetamol as alternative analgesics. Hemodynamic parameters, pain scores, and opioid usage were measured at various time points. Adverse effects were also captured.

Results: OFA resulted in significantly lower mean arterial blood pressure and significantly lower postoperative VAS score. The total consumption of opioid in the form of pethidine was significantly reduced in the OFA group than the OBA group (40.4 ± 28.21 vs. 71.8 ± 35.73 respectively, P <0.001). However, a slightly superior recovery score was observed in the OBA group (median; 6.7 vs. 7.25, P=0.008). No statistically significant difference was discovered between the two groups for any side effects, including postoperative nausea and vomiting (C) (P-value > 0.05).

Conclusions: Anesthesia management for morbidly obese individuals undergoing laparoscopic cholecystectomy under general anesthesia may benefit from the use of anesthesia devoid of opioids.

Keywords: Opioid free, Morphine, Paracetamol, Dexamethasone, Lidocaine.

INTRODUCTION

Postoperative pain following laparoscopic cholecystectomy is multifactorial, additionally; there is a rising demand for efficient pain control. Pain is now considered an important vital sign, often referred to as the fifth vital indicator, and is closely associated with quality control in the healthcare system [1]. In addition to postoperative pain, obesity may harm tight lungs by mechanically compressing the diaphragm, lungs, and chest cavity. Additionally, extra fat decreases the compliance of the entire respiratory system, heightens pulmonary resistance, and lowers the strength of the respiratory muscles [2].

While opioids continue to be a vital part of anesthesia and provide reasonably priced analgesia, their efficacy varies. Opioids are more effective in alleviating resting pain compared to pain connected with physical activity, and large dosages can result in tolerance or hyperalgesia. Additionally, opioids have several side effects such as respiratory depression, postoperative nausea and vomiting (PONV), pruritus, difficulties in urination, and

ileus, which can impact patient satisfaction and hospital stay duration. Consequently, their contribution to patients' functional recovery in the face of ongoing postoperative pain remains debatable [3].

Recently, opioid-free analgesia (OFA) has gained popularity. An efficient OFA approach combines pharmacological and non-pharmacological approaches that target various pain mechanism pathways [3]. Anti-nociceptive drugs impede information processing by interfering with a number of neurotransmitters and neuronal relays in both the ascending and descending pathways of the nociceptive system [4]. By using evidence-based therapies during the perioperative period, patient outcomes may be improved, according to the enhanced recovery after surgery (ERAS) approach. The goal of ERAS procedures is to lessen the physiological reaction to surgical stimuli and incorporate new research to reduce problems [5].

In this study, obese patients undergoing laparoscopic cholecystectomy were given either an opioid-based or opioid-free anesthetic to compare for safety and effectiveness.

PATIENTS AND METHODS

Study design: This is a randomized, prospective double-blind clinical study that was enrolled on 50 patients at Benha University Hospital through the period from August 2022 to February 2023. Patients whose laparoscopic cholecystectomy was scheduled as an elective procedure provided written informed consent.

Sample size: G. power 3.1.9.2 (Universität Kiel, Germany) was employed to determine the sample size. The following factors were taken into account when determining the sample size: 90% study power, a 0.05 α error, and the total analgesic requirement (in mg), which was 226 ± 48 in opioid-based group and was 64 ± 69 in the opioid-free group (P < 0.001) according to a previous study [7]. In order to prevent dropout, 3 cases were added to each group. 25 patients were therefore divided among the groups.

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Inclusion criteria: Patients between the ages of 18 and 60 years, who had a BMI between 30 and 35 kg/m², and who had an ASA I or II physical status.

Exclusion criteria: Peoples who refused to participate, those with an ASA physical status > II, a BMI > 35 kg/m², drug allergies, pregnant women, people with comorbid conditions like uncontrolled diabetes mellitus, people taking antihypertensive medications and people with asthma.

Randomization: The computer-generated random numbers were employed to split the eligible patients into two equal groups:

Group (I): Opioid-based anesthesia (25 patients), prior to triggering general anesthesia, a bolus dose of IV fentanyl (2 µg/kg) was delivered and then an intraoperative infusion of 1 µg/kg/hr to maintain hemodynamic changes within 20% of the baseline.

Group (II): Opioid-free anesthesia (25 patients), prior to triggering general anesthesia, patients obtained 1000 mg paracetamol, dexamethasone 0.1 mg/kg, and lidocaine 1 mg/kg. After that, magnesium sulphate (10 mg/kg/hr) and lidocaine (2 mg/kg/hr) were continuously infused.

The basis for all drug computations was adjusted body weight, which was determined by applying the following formula to the total and ideal body weights: Adjusted body weight = ideal body weight + [0.4 × (actual body weight – ideal body weight)] [6].

A well-trained anesthesia resident, who did not participate in the study, prepared and administered the medications. The grouping was kept blind for all participants, including the patients themselves, until the completion of the study. Another anesthesiologist, not involved in the study, was responsible for collecting postoperative data.

Procedure: On the night of the operation, the visual analogue scale (VAS) was described to the patients as an efficient, simple, and non-invasive method for measuring pain intensity. Standard monitoring equipments comprising non-invasive blood pressure, pulse oximetry, electrocardiography leads, and capnography cannula, were applied to all patients. Equipments for difficult intubation were also readily available. All patients were preoxygenated for 5 minutes before induction. To enable endotracheal intubation, anesthesia was produced with 2 mg/kg IV propofol and 0.5 mg/kg IV atracurium, followed by subsequent medication infusions based on the allocated groups.

Maintenance: Bolus doses of atracurium were administered to maintain optimal surgical conditions, and isoflurane inhalation (1.2-2%) was employed to keep mean arterial pressure (MAP) within 20% of the starting point. Volume-controlled mode ventilation, a tidal volume of 8–10 ml/kg, and a gas combination of 70% oxygen and 30% air were used to provide ventilation. The end-tidal carbon dioxide ($ETCO_2$) levels were targeted to be between 35 and 45 mmHg. Positive end-expiratory pressure (PEEP) of 5 cm H_2O was maintained utilizing a closed-circuit system with a 4 L/min overall fresh gas flow rate.

After gallbladder removal, continuous IV infusion was stopped in both groups. Local infiltration with 0.25% bupivacaine was performed at the sites of the three ports in both groups. Intraoperative measurements of MAP, HR, and oxygen saturation were recorded at baseline and every 5 minutes until the end of the procedure. At the conclusion of the process, neostigmine (0.05 mg/kg) with atropine (0.01 mg/kg) were administered to all patients to reverse the neuromuscular blockade caused by atracurium.

Measurements: In the recovery room, postoperative measurements were recorded, including the interval between the cessation of analgesic usage and a score of 9 on the Aldrete scale for release from the post-anesthesia care unit (PACU), as well as MAP and HR at 0, 2, 4, 8, 12, and 24 hours postoperative. Postoperative pain was determined using the VAS at 0, 2, 4, 8, 12, and 24 hours postoperative. For postoperative analgesia, pethidine was administered.

The total analgesic requirement during the first 24 h after extubation was recorded. The incidence of PONV episodes within 24 hours after extubation was also recorded, and treatment with metoclopramide (0.25 mg/kg IV, injected over 5 minutes) was provided. Severe cases were treated with ondansetron (8 mg IV).

HR, BP and VAS were considered primary outcomes, while secondary outcomes included postoperative opioid consumption over 24 hours, time to reach an Aldrete score of 9, and postoperative side effects (PONV).

Ethical Approval: This study was ethically approved by The Institutional Review Board of the Faculty of Medicine, Benha University. Written informed consents were obtained from all participants. This study was executed according to the code of ethics of The World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The statistical analysis was performed utilizing SPSS version 26 (IBM Inc., Chicago, IL, USA). The mean and standard deviation (SD) of quantitative parametric data were reported, and an unpaired student t-test was employed to assess the data. Mann Whitney-test was employed to evaluate quantitative non-parametric data that were provided as median and interquartile range (IQR). When qualitative variables were presented as frequency and percentage, either the chi-square test or Fisher's exact test was used to assess them. A two-tailed P-value of less than 0.05 was viewed as statistically significant.

RESULTS

This study enrolled 50 obese patients scheduled for laparoscopic cholecystectomy. Two equal groups were formed by random selection: OFA group and the OBA group, with 25 patients in each group [Figure 1].

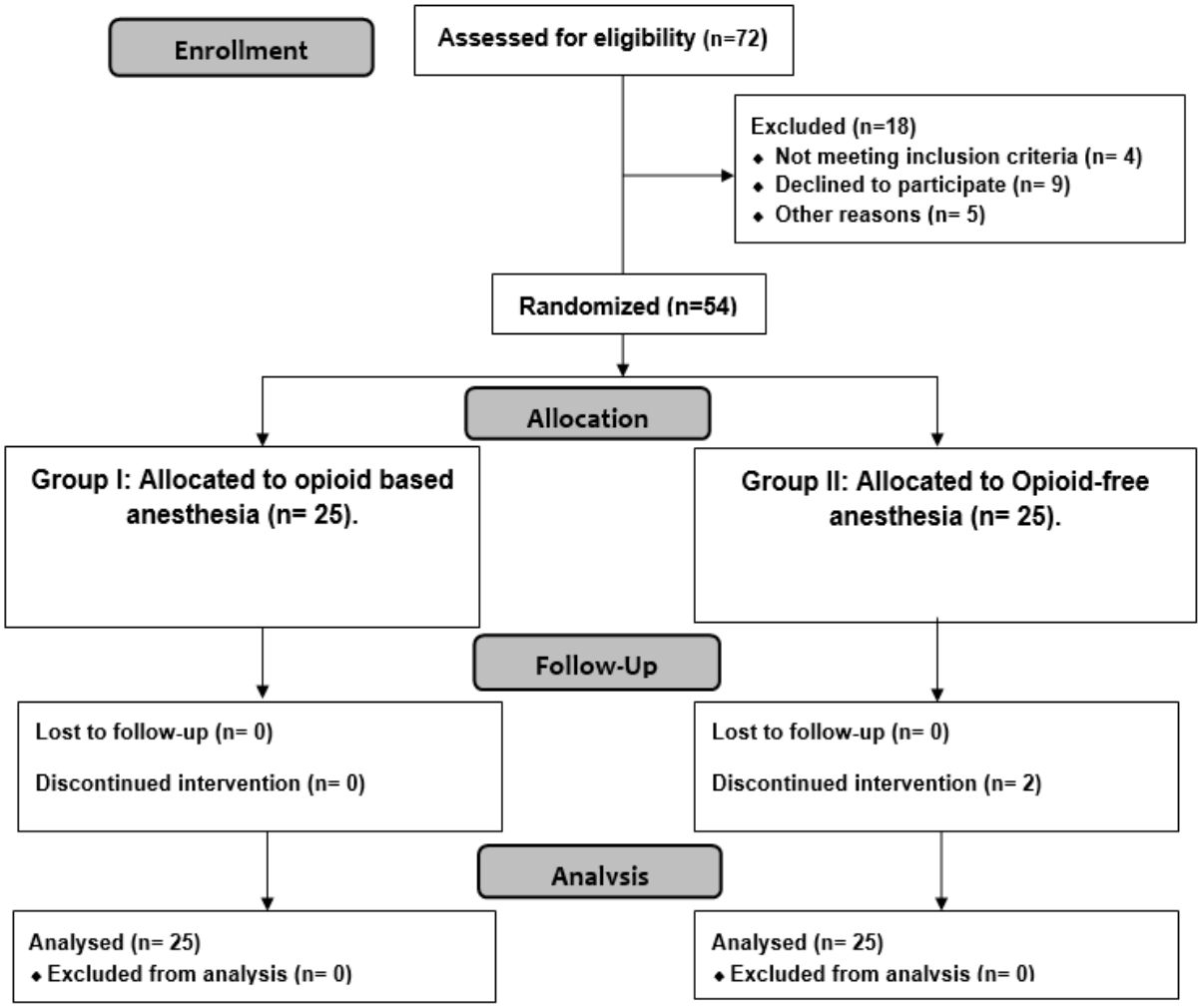

Figure (1): CONSORT flowchart of the studied patients.

Demographic data (age, body mass index and sex), ASA physical status and length of surgery were insignificantly different between the studied groups [Table 1].

Table (1): Demographic data of the studied group

		Group (OBA) (n=25)	Group (OFA) (n=25)	P value
Age (years)		35.32 ± 9.55	37.04 ± 11.17	0.561
Sex	**Male**	6 (24%)	8 (32%)	0.753
	Female	19 (76%)	17 (68%)	
BMI (kg/m^2)		33.0 ± 1.55	32.48± 1.73	0.270
ASA	**I**	16 (64%)	18 (72%)	0.762
	II	9 (36%)	7 (28%)	
Duration of surgery (min)		34.44 ± 3.61	34.08 ± 2.68	0.690

Data displayed as mean ± SD or frequency (%), BMI: body mass index, ASA: the American society of anaesthesiologists
Regarding postoperative analgesic consumption, group II consumed significantly less pethidine overall than group I. (71.8 ± 35.73 vs. 40.4 ± 28.21, P <0.001) [Table 2].

Table (2): Total pethidine consumption of the studied group

	Group (OBA) (n=25)	Group (OFA) (n=25)	P value
Total pethidine consumption (mg)	71.8 ± 5.73	40.4 ± 8.21	**<0.001***

Data displayed as mean ± SD, *: statistically significant as P value <0.05

Regarding the postoperative adverse effects, nausea occurred in 5 (20%) patients in group I and 2 (8%) patients in group II and vomiting occurred in 3 (12%) patients in group I and 1 (4%) patient in group II. Incidence of postoperative adverse effects (nausea and vomiting) were insignificantly different between both groups [Table 3].

Table (3): Adverse effects of the studied group

	Group (OBA) (n=25)	Group (OFA) (n=25)	P value
Nausea	5 (20%)	2 (8%)	0.417
Vomiting	3 (12%)	1 (4%)	0.609
Total adverse effects	8 (32%)	3 (12%)	0.171

Data presented as frequency (%).

Postoperative heart rate at 0, 2, 4, 8, 12 and 24h was insignificantly different between both groups. Postoperative mean arterial blood pressure was significantly less in group II than in group I at all measurements (0, 2, 4, 8, 12 and 24h) (P <0.001) [Figure 2 A and B].

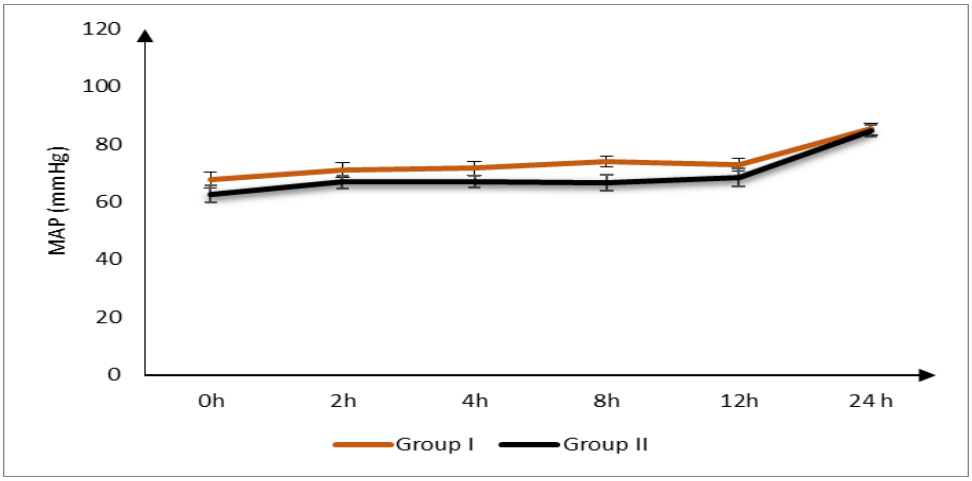

Figure (2 A): Heart rate between the studied groups.

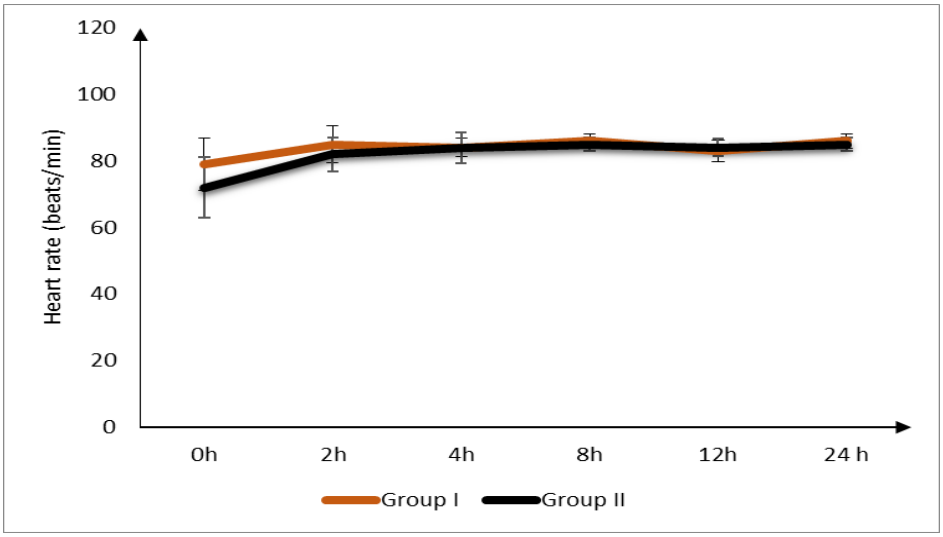

Figure (2 B): MAP between the studied groups.

Aldrete score was significantly better in group I than in group II (median; 6.7 vs. 7.25, P=0.008) [Figure 3].

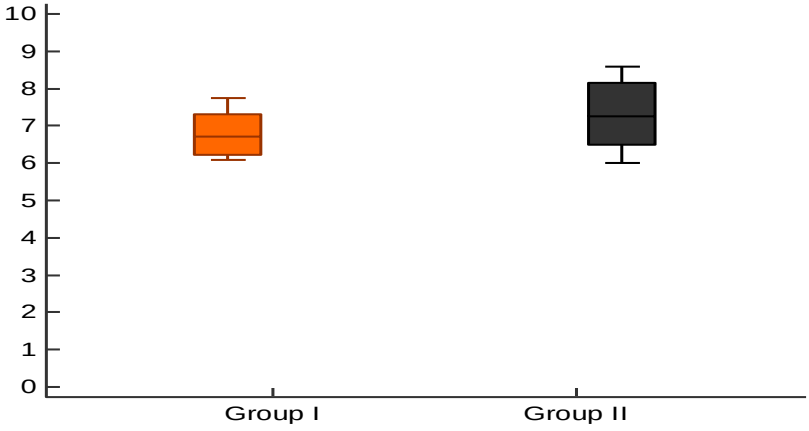

Figure (3): Aldrete score between the studied groups

VAS was insignificantly different at 0 and 2 h between both groups then significantly lower in group II than in group I at 4, 8, 12 and 24h (P <0.05) [Figure 4].

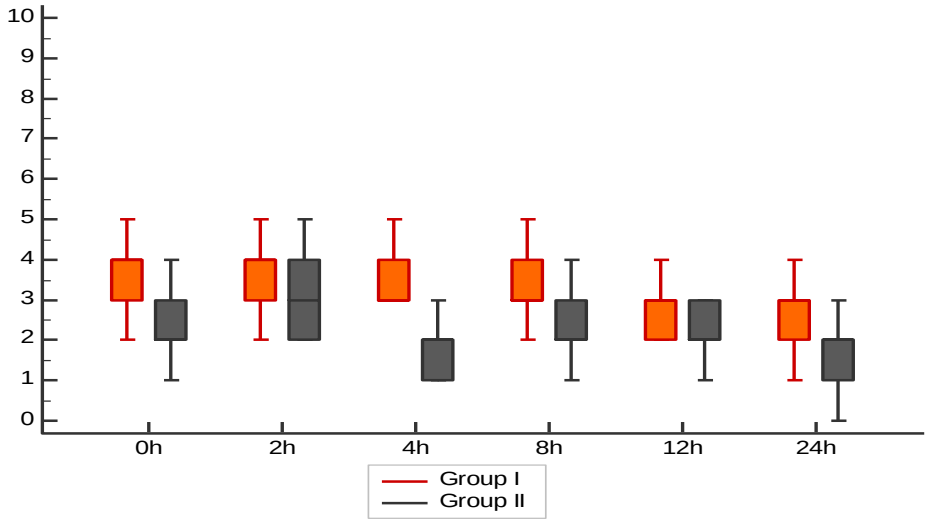

Figure (4): Postoperative visual analogue scale (VAS) between the studied groups.

DISCUSSION

Several analgesic techniques are available for the management of pain associated with this procedure, however no single modality has demonstrated superior efficacy [8, 9]. Traditionally, intravenous opioids have been utilized for patient-controlled analgesia (PCA) in many centers. However, these drugs are associated with a range of undesirable side effects. Epidural analgesia and opioid-sparing techniques, such as intrathecal administration, have been explored as alternatives [10]. However, epidural analgesia carries a high failure rate and may interfere with postoperative neurologic evaluations. Intrathecal morphine, while effective in providing pain relief, can lead to urinary retention, respiratory depression, and itching as potential side effects [11].

Current studies have indicated that OFA, which involves multimodal pain management, improves the quality of analgesia and reduces adverse effects, particularly those associated with opioids [12]. One suggested approach is to avoid the use of opioids during surgery and replace them with hypnotic or analgesic drugs to manage the effects of surgical trauma under anesthesia. However, further research is needed to investigate this suggestion [13].

Our research compared the safety and effectiveness of OBA against opioid-free anesthesia in obese patients having laparoscopic cholecystectomy. Our findings revealed that OFA resulted in significantly lower mean arterial blood pressure, significantly lower postoperative VAS score. Moreover, the total consumption of opioid pain medication, specifically pethidine, was significantly reduced in OFA group. However, a slightly superior recovery score was observed in OBA group. Regarding side effects, comprising PONV, the two groups did not differ statistically significantly from one another. Our findings align with those of **Bhardwaj *et al.*** [7], who included 80 patients between the ages of 20 and 60 who were having laparoscopic urological surgery done under general anesthesia. The OFA group needed significantly less rescue analgesia. Also, the opioid-based groups also required a considerably higher total analgesic dosage in the form of tramadol in contrast to the opioid-free groups. **Abdelmoniem *et al.*** [14] demonstrated that OFA group had a lower VAS score and consumed more pethidine after surgery in patients having laparoscopic cholecystectomy. Similar results were obtained by **Boysen *et al.*** [15], who used lidocaine and dexmedetomidine infusion in stent placement for chronic pancreatitis. Postoperatively, patients received intravenous acetaminophen (1 gm/6 h), and pain relief was achieved without the use of opioids. **Mendoca *et al.*** [16] demonstrated in their study that patients who obtained both lidocaine and magnesium sulfate consumed less rescue analgesia in the form of alfentanil during surgery.

In a case report of lumbosacral posterior spinal fusion, **Kim *et al*.** [17] utilized dexmedetomidine and lidocaine (without intraoperative opioids) for a 65-year-old man undergoing spine surgery. Postoperatively, the numeric rating scale of pain was reported as 3/10. In addition, the findings obtained by **Mulier *et al*.** [18] are consistent with our results. They found that OFA led to lower opioid consumption and higher quality of recovery compared to OBA in patients undergoing laparoscopic bariatric surgery. **Soudi *et al.*** found in their study that patients having laparoscopic bariatric surgery under general anesthesia experienced significantly lower pain levels and nalbuphine consumption in the OFA group compared to the traditional balanced anesthesia group [19].

In contrast to our study, **Ahmed *et al*.** [20] carried out research on 62 patients who went through laparoscopic cholecystectomy. The study revealed that in both OBA and OFA there were no statically significant differences regarding analgesic consumption and VAS score postoperatively. These differences in the specific medications and their dosages, as well as the management of hemodynamics and co-analgesics, could contribute to the contrasting findings between our study and study of **Ahmed *et al.*** [20] study. Additionally, they stated that there was no significant difference between the two groups in terms of the Aldrete score.

The findings of our study reported insignificantly different postoperative heart rate between both groups suggesting that the type of anesthesia (OFA vs. OBA) did not have a significant impact on heart rate during the postoperative period, however hear rate was slightly less in group II when in contrast to group I. This indicated that other factors, such as the surgical procedure itself or the patient's physiological response, might had a more prominent influence on heart rate. On the other hand, the significantly lower postoperative mean arterial blood pressure observed in group II (OFA) in contrast to group I (OBA) at all measured time points could be attributed to several factors. Opioids have a well-known effect of causing vasodilation, which can lead to a decrease in blood pressure. In OFA group, the absence or reduced usage of opioids might have contributed to less vasodilation, resulting in comparatively lower mean arterial blood pressure. Additionally, the specific medications and techniques used in OFA, such as lidocaine infusion and magnesium sulfate, may have played a role in maintaining blood pressure stability. In line with our research, **Bhardwaj *et al.*** [7] has been proven that in the postoperative period, OFA group's hemodynamic parameters, such as HR and MAP, were much lower (and more stable) than those in OBA group. Perioperative HR and MAP showed a statistically significant decline, according to **Abdelmoniem *et al*.** [14]. Concerning **Gaszynski *et al.*** [21], 42 patients undergoing bariatric surgery were evaluated, and they were divided into two groups: One receiving OFA utilising dexmedetomidine, and the other receiving fentanyl-based anesthesia. It was discovered that the OFA group's HR and MAP significantly decreased.

Additionally, **Shalaby *et al*.** [22] discovered that in patients scheduled for elective laparoscopic cholecystectomy, there was a significant drop in HR and MAP in the dexmedetomidine OFA group compared to the fentanyl group after intubation, following pneumoperitoneum, until 60 min after induction.

Al Bahar *et al*. [23] conducted a trial on 60 patients who were split into two groups: OBA group and OFA group. In morbidly obese patients undergoing laparoscopic cholecystectomy, they reported that OFA offered perioperative hemodynamic stability, postoperative pain alleviation, decreased incidence of PONV, and less analgesic consumption postoperatively than that of the OBA. In a retrospective matched case-controlled study in China by **Ma *et al*.** [24] on a total of 44 patients who underwent laparoscopic sleeve gastrectomy and were given either an opioid-based approach (OBA group) or an opioid-sparing technique (OSA group). They discovered that the OSA group's opioid intake had significantly dropped (48.79 ± 4.85 vs. 10.57 ± 0.77, $p < 0.001$).

Of note, it is crucial to observe that individual patient responses and variations in surgical factors can also influence blood pressure changes. Other factors, such as patient comorbidities, baseline blood pressure, and overall surgical management, may have contributed to the observed differences in MAP between the two groups.

Regarding PONV, the two studied groups did not differ statistically significantly from one another although there was a decrease in PONV incidence in the OFA group. Similar to our results, studies by **Ahmed *et al*.** [20], **Kim *et al*.** [17] and **Abdelmoniem *et al*.** [14] demonstrated a reduction in adverse effects such as PONV with the use of OFA. These findings are consistent with a study conducted by **Samuels *et al*.** [24] who reviewed all surgical cases performed by an anesthesiologist who switched from OSA to OFA and compared patient groups with a control group who underwent traditional opioid anesthesia (OA). According to their findings, patients in the OFA group had less nausea and vomiting than those in the other groups. They also noted that the OA and OSA groups required twice as much opioid medication in the PACU as the OFA group did.

Lastly, there were several restrictions on this study, first of all, the study had a single center and a modestly sized sample. Second, the study concentrated primarily on obese individuals with ASA I or II physical status and a BMI between 30 and 35 kg/m^2. Therefore, the findings might not be relevant to patients with higher BMI or different physical statuses. Thirdly, long-term outcomes, such as postoperative recovery, patient satisfaction, and complications beyond the first 24 hours, were not evaluated. Therefore, future studies focusing on these limitations would further improve our comprehension of the benefits and limitations of OFA in diverse patient populations and surgical procedures.

CONCLUSION

This study showed that OFA provided more intraoperative hemodynamic stability, less postoperative pain, less analgesic requirement postoperatively. For the anesthetic management of morbidly obese individuals having laparoscopic cholecystectomy under general anesthesia, OFA may be a useful choice.

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- **Duration of interest Sponsors, and funding sources:** Nil.
- **Conflict of interests:** Nil.

REFERENCES

1. **Thota R, Ramkiran S, Garg R *et al*. (2019)** : Opioid-free onco-anesthesia: Is it time to convict opioids? A systematic review of literature. J Anaesthesiol Clin Pharmacol., 35 (4) :441-52.
2. **Chung F, Liao P, Elsaid H *et al*. (2012):** Sun Y. Oxygen desaturation index from nocturnal oximetry: a sensitive and specific tool to detect sleep-disordered breathing in surgical patients. Anesth Analg., 114 (5): 993-1000.
3. **Echeverria M, Stoicea N, Todeschini A *et al*. (2020)**: Enhanced Recovery After Surgery (ERAS): A Perspective Review of Postoperative Pain Management Under ERAS Pathways and Its Role on Opioid Crisis in the United States. Clin J Pain., 36 (3): 219-26.
4. **Brown E, Pavone K, Naranjo M (2018)**: Multimodal General Anesthesia: Theory and Practice. Anesth Analg., 127 (5): 1246-58.
5. **Greenshields N, Mythen M (2020)**: Enhanced Recovery After Surgery. Current Anesthesiology Reports, 10: 49-55.
6. **Servin F, Farinotti R, Haberer P *et al*. (1993):** Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology,78 (4): 657-65.
7. **Bhardwaj S, Garg K, Devgan S (2019)**: Comparison of opioid-based and opioid-free TIVA for laparoscopic urological procedures in obese patients. J Anaesthesiol Clin Pharmacol., 35 (4): 481-6.
8. **Kaye D, Urman R, Rappaport Y *et al*. (2019)**: Multimodal analgesia as an essential part of enhanced recovery protocols in the ambulatory settings. J Anaesthesiol Clin Pharmacol., 35 (1): 40-45.
9. **Schwenk S, Mariano R (2018)**: Designing the ideal perioperative pain management plan starts with multimodal analgesia. Korean J Anesthesiol., 71 (5): 345-52.
10. **Bajwa J, Haldar R (2015):** Pain management following spinal surgeries: An appraisal of the available options. J Craniovertebr Junction Spine, 6 (3): 105-10.
11. **Ye J, Myung K, Packiasabapathy S *et al*. (2020)**: Methadone-based Multimodal Analgesia Provides the Best-in-class Acute Surgical Pain Control and Functional Outcomes With Lower Opioid Use Following Major Posterior Fusion Surgery in Adolescents With Idiopathic Scoliosis. Pediatr Qual Saf., 5 (4): 336-45.
12. **Li Y, Swallow J, Robbins C *et al*. (2021)**: Gabapentin and intrathecal morphine combination therapy results in decreased oral narcotic use and more consistent pain scores after posterior spinal fusion for adolescent idiopathic scoliosis. J Orthop Surg Res., 16: 672.
13. **Salomé A, Harkouk H, Fletcher D *et al*. (2021)**: Opioid-Free Anesthesia Benefit-Risk Balance: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Clin Med., 10 (10): 2069.
14. **Abdelmoniem M, Farran A, Soliman S *et al*. (2020)**: Opioid free anesthesia in patients undergoing three-ports laparoscopic cholecystectomy. AIMJ.,1 (2): 160-5.
15. **Boysen G, Pappas M, Evans B(2018):** An Evidence-Based Opioid-Free Anesthetic Technique to Manage Perioperative and Periprocedural Pain. Ochsner J., 18 (2): 121-5.
16. **Mendonça T, Pellizzaro D, Grossi J *et al*. (2020):** Synergistic effect of the association between lidocaine and magnesium sulfate on peri-operative pain after mastectomy: A randomised, double-blind trial. Eur J Anaesthesiol., 37 (3): 224-34.
17. **Kim J, Bengali R, Anderson A (2017):** Opioid-free anesthesia using continuous dexmedetomidine and lidocaine infusions in spine surgery. Korean J Anesthesiol., 70 (6): 652-653.
18. **Mulier P, Wouters R, Dillemans B *et al*. (2018):** . A randomized controlled, double-blind trial evaluating the effect of opioid-free versus opioid general anesthesia on postoperative pain and discomfort measured by the QoR-40. J Clin Anesth Pain Med., 2 (1): 2-6.
19. **Soudi M, Hammad A, ElShafie M *et al*. (2020):** Comparing opioid free general anesthesia to traditional balanced general anesthesia regarding achievement of enhanced recovery in laparoscopic bariatric surgeries. Ain-Shams Journal of Anesthesiology, 14: 24-9.
20. **Ahmed H, Noor El-Din M, Ali M (2020):** Opioid Free Anesthesia in Laparoscopic Cholecystectomy (Comparative Clinical Study). EJHM.,78 (3): 200-11.
21. **Gaszyński T, Czarnik K, Łaziński Ł *et al*. (2016):** Dexmedetomidine for attenuating haemodynamic response to intubation stimuli in morbidly obese patients anaesthetised using low-opioid technique: comparison with fentanyl-based general anesthesia. Anaesthesiol Intensive Ther., 48 (5): 275-9.
22. **Shalaby M, Abdalla M, Mahmoud S (2018):** Nonopioid versus Opioid Based General Anesthesia Technique for Laparoscopic Cholecystectomy. EJHM., 73 (2): 6206-12.
23. **Al Bahar M, Elbakry E, El Hennawy T *et al*. (2022):** A randomized trial with opioid-free versus opioid anesthesia in morbidly obese patients during laparoscopic cholecystectomy. Menoufia Medical Journal, 35: 686-93.
24. **Ma Y, Zhou D, Fan Y *et al*. (2022):** An Opioid-Sparing Strategy for Laparoscopic Sleeve Gastrectomy: A Retrospective Matched Case-Controlled Study in China. Front Pharmacol., 13: 879831.
25. **Samuels D, Abou-Samra A, Dalvi P *et al*. (2017):** Camporesi EM. Opioid-free anesthesia results in reduced postoperative opioid consumption. J Clin Anesth Pain Med.,1 (2): 2-4.

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