Comparative study between the effect of opioid-free anesthesia versus opioid-based anesthesia in morbid obese patients

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Introduction Multimodal techniques for pain management involve using two or more analgesic drugs with different mechanisms of action working in synergy. These drugs may be given by either the same or different routes of administration preoperatively, intraoperatively, and/or postoperatively [1]. By targeting different pain pathways within the central and peripheral nervous systems, the use of multiple agents with different mechanisms of action allows for lower doses of individual agents, which in turn results in a lower risk of adverse effects.

Aim We have conducted this study to compare the effect of opioid-free anesthesia (OFA) with opioid-based anesthesia (OA) on postoperative pain relief as a primary outcome and hemodynamic variables, including mean arterial blood pressure (MAP), heart rate (HR) and oxygen saturation%, total pethidin consumption 24 h postoperatively, and postoperative complications developed in postanesthetic care unit (PACU), such as hypoxia, shivering, nausea, and vomiting as secondary outcomes in morbid obese patients.

Patients and methods A total of 40 patients (morbidly obese) aged 25–50 years with BMI of at least 35, having ASA status II scheduled for laparoscopic cholecystectomy were divided into two groups in a randomized controlled fashion: group 1 was the OA group (n=20), which received general anesthesia with propofol, muscle relaxant (rocuronium), and fentanyl as the main anesthetic adjuvant and analgesic, and group 2 was the OFA group (n=20), which received general anesthesia with propofol, muscle relaxant (rocuronium), dexmedetomidine, magnesium sulfate, and lidocaine as anesthetic adjuvant and analgesic. Hemodynamic variables such as MAP, HR, and oxygen saturation% were recorded preoperatively, postintubation, and every 15 min till the end of surgery. Postoperative visual analog scale done immediately postoperatively, and at 2, 6, 12, and 24 h postoperatively; total pethidine consumption in 24 h postoperatively; and postoperative complications developed in PACU such as hypoxia, shivering, nausea, and vomiting were also recorded for each patient.

Results There were no differences between the two groups regarding demographic data. There was a statistically significant decrease in HR in OFA group compared with OA group from 15 min after induction to 15 min postoperatively and a statistically significant decrease in MAP in group II (OFA) compared with group I (OA) from 30 min after induction to 90 min postoperatively in PACU. Visual analog scale for pain postoperatively was lower in nonopioid group than opioid group. The postoperative pethidine consumption was significantly lower in OFA versus OA. Postoperative complications like nausea, vomiting, shivering, and hypoxia were significantly higher in the OA group.

Conclusion OFA provides postoperative pain relief and intraoperative hemodynamic stability without significant associated adverse effects compared with OA.

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Introduction

Multimodal techniques for pain management involve using two or more analgesic drugs with different mechanisms of action working in synergy. These drugs may be given by either the same or different routes of administration preoperatively, intraoperatively, and/or postoperatively [1]. By targeting different pain pathways within the central and peripheral nervous systems, the use of multiple agents with different mechanisms of action allows for lower doses of individual agents, which in turn results in a lower risk of adverse effects [2]. The lower incidence of adverse effects and improved pain management may further result in shorter hospitalization times, improved patient recovery and rehabilitation, and decreased costs of care [3]. Dexmedetomidine is a highly selective α2 adrenoceptor agonist that produces dose-dependent sedation, anxiolysis, and analgesia (involving spinal and supraspinal sites) without respiratory depression [4]. It enhances anesthesia produced by other anesthetic drugs, causes perioperative sympatholysis, and decreases blood pressure by stimulating central α2 and imidazoline receptors [5]. Lignocaine is an essential drug on WHO essential drug list and is considered efficacious, safe, and cost-effective for any healthcare system [6]. The antinociceptive effects of lignocaine are thought to be attributable to the blockade of neuronal sodium channels and

potassium currents, and the blockade of presynaptic muscarinic and dopamine receptors [7]. Magnesium is a calcium channel blocker and noncompetitive *N*-methyl-d-aspartate receptor antagonist with antinociceptive effects. Magnesium sulfate has been investigated as a possible adjuvant for intraoperative and postoperative analgesia in different kind of surgeries [8]. The objective of this study is to evaluate and compare opioid-free anesthesia (OFA) by using multimodal techniques for pain management with opioid-based anesthesia (OA) on postoperative pain relief as a primary outcome and hemodynamic variables, including mean arterial blood pressure (MAP), heart rate (HR), and oxygen saturation%, total pethidine consumption 24 h postoperatively, and postoperative complications developed in postanesthetic care unit (PACU) such as hypoxia, shivering, nausea, and vomiting as secondary outcomes in morbid obese patients.

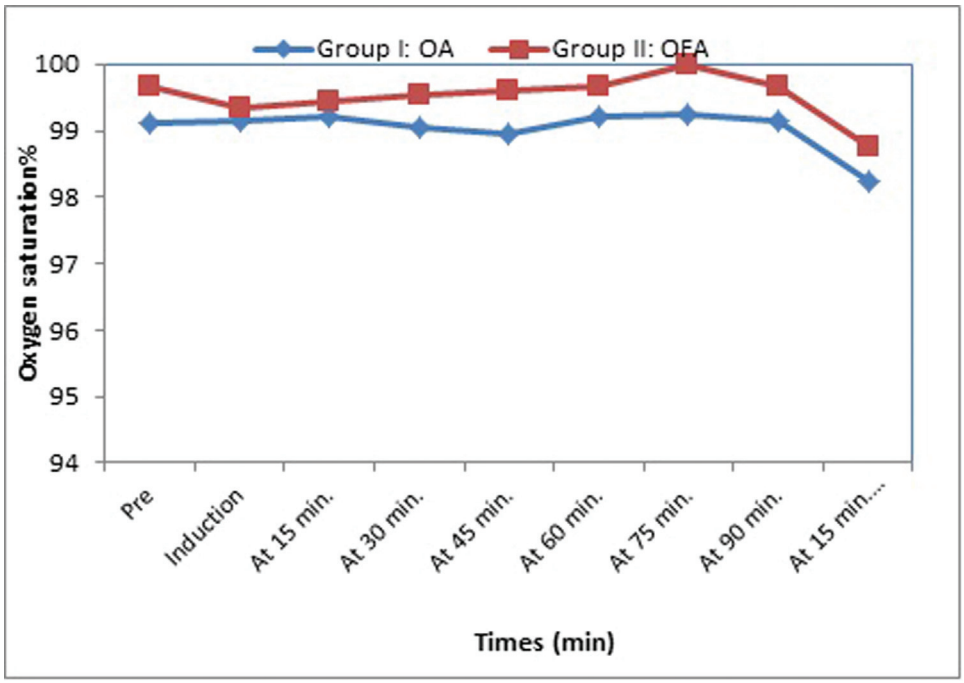
Patients and methods

This prospective randomized controlled study was conducted at Al-Zahraa University Hospital on 40 adult obese patients subjected to laparoscopic cholecystectomy that started from January 2019 to May 2019 after approval of the study protocol by Local Ethical Committee of Al-Zahraa University Hospital, Al-Azhar University and a written, informed consent from the patients. Patients aged between 25 and 50 years, of both sexes, having ASA status II and BMI of at least 35 (as inclusion criteria) were enrolled in this study. Exclusion criteria included pregnant or nursing woman, patients currently on antihypertensive drugs even controlled, patients currently taking opioid for chronic pain, patients with allergies to study medication, patients with obstructive sleep apnea syndrome, patients with unstable cardiorespiratory disorder, and patients with hepatic and renal insufficiency. Patients were randomly assigned by computer-generated random number and sealed opaque envelopes into two groups: group I was the OA group (*N*=20 patients), where fentanyl (1–2 μg/kg, intravenously) was administered before induction of general anesthesia and intermittent boluses of fentanyl (50 mic) was given intraoperatively when needed to maintain the change in hemodynamics within 20% of the baseline. Group II was the OFA group (*N*=20 patients), where a loading dose of dexmedetomidine (0.5 μg/kg, intravenously, over 10 min) was given before induction of general anesthesia and then infusion of dexmedetomidine was maintained at a rate of 0.25 μg/kg/h intraoperatively and stopped before end of surgery. Loading dose of lidocaine was 1 mg/kg, and then lidocaine was maintained at rate of 1 mg/kg/h. Loading dose of magnesium sulfate was 30 mg/kg, and then infusion of magnesium sulfate was maintained at a rate of 10 mg/kg/h. All patients were monitored as ASA standard monitoring by Drager (Vista 120) monitor manufactured by Drager Medical System Inc. (fabius GS Germany), including noninvasive blood pressure, ECG, pulse oximetry for O_2 saturation, end tidal CO_2 values by capnography (using Penlon SP M5 InterMed, Penlon Limited, Abingdon Science Park, Barton Lane, Abingdon, OX14 3NB, Oxford, UK), and bispectral index for depth of anesthesia. Patients from both groups were pre-oxygenated for 5 min before induction, and anesthesia was induced with propofol (2 mg/kg, intravenously) according to ideal body weight, rocuronium (0.5 mg/kg, intravenously) according to lean body weight, and 1 g of paracetamol was given with induction. After induction and intubation, muscle relaxation was maintained with boluses of rocuronium (10–20 mg) to provide optimal surgical conditions, and general anesthesia was maintained with inhalation anesthetics (desflurane) based on BIS value between 50 and 60%. The ventilation in both groups was achieved with a volume-controlled mode and was adjusted to maintain normocarbia using a closed circle system with a total fresh gas flow rate of 3 l/min. The bispectral index was maintained in both groups between 50 and 60%. At the end of surgery, muscle relaxation was reversed with neostigmine (≤5 mg) and atropine (0.2–0.8 mg). Boluses of ephedrine (3–9 mg/dose) and atropine (0.4–0.8 mg/dose) were used to correct oversympatholysis and to maintain the change in hemodynamics within 20% of baseline. Assessment parameters include demographic data (age, sex, BMI and duration of surgery); perioperative hemodynamic changes (MAP, HR and oxygen saturation%) preoperatively, postintubation, and every 15 min till the end of surgery; postoperative visual analog scale (VAS) score for pain immediately postoperatively and after 2, 6, 12 and 24 h postoperatively; total pethidine (0.5 mg/kg, intramuscular) consumption in 24 h postoperatively guided by VAS scores; and postoperative complications developed in PACU such as hypoxia, shivering, nausea, and vomiting.

Sample size justification

MedCalc version 12.3.0.0 program (MedCalc Software, Ostend, Belgium) was used for calculations of sample size, which is a statistical calculator based on 95% confidence interval and power of the study 80% with α error of 5%. According to a previous study, Jan *et al.* [10] showed that the median (interquartile range) of

Figure 1



Comparison between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to oxygen saturation%.

Figure 2

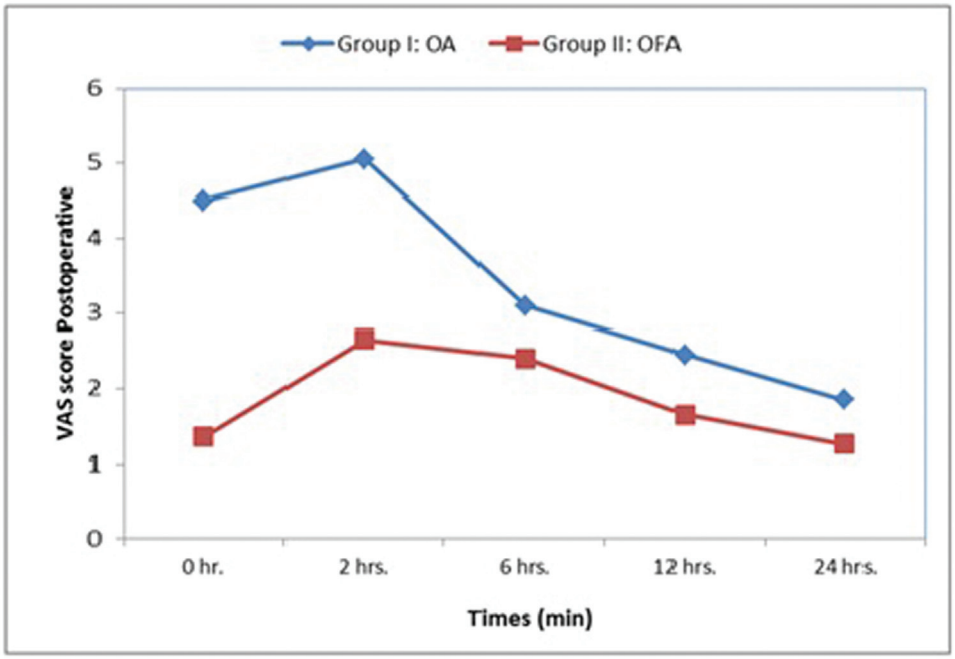


Chart between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to visual analog scale score postoperative.

VAS score of OA group was 3.3 (0.7) versus 2.0 (0.7) for the OFA group, with *P* value 0.016. So it can be relied upon in this study. Based on this assumption, the sample size was calculated according to these values. A minimal sample size of 38 cases was enough to find such a difference. Assuming a dropout ratio of 5%, the sample size was 20 cases in each group.

Statistical analysis

Recorded data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean±SD. Qualitative data were expressed as frequency and percentage. The following tests were done: independent-samples *t*-

Table 1 Comparison between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to demographic data

Demographic data	Group I: opioid-based anesthesia (*n*=20)	Group II: opioid-free anesthesia (*n*=20)	t/χ^2	*P* value
Age (mean±SD) (years)	37.80±8.46	35.30±7.78	1.577	0.139
Sex				
Female	15 (75.0)	14 (70.0)	0.125 (χ^2)	0.723
Male	5 (25.0)	6 (30.0)		
BMI (mean±SD) (weight/height^2)	40.60±4.01	39.65±2.43	0.822	0.370
Duration of surgery (mean±SD) (min)	74.00±22.34	69.50±19.32	0.464	0.500

P>0.05, NS.

Table 2 Comparison between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to heart rate (beat/min)

Heart rate (beat/min)	Group I: opioid-based anesthesia (*n*=20)	Group II: opioid-free anesthesia (*n*=20)	*t*-Test	*P* value
Preinduction (mean±SD)	86.75±8.93	89.65±6.20	1.424	0.240
Postinduction (mean±SD)	85.90±12.62	84.85±8.79	0.482	0.788
At 15 min (mean±SD)	83.00±12.59	76.85±8.19	3.355	0.045*
At 30 min (mean±SD)	83.15±13.45	76.15±7.84	4.043	0.047*
At 45 min (mean±SD)	80.35±10.66	75.40±6.36	3.179	0.033*
At 60 min (mean±SD)	81.93±10.61	72.29±4.96	11.284	0.002*
At 75 min (mean±SD)	85.25±12.24	69.00±5.59	9.367	0.007*
At 90 min (mean±SD)	81.63±9.40	68.67±2.58	10.609	0.006*
At 15 min postoperative (mean±SD)	82.05±13.30	75.75±5.05	3.921	0.034*

P>0.05, NS. **P*<0.05, significant.

Table 3 Comparison between opioid-based anesthesia group and opioid-free anesthesia group according to mean arterial blood pressure (mmHg)

Mean arterial blood pressure (mmHg)	Group I: opioid-based anesthesia (*n*=20)	Group II: opioid-free anesthesia (*n*=20)	*t*-Test	*P* value
MABP: Pre (mean±SD)	93.75±12.44	94.40±8.36	0.038	0.847
Induction (mean±SD)	94.75±17.02	88.50±13.87	1.621	0.211
At 15 min (mean±SD)	85.90±14.82	79.10±11.21	2.678	0.110
At 30 min (mean±SD)	86.80±12.16	77.05±8.98	8.315	0.006*
At 45 min (mean±SD)	91.60±11.98	74.55±5.00	34.502	<0.001**
At 60 min (mean±SD)	87.67±12.63	72.82±6.69	17.855	<0.001**
At 75 min (mean±SD)	94.92±15.01	65.33±7.50	20.307	<0.001**
At 90 min (mean±SD)	88.50±10.14	68.00±5.44	19.920	<0.001**
At 15 min postoperative (mean±SD)	88.95±10.90	78.10±9.49	11.272	0.002*

P>0.05, NS. **P*<0.05, significant. ***P*<0.001, highly significant.

test of significance was used when comparing between two means, Mann–Whitney *z* test was used for two-group comparisons in nonparametric data, and χ^2-test of significance was used to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P* value was considered significant as follows: *P* value up to 0.05 was considered significant, *P* value up to 0.001 was considered as highly significant, and *P* value more than 0.05 was considered insignificant.

Results

The variables in demographic data did not show a statistically significant difference between groups with respect to age, sex, BMI, and duration of surgery, as shown in Table 1.

Regarding HR (beat/min), there was a statistically significant decrease in OFA group compared with OA group from 15 min after induction to 15 min postoperatively (Table 2).

Regarding the MAP (mmHg), there was a statistically significant decrease in group II (OFA) compared with group I (OA) from 30 min after induction to 90 min postoperatively (Table 3).

Regarding oxygen saturation, there was no statistically significant difference between both groups (Fig. 1).

Regarding VAS score, there was a statistically significant decrease in group II (OFA) compared with group I (OA) according to VAS score postoperatively, from 0 h postoperatively to after 24 h postoperatively (Fig. 2).

Table 4 Comparison between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to total pethidine consumption in 24 h postoperative

Total pethidine consumption in 24 h postoperative	Group I: opioid-based anesthesia (*n*=20) [*n* (%)]	Group II: opioid-free anesthesia (*n*=20) [*n* (%)]	χ^2	*P* value
100 mg	7 (35.0)	0	6.234	0.013*
50 mg	10 (50.0)	6 (30.0)	0.937	0.334
No	3 (15.0)	14 (70.0)	8.291	0.009*

P>0.05, NS. **P*<0.05, significant.

Regarding total pethidine consumption, there was a statistically significant difference between the groups in 24 h postoperatively, where it was lower in OFA group than OA group, as there were only three from 20 patients in the OA group who did not need postoperative pethidine, whereas in OFA group, 14 patients did not need pethidine as a postoperative analgesia (Table 4).

Regarding postoperative complications in PACU, there was a statistically significant difference between groups according to nausea, shivering, and vomiting and no significant difference regarding hypoxia (Table 5).

Table 5 Comparison between group I (opioid-based anesthesia) and group II (opioid-free anesthesia) according to postoperative complications in postanesthetic care unit

Postoperative complications in postanesthetic care unit	Group I: opioid-based anesthesia (*n*=20) [*n* (%)]	Group II: opioid-free anesthesia (*n*=20) [*n* (%)]	χ^2	*P* value
Hypoxia	2 (10.0)	3 (0.0)	0.526	0.468
Nausea	12 (60.0)	0	14.405	<0.001**
Shivering	12 (60.0)	3 (15.0)	6.827	0.009*
Vomiting	8 (40.0)	0	7.656	0.006*

P>0.05, NS. **P*<0.05, significant. ***P*<0.001, highly significant.

Discussion

This study was designed to compare between the effects of OA and OFA in morbid obese patients regarding hemodynamics (HR, MAP), quality of pain relief using (VAS), total amount of pethidine consumption postoperatively, and postoperative complications in PACU such as nausea, vomiting, shivering, and hypoxia. Regarding demographic data, the two groups were found to be similar in terms of age, sex, BMI, and duration of surgery. Concerning the hemodynamic changes (HR and MAP), there was a statistically significant decrease in HR in OFA group compared with OA group from 15 min after induction to 15 min postoperatively and a statistically significant decrease in MAP in group II (OFA) compared with group I (OA) from 30 min after induction to 90 min postoperatively in PACU. In agreement with the results of this study, the study done by Shalaby *et al.* [9] compared the effect of OFA (using dexmedetomidine and propofol) and OA (using fentanyl and propofol) total intravenous anesthesia (TIVA) techniques on hemodynamic stability, sedation postoperative pain intensity, and the incidence of side effects on 80 patients scheduled for elective laparoscopic cholecystectomy. The patients were randomized into nonopioid group, which received dexmedetomidine (1 μg/kg) over 10 min before induction of anesthesia followed by continuous infusion of 0.5 μg/kg/h, and opioid group, which received fentanyl (1.0 μg/kg) over 10 min before induction of anesthesia followed by continuous infusion of 0.4 μg/kg/h. There were significant differences between the two groups regarding HR and MAP, both being lower in nonopiod group than opioid group. However, in contrary to this study, Jan *et al.* [10] measured the quality of recovery after OFA on 50 patients undergoing elective laparoscopic bariatric surgery. Before induction, the OA group received 0.5 μg/kg sufentanil, whereas the OFA group received 0.5 μg/kg dexmedetomidine, 0.25 mg/kg ketamine, and 1.5 mg/kg lidocaine. The study showed no differences in HR and MAP between the two groups intraoperatively. This may be owing to the use of sufentanil in the opioid group instead of fentanyl, which maintains myocardial stability and is more potent than fentanyl, and thus makes no change in intraoperative hemodynamics. Regarding oxygen saturation, in this study, there was no statically significant difference between two groups according to oxygen saturation%. In agreement with the results of this study, the study done by Mansour *et al.* [11] evaluate the efficacy and safety of giving general anesthesia without the use of any opioids either systemic or intraperitoneal on 28 obese patients (BMI>50 kg/m^2) undergoing laparoscopic sleeve gastrectomy. Preoperatively, all patients received ranitidine 50 mg as H2 receptor antagonist, metoclopramide 10 mg intravenously and dexamethasone 8 mg intravenously as postoperative nausea and vomiting (PONV) prophylaxis, and midazolam 10 mg orally for sedation. Patients in the nonopioid group had coinduction of propofol 2 mg/kg and analgesic dose of ketamine 0.5 mg/kg and rocuronium 0.5 mg/kg followed by intubation. Patients in the opioid group had coinduction of propofol 2 mg/kg and analgesic dose of fentanyl 2.5 mcg/kg and rocuronium 0.5 mg/kg followed by intubation. There is no statically significant difference between two groups according to oxygen saturation%.

Regarding VAS score, in this study, we found that there was a highly statistically significant decrease at 0 h

postoperatively in comparison with the other postoperative hours and also between two studied groups. Moreover, there was a significant difference between OA group and OFA group during the whole period study as determined by VAS, where it was lower in nonopioid group than opioid group. In agreement with the results of this study, the study done by Shalaby *et al.* [9] demonstrated that there were significant differences between two groups regarding VAS scores at 20, 60 min, and 6 h postoperatively, where it was lower in dexmedetomidine group than fentanyl group. On the contrary, Choi *et al.* [12] compared intraoperative infusion of dexmedetomidine, fentanyl, and remifentanyl on perioperative hemodynamics, sedation quality, and postoperative pain control in laparoscopic total hysterectomy and observed that VAS scores of postoperative pain were not significantly different among dexmedetomidine, fentanyl, and remifentanil groups. This may be because the analgesic effect of fentanyl and remifentanyl are stronger than that of dexmedetomidine when it is used alone to achieve an OFA technique.

Regarding total pethidine consumption in 24 h postoperative, in this study, there was a statistically significant difference between the two groups in total pethidine consumption, where it was lower in OFA group than OA group. In agreement with this study, the study performed by Hontoir *et al.* [13] included 66 female patients scheduled for breast cancer surgery and randomized them into two groups: induction in the opioid group started with a target-controlled infusion of remifentanil, and the opioid-free group received a loading dose of clonidine (0.2 μg/kg). Both groups then received a bolus of ketamine (0.3 mg/kg), lidocaine (1.5 mg/kg), and propofol (2–3 mg/kg). A statistically significant difference in postoperative piritramide (a synthetic opioid analgesic) consumption was observed. Our findings are also in agreement with the results of the study performed by Samuels *et al.* [14] who found in a retrospective analysis that OFA needed 50% less opioids postoperatively, whereas opioid-sparing anesthesia did not make any difference. In contrast, the result of our study are against the result concluded by Ziemann-Gimmel *et al.* [15] who performed a randomized, parallel group, single-center study that included a premedication with 2–4 mg of midazolam. Induction was performed using propofol and either succinylcholine or rocuronium in both groups. They also received 1 g of acetaminophen intravenously 20 min after induction and 30 mg of ketorolac 20 min before emergence. The classic group received fentanyl (0.5–1 μg/kg) during induction, and general anesthesia was maintained with either sevoflurane or desflurane. Opioids, including fentanyl, morphine, or hydromorphone, were given intraoperative at the provider's judgment. In the other group, a loading dose of dexmedetomidine (0.5 μg/kg) was administered, and then a drip was started at 0.1–0.3 μg/kg, along with an infusion of propofol at 75–150 μg/kg as TIVA. They found no difference in opioid consumption postoperatively for the same VAS scores but did not explain what postoperative period was compared. This may be owing to the use of dexmedetomidine only in TIVA group as an OFA regimen.

Regarding postoperative complications in PACU, in this study, there was a significant difference between the studied groups regarding nausea, vomiting, and shivering, but there were no significant differences between the study groups regarding hypoxia. In agreement with the results of this study, the study done by Jan *et al.* [10] measured the quality of recovery after OFA on 50 patients undergoing elective laparoscopic bariatric surgery and showed that the OFA patients had fewer PONV, shivering, and hypoxia in the PACU. In disagreement with this study, the study done by Mansour *et al.* [11], which included 28 obese patients (BMI>50 kg/m^2) undergoing laparoscopic sleeve gastrectomy, showed that there was no statistically significant difference between the groups regarding postoperative complications in PACU. This may be because all patients received ranitidine 50 mg as H2 receptor antagonist and metoclopramide 10 mg intravenously and dexamethasone 8 mg intravenously as PONV prophylaxis.

Conclusion

This study concluded that OFA provides intraoperative hemodynamic stability and postoperative analgesia without significant associated adverse effects compared with OA.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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