Original Article

Comparison of opioid-based and opioid-free TIVA for laparoscopic urological procedures in obese patients

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Abstract

Background and Aims: Perioperative pain management in an obese patient is challenging. The incidence of respiratory depression is higher in obese patients and is exaggerated with opioids. We evaluated the efficacy of opioid-free anesthesia with propofol, dexmedetomidine, lignocaine, and ketamine in obese patients undergoing urological laparoscopic procedures with reference to postoperative analgesic consumption, hemodynamic stability, and respiratory depression.

Material and Methods: In this prospective, randomized, blinded controlled study, patients were randomized to receive either opioid-based (opioid group) or opioid-free (opioid-free group) anesthesia. Postoperative pain was assessed using visual analog score (VAS) 30 min after recovery, hourly for 2 h and every 4 hourly for 24 h. The primary outcomes studied were respiratory depression, mean analgesic consumption and time to rescue analgesia. Intraoperative hemodynamic parameters, mean SpO_2, respiratory rate and postanesthesia care unit (PACU) discharge time were secondary objectives.

Results: There were no differences in the demographic and intraoperative hemodynamic profile between the groups. Incidence of respiratory depression, defined as fall in saturation, was more in opioid-based group. Postoperative analgesic requirement (225 ± 48.4 vs 63.6 ± 68.5 mg of tramadol with *P* value of <0.001) and PACU discharge times (18.1 ± 5.4 vs 11.7 ± 4.3 hours with *P* value of <0.001) were significantly less in the opioid-free group.

Conclusions: Opioid-free anesthesia is a safer and better form of anesthesia in obese patients undergoing laparoscopic urological procedures as there is a lower requirement of postoperative analgesia.

Keywords: Dexmedetomidine, ketamine, laparoscopic urological procedures, obese patients, propofol

Introduction

Obesity leads to a restrictive lung disease, causing reduction in functional residual capacity and total lung compliance.[1,2] Severe Obstructive Sleep apnea occurs in 10–20% of patients with body mass index (BMI) >35 kg/m^2 and is often undiagnosed. When an obese patient is supine and anesthetised, the depressant effects of many anesthetic agents and analgesics, particularly opioids, further decrease the lung compliance, leading to increased hypoxemia.[3] Opioid-based general anesthesia in these patients increases the incidence of postoperative respiratory depression, atelectasis, and pneumonia. Also, pain relief with opioids is associated with sedation, hence impeding rapid recovery and early mobilization.[3] Opioid-free total intravenous anesthesia (TIVA) is an alternative to this.

Opioid-free anesthesia is the use of multimodal or balanced analgesia. The principle of this is to gain additive analgesic effects from different drugs while minimizing side-effects, particularly those of opioids. Studies have shown that

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Access this article online

Quick Response Code:

Website: www.joacp.org

DOI: 10.4103/joacp.JOACP_382_18

How to cite this article: Bhardwaj S, Garg K, Devgan S. Comparison of opioid-based and opioid-free TIVA for laparoscopic urological procedures in obese patients. J Anaesthesiol Clin Pharmacol 2019;35:481-6.

opioid-free anesthesia fast tracks surgery, reduces hospital stay, promotes early mobilization and enteral nutrition.[4]

Prior studies which investigated opioid-free techniques are based on the combination of drugs acting on sympathetic nervous system, perioperative administration of local anesthetics, nonsteroidal anti-inflammatory drugs, and of adjuvant drugs, such as ketamine, magnesium etc.[5-9]

Laparoscopic urological surgery is more challenging in obese patients since they have excessive pneumoperitoneal insufflation pressures, longer anesthetic, surgical, and recovery times. Moreover, these procedures are usually done in Trendelenburg position which further leads to increased airway resistance. This along with reduced chest wall and diaphragmatic tone during general anesthesia causes increased incidence of atelectasis and retention of secretions leading to rapid deterioration during hypoventilation or apnea.[3] However, scant data are available regarding the safety and efficacy of opioid-free anesthesia in obese patients undergoing laparoscopic urological procedures. We, therefore, aimed to compare the efficacy of opioid-free and opioid-based anesthesia in terms of analgesia and hemodynamic stability in obese patients undergoing laparoscopic urological procedures.

Material and Methods

We enrolled 80 patients aged 20–60 years with American Society of Anesthesiologists (ASA) classification II or III physical status with BMI of 30 kg/m^2 or more undergoing laparoscopic urological procedures under general anesthesia in this blinded randomized controlled study. Approval of the Institutional Ethics Committee was taken and an informed consent was obtained from all patients enrolled in the study. Patients with history of known allergies to study drugs, opioid use 1 month prior to surgery, chronic opioid addiction, inability to comprehend visual analog scale (VAS), pregnant or lactating mothers and those with a history of significant hepatic, renal, or cardiac disease were excluded. Patients were randomized using computer-generated random numbers to receive either opioid-based (opioid group) or opioid-free (opioid-free group) anesthesia (n = 40, each group). A thorough preanesthetic check-up was conducted prior to surgery which included detailed history, general physical, and systemic examination of all patients. Relevant investigations were done prior to surgery. Patients were educated regarding use of visual analog scale (VAS) scoring system prior to the surgery.

Patients were kept nil orally from the midnight before surgery. They were premedicated with 0.25 mg alprazolam orally at 6:00 am on the day of surgery. In the operation theatre standard monitors were attached to the patient (electrocardiogram, noninvasive blood pressure, and pulse oximeter) and baseline parameters were recorded. Intravenous access was established with an 18G intravenous cannula. Patients, investigator assessing the postoperative parameters, and the data analyst were blinded to the study. The anesthetist providing anesthesia was not blinded to the study drugs administered. All patients received 1 mg of midazolam before induction of general anesthesia. Preoxygenation was done for 3 minutes before induction of anesthesia.

In the opioid-based group, anesthesia was induced with fentanyl 2 μg/kg and propofol 2.5 – 3.5 mg/kg, followed by atracurium 0.5 mg/kg for tracheal intubation, and maintained with continuous infusion of propofol 50 – 200 μg/kg/min and intermittent fentanyl 0.5 μg/kg bolus for maintaining bispectral index (BIS) between 40 and 60. In the opioid-free group, after a loading dose of dexmedetomidine 0.5 μg/kg over 10 min, anesthesia was induced with propofol 2.5 – 3.5 mg/kg, followed by atracurium 0.5 mg/kg, and maintained with continuous infusion of propofol 50 – 200 μg/kg/min and dexmedetomidine 0.1 – 0.3 μg/kg/h for maintaining BIS between 40 – 60. Lignocaine 1.5 mg/kg was administered at induction and an infusion of 0.1 mg/kg/h was started immediately after the loading dose. Ketamine 0.5 mg/kg was given before incision.

After intubation, patient's lungs were mechanically ventilated with an oxygen–air mixture to maintain end-tidal CO_2 between 35 and 40 mmHg. At the end of surgery, neuromuscular blockade was reversed using intravenous neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg). The trachea was extubated when adequate spontaneous ventilation (tidal volume >4 ml/kg) was established. Heart rate, mean arterial pressure, respiratory rate, and saturation were recorded intraoperatively. Dexamethasone (8 mg i.v.) was administered 15 min after induction of general anesthesia and ondansetron (4 mg i.v.) 20 min before the end of the operation in both the groups. All the patients received i.v. diclofenac (75 mg) 30 min after induction and i.v. paracetamol (1 gm) 20 minutes before emergence.

On arrival in the recovery room patients were asked to rate their pain using VAS rulers with slide indicator with 0–10 analog scale attached in front, with '0' mark corresponding to no pain and '10' mark representing worst imaginable pain. Patients were monitored for postoperative pain and any analgesic requirement 30 minutes after recovery, hourly for 2 h and every 4 hourly for a period of 24 h. Any patient showing VAS ≥4 at any point of time was administered intravenous tramadol initially as a bolus of 100 mg slowly over 2–3 minutes and if required an additional dose of 50 mg every 30 minutes after

90 minutes of initial bolus up to a total dose of 250 mg. Time of first rescue analgesic and total rescue analgesic consumed postoperatively were noted. Adverse effects of the drugs, if any, were also evaluated.

Demographic characteristics of the patients, amount of intraoperative propofol used, hemodynamic parameters, and the amount of rescue analgesic used in the postoperative period for 24 h, VAS, time of first rescue analgesic administration, extubation, orientation, and postanesthesia care unit (PACU) discharge times were noted.

Statistical analysis

Data were described in terms of range; mean ± standard deviation (±SD), median, frequencies (number of cases), and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups was done using Student's *t*-test and Mann–Whitney *U* test for independent samples for parametric and nonparametric data, respectively. For comparing categorical data, χ^2 test was performed and exact test was used when the expected frequency was less than 5. A *P* value less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows. The direction of null hypothesis was two-tailed.

Results

We excluded patients in whom the sugical procedure was converted to the open procedure were excluded. There was no significant difference between the two groups with respect to demographic profile [Table 1]. Intraoperative heart rate and mean arterial pressure and respiratory rate [Figure 1] were comparable between the two groups with an overall trend to decrease during the procedure. However, there is a significant drop of intraoperative SpO_2 values in opioid-based group which persists till 40 minutes compared to opioid-free group (*P* value <0.005 and 95% confidence interval 0.001–0.003). Propofol consumption was significantly higher in opioid-free group compared to opioid-based group whereas intraoperative BIS values were comparable between two groups. Extubation and orientation times at the end of surgery were significantly higher in patients of opioid-free group [Table 2].

Postoperatively, the hemodynamic parameters like heart rate, mean arterial pressure, and respiratory rate were significantly lower (more stable) in opioid-free group compared to opioid-based group whereas saturation remained comparable in both the groups [Figures 2 and 3]. Significantly fewer patients in the opioid-free group required rescue analgesia (95% confidence interval 44.1–85.9) [Table 3].

The need for the first dose of rescue analgesic was significantly earlier in the opioid-based group compared to the opioid-free group.The total analgesic dose requirement was also significantly greater in the opioid-based group compared to opioid-free group [Table 4]. Additionally, PACU discharge time was significantly lower in opioid-free group patients. In our institute, we follow Modified Aldrete system for PACU discharge [Table 5]. None of the patients developed skin rash, hypotension, hypertension, hypoxemia, sedation, bradycardia,

Table 1: Baseline characteristics of the two study groups

	Mean (SD)		*P*	95% Confidence interval of the difference	
	Opioid-based group	Opioid-free group		Lower	Upper
Gender	M: 14 (35%) F: 26 (65%)	M: 22 (55%) F: 18 (45%)	0.204		
Age (years)	46 (12)	46 (8)	0.988	−7	6
Weight (kg)	102 (15)	99 (12)	0.512	−6	11
BMI (kg/m^2)	37 (5)	35 (4)	0.217	−1	5
ASA physical status II ASA physical status III	22 (55%) 18 (45%)	16 (40%) 24 (60%)	0.179		

Data are expressed as mean and SD or numbers. SD=Standard deviation, ASA=American Society of Anaesthesiologists, BMI=Body Mass Index, M=Male, F=Female

Table 2: Comparison of perioperative data of patients in the two groups

	Mean (SD)		*P*	95% Confidence interval of the difference	
	Opioid-based group	Opioid-free group		Lower limit	Upper limit
Propofol dose for maintainence (mg/kg/h)	4 (1)	6 (1)	<0.001	−3	−1
Extubation time (min)	11 (2)	15 (3)	<0.001	−6	−3
Orientation time (min)	16 (2)	24 (4)	<0.001	−10	−6
BIS	50 (3)	48 (4)	0.126	−1	458

Data are expressed as mean±SD. SD=Standard deviation, BIS=Bispectral index

tachycardia, or recall of intraoperative events. The incidence of nausea and vomiting was not found to be statistically different between the two groups [Table 6].

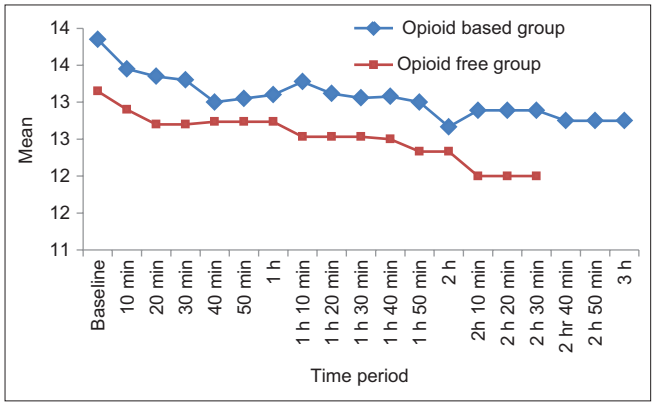

Figure 1: Changes of mean respiratory rate during intraoperative period in the two studied groups

Discussion

The results of our study indicate that opioid-free anesthesia is associated with lower rescue analgesic consumption in the postoperative period and earlier PACU discharge times compared to opioid-based TIVA. Opioids cause respiratory depression in obese patients, suggesting that alternative analgesics or sedatives are needed to improve pain

Table 3: Number of patients requiring rescue analgesic in each group

	Group		*P*
	Opioid-based group (*n*=40)	Opioid-free group (*n*=40)	
Patients requiring analgesia			
No	6 (15%)	32 (80%)	<0.001
Yes	34 (85%)	8 (20%)	

n=Number of patients in each group

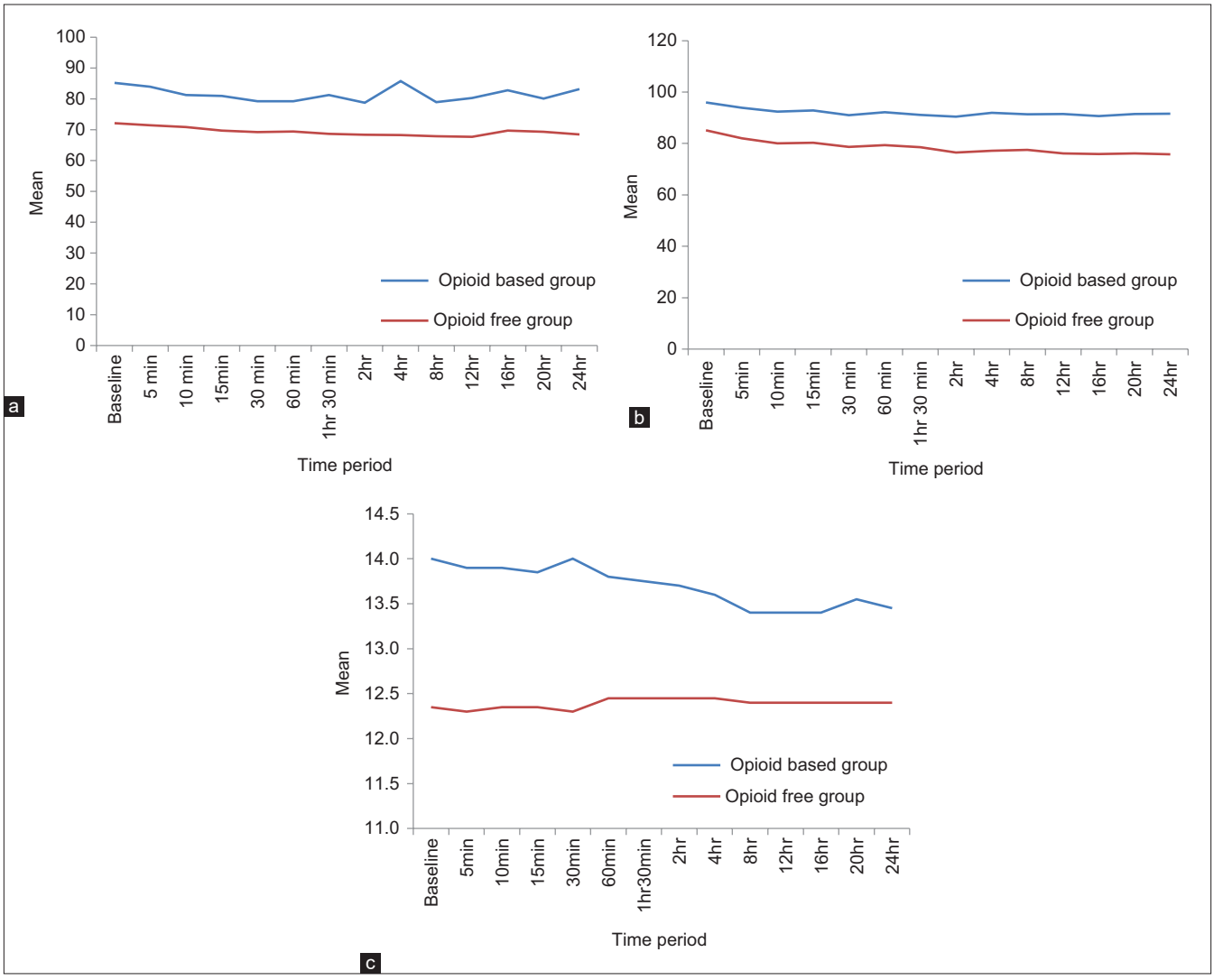

Figure 2: (a) Changes of mean heart rate during the 24 postoperative hours in the two studied groups. (b) Changes of mean arterial pressure during the 24 postoperative hours in the two studied groups. (c) Changes of mean Respiratory Rate during the 24 postoperative hours in the two studied groups

Table 4: Rescue analgesic requirement and VAS at that time interval

	Mean (SD)		*P*	95% Confidence interval of the difference	
	Opioid-based group	Opioid-free group		Lower limit	Upper limit
Time when first dose of rescue analgesic is required dose (h)	2 (1)	5 (1)	0.002	−4	−1
VAS	5 (1)	5 (1)	0.487	−1	−1
Total analgesic requirement (in mg)	226 (48)	64 (69)	<0.001		

SD=Standard deviation, VAS=Visual Analog Score

Table 5: Postanesthesia care unit discharge time

	Mean (SD)		*P*	95% confidence interval of the difference	
	Opioid-based group	Opioid-free group		Lower limit	Upper limit
Postanesthesia Care Unit Discharge time (h)	18 (5)	12 (4)	<0.001	3	10

SD=Standard deviation

Table 6: Incidence of postoperative nausea and vomiting

	Group		*P*
	OBA (*n*=40)	OFA (*n*=40)	
Nausea	10 (25%)	2 (5%)	1
Vomiting	5 (12.5%)	1 (2.5%)	
Total	15	3	

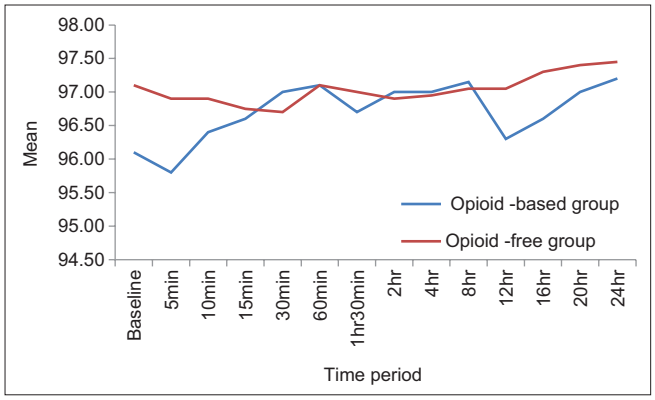

Figure 3: Changes of mean SpO2 during the 24 postoperative hours in the two studied groups

management in obese patients. The advent of newer and lesser cardio-depressant drugs form the basis of opioid-free anesthesia.[5-7]

Dexmedetomidine (α-2 adrenergic agonist) has been widely used for its analgesic, sedative/hypnotic, anxiolytic, and sympatholytic properties.[10] Turgut *et al.* found that propofol–dexmedetomidine combination leads to lower requirement of postoperative analgesics with stable hemodynamics compared with propofol–fentanyl in 50 patients undergoing elective spinal laminectomy.[11] In fact, numerous studies have validated the substitution of opioids with dexmedetomidine[11-14] with better postoperative analgesia and sedation without respiratory depression. In our study fewer patients reported pain and demanded rescue analgesic in the opioid-free group over 24 h.

Various clinical trials have suggested that intravenous lignocaine reduces postoperative pain[15] and dexmedetomidine further enhances this action Xu *et al.* demonstrated that the combination of intravenous lignocaine and dexmedetomidine infusion is superior in controlling pain.[16]

We used a subanesthetic dose of intravenous ketamine as it provides effective analgesia with clinical safety comparable to that of intravenous morphine.[17] Thus, combination of these drugs along with other nonopioid analgesic drugs in a multimodal approach can result in additive or synergistic analgesia leading to a reduction or avoidance of opioids during perioperative period. The total rescue analgesic demand decreased by 72% for 24 h postoperatively in opioid-free anesthesia. Rescue analgesic was demanded earlier in the opioid-based group compared to patients in the opioid-free group indicating superior pain relief with the use of opioid-free anesthesia technique.

Extubation and orientation times were prolonged in the opioid-free group. The use of dexmedetomidine might have delayed recovery.[8,9,18] A parallel increase in propofol consumption was seen which might have delayed the recovery further. In the postoperative period, hemodynamic parameters correlated well with the patient's comfort level.[19,20] There was a significant fall in SpO_2 values from baseline till 40 min of surgery in opioid-based anesthesia suggesting that opioids lead to respiratory depression in obese patients. PACU discharge times were shorter in opioid-free group patients because of better pain control, decreased opioid requirements, and hence fewer side effects.

The incidence of nausea and vomiting was not found to be statistically different between the two which can be ascribed to smaller sample size to detect differences in PONV.

In addition to the anesthetic agents used in this study, perioperative administration of dexamethasone[21] appears to be effective in combination with paracetamol and diclofenac[22] used as multimodal strategies to reduce postoperative pain and opioid consumption.

Limitations

None of our patients fall in super obese group, as in our study the BMI ranges from 30 to 36 kg/m^{-2}. We could not assess the sedation caused by opioids in our study. The data of modified Aldrete score were not available with us. We restricted our study to laparoscopic urological procedures and did not take other laparoscopic procedures in obese patients.

Conclusion

In obese patients, opioid-free anesthesia with dexmedetomidine, lignocaine, ketamine provides better postoperative analgesia and hemodynamics, with lesser postoperative tramadol requirement. Further studies are needed to support our findings and create awareness in clinical practice.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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