Original Article

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Opioid-based Anaesthesia versus Opioid Free Anaesthesia in Laparoscopic Cholecystectomies: A Randomised Clinical Study

Anaesthesia Section

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ABSTRACT

Introduction: Intravenous opioids have been frequently used to provide analgesia and supplemental sedation during general anaesthesia or monitored anaesthesia care. Opioid Free Anaesthesia (OFA) is a multimodal approach which combines different drugs likes lignocaine, dexamethasone, paracetamol and dexmedetomidine with different techniques- such as hypnosis, sedation, analgesia and sympatholysis. Thus, reducing and avoiding opioids perioperatively will lead to decrease in opioid related adverse effects with better postoperative outcomes.

Aim: To compare OFA and Opioid-based Anaesthesia (OBA) in terms of haemodynamic stability, speed and quality of recovery, postoperative pain score and analgesic requirement.

Materials and Methods: The present study was a randomised study conducted in the Department of Anaesthesiology, Mahatma Gandhi Memorial Medical Colledge, Indore, Madhya Pradesh, India, from June 2021 to September 2022. The study has enrolled 90 patients of American Society of Anaesthesiologists (ASA) Grade I, II, 20-60 years of age undergoing elective Laparoscopic Cholecystectomy (LC) were divided into OBA fentanyl and OFA-lignocaine and dexmedetomidine. A standard general anaesthesia protocol of the institute was followed. OBA group received fentanyl (2 µg/kg) over 10 minutes before induction of anaesthesia and OFA group received lignocaine (2 mg/kg) and dexmedetomidine (0.5 µg/kg) both intravenously over 10 minutes before induction of anaesthesia. In OFA group analgesia was maintained by infusion of lignocaine 2 mg/kg/hr and dexmedetomidine 0.5 µg/kg/hr, whereas in OBA group fentanyl 0.5 µg/kg was given whenever required till the gall bladder was resected. Postoperative intraperitoneal instillation of gall baldder fossa was done with 20 mL 0.5% bupivacaine. Intraoperative mean Heart Rate (HR) and Mean Arterial Pressure (MAP) were recorded. Postoperative speed and quality of recovery, pain score, analgesic requirements and incidence of Postoperative Nausea and Vomiting (PONV) were noted. Paracetamol 15 mg/kg was given intravenously whenever Numerical Rating Scale (NRS) score was ≥6. Comparison of means between the two groups was done using unpaired t-test, association between two non parametric variables was done using Pearson Chi-square (χ^2 test) test.

Results: The mean age, sex, weight, ASA and duration of surgery were comparable in both the groups. The mean HR was significantly lower in OFA group compared to the OBA group at all the time points (p-value ≤0.05). The mean MAP was significantly lower in OFA group at induction, after trochar insertion, after abdominal deflation and after extubation. Although, postoperative speed of recovery was slower in OFA group, the overall quality of recovery was better. The postoperative pain score, analgesic requirement and incidence of nausea and vomiting were all significantly less in OFA group as compared to OBA group with p-values of 0.02, 0.001 and 0.02, respectively.

Conclusion: OFA is new anaesthetic approach that provides better perioperative haemodynamic stability, postoperative pain control with less PONV and thus can be used safely and successfully.

Keywords: Cholecystectomy, Dexmedetomidine, Fentanyl, Lignocaine

INTRODUCTION

Opioids have long been used for providing analgesia during general anaesthesia and postoperative pain management. They are associated with nausea, vomiting, dizziness, constipation, respiratory depression, opioid-induced tolerance and hyperalgesia. The dose-dependent side-effects can be very disabling for the patient and can delay postoperative rehabilitation [1]. Thus, there has been a consistent search for sparing techniques in anaesthesia. So OFA, a multimodal approach with the use of non opioid analgesics and sympatholytic medications can reduce the requirement for perioperative analgesics [2]. The respiratory depression is most significant opioid side-effect [3]. This is crucial for individuals with conditions including obesity, sleep apnoea, chronic obstructive pulmonary disease and surgeries that have a high incidence of postoperative respiratory failure [4]. Indeed, modern postoperative analgesia is based on opioid sparing, synthetic opioids were widely adopted to limit the effects of hypnotic agents by reducing their doses, maintaining haemodynamic stability, reducing cardiac out putmaintaing coronary perfusion, spontaneous breathing and facilitating mechanical ventilation. By using Multimodal Analgesia (MMA) with an opioid-sparing strategy, OFA has been made practicable [2,5]. MMA is based on the synergistic combination of medicines with various mechanisms of action causing additive pain relief that targets various nociceptors throughout the pain pathway. Thus, the combination of medications and/or methods enables a good quality general anaesthesia without the use of opioids [6,7]. So far very limited studies have been done on opioid sparing techniques for general anaesthesia.

Since, OFA avoids opioid-related adverse effects, an OFA regimen consisting of dexmedetomidine and lignocaine infusions along with paracetamol as a co-analgesic can be an effective anaesthetic technique for patients undergoing LC compared to the standard OBA regimen [8,9]. It is also associated with intraoperative haemodynamic stability, lower postoperative pain intensity, lower analgesic requirements in the early postoperative period and less incidence of PONV and also enables earlier mobilisation with enhanced rehabilitation, faster discharge and improved patient satisfaction [10,11].

Hence, the present study was done to compare OFA and OBA in terms of intraoperative haemodynamic stability, speed of recovery and postoperative pain score as primary measures and total requirement of postoperative analgesic (Paracetamol) and antiemetic (Ondansetron), quality of recovery, incidence of postoperative side-effects both postoperatively as secondary measures.

MATERIALS AND METHODS

This double-blind, randomised, clinical study was conducted in the Department of Anaesthesiology, Mahatma Gandhi Memorial Medical Colledge, Indore, Madhya Pradesh, India, from June 2021 to September 2022. The patient and the observer both were blinded in the study. Approval from the Institutional Ethics and Scientific Committee was obtained (Letter No. EC/MGM/JUNE 21-22, date: 9, June).

Inclusion criteria: ASA I,II patients aged from 20 to 60 years of either gender scheduled for LC under general anaesthesia were included in the study.

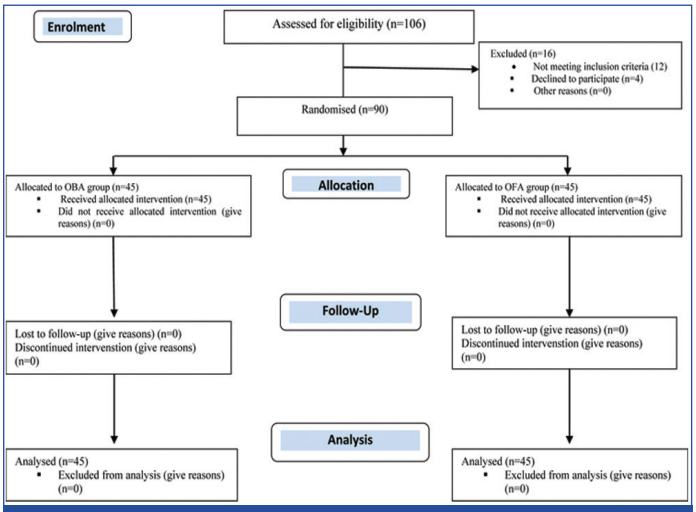
Exclusion criteria: Patients with allergy to study medication, history of analgesic dependence and opiate tolerance, epilepsy and psychiatric disturbances, pre-existing diseases like cardiopulmonary diseases, hepatic dysfunction, renal dysfunction, psychiatric illness, pregnancy and lactation were excluded from the study.

Sample size calculation: Sample size calculation was based on difference of means of two independent samples. The following formula was used for sample size estimation:

$$n_i = 2\left(\frac{Z_{1-\alpha/2}+Z_{1-\beta}}{ES}\right)^2$$

where ni is the sample size required in each group (i=1,2), α is the selected level of significance and Z 1-α/2 is the value from the standard normal distribution holding 1-α/2 below it, and 1-β is the selected power and Z 1-β is the value from the standard normal distribution holding 1-β below it. ES is the effect size=0.599, Sample size was calculated using G power, software version 3.1.9.2. The sample size obtained at 95% confidence interval with an 80% power of the study. Where a (type-I error rate)=0.05, b (power of the study)=0.8, non centrality parameter=2.8414, critical t=1.98, df=88. A total of 90 patients were included in the study.

Allocation: A thorough preanaesthetic evaluation was performed. Ninety patients satisfying inclusion criteria were randomly allocated by sealed envelope method into two groups with 45 patients in each. Opioid based (fentanyl) group-OBA and opioid free (lignocaine+dexmedetomidine) group-OFA [Table/Fig-1].



[Table/Fig-1]: Consort flow chart.

Procedure

On the day of the surgery, patient was allocated to the group as per randomisation and informed/written consent was taken. Standard fasting guidelines were followed. Patients were taught to express pain by using NRS depicted by a 10 cm line with 0 at one end and 10 at the other [12].

Baseline parameters HR, MAP and Oxygen Saturation (SpO_2) and End Tidal CO_2 ($ETCO_2$) were recorded and the patients were pre-medicated with inj. midazolam 0.05 mg/kg intravenously and inj-glycopyrrolate 10 µg/kg intramuscularly 30 minutes before induction of anaesthesia. Inj. dexamethasone 0.2 mg/kg and inj. paracetamol 15 mg/kg were both given intravenouslyover 10 minutes [13]. OBA group received fentanyl (2 µg/kg) over 10 minutes before induction of anaesthesia and OFA group received lignocaine (2 mg/kg) and dexmedetomidine (0.5 µg/kg) both intravenously over 10 minutes before induction of anaesthesia [14]. Induction was achieved by inj. propofol 2.5 mg/kg intravenously in both the groups. In both groups, intubation of trachea was facilitated by inj. succinylcholine 1.5 mg/kg intravenously and the airway was secured by appropriate size Endo-Tracheal Tube (ETT). Anaesthesia was maintained with O_2:N_2O 50:50 and isoflurane 0.6-1.6 vol% in a titrated manner. Muscle-relaxation was maintained with inj. vecuronium 0.1 mg/kg, intravenously as loading dose followed by top-up doses ($1/4^{th}$ of loading dose) as and when required.

In OBA group, additional fentanyl 0.5 µg/kg was given whenever HR was above 20% of baseline or MAP increased by 20% of baseline. In OFA group, a continuous infusion of inj. dexmedetomidine was maintained at a rate of 0.5 µg/kg/h with inj. lignocaine 2 mg/kg/hr till the gallbladder was resected. After removal of gallbladder, intraperitoneal instillation of 20 mL of 0.5% bupivacaine was done in gallbladder fossa in patients of both the groups [15]. At the end of surgery, reversal of neuromuscular blockade was done by inj. neostigmine 50 µg/kg and inj. glycopyrrolate 10 µg/kg intravenously. Tracheal extubation was performed when patients were conscious and achieved a regular spontaneous breathing pattern.

HR, MAP, SpO_2 and $ETCO_2$ were recorded at baseline, induction (after analgesic), induction (after propofol), after intubation, after trochar insertion, after CO_2 insufflation, after abdominal deflation and after extubation. Postoperative pain scores were assessed using NRS at 4 hours, 8 hours, 12 hours, 16 hours, 20 hours and 24 hours, postoperatively. Inj. paracetamol was given 15 mg/kg intravenous bolus whenever NRS was ≥6 for the first 24 hours in both groups. Speed of recovery in terms of time to spontaneous eye opening and time to extubation after switching off inhalational anaesthetics agents was assessed [16]. Quality of recovery was also recorded in two groups using a 15-item questionnaire [Table/Fig-2] [17,18]. In 24 hours the incidence of PONV and total postoperative antiemetic (ondansetron) used were also noted.

S. No.	Quality of recovery (QoR)-15 items	Score
1.	Able to breath easily	
2.	Been able to enjoy food	
3.	Feeling rested	
4.	Have had a good sleep	
5.	Able to look after personal toilet and hygiene unaided	
6.	Able to communicate with family or friends	
7.	Getting support from hospital doctors and nurses	
8.	Able to return to work or usual home activities	
9.	Feeling comfortable and in control	
10.	Having a feeling of general well-being	
11.	Moderate pain	
12.	Severe pain	
13.	Nausea or vomiting	
14.	Feeling worried or anxious	

15.	Feeling sad or depressed	

Where score 0, 1 and 2 is given for no satisfaction, average and good patient satisfaction respectively, and total score was added to give quality of recovery. Inter-item Correlation Matrix for the QoR-15 at 24 hour and 48 hour postoperatively. QoR-15 before surgery (but not on day of surgery) and 48 hour postoperatively provided a useful and feasible assessment of patient reported outcome after surgery.

[Table/Fig-2]: Quality of recovery (QoR)-15 items.

STATISTICAL ANALYSIS

After collecting the data, the statistical analysis was performed using Excel 2007 and IBM Statistical Package for the Social Sciences (SPSS) version-20.0. Appropriate test of significance was applied wherever necessary for calculating the p-values. Comparison of means between the two groups was done using unpaired t-test, association between two non parametric variables was done using Pearson Chi-square (χ^2 test) test. Quantitative data were described using mean, Standard Deviation (SD) and range. Categorical data were presented as frequencies and percentages. Changes in intraoperative haemodynamics among the two groups were analysed with one-way repeated measures Analysis of Variance (ANOVA). The p<0.05 was considered statistically significant.

RESULTS

The mean age, weight and ASA status of the patients were all comparable in two groups whereas a female preponderance was there in both the groups. The durations of surgery were also comparable in both the groups [Table/Fig-3].

Variable		OBA group	OFA group	p-value
Mean age		44.66±11.10	42.2±12.32	0.32[a]
Sex	Male	16 (35.6%)	14 (31.1%)	0.655[b]
	Female	29 (64.4%)	31 (68.9%)	
Weight (kg)		72.47±6.39	71.91±6.59	0.686[a]
ASA status- I/II		30/15	27/18	0.661[b]
Duration of surgery (min)		85.44±14.26	80.80±13.45	0.123[a]

[Table/Fig-3]: General characteristics and distribution of patients according to demographic data of studied groups (n=90).
a-unpaired t-test, b-Chi-square t-test

The mean baseline HR and mean MAP were comparable between the two groups (p-value >0.05). The mean HR was significantly lower in OFA group compared to the OBA group at all the time points (p-value <0.05) [Table/Fig-4]. Except for two time points (after intubation and after CO_2 insufflation), the mean MAP was significantly lower in OFA group compared to the OBA group (p-value <0.05) [Table/Fig-5].

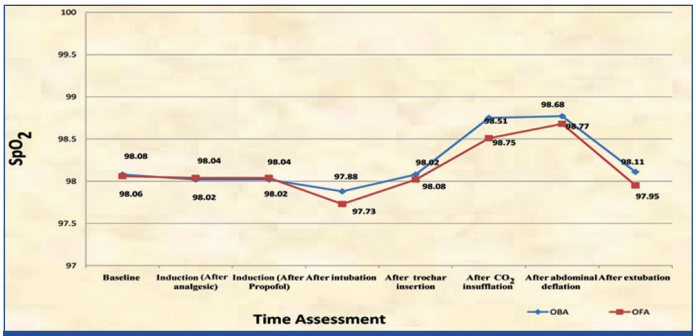
HR (beats/min)	OBA (Mean±SD)	OFA (Mean±SD)	t-value	p-value
Baseline	85.89±7.25	85.11± 8.62	0.46, df=88	0.643, NS
Induction (After analgesic)	90.38±5.69	76.73±8.05	9.27, df=88	**0.001***
Induction (After propofol)	80.13±7.15	69.33±7.08	7.19, df=88	**0.001***
After intubation	94.78±5.19	88.36±8.24	4.42,df=88	**0.001***
After trochar insertion	85.42±5.86	80.80±8.03	3.11, df=88	**0.002***
After CO_2 insufflation	89.00±8.27	84.62±4.94	3.04, df=88	**0.003***
After abdominal deflation	76.93±6.71	71.18±6.14	4.24, df=88	**0.001***
After extubation	88.16±5.63	82.31±5.14	5.14, df=88	**0.001***

[Table/Fig-4]: Comparison of mean HR between OBA and OFA groups.
*Significant (p-value <0.05)

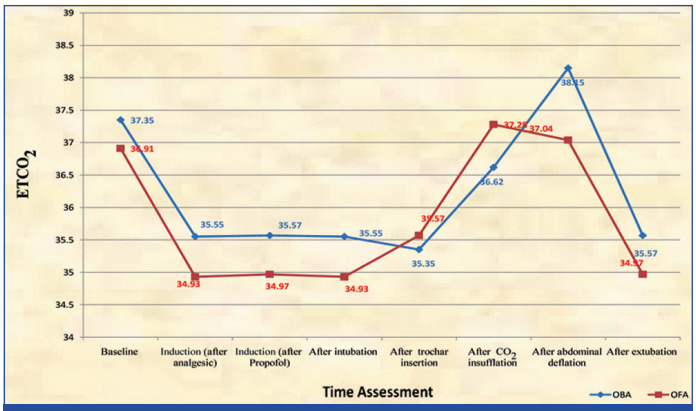
MAP	OBA (Mean±SD)	OFA (Mean±SD)	t-value	p-value
Baseline	94.58±7.70	93.40±9.29	0.65, df=88	0.515, NS
Induction (after analgesic)	95.04±4.86	86.00±5.68	8.11, df=88	**0.001***
Induction (after propofol)	84.07±5.04	77.47±6.25	5.51, df=88	**<0.001***
After intubation	83.47±6.15	84.76±5.95	-1.01, df=88	0.315, NS
After trochar insertion	80.27±5.84	75.11±5.87	4.17, df=88	**0.001***
After CO_2 insufflation	85.42±5.98	84.02±5.25	1.18, df=88	0.241, NS
After abdominal deflation	77.84±6.46	71.04±4.49	5.80,df=88	**0.001***
After extubation	86.60±6.29	79.27±5.28	5.99, df=88	**0.001***

[Table/Fig-5]: Comparison of mean MAP between OBA and OFA groups.
*Significant (p-value <0.05)

The mean baseline SpO_2 and $ETCO_2$ in patients of OBA group and OFA group were 98.08±0.87 versus 98.06±0.88 and 37.35±4.38 mmHg versus 36.91±4.24 mmHg respectively. Thereafter no significant changes were noted in both the values of two group at all points of time [Table/Fig-6,7].



[Table/Fig-6]: Comparison of mean SpO_2 between OBA and OFA group.



[Table/Fig-7]: Comparison of mean $ETCO_2$ between OBA and OFA group.

The postoperative mean NRS score was found to be significantly lower in OFA group in comparison to OBA group at 4, 8, 12, 16, 20 and 24 hours postoperative (p-value <0.05) [Table/Fig-8]. Thirteen (28.9%) out of 45 patients required paracetamol postoperatively in OFA group as compared to 31 (68.9%) patients in OBA group which was statistically significant (p-value <0.05) [Table/Fig-9]. There were 14 (31.1%) patients in OBA group who had PONV compared to 5 (11.1%) patients in OFA group (p-value=0.020) [Table/Fig-9].

Postoperative NRS score	OBA (Mean±SD)	OFA (Mean±SD)	t-test	p-value
4 hours	4.40±1.37	3.71±1.39	2.365, df=88	**0.020***
8 hours	4.33±1.39	3.62±1.05	2.728, df=88	**0.008***
12 hours	4.38±1.32	3.78±1.18	2.270, df=88	**0.026***
16 hours	4.27±1.16	3.78±0.90	2.237, df=88	**0.028***
20 hours	3.91±0.99	3.51±0.55	2.360, df=88	**0.020***
24 hours	3.84±0.99	3.44±0.63	2.278, df=88	**0.025***

[Table/Fig-8]: Comparison of postoperative mean NRS scores between OBA and OFA groups.
*Significant (p-value <0.05)

In present study, speed of recovery from anaesthesia i.e. mean time to spontaneous eye opening and to extubation in OBA versus OFA group were 23.58±3.27 minutes v/s 31.40±3.03 minutes and 27.16±3.01 minutes v/s 36.56±2.59 min respectively (p-value

	OBA (n=45)	OFA (n=45)	χ^2 test	p-value
Patients who required paracetamol	31 (68.9%)	13 (28.9%)	14.407, df=1	**0.001***
Patients who required ondansetron	14 (31.1%)	5 (11.1%)	5.404, df=1	**0.020***

[Table/Fig-9]: Comparison of postoperative analgesic (paracetamol) and antiemetic (ondansetron) requirement between OBA and OFA groups.
*Significant (p-value <0.05)

<0.05) [Table/Fig-10]. The mean QoR-15 score was 24.58±1.76 in OBA group and 25.93±1.42 in OFA group which is significantly better in OFA group as compared to OBA group (p-value=0.001) [Table/Fig-11].

	OBA (Mean±SD)	OFA (Mean±SD)	t-value, df	p-value
Time to spontaneous eye opening (min)	23.58±3.27	31.40±3.03	-11.789, df=88	**0.001***
Time to extubation (min)	27.16±3.01	36.56±2.59	-15.866, df=88	**0.001***

[Table/Fig-10]: Comparison of speed of recovery between OBA and OFA groups.
*Significant (p-value <0.05)

	OBA (Mean±SD)	OFA (Mean±SD)	't' value, df	p-value
(QoR)-15	24.58±1.76	25.93±1.42	-4.014, df=88	**0.001***

[Table/Fig-11]: Comparison of postoperative mean quality of recovery (QoR)-15 score between OBA and OFA groups.
*Significant (p-value <0.05)

DISCUSSION

The goal of providing OFA has been made possible by MMA. MMA is based on the synergistic use of drugs with different modes of action, leading to additive pain management that works at different nociceptors along the pain pathway. So, intraoperative anaesthesia evolved from single agent anaesthesia to opioid based anaesthesia and the multimodal or balanced anaesthesia [2]. Now-a-days, balanced OFA is feasible as it allows opioid sparing and is based on the concept that one drug will not replace opioid, rather it is the association of drugs and/or techniques that allows a good quality general anaesthesia with no need for opioids [5]. So the present randomised clinical study was conducted to compare two techniques i.e., OFA versus OBA for patients undergoing LC. The study findings showed that patients in OFA group had a better intraoperative haemodynamic stability than patients in OBA group. They also had lower pain scores with lesser postoperative analgesic requirement. Although the speed of recovery from anaesthesia was slower in OFA group as compared to OBA group due to sedative effects of dexmedetomidine, the overall quality of recovery was better in OFA group.

In the present study, intraoperative mean HR and mean MAP were significantly lower intraoperatively in OFA group compared to the OBA group and the differences were statistically significant (p-value <0.05) [Table/Fig-4,5]. These results were coherent with the findings of the study performed by Vora KS et al., in 70 patients scheduled for elective laparoscopic surgeries, who received bolus infusion of dexmedetomidine (Group D) or saline (Group S) 1 mcg/kg/h, followed by continuous infusion of the same at the rate of 0.5 mcg/kg/h, where intraoperative mean HR was found to be lower in Group D than Group S (p-value <0.05) [19]. These results were contradictory with the findings of a study performed by Ahmed OH and Noor El-Din TM, in which 62 patients were scheduled for LC which compared fentanyl with the combination of dexmedetomidine, ketamine and paracetamol as anaesthetic adjuvant in perioperative analgesics [20]. The intraoperative HR, mean BP were lower in OFA, although statistically insignificant. This could be because of ketamine used in their study which is a sympathetic stimulant. The better haemodynamic stability and lower reading of mean HR and mean MAP in the present study may be due to additive negative inotropic effects of lignocaine and sympatholytic effects of dexmedetomidine.

In the present study, mean NRS score were found to be lower in OFA group in comparison to OBA group at 4, 8, 12, 16, 20 and 24 hours postoperatively (p-value <0.05). In OFA group, 13 (28.9%) out of 45 patients required paracetamol postoperatively as compared to 31 (68.9%) patients in OBA group which is statistically significant (p-value <0.05). The results of the current study were nearly consistent with the study done by Shalaby M et al., on 80 patients scheduled for elective LC which showed that NRS scores were lower at 20 minutes, 60 minutes and six hours postoperatively in OFA group than the OBA group the difference was statistically significant [21]. The results of the current study were again consistent with the study done by Toleska M and Dimitrovski A on 60 patients scheduled for elective LC, which compared general balanced anaesthesia with fentanyl (F-group) and opioid-free general anaesthesia (OFA-group) [22]. In the postoperative period, patients in the fentanyl group had higher pain scores as compared to those in OFA group. The total opioid requirement in the postoperative period was significantly higher in the fentanyl group as compared to the OFA group.

The speed of recovery from anaesthesia in terms of mean time to spontaneous eye opening and mean time to extubation both were delayed in dexmedetomidine (OFA) group as compared to fentanyl (OBA) group which was statistically significant (p-value <0.05). These results were coherent with the findings of study performed by Siddiqui T et al., in patients posted for LC [23]. Dexmedetomidine group had longer on table recovery time and time to discharge from Postanesthesia Care Unit (PACU) (p-value <0.001) as compared to fentanyl group. The slower speed of recovery from anaesthesia in OFA group in present study could be attributed to sedative and hypnotic effects of dexmedetomidine, which is an alpha-2 adrenergic agonist.

In the present study, mean QoR-15 score of 25.93±1.42 in OFA group was better than 24.58±1.76 in OBA group with a statistically significantly difference (p-value <0.05). QoR-15 score shows the overall quality of anaesthesia i.e., less PONV, less postoperative pain, early mobilisation and rehabilitation. The results of the current study were supported with a study conducted by Al Bahar MY et al., who compared the effectiveness of OA versus OFA on 60 morbidly obese patients undergoing LC under general anaesthesia [24]. The patients of OBA group received general anaesthesia with propofol, muscle relaxant and fentanyl as the main anaesthetic adjuvant and analgesic and those of OFA group received general anaesthesia with propofol, muscle relaxant, dexmedetomidine, ketamine and lidocaine as anaesthetic adjuvant and analgesic. OFA provided perioperative haemodynamic stability, postoperative pain relief with less analgesic consumption, less incidence of PONV, acceptable patient sedation and satisfaction than that of the opioid based anaesthesia in morbidly obese patients.

In the present study, in OBA group 14 (31.1%) out of 45 patient required ondansetron postoperatively as compared to 5 (11.1%) patient in OFA group the difference being statistically significant (p-value=0.020).

Limitation(s)

The present study was done on ASA I,II group patients which limit the application of this protocol in practice setting with lower co-morbidities. So specific patient's population those with obesity, obstructive sleep apnoea and chronic pain should be targeted specifically in future studies on more complex surgeries which require longer period of hospitalisation and recovery to allow better assessment of OFA effects.

CONCLUSION(S)

From the observation and result of above study, it may be concluded that OFA eliminates opioid-related side-effects, provides better perioperative haemodynamic stability and postoperative pain

relief with less analgesic requirement and less incidence of PONV in patients undergoing elective LC as compared to opioid based anaesthesia. Thus, it can be adopted as a feasible and emerging technique of general anaesthesia in future.

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