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Opioid Free Anesthesia is Not Always the Ideal Paradigm; Balanced Opioid-Free Anesthesia with Dexmedetomidine Versus Balanced Opioid Sparing Anesthesia with Fentanyl for Laparoscopic Bariatric Surgeries: A Randomized Study

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Abstract

Background: Opioid drawbacks on bariatric patients make a scientific revolution by administering a technique that limits or excludes opioid use. The role of opioid-free anesthesia remains controversial.

Objective: Investigate the cost-benefit of using intraoperative balanced opioid-free anesthesia with dexmedetomidine in comparison to opioid-sparing anesthesia with fentanyl after laparoscopic bariatric surgeries.

Methods: This prospective randomized double-blind was conducted on 60 adult patients, aged 18-60 years, body mass index between 35-45 kg/m^2, and scheduled for elective laparoscopic bariatric surgery. Patients were randomized into two equal groups. Fentanyl group: received opioid-sparing anesthesia and dexmedetomidine group received opioid-free anesthesia.

Results: Postoperative hypoxemia was observed at 60% and 43% in the DEX and fentanyl groups, respectively, without statistical significance but with clinical significance. Bradycardia (<45 bpm) was clinically significantly more common in the DEX group (19 cases). Additionally, PONV was more clinically significant in the fentanyl group, without statistical significance. The total postoperative tramadol requirement within 24 hours was 175 mg in the fentanyl group and 50 mg in the dexmedetomidine group ($P \leq 0.001$). The time of extubation was significantly higher in the dexmedetomidine group than in the other group (37.3 minutes and 12.4 minutes, respectively) ($P \leq 0.001$).

Conclusion: opioid-sparing anesthesia is preferable to opioid-free anesthesia in bariatric surgeries because patients on opioid-free anesthesia with dexmedetomidine experienced more intraoperative significant bradycardia, postoperative hypoxemia, a longer time for extubation, and a longer stay in the post-anesthesia care unit despite reduced postoperative opioid intake and postoperative nausea and vomiting.

Keywords: Dexmedetomidine; Fentanyl; Laparoscopic Bariatric Surgeries; Opioid-Free Anesthesia; Opioid Sparing Anesthesia; Opioid drawbacks

Introduction

Immobility, antinociception, amnesia, and unconsciousness are all components of balanced general anesthesia (GA). Production of signals of nociception are continuous under GA. GA may have detrimental physiological consequences and increases the chance of awareness [1, 2]. Opioids function as principal antinociception agents and arousal is reduced by modulating receptor activity at several levels. Sedative-hypnotics are not required for induction and maintenance of general anesthesia when opioids are utilized in conjunction with other GA components as an adjuvant [3, 4].

Anesthesiologists are embracing a paradigm shift or scientific revolution by administering a technique that limits or excludes opioid use. Bariatric centers worldwide have accumulated data using an opioid-free regime that could be useful in many clinical scenarios, relying on non-pharmacological agents to control intraoperative nociception [5].

The objectives of opioid avoidance in surgeries are reducing or preventing opioid-induced hyperalgesia (OIH) [6], pharyngeal muscle weakness, tolerance and addiction, vomiting, central muscle rigidity, respiratory depression, ileus, constipation, dizziness, excessive somnolence, the possibility of inferior outcomes in oncology, obstructed breathing, nausea and urinary retention [7].

OIH has been observed in human volunteers and animal models. Remifentanil, fentanyl, morphine, and diamorphine have been identified as opioids that may induce OIH under these experimental settings [6]. Owing to the reduction of opioid-induced adverse effects, opioid-free anesthesia (OFA) has been utilized for a number of years to enhance postoperative recovery and reduce risks. In the context of OFA, anaesthetic adjuncts, including lidocaine, ketamine, magnesium and dexmedetomidine (DEX) are utilised in place of opioids. To reduce postoperative nausea and vomiting (PONV) and pain after surgery, The application of OFA in a variety of surgical procedures has been studied (e.g., cardiac surgery, bariatric surgery, gynecologic surgery, orthopedic surgery, and urological surgery. Furthermore, there is evidence that OFA enhances recovery after surgery [8]. However, these studies were limited by observational design thus we conducted this RCT to generalize these findings.

Objective of Study: to determine whether balanced OFA with DEX decreases the need of opioids after surgery and related adverse events compared to balanced anesthesia with fentanyl after laparoscopic bariatric surgeries.

Materials and Methods

This prospective randomized double-blind was carried out on 60 adult patients, both sexes, aged 18-60 years old, classified by the American Society of Anesthesiologists (ASA) class II and III, with body mass index (BMI) between 35 and 45 kg/m2, and scheduled for elective laparoscopic bariatric surgery. The study was done from January 2022 to December 2022, after the institutional ethics committee approval Anesthesia and Intensive Care department, Tanta University Hospitals, Tanta, Egypt, (approval code: 35221/1/22). The protocol was registered in the Pan African Clinical Trial Registry (PACTR202203767098081). (https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=21484). Written informed consent was obtained from all patients. Exclusion criteria were chronic opioid or beta-blocker use, renal or hepatic insufficiency, known allergy to study drugs, epilepsy, atrioventricular block type II & III, and thyroid gland disorders.

Randomization and blindness

Using a computer-generated random number, the cases were randomized into two equal groups. Fentanyl group: received opioid-sparing anesthesia (OSA), DEX group: received intraoperative OFA.

Cases, and outcome assessors were blinded. A blindfolded nurse who was not involved in the study or data collecting read the number on the envelope and assigned the patients to their groups. A second anesthesiologist, who was not informed of the group assignment, assessed intraoperative and postoperative measures.

Laboratory investigations were performed in addition to general and physical examinations and history collection for each case. Cases were informed about Numerical Rating Scale (NRS) [ranges from 0 to 10, with 0 denoting no pain and 10 denoting the most excruciating pain imaginable].

Upon entering the operating room, an 18-gauge intravenous (IV) cannula was attached to each patient, who then underwent standard monitoring, including electrocardiogram (ECG), non-invasive blood pressure measurement, pulse oximetry, temperature probe, and capnogram. Each patient received dexamethasone (4 mg IV) at the beginning of surgery and ondansetron (4 mg IV) at the end of surgery as a prophylaxis to PONV. No sedatives were given.

All patients had pre-oxygenation for a duration of three minutes at a fraction of inspired oxygen (FiO_2) adjustment of 1.0, while maintaining a head-up posture of 25º. All doses were adjusted to the ideal body weight (IBW). Thereafter, anesthesia was induced with lidocaine 1.5 mg/kg IV, fentanyl 1-2 mcg/kg, propofol 2 mg/kg, ketamine 25 mg, and cis-atracurium 0.15 mg/kg for intubation. Anesthesia was maintained with sevoflurane in 50% air at a minimum alveolar concentration (MAC) of 2-3% and cis-atracurium 0.03 mg/kg increments guided with a nerve stimulator.

All patients received magnesium in doses of 30 to 50 mg/kg IV bolus [to reduce hemodynamic variability during surgery, pain control and to provide stable anesthesia], followed by a 10- to 15-mg/kg/h infusion [9], along with lidocaine infusion of 40 mcg/kg/min during surgery [to provided analgesic effect], which de-escalated to 0.5-1 mg/min at the end of surgery [10].

Low tidal volumes (6–8 ml/kg IBW) and a PEEP of 10 cmH_2O were utilized as lung protective ventilation techniques. A rate adjustment was made to keep the end-tidal CO_2 pressure (40 mmHg). A 30 cm H_2O maximum peak pressure was permitted. The starting FiO_2 was 0.5 under anesthesia, and it was adjusted based on the SpO_2. The intraoperative aim was to maintain an adequate depth of anesthesia (bi-spectral index between 40 and 60).

Hypertension and tachycardia were frequent clinical manifestations of insufficient analgesia [2].

Enrolled patients were assigned to manage inadequate analgesia either by fentanyl 25-50 mcg through fast infusion *(fentanyl group)* or DEX administered IV at an infusion rate of 0.25 to 1 mcg/kg/h adjusted according to the patient's hemodynamics *(DEX group)*. Fentanyl and DEX ceased after the surgery was ended.

Placebo infusion at a rate of 0.25 to 1 mcg/kg/h was administered in fentanyl group, and placebo boluses in case of inadequate antinociception were taken in DEX group to ensure blindness of the research.

After surgery Reversal was done using atropine 0.02 mg/kg and neostigmine 0.05 mg/kg at the surgery end. The trachea was extubated in a head-up posture with a positive pressure of 10 cm H_2O at an adjusted FiO_2 of 1.0 when the patient was completely awake and breathing independently.

In the post-anesthesia care unit (PACU), in the case of NRS score ≥ 3, tramadol 100 mg in 100 ml saline was administered I.V.

The primary outcome was adverse effects related to the analgesic modality utilized, including postoperative hypoxemia, perioperative bradycardia, and PONV. The secondary outcomes included postoperative pain and the total 24-hour postoperative analgesic requirement.

Calculation of the Sample Size

Calculation of the sample size was done by G*Power 3.1.9.2 (Universitat Kiel, Germany). Based on the findings of a prior study, required a minimum of 25 cases in each group [11] to detect a 8 mg reduction in overall opioid intake, with a 0.05 error, a 9.8 standard deviation, and an 80% research power. To overcome dropouts, we enrolled 30 cases in each group.

Statistical Analysis

SPSS 26 (SPSS Inc., Chicago, IL, USA) was the statistical analysis program used in this study. The Shapiro-Wilk test was employed to assess the normality of the data. Quantitative variables were presented as mean and standard deviation (SD), and Student's independent t-test was used to compare between the two groups. Analyses of quantitative non-parametric data were conducted using the Mann Whitney test and were provided as the median and interquartile range (IQR). The Chi-square test or Fisher's exact test was used to evaluate categorical data, which were presented as the number of patients and a percentage (%) where suitable. A two--tailed P value less than 0.05 was deemed to be significant.

Results

Eleven of the seventy-one patients who were considered for inclusion in the study were rejected; six of them did not match the requirements, and five patients declined to take part. The remaining sixty patients were randomly divided into two study groups, thirty patients each. Figure 1

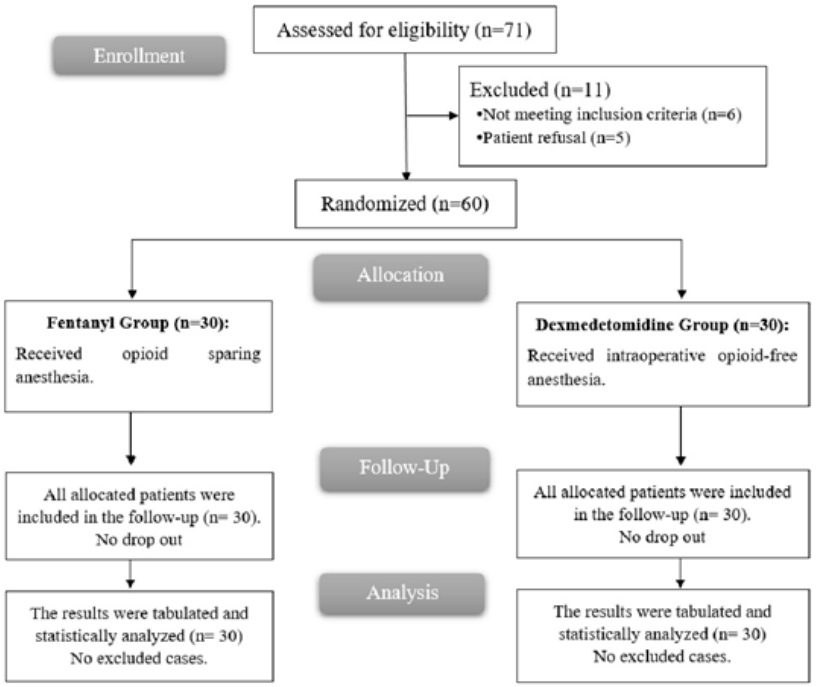

Figure 1: CONSORT flowchart of the enrolled patients

The patient characteristics (age, gender, body weight, and BMI) of both groups were comparable. Table 1

Table 1: Demographic data of the studied groups

	Fentanyl group (n=30)	DEX group(n=30)	P value	95%CI
Age (years)	34.97 ± 12.6	35.93 ± 12.89	0.770	-7.56: 5.62
Gender	16 (53.33%)	17 (56.67%)	0.786	0.61:1.46
Weight (kg)	116.2 ± 16.23	119.13 ± 12.9	0.441	-10.51: 4.64
BMI (kg/m^2)	42.11 ± 3.68	42.37 ± 3.11	0.763	-2.03: 1.49

Data are presented as mean ± SD or frequency (%). CI: Confidence interval.

Postoperative hypoxemia was observed in 18 patients (60%) in the DEX group and 13 patients (43%) in the fentanyl group, without statistical significance (P = 0.196, CI 0.44:1.19) but with clinical significance. Furthermore, bradycardia less than 45, requiring administration of atropine, was clinically significantly more prevalent in the DEX group [19 cases] compared to the fentanyl group [13 cases]. Table 2 Additionally, PONV was clinically significant in the fentanyl group with 11 cases compared to 6 cases in the DEX group, without statistical significance (P = 0.152, CI 0.78:4.32).

	Fentanyl group (n=30)	DEX group (n=30)	P	95%CI
PONV	11 (100%)	6 (100%)	0.152	0.78:4.32
Hypoxemia	13 (100%)	18 (100%)	0.196	0.44:1.19
Bradycardia	13 (43.3%)	19 (63.3%)	0.120	

Table 2: Perioperative adverse events of Fentanyl and DEX groups

Presentation of data is as number (%). P < 0.05 is significant. PONV: postoperative nausea and vomiting. DEX: Dexmedetomidine. CI: Confidence interval.

The total postoperative tramadol requirement within 24 hours was 175 mg [100-250] in the fentanyl group and 50 mg [50-100] in the DEX group (P ≤ 0.001, CI 67.42: 130.98). The prolonged time of extubation was significantly higher in the DEX group than in the other group (37.3 minutes and 12.4 minutes, respectively) (P ≤ 0.001, CI -29.7: -20.03). Table 3

	Fentanyl group (n=30)	DEX group (n=30)	P	95%CI
Tramadol consumption (mg)	175 (100-250)	50 (37.50-100)	<0.001*	67.42: 130.98
Extubation time (min)	12.43±4.18	37.3±12.5	<0.001*	-29.7: -20.03
Time to reach Aldert score >9 (min)	62.2±20.9	89.5±30.1	<0.001*	-40.75: -13.95

Table 3: Tramadol consumption, extubation time and time to reach Aldert score >9 of Fentanyl andDEX groups

Presentation of data is as mean ± SD or median (IQR). *: Significant, P < 0.05 is significant. DEX: Dexmedetomidine. CI: Confidence interval.

However, the number of episodes where the number of patients with an NRS scale was greater than 3 after surgery during the first 12 hr. was significantly lower in DEX group compared to Fentanyl group (P=0.020, CI -0.29: 0.69). Table 4

	Fentanyl group (n=30)	DEX group (n=30)	P
0 time	2 (6.6%)	1 (3.3%)	0.553
30 min	3 (10%)	4 (13%)	0.687
1 h	3 (10%)	4 (13%)	0.687
6 h	14 (46.6%)	10 (33%)	0.291
12 h	20 (66.6%)	11 (36.6%)	0.020*

Table 4: Number of patients with NRS>3 of Fentanyl and DEX groups

Presentation of data is as number (%). *: Significant, P < 0.05 is significant. NRS: Numerical Rating Scale. DEX: Dexmedetomidine.

Moreover, the time of recovery was prolonged in the DEX group [89 minutes] in comparison to the fentanyl group [62 minutes] (P ≤ 0.001, CI -40.75: -13.95).

Discussion

Perioperative liberal use of opioids, opioid-sparing, and OFA are three modalities used as anesthetic techniques for obese individuals undergoing bariatric procedures. Despite the advantages of opioids, because of their known short-term drawbacks they need to be used cautiously, which can affect cost and patient-important outcomes [12].

In this double-blind randomized trial, we emphasized demonstrating the benefits and drawbacks of opioid-free balanced anesthesia with DEX in comparison to OSA with fentanyl in patients undergoing elective bariatric surgery. DEX opioid-free balanced anesthesia was linked to an increased frequency of perioperative severe adverse events than OSA with fentanyl. Patients in the OFA with DEX group experienced greater intraoperative bradycardia, greater postoperative hypoxemia, and delayed emergence, without substantially affecting the pain score after surgery. Conversely, DEX bounty is not denied. Less tramadol was used and there were fewer instances of postoperative nausea and vomiting during OFA. One can speculate that the decrease in postoperative nausea and vomiting may not be due to tramadol sparing alone. As was already established, DEX may have a protracted antiemetic effect [13].

Overall, our findings show prolonged sedation in the OFA group, while DEX responds to dose tapering. Therefore, no bolus dose of DEX was decided to be administered, but rather a starting dose of the infusion of 0.25 mcg/kg/h, and researchers were instructed to modify the continuous infusion dose based on the patient's heart rate (with an upper limit of 1 mcg/kg/h).

Moreover, this dose gains hemodynamic stability with minimal bradycardia or hypotension.

This study is in accordance with the research carried out by Beloeil et al. [14]. They classified 314 cases undergoing noncardiac surgery into two groups, a remifentanil group and a DEX group. Less morphine is used when anesthesia is free of opioids. There are also fewer cases of postoperative nausea and vomiting. This trial disproved the idea that OFA with DEX would lead to less adverse outcomes associated to opioids after surgery compared to remifentanil. However, it did lead to a higher occurrence of significant adverse effects, particularly bradycardia, hypoxemia, and somnolence.

In another words, SOFA trial 2024 concluded that opioid-free anesthesia protocol improving quality of recovery after major elective surgery in a statistically but not clinically significant manner when compared to standard anesthesia [15].

On the near path; Feenstra ML. et al [16] in their recent systematic review on OFA, there is moderate quality evidence from 38 studies demonstrating that there is no clinically relevant change with OFA on opioid use or Numeric Rating Scale (NRS) ratings throughout the postoperative period. The compound is on less PONV with OFA.

On the other hand, our research is not incoherent with Ulbing et al. [17]. They favor OFA in bariatric surgeries. The nature of conflict attributed to the use of remifentanil in a liberal manner making mentioned OIH and giving superiority to OFA.

Also in bariatric surgeries, Mulier reported [5] that the OFA was accompanied with better emergence, decreased PONV, as well as morphine consumption and oxygen desaturation postoperatively. In another study with his colleague in 2019, similar outcomes were also observed by a sizable retrospective analysis that included 9,246 patients who underwent bariatric surgery [18].

Frauenknecht et al. [19] meta-analysis and systematic review have also mentioned the advantages of OFA. The substantial degree of study heterogeneity contained calls for care in the analysis of the findings.

Regarding the impact of OFA on overall sedation during emergence, prolonged postoperative sedation, PACU stay, extubation time, previous research has shown inconsistent results[20, 21]. These differences can be brought on by the various DEX doses used.

The effective optimum DEX dosage needed during general anesthesia to maintain hemodynamic stability while minimizing adverse effects has not been identified. Doses vary from one study to another. According to our study, we support the infusion of 0.25 mcg/kg/h (with an upper limit of 1 mcg/kg/h) as mentioned.

In our study and the majority of earlier studies, bradycardia was observed when DEX was injected intraoperatively during OFA or even when it was given in an intensive care unit [22]. Warnings from this were stated in a meta-analysis that provided evidence of great confidence of a risk of bradycardia [23] and confirmed in Feenstra ML. et al systematic review [16].

Concerning the prevalence of hypoxemia observed in our research, it was obvious in the balanced OFA with the DEX group to be due to the sedative effect of DEX, and it could have contributed to the increased frequency of serious adverse events [24].

Limitations to Our Study: include the small sample size involved making clinical significant results are not statistically significant. Unfortunately, bariatric surgeries are still not in the desired zone for inclusion larger number of patients in our community. Also, the trial's design predicated the analgesic dosage on the patient's hemodynamics as there are no validated nociception monitors available for use during OFA.

Future Research Directions: preparing already multicenter research on three groups; opioid liberal group, opioid sparing group, and OFA group to make powerful research and more conclusive research.

Conclusion

OSA is preferable to OFA in bariatric surgeries because patients on OFA with DEX experienced more intraoperative significant bradycardia, postoperative hypoxemia, a longer time for extubation, and a longer stay in the PACU despite reduced postoperative opioid intake and PONV compared to patients receiving fentanyl.

Ethics Approval and Consent to Participate

The study was done from January 2022 to December 2022, after the institutional ethics committee approval Anesthesia and Intensive Care department, Tanta University Hospitals, Tanta, Egypt, (approval code: 35221/1/22). The protocol was registered in the Pan African Clinical Trial Registry (PACTR202203767098081). (https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=21484). Written informed consent was obtained from all patients.

Human and Animal Rights

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research com

Consent for Publication

Informed consent was obtained from the participants prior to participation. mittees.

Availability of Data and Materials

Every data produced or analyzed while this research is available for sharing from the corresponding author upon reasonable request.

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Conflict of Interest

None to be declared

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There is none to be declared

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