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## **Effects of opioid-free anesthesia on postoperative morphine consumption after bariatric surgery**

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## Abstract

**Study objectives:** The objective of this study was to determine whether postoperative morphine requirement in obese patients undergoing laparoscopic bariatric surgery was reduced by opioid-free anesthesia (OFA), as compared to an anesthetic strategy using opioids (opioid balanced anesthesia (OBA)) and to investigate the differences that may exist between the use of clonidine and dexmedetomidine in the context of OFA.

**Design:** Retrospective cohort study.

**Setting:** Academic medical center in Lyon, France.

**Patients:** 257 patients who underwent laparoscopic bariatric surgery between March 2017 and March 2019. 77 patients were included in the OBA group and 180 in the OFA group. The OFA group was subdivided in two: 90 patients received OFA with clonidine (OFAC) and 90 received OFA with dexmedetomidine (OFAD).

**Measurements:** Proportion of patients who did not receive morphine during the first 24 postoperative hours.

**Main results:** During the first 24 postoperative hours, the proportion of patients who did not require morphine was significantly higher in the OFA (87%) than in the OBA (52%) group (OR: 6.31; 95% CI [3.38; 11.80],  $P < 0.001$ ). This difference remained significant after adjustment for age, body mass index, sex, type and duration of surgery (OR: 7.99; 95% CI [4.05; 16.48],  $P < 0.001$ ). A greater proportion of patients in the OFAD (93%) than in the OFAC group (81%,  $P = 0.026$ ) did not receive morphine during the same period.

**Conclusions:** OFA is associated with a lower morphine requirement than with OBA during the first 24 hours after bariatric surgery. In addition, OFAD seems to be more effective than OFAC in order to reduce morphine consumption.

## Introduction

Opioids are widely used for perioperative analgesia. However, their perioperative use is associated with postoperative hyperalgesia with increased analgesic requirements, postoperative nausea and vomiting (PONV), ileus, urinary retention, and respiratory adverse events [1–5]. Multimodal analgesia, which is recommended by the Enhanced Recovery After Surgery (ERAS) guidelines, is an example of an opioid-sparing technique which aim is to decrease postoperative pain with a reduced use of intra- and postoperative opioids and their adverse effects [6–8].

This idea has recently been pushed further with the use of opioid-free anesthesia (OFA), a multimodal analgesia strategy based on the use of other drugs [9,10]. For instance, alpha-2 agonists (clonidine and dexmedetomidine) have been proposed to ensure intraoperative hemodynamic stability as they are direct sympathetic blockers [11,12]. These drugs exhibit interesting pharmacological characteristics (*i.e.* sedation, hypnosis, anxiolysis, sympatholysis, and analgesia) in the context of multimodal analgesia [11,12]. Their intraoperative use has been associated with a decrease in morphine consumption and respiratory events [13].

This property seems particularly interesting in severe obese subjects, a patient population experiencing frequent episodes of oxygen desaturation after laparoscopic bariatric surgery [14]. Moreover, these patients are at high risk of PONV and avoiding morphine consumption in the postoperative period can reduce the PONV occurrence [15]. However, the evidence of the reduction of opioid-related complications with the use of OFA remains low and the incidence of bradycardia reported with dexmedetomidine seems significant [16]. Concerning clonidine, only one study assessed its effectiveness in OFA [17]. Furthermore, no study has ever compared clonidine-based OFA, dexmedetomidine-based OFA, and opioid balanced anesthesia.

We therefore conducted a cohort study which primary aim was to test the hypothesis

that postoperative morphine requirement in obese patients undergoing laparoscopic bariatric surgery could be decreased when using OFA as compared to an anesthetic strategy using opioids. One of the secondary objectives was to compare OFA with dexmedetomidine (OFAD) and OFA with clonidine (OFAC) in order to determine the optimal molecule to use.

## **Materials and Methods**

### **Study Design and Setting**

This historical cohort study was approved by the institutional review board of the Hospices Civils de Lyon; 5 Quai des Celestins; 69002 Lyon France (Chairperson, Pr Guérin) on May 13, 2020 (Ethical Committee N°IRB 20-60) and by the National Commission for Information Technology (*Commission Nationale de l'Informatique et des Libertés*, CNIL), according to French law [18]. An information letter was sent to each eligible patient after their surgery, providing also the possibility to refuse to be included in the study.

Patients who underwent elective laparoscopic bariatric surgery (bypass or sleeve gastrectomy) between March 6, 2017 and March 25, 2019 were identified in the anesthesia database and in electronic patient records (Edouard Herriot hospital, Hospices Civils de Lyon, Lyon, France). This study period allowed for the inclusion of patients who received an anesthetic strategy using opioids and others who received OFA. Practice evolved in December 2017, when we stopped using intraoperative opioids, first using clonidine from December 5, 2017 to September 21, 2018, and then using dexmedetomidine from September 24, 2018 to March 25, 2019, allowing for the distinction of 3 periods of time. No other changes in the anesthesia management of patients were implemented. Our observational study follows the Strengthening the Reporting of Observational studies in Epidemiology guidelines and was conducted in accordance with the Declaration of Helsinki.

### **Patients**

All patients aged 18 years or above who had undergone bariatric surgery during this period were eligible. Non-inclusion criteria were atrioventricular conduction disorders, coronary heart disease with stenting during the past year, allergy to neuromuscular blocking agents, cirrhosis, laparotomy conversion, opioid treatment before surgery.

## **Anesthesia management**

For all patients, general anesthesia was induced with 3 mg/kg propofol (current body weight, CBW), then maintained with volatile anesthetics (sevoflurane or desflurane) or continuous infusion of propofol depending on the choice of the anesthetist. In all cases, anesthesia depth was monitored with the bispectral index of the encephalogram with values maintained between 40 and 60 by adapting the dosage of hypnotics (sevoflurane, desflurane or propofol) administration. After induction of anesthesia, an intravenous 1.5 mg/kg lidocaine bolus was administered over 10 min (with a maximal dose of 100 mg) followed by a continuous infusion of lidocaine 2 mg/kg/h. After skin closure, lidocaine infusion rate was reduced to 1 mg/kg/h until discharge from the post-anesthesia care unit (PACU). Lidocaine dosage was based on the adjusted body weight (ABW) defined by the following formula:  $ABW = \text{ideal body weight (IBW)} + 0.4 \times (\text{CBW} - \text{IBW})$  [19]. Muscle relaxation was achieved with 0.2 mg/kg cisatracurium (ABW) and monitored using post-tetanic count and train of four, succinylcholine was used if rapid sequence induction was required (1 mg/kg CBW). All patients received 50 mg/kg magnesium (ABW) and 0.15 mg/kg dexamethasone (ABW) during anesthesia induction and 1.25 mg droperidol at the end of surgery.

In order to avoid deep and/or prolonged hypotension and, in accordance with the principle of personalized care for each patient, the anesthesiologist in charge used ephedrine, phenylephrine and/or norepinephrine to maintain the blood pressure close to the patient's usual values (within 80 to 120% of baseline value). Volume-controlled mechanical ventilation was initiated using a tidal volume between 6 and 8 ml/kg based on IBW and a positive expiratory end pressure between 8 and 10 cm of water. Ventilator frequency was adjusted to obtain an end-tidal carbon dioxide close to 40 mmHg and inspired oxygen fraction in air was titrated to have a pulse oxygen saturation above 96%. Recruitment maneuvers were performed after orotracheal intubation and then every 30 minutes until the end of the procedure.

Postoperative analgesia was provided by the combination of acetaminophen (1 or 2 g intravenously 30 min before the end of surgery then every 6 h if needed), ketoprofen (100 mg intravenously during induction and then 50 mg every 6 h if needed), nefopam (20 mg intravenously 30 min before the end of surgery and then every 4 h if needed), and/or tramadol (100 mg intravenously 30 min before the end of surgery and then every 8 h if needed).

The Opioid Balanced Anesthesia (OBA) group included patients operated between March 2017 and December 2017. The OBA group received remifentanyl (Target Controlled Infusion, TCI, Minto model) during the whole anesthesia and 0.2 mg/kg ketamine (IBW) during induction. Morphine was delivered intravenously 30 min before the end of surgery for postoperative analgesia (0.05 mg/kg ABW).

The OFA group with clonidine adjuvant (OFAC) included patients operated between December 2017 and September 2018. The OFAC group received a clonidine bolus of 2 or 3  $\mu\text{g}/\text{kg}$  (ABW) over 10 minutes before induction. During the intraoperative period, a second administration of clonidine 0.5  $\mu\text{g}/\text{kg}$  (ABW) was performed in case of tachycardia or hypertensive episode.

The OFA group with dexmedetomidine adjuvant (OFAD) included patients operated between September 2018 and March 2019. Dexmedetomidine dosage was based on CBW. Before induction patients received a loading dose of dexmedetomidine 1.4  $\mu\text{g}/\text{kg}/\text{h}$  during 10 min, followed by a continuous infusion stopped after exsufflation. Intraoperative infusion of dexmedetomidine was let at the discretion of the anesthetist in charge but should always be comprised between 0.5 to 1  $\mu\text{g}/\text{kg}/\text{h}$ .

The OFA group included all patients from the OFAC and OFAD groups. All these patients received 0.5 mg/kg ketamine (IBW) before induction. For all of them, the anesthetist in charge was free to start administration of remifentanyl during the intraoperative period if he deemed it necessary.



In the PACU, postoperative pain was managed for the three groups with an intravenous morphine titration to keep visual analogue scale (VAS) below 4, after approval of the anesthesiologist in charge. Patients complaining of PONV in the PACU received ondansetron.

Lastly, the team in charge consisted of anesthesiologists familiar with the use of OFA as well as surgeons with extensive experience in the practice of bariatric surgery. The members of this team were the same during the whole study period.

## **Outcomes**

The time when observation started was set at the patient arrival in the operating room. The following patient characteristics were recorded: age, sex, body mass index (BMI), presence of obstructive sleep apnea syndrome, type (sleeve gastrectomy or bypass), administered intraoperative dose of remifentanyl or alpha-2 agonists (clonidine or dexmedetomidine), morphine consumption during the first 24 postoperative hours, readmission during the 30 postoperative days for PONV. During surgery, non-invasive blood pressure, heart rate, vasopressor use, type of hypnotic used for the maintenance of anesthesia (sevoflurane, desflurane or continuous infusion of propofol) and duration of surgery were recorded. During the PACU stay, antiemetic and morphine consumption, non-invasive blood pressure, heart rate, length of stay and VAS were recorded. In the ward, VAS, antiemetic consumption and length of stay were recorded.

The primary effectiveness endpoint was, for each group, the proportion (%) of patients who did not receive morphine during the first 24 postoperative hours. Secondary endpoints were antiemetic consumption, VAS, morphine consumption, maximum and minimum systolic blood pressure, and heart rate during the PACU stay; intraoperative occurrence of cardiovascular events (defined as change in heart rate or arterial pressure of more than 20% from pre-induction value) and need for vasopressor use; lengths of PACU and hospital stay;

antiemetic consumption and VAS in the ward; and proportion of readmission during the first 24 postoperative hours.

### **Statistical Analyses**

At the time of the study design, the number of patients of the OFAC group was known and could not be changed ( $n = 90$ ). It was agreed to return to patient records to obtain approximately the same number of patients in the OBA group, and to wait for recruitment of the same number of patients in the OFAD group. Assuming a mean percentage of patients without morphine during the first 24 postoperative hours of 20% across all groups, a percentage of 10% in the OBA group, of 20% in the OFAC group, and of 40% in the OFAD one (corresponding to a variance of 0.016 between groups of this percentage), the inclusion of 90 patients per group resulted in a power greater than 90% [20]. Continuous variables are expressed as mean  $\pm$  standard deviation (SD) or as median [1<sup>st</sup> and 3<sup>rd</sup> quartile] and categorical variables as frequency and percentages. Comparisons of outcomes between groups were performed using Wilcoxon and Kruskal-Wallis tests, or by the Fisher's exact and Chi-squared tests. Treatment effect (OBA/OFA) was quantified by odds ratios with 95% confidence intervals (CI). Multivariate analyses were adjusted on age, sex, BMI, as well as type and duration of surgery for morphine use, and on sex and intraoperative use of continuous propofol infusion for antiemetic rescue medication. A p-value less than 0.05 was considered as statistically significant. Analyses were performed using R software (R Development Core Team (2019) R: A language and environment for statistical computing R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Patients

A total of 274 consecutive patients were screened for eligibility and 257 were included in the study with 77 patients in the OBA group, 90 in the OFAC group, and 90 in the OFAD group (Figure 1). No significant difference was observed between the 3 groups in terms of patient and surgery baseline characteristics such as age, BMI, sex, occurrence of preoperative obstructive sleep apnea syndrome as well as type and mean duration of surgery (Table 1).

### Morphine consumption during the first 24 postoperative hours

During the first 24 postoperative hours, the proportion of patients who did not require morphine was significantly higher in the OFA (87%) than in the OBA (52%) group (OR: 6.31; 95% CI [3.38; 11.80],  $P < 0.001$ ). This difference remained significant after adjustment for age, BMI, sex, as well as type and duration of surgery (OR: 7.99; 95% CI [4.05; 16.48],  $P < 0.001$ ). A greater proportion of patients in the OFAD (93%) than in the OFAC (81%;  $P = 0.026$ ) group did not receive morphine during the same period. The mean  $\pm$  SD morphine [1<sup>st</sup> and 3<sup>rd</sup> quartiles] consumption during the first 24 postoperative hours was  $2 \pm 3$  [0, 4] mg in the OBA group,  $1 \pm 3$  [0, 0] mg in the OFAC group, and  $1 \pm 4$  [0, 0] mg in the OFAD group ( $P < 0.001$ ). In the OFAC group, the proportion of patients who did not require any morphine during the first 24 postoperative hours was significantly higher in patients who did not receive remifentanyl (85%) compared to those who did (44%;  $P = 0.011$ ). Moreover, in the OFAC group, the mean  $\pm$  SD morphine [1<sup>st</sup> and 3<sup>rd</sup> quartiles] consumption during the first 24 postoperative hours was  $1 \pm 3$  [0, 0] mg in patients who did not receive any remifentanyl and  $3 \pm 4$  [0, 5] mg in patients who received remifentanyl ( $P = 0.003$ ).

### Postoperative nausea and vomiting

In PACU, a statistically lower proportion of patients in OFA group (4%) required antiemetic rescue medication than in the OBA (17%) group (OR: 0.20; 95% CI [0.08-0.52],  $P$

= 0.001). This reduction remained significant after adjustment for sex and intraoperative use of continuous infusion of propofol (OR: 0.1; 95% CI [0.02; 0.41],  $P < 0.001$ ). No significant difference in the frequency of antiemetic rescue medication use in PACU was observed between the OFAC (3%) and OFAD groups (4%;  $P = 1$ ). During the first 24 postoperative hours, the proportion of patients who required antiemetic rescue medication was not significantly different between the OBA (36%) and the OFA (41%) groups ( $P = 0.566$ ). No significant difference was found between the OBA and OFA groups concerning the proportion of patients readmitted during the 30 postoperative days due to PONV: 1% in the OBA group vs. 2% in the OFA group ( $P = 1$ ).

### **Perioperative hemodynamic parameters, VAS score and hospital length of stay**

During surgery, patients in the OFA group received less vasopressors but experienced more episodes of hypertension than those from the OBA group (Table 2). In PACU, patients from the OFA group exhibited lower VAS score and longer length of stay than those from the OBA group (Table 2). During surgery, patients in the OFAC group presented more tachycardia episodes and required more frequently intraoperative remifentanyl rescue therapy due to hemodynamic instability than those from the OFAD group (Table 3). No significant difference was found between the OBA and OFA groups concerning the mean  $\pm$  SD hospital length of stay ( $3 \pm 3$  days vs.  $3 \pm 2$  days;  $P = 0.583$ ).

## Discussion

The present study found that the use of OFA during bariatric surgery was associated with a lower morphine requirement during the first 24 postoperative hours compared to an anesthetic strategy using opioids and that OFAD reduced postoperative morphine requirements compared to OFAC. Moreover, the use of OFA appeared safe and was associated with a reduction of antiemetic rescue medication in the PACU compared to an anesthetic strategy using opioids.

Patients from the OBA group exhibited higher postoperative pain scores in the PACU compared to those from the OFA group. This may be partly related to the stimulation of alpha-2 receptors in the brain and spinal cord by alpha-2 agonists (clonidine, dexmedetomidine) which inhibit neuronal firing leading to analgesia: pain transmission is suppressed by hyperpolarization of interneurons and reduction of the release of pronociceptive transmitters such as substance P and glutamate [12]. A second explanation could be related to the reduction of opioid-induced hyperalgesia, which is characterized by a state of nociceptive sensitization caused by exposure to opioids [1,21]. Furthermore, intraoperative administration of opioids, especially remifentanyl, is known to be associated with a significant pain increase after surgery [22]. This was confirmed herein as avoiding the intraoperative use of remifentanyl led to a positive impact on postoperative pain and morphine consumption. In addition, decreasing opioid consumption could have other benefits, particularly in the setting of bariatric surgery as suggested by the ERAS guidelines [6]. For instance, the high incidence of obstructive sleep apnea syndrome in obese patients exposes them to the risk of perioperative respiratory events [14,23]. As perioperative opioid consumption is known to be associated with an increased occurrence of apnea [24,25], OFA could also be associated with fewer postoperative respiratory complications as reported by Mulier *et al.* who found that OFA led to fewer patients with postoperative oxygen desaturation in the PACU [13]. Morphine consumption is also known to

increase the occurrence of PONV, which is also one of the most common postoperative complications after bariatric surgery [15,26]. Herein, OFA was associated with a reduction in the proportion of patients using antiemetic rescue medication in the PACU. This result remained significant even after adjustment for sex and intraoperative use of continuous infusion of propofol, a medication known to reduce PONV as compared to inhaled anesthetics [2,27]. This reduction in PONV linked to the OFA use is supported by a randomized controlled study that demonstrated, during bariatric surgery, a significant decrease in their occurrence in the OFA group [28]. This potential reduction of PONV is of particular interest because patients undergoing bariatric surgery, as stated in the ERAS guidelines, often present many risk factors of PONV [6].

OFA requires the use of a drug ensuring hemodynamic stability. Like most of the published studies on OFA [29–31], we chose to use alpha-2 agonists to meet this need. However, as they are direct sympathetic blockers, concerns remain regarding the occurrence of perioperative hypotension associated with their use, as described by Feld *et al.* [29]. In the present study, we found that the use of OFA was associated with a lower intraoperative use of ephedrine and vasopressors than with OBA. Although the occurrence of intraoperative hypotension was similar in the two groups, the reduction in the use of vasopressors associated with OFA suggests that hypotensive episodes in this group were less profound and/or shorter. This is of particular interest as intraoperative hypotension is associated with postoperative complications such as PONV, acute kidney injury and myocardial injury [32,33]. Conversely, OFA was associated with higher frequency of intraoperative hypertension. These results are consistent with those reported by Bello *et al.* who used OFA in the setting of thoracic surgery [17]. None of the patients herein, however, required the use of other antihypertensive drugs, suggesting that hypertensive episodes were short and/or moderate. Interestingly, during the PACU stay, we observed more frequent episodes of hypertension in the OBA group than in the

OFA group, as previously described by Mulier *et al.* [13]. This result could be linked to the lower pain observed in the OFA group.

The use of OFA remains controversial, particularly because of its potential bradycardic effects. The Postoperative and Opioid-free Anesthesia (POFA) trial was stopped prematurely because of five cases of severe bradycardia in the dexmedetomidine group [16]. We did not observe any severe bradycardia event in our cohort. This difference may be explained by the higher dosage of dexmedetomidine used in the POFA trial (the mean dosage of the continuous infusion was  $1.2 \pm 2 \mu\text{g/kg/h}$  in the POFA trial whereas patients from our study received a loading dose of dexmedetomidine  $1.4 \mu\text{g/kg/h}$  during 10 min followed by a continuous infusion of 0.5 to  $1 \mu\text{g/kg/h}$ ). Moreover, in the POFA trial, the use of dexmedetomidine was more prolonged (dexmedetomidine stopped at the end of surgery in the POFA trial vs. stopped at exsufflation in our study). These results raise the key question of the optimal dosage of dexmedetomidine, which remains at this time unclear. In our study, dexmedetomidine infusion rate was left at the discretion of the anesthetist but had to remain below  $1 \mu\text{g/kg/h}$ . With this administration protocol, we do not report any increased risk of bradycardia, suggesting that OFA may safely be used with a lower dosage in the context of laparoscopic bariatric surgery.

A higher proportion of patients in the OFAD group did not receive morphine during the first 24 hours after surgery as compared to patients in the OFAC group. This finding is consistent with the data from Blaudszun *et al.* who report that morphine sparing after surgery performed during general anesthesia using dexmedetomidine was more pronounced than with the use of clonidine [34]. This result is reinforced by the fact that patients in the OFAC group herein experienced more frequently tachycardia and required more frequently intraoperative remifentanyl rescue therapy due to hemodynamic instability than those in the OFAD group. This could be explained by the pharmacological characteristics of dexmedetomidine. Even if dexmedetomidine has a shorter half-life than clonidine (2 hours vs. 15 hours), its affinity for

alpha-2 receptors is eight times that of clonidine [35]. This could also explain the prolonged PACU length of stay in the OFAD group (which had no impact on hospital length of stay) which has also been reported by Choi *et al.* in the dexmedetomidine group after thyroid surgery [36].

The study, however, has certain limitations. First, it is retrospective, which could explain why some data are missing. Nevertheless, this concerned only the total dose of dexmedetomidine administered in few patients, and therefore does not affect the conclusions of the study. Second, we could not evaluate postoperative respiratory events because patients were not continuously monitored in the ward. Third, given the retrospective and observational design of this study, we cannot establish any causal relationship. Fourth, since the present study is not a randomized controlled trial, other confounding factors may also have interfered with our results such as the use of continuous infusion of propofol vs. the use of volatile anesthetics. Nevertheless, the major prognostic factors were taken into account in the multivariate analysis. Likewise, 2 years separate the first and the last patients included. During this time, anesthesiologists' practices slightly evolved, with an increase in ketamine dosage for induction (from 0.2 mg/kg in the OBA group to 0.5 mg/kg in the OFA group). However, as a single dose bolus only was administered, it is unlikely to be responsible for differences that persist 24 hours [37,38]. Fifth, only 77 patients were included in the OBA group but this did not prevent from showing some significant differences between groups. This could be explained by the increase over time of the number of patients undergoing laparoscopic bariatric surgery in our hospital: the OBA period lasted approximately 9 months with 77 patients included whereas the OFAD period lasted approximately 6 months with 90 patients included. Finally, the anesthesiologist from the PACU, responsible for morphine and antiemetic prescriptions within the PACU, was not aware of this retrospective study but was aware of each patient's protocol (OBA, OFAC, or



OFAD). Thus, subjectivity may also have slightly influenced morphine and antiemetic administration in the PACU.

## **Conclusion**

In obese patients undergoing bariatric surgery, OFA was safely associated with a reduction in morphine consumption during the first 24 postoperative hours as compared to OBA. Interestingly, OFAD was associated with a lower morphine requirement than OFAC.

## References:

- [1] Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006;104:570–87. <https://doi.org/10.1097/00000542-200603000-00025>.
- [2] Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br J Anaesth* 2012;109:742–53. <https://doi.org/10.1093/bja/aes276>.
- [3] Cali RL, Meade PG, Swanson MS, Freeman C. Effect of Morphine and incision length on bowel function after colectomy. *Dis Colon Rectum* 2000;43:163–8. <https://doi.org/10.1007/BF02236975>.
- [4] Baldini G, Bagry H, Aprikian A, Carli F. Postoperative urinary retention: anesthetic and perioperative considerations. *Anesthesiology* 2009;110:1139–57. <https://doi.org/10.1097/ALN.0b013e31819f7aea>.
- [5] Broens SJ, He X, Evley R, Olofsen E, Niesters M, Mahajan RP, et al. Frequent respiratory events in postoperative patients aged 60 years and above. *Ther Clin Risk Manag* 2017;13:1091–8. <https://doi.org/10.2147/TCRM.S135923>.
- [6] Stenberg E, Dos Reis Falcão LF, O’Kane M, Liem R, Pournaras DJ, Salminen P, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations: A 2021 Update. *World J Surg* 2022;46:729–51. <https://doi.org/10.1007/s00268-021-06394-9>.
- [7] Rasmussen ML, Mathiesen O, Dierking G, Christensen BV, Hilsted KL, Larsen TK, et al. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. *Eur J Anaesthesiol* 2010;27:324–30. <https://doi.org/10.1097/EJA.0b013e328331c71d>.
- [8] Memtsoudis SG, Poeran J, Zubizarreta N, Cozowicz C, Mörwald EE, Mariano ER, et al. Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study. *Anesthesiology* 2018;128:891–902. <https://doi.org/10.1097/ALN.0000000000002132>.
- [9] Beloeil H. Opioid-free anesthesia. *Best Pract Res Clin Anaesthesiol* 2019;33:353–60. <https://doi.org/10.1016/j.bpa.2019.09.002>.
- [10] Sultana A, Torres D, Schumann R. Special indications for Opioid Free Anaesthesia and Analgesia, patient and procedure related: Including obesity, sleep apnoea, chronic obstructive pulmonary disease, complex regional pain syndromes, opioid addiction and cancer surgery. *Best Pract Res Clin Anaesthesiol* 2017;31:547–60. <https://doi.org/10.1016/j.bpa.2017.11.002>.
- [11] Nguyen V, Tiemann D, Park E, Salehi A. Alpha-2 Agonists. *Anesthesiol Clin* 2017;35:233–45. <https://doi.org/10.1016/j.anclin.2017.01.009>.
- [12] Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. *Clin Pharmacokinet* 2017;56:893–913. <https://doi.org/10.1007/s40262-017-0507-7>.
- [13] Mulier JP, Wouters R, Dekock M. Opioid-Free Versus Opioid General Anaesthesia on Postoperative Pain 2018;2:6.
- [14] Ahmad S, Nagle A, McCarthy RJ, Fitzgerald PC, Sullivan JT, Prystowsky J. Postoperative hypoxemia in morbidly obese patients with and without obstructive sleep apnea undergoing laparoscopic bariatric surgery. *Anesth Analg* 2008;107:138–43. <https://doi.org/10.1213/ane.0b013e318174df8b>.
- [15] Ziemann-Gimmel P, Hensel P, Koppman J, Marema R. Multimodal analgesia reduces narcotic requirements and antiemetic rescue medication in laparoscopic Roux-en-Y gastric bypass surgery. *Surg Obes Relat Dis* 2013;9:975–80. <https://doi.org/10.1016/j.soard.2013.02.003>.

- [16] Beloeil H, Garot M, Lebuffe G, Gerbaud A, Bila J, Cuvillon P, et al. Balanced Opioid-free Anesthesia with Dexmedetomidine versus Balanced Anesthesia with Remifentanyl for Major or Intermediate Noncardiac Surgery. *Anesthesiology* 2021;134:541–51. <https://doi.org/10.1097/ALN.0000000000003725>.
- [17] Bello M, Oger S, Bedon-Cardre S, Vielstadte C, Leo F, Zaouter C, et al. Effect of opioid-free anaesthesia on postoperative epidural ropivacaine requirement after thoracic surgery: A retrospective unmatched case-control study. *Anaesth Crit Care Pain Med* 2019;38:499–505. <https://doi.org/10.1016/j.accpm.2019.01.013>.
- [18] Toulouse E, Maseguin C, Lafont B, McGurk G, Harbonn A, A Roberts J, et al. French legal approach to clinical research. *Anaesth Crit Care Pain Med* 2018;37:607–14. <https://doi.org/10.1016/j.accpm.2018.10.013>.
- [19] Acute Respiratory Distress Syndrome Network, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–8. <https://doi.org/10.1056/NEJM200005043421801>.
- [20] Lachin JM. Sample size determinants for r X c comparative trials. *Biometrics* 1977;33:315–24.
- [21] Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician* 2011;14:145–61.
- [22] Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth* 2014;112:991–1004. <https://doi.org/10.1093/bja/aeu137>.
- [23] Gali B, Whalen FX, Schroeder DR, Gay PC, Plevak DJ. Identification of patients at risk for postoperative respiratory complications using a preoperative obstructive sleep apnea screening tool and postanesthesia care assessment. *Anesthesiology* 2009;110:869–77. <https://doi.org/10.1097/ALN.0b013e31819b5d70>.
- [24] Dahan A, Romberg R, Teppema L, Sarton E, Bijl H, Olofsen E. Simultaneous measurement and integrated analysis of analgesia and respiration after an intravenous morphine infusion. *Anesthesiology* 2004;101:1201–9. <https://doi.org/10.1097/00000542-200411000-00021>.
- [25] Pattinson KTS. Opioids and the control of respiration. *Br J Anaesth* 2008;100:747–58. <https://doi.org/10.1093/bja/aen094>.
- [26] Apfel CC, Philip BK, Cakmakkaya OS, Shilling A, Shi Y-Y, Leslie JB, et al. Who is at risk for postdischarge nausea and vomiting after ambulatory surgery? *Anesthesiology* 2012;117:475–86. <https://doi.org/10.1097/ALN.0b013e318267ef31>.
- [27] Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, et al. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004;350:2441–51. <https://doi.org/10.1056/NEJMoA032196>.
- [28] Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *Br J Anaesth* 2014;112:906–11. <https://doi.org/10.1093/bja/aet551>.
- [29] Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. *J Clin Anesth* 2006;18:24–8. <https://doi.org/10.1016/j.jclinane.2005.05.009>.
- [30] Bakan M, Umutoglu T, Topuz U, Uysal H, Bayram M, Kadioglu H, et al. Opioid-free total intravenous anesthesia with propofol, dexmedetomidine and lidocaine infusions for laparoscopic cholecystectomy: a prospective, randomized, double-blinded study. *Braz J Anesthesiol* 2015;65:191–9. <https://doi.org/10.1016/j.bjane.2014.05.001>.
- [31] Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanyl in postoperative pain control after spinal surgery: a randomized controlled study. *BMC Anesthesiol*

2015;15:21. <https://doi.org/10.1186/s12871-015-0004-1>.

[32] Nakatani H, Naito Y, Ida M, Sato M, Okamoto N, Nishiwada T, et al. Association between intraoperative hypotension and postoperative nausea and vomiting: a retrospective analysis of 247 thyroidectomy cases. *Braz J Anesthesiol* 2021;S0104-0014(21)00094-4. <https://doi.org/10.1016/j.bjane.2021.02.029>.

[33] Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013;119:507–15. <https://doi.org/10.1097/ALN.0b013e3182a10e26>.

[34] Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic  $\alpha_2$  agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 2012;116:1312–22. <https://doi.org/10.1097/ALN.0b013e31825681cb>.

[35] Paris A, Tonner PH. Dexmedetomidine in anaesthesia. *Curr Opin Anaesthesiol* 2005;18:412–8. <https://doi.org/10.1097/01.aco.0000174958.05383.d5>.

[36] Choi EK, Seo Y, Lim DG, Park S. Postoperative nausea and vomiting after thyroidectomy: a comparison between dexmedetomidine and remifentanyl as part of balanced anesthesia. *Korean J Anesthesiol* 2017;70:299–304. <https://doi.org/10.4097/kjae.2017.70.3.299>.

[37] Kamp J, Olofsen E, Henthorn TK, van Velzen M, Niesters M, Dahan A, et al. Ketamine Pharmacokinetics. *Anesthesiology* 2020;133:1192–213. <https://doi.org/10.1097/ALN.0000000000003577>.

[38] Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol* 2014;77:357–67. <https://doi.org/10.1111/bcp.12094>.

## Tables

**Table 1: Patient and surgery baseline characteristics**

	OBA (n = 77)	OFAC (n = 90)	OFAD (n = 90)	P value
Age, years	47 [37-53]	44 [31-53]	47 [37-55]	0.092†
Body Mass Index, kg/m <sup>2</sup>	43 [38-47]	42 [39-47]	43 [39-47]	0.785†
Women, n (%)	49 (64)	64 (71)	64 (71)	0.495‡
OSAS, n (%)	40 (52)	38 (42)	47 (52)	0.319‡
Type of surgery, n (%)				
Bypass	45 (58)	42 (47)	46 (51)	0.312‡
Sleeve	32 (42)	48 (53)	44 (49)	
Length of surgery, min	125 [97-157]	114 [92-139]	106 [83-145]	0.082†
Total dose clonidine, µg	0 [0-0]	270 [240-300]	0 [0-0]	
Total dose dexmedetomidine, µg*	0 [0-0]	0 [0-0]	237 [185-290]	
Total dose remifentanyl, µg	1210 [1030-1420]	535 [398-756] **	0 [0-0]	
Hypnotics, n (%)				
Sevoflurane	5 (7)	4 (4)	3 (4)	0.707***
Desflurane	70 (90)	47 (52)	21 (23)	0.001‡
Propofol	2 (3)	39 (43)	66 (73)	<0.001‡

Data are expressed as median [interquartile range] or number (percentage).

\*Total dose of dexmedetomidine was missing for 6 patients in the OFAD group.

\*\*Total dose of remifentanyl only among patients who received remifentanyl in the OFAC group (n = 9).

\*\*\*Fisher's exact Test

†Kruskall-Wallis test

‡Chi-squared test

OSAS: obstructive sleep apnea syndrome; OBA: opioid balanced anesthesia; OFAC: opioid-free anesthesia with clonidine adjuvant; OFAD: opioid-free anesthesia with dexmedetomidine adjuvant.  
OSAS: obstructive sleep apnea syndrome.

**Table 2: Intra- and postoperative parameters in the OBA and OFA groups**

		OBA	OFA	P value
		(n = 77)	(n = 180)	
Intraoperative parameters	Bradycardia, n (%)	58 (75)	115 (64)	0.100*
	Tachycardia, n (%)	53 (69)	114 (63)	0.482*
	Hypotension, n (%)	76 (99)	177 (98)	1**
	Hypertension, n (%)	29 (38)	100 (56)	0.013*
	Ephedrine use, mg	30 [18-30]	20 [12-30]	0.007†
	Vasopressor use, n (%)	49 (64)	72 (40)	0.001*
	Continuous infusion of propofol, n (%)	2 (3)	105 (58)	< 0.001*
PACU	Highest SAP, mmHg	146 [133-163]	121 [110-132]	< 0.001†
	Lowest SAP, mmHg	122 [113-139]	98 [89-108]	< 0.001†
	Highest heart rate, beats/min	99 [90-108]	87 [79-97]	< 0.001†
	Lowest heart rate, beats/min	82 [70-90]	69 [61-76]	< 0.001†
	PACU length of stay, min	73 [60-90]	88 [71-121]	< 0.001†
	Morphine administered, mg***	2 ± 3, 0 [0-4]	0 ± 2, 0 [0-0]	< 0.001†
	Patients not requiring morphine, n (%)	43 (56)	166 (92)	< 0.001*
	Highest VAS score	3 [1-6]	1 [0-4]	< 0.001†
Ward	Highest VAS score in the first 24 postoperative hours	3 [1-6]	3 [2-5]	0.583†

Data are expressed as median [interquartile range] or number (percentage).

\* Chi-squared test

\*\*Fisher test

\*\*\*Due to the high number of 0 concerning morphine administered in PACU, the median is equals to 0 in the two groups. Because of a non-Gaussian distribution concerning morphine administered in PACU and to be more informative, data are expressed as mean ± standard deviation and as median [interquartile range].

†Wilcoxon test



OBA: opioid balanced anesthesia; OFAC: opioid-free anesthesia with clonidine adjuvant; OFAD: opioid-free anesthesia with dexmedetomidine adjuvant. PACU: post-anesthesia care unit. SAP: systolic arterial pressure.

**Table 3: Intra- and postoperative parameters according to the type of alpha-2 adjuvant used for opioid-free anesthesia.**

		OFAC (n = 90)	OFAD (n = 90)	<i>P</i> value
Intraoperative parameters	Bradycardia, n (%)	57 (63)	58 (64)	1*
	Tachycardia, n (%)	64 (71)	50 (56)	0.044*
	Hypotension, n (%)	87 (97)	90 (100)	0.246**
	Hypertension, n (%)	48 (53)	52 (58)	0.653*
	Remifentanil administration (rescue), n (%)	9 (10)	0 (0)	0.003**
PACU	Highest SAP, mmHg	127 [117-136]	117 [106-128]	< 0.001†
	Lowest SAP, mmHg	103 [93-113]	95 [87-102]	< 0.001†
	Highest heart rate, beats/min	94 [85-104]	83 [76-90]	< 0.001†
	Lowest heart rate, beats/min	73 [67-84]	64 [59-71]	< 0.001†
	Patients not requiring morphine, n (%)	73 (81)	84 (93)	0.026*
	PACU length of stay, min	84 [65-102]	100 [76-130]	0.003†
	Morphine administered, mg***	1±2, 0 [0-0]	0±1, 0 [0-0]	0.001†
Ward	Highest VAS score	3 [1-5]	0 [0-1]	< 0.001†
	Highest VAS score in the first 24 postoperative hours	3 [1-4]	3 [2-6]	0.054†

Data are expressed as median [interquartile range] or number (percentage).

\*Chi-squared test

\*\*Fisher test

\*\*\* Due to the high number of 0 concerning morphine administered in PACU, the median is equals to 0 in the two groups. Because of a non-Gaussian distribution concerning morphine administered in PACU and to be more informative, data are expressed as mean ± standard deviation and as median [interquartile range].

†Wilcoxon test

OFAC: opioid-free anesthesia with clonidine adjuvant; OFAD: opioid-free anesthesia with dexmedetomidine adjuvant. PACU: post-anesthesia care unit. SAP: systolic arterial pressure.

Figures

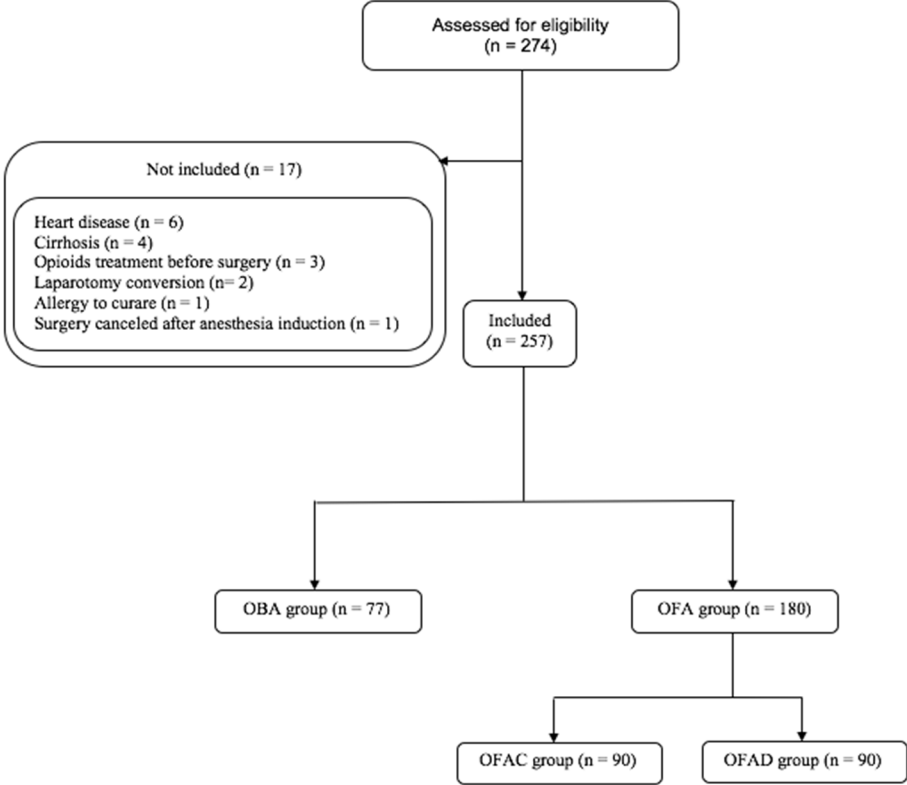


Fig. 1. Study flow chart