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Original study

Impact of opioid free Anaesthesia versus opioid Anaesthesia on the immediate postoperative oxygenation after bariatric surgery: a prospective observational study

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Abstract

Introduction: **Opioid induced respiratory depression (OIRD) is a preventable aetiology of postoperative respiratory depression with 85% of the episodes taking place in the first 24 postoperative hours. Due to altered respiratory functional metrics and frequently coexisting comorbidities, obese patients are at a particularly higher risk for such complications. The present study aimed to assess if an opioid-free anesthesia (OFA) was associated with a reduced immediate postoperative OIRD when compared to Opiod-based anesthesia (OA).**
Methods: **Obese patients presenting for bariatric surgery were consecutively included in a non-randomized fashion. Lung protective ventilation strategies applied in both groups. In the OA group, Sufentanil was used for intraoperative analgesia in a liberal fashion. In the OFA group, patients received a pre-induction dexmedetomidine loading, followed by a lidocaine, ketamine and dexmedetomidine bolus immediately before induction, further maintained throughout the intraoperative period. Plethysmographic saturations were obtained before induction as well as after extubation and in the Post-anesthesia care unit (PACU). Opioid requirement and Postoperative Nausea and Vomiting incidence were similarly registered.**
Results: **Thirty-four patients were included in the OFA group, and 30 in the OA group. No significant anthropometric and comorbidity differences were found between both groups. OFA patients had significantly lower pre-induction saturations after dexmedetomidine loading. No difference was found for post-extubation saturations as well as well as pre-PACU discharge. The need for supplemental oxygen at the PACU was higher in the OA group. Opioid requirement and cumulative consumption (MEDs) were significantly higher with OA.**
Conclusion: **OFA was not associated with significant postoperative saturation changes but led to a lower need of postoperative supplemental oxygen therapy. OA led to higher opioid rescue need. No fatal respiratory complications were registered in both groups in the immediate postoperative period.**

Keywords: **Not included**

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Introduction

Postoperative respiratory failure is a frequent phenomenon with a reported incidence varying between 0.3 and 17% depending the used metrics[1]. It is associated with significant morbidity and mortality, as well as increases in resource utilization and thus global healthcare costs[1,2]. Despite such known consequences, postoperative desaturation

is still deemed a significantly underreported postoperative phenomenon. In fact, not only do standard nursing records miss more than 90% of hypoxemic episodes in ward/downscale units, but also more than third of postoperative patients have been estimated to undergo prolonged hypoxemic episodes (defined as a plethysmographic saturation under 90%) during the first postoperative hours[3].
Amongst the various etiologies of postoperative respiratory depression, opioid-induced respiratory depression (OIRD) has gained increased attention as a potentially preventable cause of death as well as of neurological impairment after surgery (1). Recent meta-analysis estimates an OIRD prevalence of 0.5%[4].

Opioids, mainly pure μ-opioid receptor agonists, lead to a reduction of the respiratory drive in a classical dose dependent fashion. Although their pharmacodynamics are characteristically idiosyncratic, opioids tend to initially result in a reduction of the depth of breathing, followed by a slowing of the respiratory rate and generation of more irregular/inconsistent breathing patterns[5]. High doses characteristically magnify these responses and potentially lead to respiratory arrest[6,7]. Lower relative doses tend to induce or aggravate obstructive breathing and episodic desaturation[8].

The first postoperative 24 hours are a high-risk period for opioid-induced adverse respiratory events, encompassing up to 85% of all postoperative OIRD episodes[4]. Its occurrence is further potentiated by not only by unmodifiable factors such as advanced age and female sex, but also by co-morbidities such as obesity, Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS), Chronic Obstructive Pulmonary Disease (COPD), Chronic kidney Disease (CKD), hepatic and cardiac disease significantly increase the risk of OIRD[4,9]. Obese patients are in fact an increasingly prevalent risk-group for the aforementioned postoperative morbidity and mortality events. The frequently displayed baseline reductions in many respiratory functional metrics (among others, compliance, elastance, and functional residual capacity), partially explains this higher risk[10,11].

The commonly employed postoperative administration of oxygen further aggravates OIRD by delaying the observation of desaturation by pulse oximetry as well as by contributing to the hyperoxic inhibition of ventilatory drive[12]. In these group of patients, OIRD diagnosis is alternatively aided by respiratory rate monitoring (f.e. impedance-derived) or capnography[1], although such methodologies are not systematically employed on both postoperative units as well as the less monitored step-down ward/ units.

Despite having known adverse effects, opioids remain a widely adopted choice for perioperative analgesia[2]. Given the undesired side effect profile of these agents on known risk populations, the AZ Sint Jan Brugge-Oostende hospital introduced and standardized opioid free anesthesia (OFA) for bariatric surgery purposes. Since its implementation in 2009, the fine-tuning of this practice allowed a 75% reduction of opioid use for analgesic rescue purposes[13].

The present study aimed to investigate whether OFA is associated with a reduced incidence of OIRD in elective bariatric surgery settings, as compared to opioid anesthesia (OA). The study's primary endpoints were incidence of hypoxia (SpO2<94%) without supplemental oxygen during the post anesthesia care unit (PACU) stay, after an eventual PACU rescue opioid therapy as well as at the time of PACU discharge. Secondary end-points included pain assessment scores and total opioid consumption in morphine equivalent dose (MED).

Methods

The present study is of a prospective and observational nature. Patient inclusion started in September 2018 and ended in 5 November 2019. Inclusion criteria filtered adult patients (> 18 years) with a body mass index (BMI) greater than 35 presenting for elective laparoscopic bariatric surgery patients. Exclusion criteria included: procedures with a surgical duration under 1 hour; chronic opioid use in the month preceding the surgery; pre-operative oxygen requirement; daytime Continuous Positive Airway Pressure (CPAP) requirement; Renal Insufficiency (KDIGO <G2); acute or chronic liver insufficiency; allergy to Acetaminophen or non-steroidal anti-inflammatory agents; spontaneous breathing attempts during general anesthesia.

The study protocol was approved by the local institutional review board prior to commencement (Commissie voor Ethiek, AZ Sint-Jan Brugge-Oostende AV, Reference B049201316611, President Prof. Dr. Ludo Vanopdenbosch) and registered at the clinicaltrials.gov database (NCT 03660306). Written informed consent was obtained before patient enrolment.

Patient allocation was not subject to randomization and treatment allocation (OA/OFA) and left at the discretion of the attending anesthesiologist. All bariatric procedures were performed or closely supervised by one senior surgeon using standardized surgical approaches.

Perioperative drug dosing was based on Ideal Body Weight as calculated by the Broca index. Pre and intraoperative oxygenation and ventilation

strategies were identically standardized in both groups and based on lung protective ventilation (LPV) principles. Induction was performed in 30° back elevation beach chair position with simultaneous application of a CPAP of 5 cmH20 at a 80% inspired oxygen fraction (FiO2). After induction and during the procedure the lungs were recruited as per judgement of the attending anaesthesiologist. Intra-operative PEEP settings between 10 and 15 cmH2O were mandated, as well as tidal volumes of 6-8 ml/kg IBW and an inspiratory:expiratory ratio of 1:1. Intra-operative Fi02 was recommended to be no lower than and as close to 40% as possible, as guided by plethysmography oxygen saturation (SpO2>94%). Anaesthesia maintenance was achieved with Sevoflurane set at an age-corrected Minimum Alveolar Concentration (MAC) of 1. Intra-operative intra-venous (IV) fluid administration (balanced crystalloid solution) was standardly set at 100 ml/hour, deep neuromuscular blockade (as defined by a post-tetanic count under 2 by means of acceleromyographic adductor pollicis monitoring) was achieved by means of continuous rocuronium infusion by automated syringes.

In the OA group, Sufentanil was used for intraoperative analgesia, with a dosage of 0.1-0.3 mcg/kg IBW given at induction and maintenance top-ups of 0.1mcg/kg during the surgery at discretion of the attending anaesthesiologist.

The OFA group received a Dexmedetomidine IV loading dose (0.3mcg/kg) 15 minutes before induction, which preceded baseline saturation measurements. At induction, a mixture of dexmedetomidine (0.1mcg/kg), lidocaine (1mg/kg) and ketamine (0.1mg/kg) was administered as an IV bolus. Before surgical incision, an IV bolus of ketamine (0.7mg/kg, max 50mg) was administered. These drugs were maintained intraoperatively as an automated IV infusion: dexmedetomidine (0.1 mcg/kg/h), lidocaine (1mg/kg/h) and ketamine (0.1mg/kg/h). After Extubation, the aforementioned drug infusion rates were all reduced by 50% and continued during PACU admission and until the patient was deemed discharge ready (up to a maximum of 5 consecutive hours).

At the end of surgery Sugammadex was administered in order to achieve full neuromuscular recovery as defined by a TOF ratio above 0.9) and extubation took place with a FiO2 lower than 60% in beach chair position (minimal back-up inclination of 20°) with a CPAP of 5 - 10 cmH20. Beach chair positioning was maintained during transport and PACU stay. Supplemental oxygen administration was initiated at any time-point post-extubation if plethysmography saturation values dropped below 94%. The choice of 94% as a cut-off pertained with local PACU early warning system reaction protocols as well as PACU discharge criteria. Analgesia was standardly provided with Paracetamol 4 gram/day after a 2 gram intra-operative loading dose, Diclofenac 150 mg/day after a 150 mg intraoperative loading dose. Pain was assessed by means of a Visual Analogue Scale (VAS) at the PACU. The presence of a score greater than 5 led to a titration of Piritramide (Dipidolor®) per 5mg boli followed by a saline flush. For the purpose of calculation of Morphine Equivalent Dose, Intravenous Piritramide was considered to have a relative potency of 0.75 when compared to Intravenous Morphine.

Plethysmography oxygen saturation readings were retrieved at the following peri-operative time-points: pre-operatively at arrival to the operation room before and after 3 deep room air breaths; at Extubation (without supplemental oxygen); the lowest saturation during the PACU stay; and immediately before PACU discharge. The total dose of morphine equivalent dose (MED) of opioids given in the PACU was calculated. The highest VAS score in the PACU was similarly noted.

Statistical processing was carried out on IBM® SPSS® Statistics (Release 27.0.0.0, 64bit ed.). Variables were subjected to normality conformity assessment prior to difference analysis. The applicable parametric/nonparametric testing was subsequently applied based on these results. Thus, unpaired normally distributed continuous data (Age and Height) were assessed with independent sample t-testing after appropriate homoscedasticity interpretation by means of Levene's test. It's non-parametric equivalent (Mann-Whitney U test) was used for non-normally distributed continuous variables. Contingency testing was used for intergroup dichotomic variable comparison through Fisher's exact testing, considering most of the anthropometric/comorbidity descriptive variables had relative low expected frequencies.

Throughout statistical testing, an alpha (α) threshold of 0.05 was retained and 95% Confidence Intervals (CI) were considered. Categorical variable's frequencies report to valid percentual values, where missing values are singled-out. Continuous variables are reported as means with corresponding standard deviations.

The estimated sample size for the primary outcomes was calculated based to allow the detection of a significant difference between study and control group at a two-sided 5% significance level, with a power of 90%, allowing for a 5% dropout rate for each variable.

The manuscript adheres to the applicable Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines[15].

Results

A total of 64 patients were uninterruptedly included in the present study. Thirty-four patients were included in the OFA group and 30 in the OA group. Both groups had proportionally more female patients, which corresponded to 81% of whole study's population. Nine patients were submitted to a Sleeve gastrectomy (3 patients in the OFA group, 6 in the OA group), being the remainder of the procedures Roux-en-Y gastric bypasses.

Descriptive anthropometric and comorbidity location statistics per anaesthesia type (Opioid versus Opioid-free) are displayed in Table I. Intergroup significance testing results are accordingly presented and revealed no differences between both groups.

The perioperative respiratory and analgesic descriptives are presented in Table II, with the corresponding clustered boxplots displayed in figures 1, 2 and 3. Significant intergroup differences were found for pre-induction saturation levels (both baseline and after 3 vital capacity breaths), saturation variation between after extubation and pre-induction periods, as well as the proportion of patients receiving supplemental oxygen therapy at the PACU. The number of patients requiring opioid rescue therapy and the corresponding total MEDs were similarly significantly different.

Table I. — Intergroup anthropometric and comorbidity location statistics.

	OA (n=30)	OFA (n=34)	Intergroup difference
Age (years)	40.7 +- 7.9	44.8 +- 12.3	t = -1.503, p = 0.139 [b]
Weight (Kg)	105.0 +- 24.0	106.9 +- 20.4	U = 393.0, p = 0.524 [a]
Height (cm)	167.3 +- 11.5	167.6 +- 8.7	t = -0.129, p = 0.898 [b]
BMI (kg/m^2)	36.9 +- 5.1	37.8 +- 5.8	U = 346.5, p = 0.780 [a]
M:F ratio	4:26	8:26	p = 0.351 [c]
Active Smoker (n [%])	2 (6.7 %)	3 (10.0 %)	p = 1.000 [c]
Home CPAP (n [%])	1 (4.0 %)	0 (0 %)	p = 0.455 [c]
PONV history (n [%])	3 (11.1 %)	2 (6.7 %)	p = 0.660 [c]
AHT (n [%])	0 (0 %)	3 (10.0 %)	p = 0.239 [c]
Type I/II DM (n [%])	0 (0 %)	2 (6.7 %)	p = 0.492 [c]

Continuous variables in median+- standard deviation; Categorical variables in cumulative incidence numbers and percentage; a Mann-Whitney U test; b Independent sample t-test; c Fisher's test.
BMI – Body Mass Index; CPAP – Continuous Positive Airway Pressure; PONV – Postoperative Nausea and Vomiting; AHT – Arterial Hypertension; DM – Diabetes Mellitus.

Table II. — Intergroup respiratory and opioid consumption statistics.

	OA (n=30)	OFA (n=34)	Intergroup difference
Baseline Pre-induction Oxygen Saturation	99.0 +- 1,4	96.6 +- 2.5	U = 176.5, p < 0.001 [a]
Pre-induction saturation after 3 vital capacity breaths	99.8 +- 0.5	98.9 +- 1.8	U = 238.0, p = 0.005 [a]
Lowest post-extubation saturation without supplemental oxygen	96.7 +- 2.7	97.5 +- 2.3	U = 370.5, p = 0.322 [a]
Saturation change pre-induction (pre-vital capacity breath) to post-extubation	-2.1 +- 3.3	0.7 +- 2.2	U = 219.5, p = 0.001 [a]
Lowest PACU Saturation after opioid rescue	94.4 +- 2.2	95.7 +- 2.7	U = 299.0, p = 0.132 [a]
Saturation change Post-extubation to post-opioid rescue	2,4 +- 2,8	2.1 +- 2.5	U = 398.0, p = 0.723 [a]
Saturation immediately before PACU discharge	95.9 +- 2.4	96.7 +- 2.3	U = 372.0, p = 0.245 [a]
Saturation change pre-PACU discharge to post-extubation	2.4 +- 18.4	2.1 +- 17.6	U = 492.0, p = 0.967 [a]
Highest PACU VAS Score	5.1 +- 2.0	4.9 +- 2.6	U = 397.5, p = 0.891 [a]
PACU total MEDs received	13.4 +- 8.9	7.2 +- 13.7	U = 152.5, p < 0.001 [a]
PACU Rescue opioids administered (n [%])	30 (100 %)	21 (70%)	p = 0.002 [b]
Supplemental oxygen administration at the PACU (n [%])	16 (53.3%)	4 (12.9 %)	p = 0.001 [b]
PONV before opioid administration (n [%])	2 (7.7 %)	5 (16.7%)	p = 0.431 [b]
PONV after opioid administration (n [%])	11 (42.3 %)	2 (6.7 %)	p = 0.003 [b]

Continuous variables in median+- standard deviation; Categorical variables in cumulative incidence numbers; Significant intergroup differences p-values highlighted in bold; a Mann-Whitney U test; b Fisher's test.
PACU – Post Anaesthesia Care Unit; VAS – Visual Analogue Score; MED – Morphine Equivalent Dose; PONV – Postoperative Nausea and Vomiting.

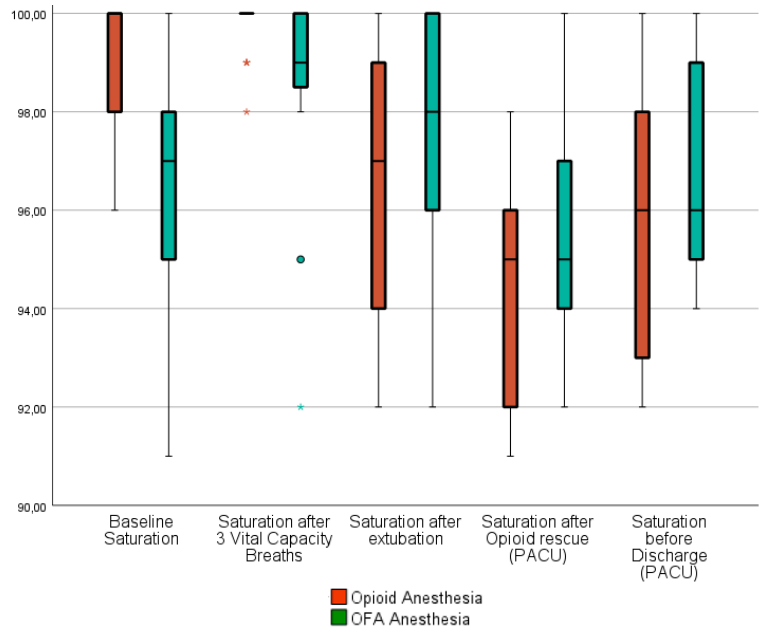

Fig. 1 — Boxplot of the main perioperative saturation variables between groups.
Green – OFA group; Orange – OA group;
y axis - Absolute Saturation values (percentual); x axis – perioperative saturation category.

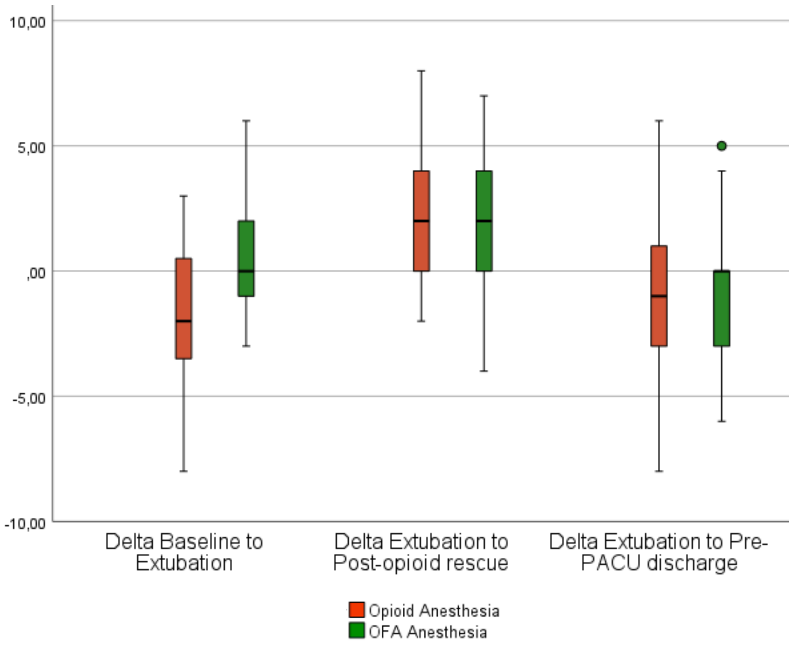

Fig. 2 — Boxplot of the perioperative saturation deltas
Green – OFA group; Orange – OA group;
y axis - Absolute Saturation variation values; x axis – perioperative saturation category.

Discussion

Aiming to report mainly on practical/point-of-care perioperative respiratory metrics (i.e. plethysmographic saturation levels), the present observational study registered mixed differences between two frequently opposed analgetic management strategy groups. The main findings of the present work were that although OFA was not associated with significant postoperative saturation changes, it led to a reduced need of oxygen administration to maintain saturations above 94%. Put differently, while overall postoperative saturations weren't different between both groups, oxygen supplementation needs were higher in the OA group. Patients receiving intraoperative opioids required postoperative rescue opioids more frequently and at higher MEDs. Considering the pre-induction period, one observes that the OA patients presented relatively higher saturation levels. This applied both to baseline and post triple vital capacity breath values. Although groups were

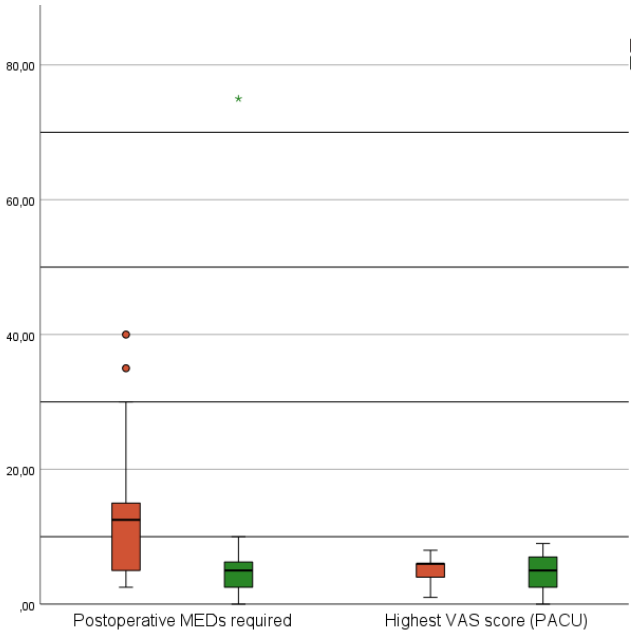

Fig. 3 — Boxplot of postoperative analgesic scores and requirements
Green – OFA group; Orange – OA group;
y axis – Absolute units (VAS Score or MEDs); x axis – PACU Analgesic category;MED – Morphine Equivalent Dose (milligrams); PACU – Post Anesthesia Care unit.

not formally case-controlled matched in statistical terms, no major anthropometric/co-morbidity intrinsic intergroup differences were registered to potentially explain the difference. As such, the abovementioned contrast can potentially be ascribed to the dexmedetomidine loading received by OFA patients prior to baseline saturation registration. On healthy non-obese volunteers, Dexmedetomidine infusions have been either reported to leave saturation, end-tidal carbon dioxide pressure and respiratory rate relatively unchanged[13], or minimally lower saturation (no lower than 95%) (16). In obese patients, loading doses up to 1ug/Kg have been reported to effectively reduce plethysmographic saturations up to 25 minutes after loading[17]. This contrasts to reported oxygenation improvements in obese patients affected by restrictive lung disease [18]. As such, in the absence of other evident causality arguments, one would potentially attribute the described differences to the dexmedetomidine infusion.

Nevertheless, such post-infusion baseline changes seem to be able to be mitigated by vital capacity breaths. In fact, although 3 OFA patients had baseline saturations lower than 94% (compared to none in the OA group), only one remained under this threshold after the vital capacity breath exercise.

Further on the perioperative period and considering the identical ventilation/oxygenation strategy in both groups, no differences could be retained on the lowest post-extubation absolute saturation levels. Nevertheless, OA patients did present a significant saturation drop when compared to baseline levels (2.1% +- 3.3%), which opposed the average resaturation of 0.7% in the OFA group (0.7%+- 2.2%). With 95% confidence intervals extending to both positive and negative variations, the present findings do not support an exclusive and clear one-sided variation in either cluster, conclusion supported by analogous studies[19]. Moreover, the lower starting saturation of OFA patients might explain the above-mentioned trend. On absolute terms, this corresponded to 5 OA patients (16.7%) and 3 OFA subjects (14.7%) presenting with post-extubation saturations below 94%.

The intraoperative saturation trends did not necessarily set forth into the PACU, and clear differences were found on the proportion of patients requiring supplemental postoperative oxygen administration. In fact, while 53.3% of OA patients required O2 therapy due to registered saturations under 94%, only 12.9% of the OFA patients did so too. These results confirm previously reported findings where, despite standard postoperative oxygen administration, obese patients receiving intra-operative opioids displayed relatively lower saturations when compared to matched opioid-free counterparts[20].

Similarly, significant differences were observed on the proportion of patients requiring opioid rescue (70% OFA vs 100% OA) despite an absence of evident differences on the highest reported VAS scores. This might partially be account for by a higher cumulative background pain control need in

OA patients, a hypothesis supported by the higher MEDs required for effective postoperative pain relief within this group. The use of opioids at the PACU did not, however, translate into significant post-rescue and pre-discharge intergroup saturation differences. Similar studies and reports have corroborated the higher comparative need for opioid rescue, as well as higher cumulative MEDs[13,19,20].

Paradoxically, OFA patients did exhibit higher (although not significantly different) PONV rates at PACU admission. In fact, although both groups were subject to the exposure of volatile agents for maintenance purposes, in the absence of significant cumulative exposure differences and other Apfel score element significant differences, such result was not expected a priori, nor confirmed by previous studies[21-23]. This trend inverted after opioid rescue, with OA patients exhibiting significantly higher PONV complaints.

The present study presents design limitations that should be taken into account when extrapolating data. In fact, for pragmatic and local practice purposes, no patient randomization took place. As such, an invariable selection bias is introduced that potentially confounds the obtained results. For that matter, the corresponding intra-operative opioid weight-adjusted load within the OA group was not accounted for when reporting postoperative respiratory and analgetic results. Given the potential accumulation of potent liposoluble opioids such as Sufentanil, a postoperative extension of their effect is thus not excluded, nor are eventual correlations for idiosyncratic opioid sensitivity, which are practically difficult to account for. Moreover, the time to first opioid rescue at the PACU was not registered in both groups, thus not allowing further speculation on a possible postoperative extension of the effect of intra-operative opioids. Additionally, actively smoking patients were not excluded from the analysis (although no intergroup differences were present for this purpose).

A trans-operative analysis where intraoperative saturations are taken into account to set continuity from pre- to post- operative oxygenation values, was not carried out. For that purpose, although no major intraoperative adverse events were reported in both groups, the intra-operative period course is at best assumed, but not confirmed, as normal and unbiased.

Finally, the present study lacks an analysis of adverse events on the step-down units to which patients are discharged after the PACU. Considering 85% of OIRD events take place in the first 24 postoperative hours, additional more encompassing studies are needed to further corroborate the respiratory safety of OFA techniques[3,4].

Conclusion

When compared to OA, OFA is not associated with significant postoperative saturation changes. However, OFA is associated with a significantly reduced need of oxygen administration. The need for opioid rescue as well as cumulative MEDs are significantly higher in OA patients. Large randomized clinical trials looking at larger postoperative time windows are needed.

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