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Impact of opioid free Anesthesia versus opioid Anesthesia on post-operative oxygenation after bariatric surgery: an observational study

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Abstract: *Introduction:* Opioid induced respiratory depression (OIRD) is a preventable etiology of post-operative 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 postoperative respiratory depression when compared to Opioid-based anesthesia (OA).
Methods: Obese patients presenting for bariatric surgery were consecutively included in a non-randomized fashion. Lung protective ventilation strategies were 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 afterextubation and in the post-anesthesia care unit (PACU). Opioid requirement and postoperative nausea and vomiting (PONV) 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 were significantly higher with OA.
Conclusion: OFA was not associated with significant post-operative saturation changes. OA lead to higher need of postoperative oxygen therapy and more opioid rescue. No fatal respiratory complicationswere registered in both groups in the immediate postoperative period.

Keywords: anesthesia; opioid; oxygen; bariatric surgery.

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, post-operative 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 post-operative patients have been estimated to undergo prolonged hypoxemic episodes (defined as aplethysmographic saturation under 90%) during the first postoperative hours. Sun Z. et al concludedthat the saturation values recorded in medical charts seriously underestimate the incidence of postoperative hypoxemia (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). A 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 opioid pharmacodynamics are characteristically idiosyncratic, these tend to initially lead to a reduction in the depth of breathing, followed by a slowing of the respiratory rate and generation of more irregular/inconsistent breathing patterns (5). High

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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 post-operative 24 hours are a high-risk period for opioid-induced adverse respiratory events, encompassing up to 85% of all post-operative OIRD episodes (4). Its occurrence is further potentiated not only by unmodifiable factors such as advanced age and female sex, but also by co-morbidities such as obesity, obstructive sleep apnea syndrome (OSAS), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), hepatic and cardiac disease (4, 9). Obese patients are in fact an increasingly prevalent risk-group for the aforementioned post-operative morbidity and mortality events. The physiological changes in obese patients that contribute to hypoventilation and hypoxemia are relatively well described. Fat in the abdomen and surrounding the chest wall contributes to the reduction of the expiratory reserve volume, with a consequent significant decrease in the functional residual capacity. Overweight patients tend to breathe at lower relative (downshifted) tidal volume ranges, especially when supine and during sleep. Fat deposits have direct mechanical effects leading to a reduction in compliance associated with greater airway resistance which contributes to an increase in total work of breathing and more limited expiratory gas flows. Gas trapping due to premature airway closure generates intrinsic positive end-expiratorypressure and favors ventilation-perfusion mismatches (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 this group of patients, OIRD diagnosis is alternatively aided by respiratory rate monitoring (for example, by impedance-derived methods or capnographic measurements), although such methodologies are not systematically employed on every ward (1).

Despite having known adverse effects, opioids remain a widely adopted choice for perioperative analgesia (2). Given their undesired dose-dependent side effect profile on known risk populations, opioid free anesthesia (OFA) protocols have been introduced and standardized in bariatric surgery reference centers. Belgian anesthesia departments with extensive bariatric anesthesia experience have reported that the fine-tuning of this practice has contributed to a reduction of opioid use for analgesic rescue purposes up to 75% (13).

Although the perioperative pain mitigation strategy is assumed to play a significant role on the incidence of post-anesthetic respiratory depression, the role and potential interplay of other anesthetic interventions should be similarly considered as determinant for this purpose. In fact, the following anesthetic and surgical approaches have been put forward as aids (or alternatives on theirown) to the prevention of respiratory depression: full reversal of paralytics at the end of surgery; locoregional anesthesia techniques; minimal invasive surgical approaches, lung protective ventilation strategies; and avoidance of perioperative benzodiazepines (3).

Although opioid sparing/free anesthetic techniques might intuitively suggest a potential relative benefit in terms of desaturation-avoidance when compared with opioid permissive strategies, previously published studies have failed to clearly demonstrate a difference between the two approaches. As such, the present study aimed to investigate whether OFA is associated with a reduced incidence of post-operative respiratory depression 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 at admission to the post anesthesia care unit (PACU), after an eventual PACU rescue opioid therapy as well as at 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 November 2019. Adult patients (18 years of age and older) with a body mass index (BMI) greater than 35 presenting for elective laparoscopic bariatric surgery at AZ Sint-Jan Brugge, were included. Exclusion criteria were: chronic opioid use in the month preceding the surgery, pre-operative oxygen requirement, Obstructive sleep apnea syndrome (OSAS), renal insufficiency, uncontrolled hypertension, acute or chronic liver insufficiency, allergy toacetaminophen or non-steroidal anti-inflammatory agents and BMI more than 60. Theaforementioned exclusion criteria lead to the exclusion of a total of 2 patients. Patients with OSAS and extreme obesity (defined as BMI more than 60) have a clear benefit from opiate free anesthesiaon postoperative respiratory function and were therefore not included.

The study protocol was approved by the local institutional review board prior to commencement aswell as registered at the clinicaltrials.gov database (NCT 03660306). Written informed consent was obtained before patient enrollment.

Patient allocation was not subject to randomization and treatment allocation (OA/OFA) 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 (IBW) 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 (14). Induction was performed in 30° back elevation beach chair position with simultaneous application of a CPAP of 5-10 cmH20 at a 80% inspired oxygen fraction (FiO2). After induction and during the procedure, the lungs were recruited whenever lung compliance dropped below 40 ml/cmH20. 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 (I:E) ratio of 1:1. Intra-operative Fi02 was recommended to be no lower than and as close to 40% as possible, as guided by a plethysmographic oxygen saturation (SpO2) above 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 of a balanced crystalloid solution was standardly set at 100 ml/hour, and deep neuromuscular blockade (as defined by a post-tetanic count under 2 by means of acceleromyographic adductor pollicis monitoring) was achieved with a 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 0,1 mcg/kg during the surgery at the discretionof the attending anaesthesiologist.

The OFA group received a dexmedetomidine IV loading dose (0,3 mcg/kg) 15 minutes before induction, which preceded baseline saturation measurements. At induction, a mixture of dexmedetomidine (0,1 mcg/kg), lidocaine (1 mg/kg) and ketamine (0,1 mg/kg) was administered as an IV bolus. Before surgical incision, an IV bolus of ketamine (0.7 mg/kg, max 50 mg) was administered. These drugs were maintained throughout the intraoperative period as an automated IV infusion: dexmedetomidine (0,1 mcg/kg/h), lidocaine (1 mg/kg/h) and ketamine (0,1 mg/kg/h). After Extubation, the aforementioned drug infusion rates were all reduced by 50% and continued throughout the PACU admission.

At the end of surgery sugammadex was administered in order to achieve full neuromuscular recovery as defined by a TOF ratio above 0,9. Extubation took place with a FiO2 lower than 60%, in beach chair position (minimal back-up inclination of 20°) and with a CPAP of 5 - 10 cmH20. Beach chair positioning was maintained during transport and PACU stay. Supplemental oxygen administration was initiated at the PACU when a drop of the plethysmographic saturation below 94% was observed by the PACU nurse. The supplemental oxygen therapy was continued, as needed, until the discharge of the PACU.

Analgesia was standardly provided with 1 gram of paracetamol every 6 hours after a 2 gram intra- operative loading dose, diclofenac 75 mg every 12 hours after a 150 mg intraoperative loading dose. Pain was assessed at the PACU by means of a visual analogue scale (VAS). The presence of a scoregreater than 5 lead to a titration of piritramide (Dipidolor®) per 5mg boli followed by a saline flush.

Plethysmographic oxygen saturation readings were retrieved at the following peri-operative time-points: at arrival to the operation room before and after 3 deep room air breaths, at extubation, the lowest saturation during the PACU stay, saturation after opioid rescue at the PACU and immediately before PACU discharge. The total dose of opioids given in the PACU was calculated and registered as morphine equivalent doses (MED). 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 edition, Armonk, New York). Variables were subject 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 manuscript adheres to the applicable strengthening the reporting of observational studies in epidemiology (TREND) 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.

Descriptive anthropometric and comorbidity location statistics per anaesthesia type (Opioid versus Opioid-free) are displayed in Table 1. Herein, intergroup significance testing results are accordingly presented, having revealed no significant differences between both groups. The relative allocation of comorbidities in both groups are illustrated in figure 1 (OA group) and figure 2 (OFA group).The perioperative respiratory and analgetic strategy descriptives are presented in table 2, 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 pre-induction and after extubation 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 1

Demographic and clinical characteristics of patients who received OA vs OFA

	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/m²)	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]
PONV history (n [%])	3 (11.0 %)	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 mean+- 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 – Post-operative Nausea and Vomiting; AHT – Arterial Hypertension; DM – Diabetes Mellitus.*

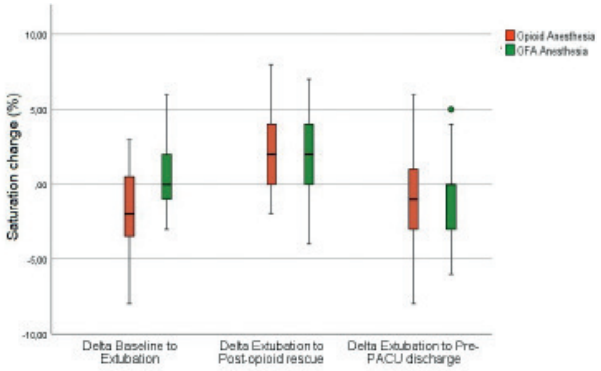

Fig. 1. — Saturation measured at different moments perioperative in OA vs OFA.

Green – OFA group; Red – OA group; y axis - Saturation values (percentual); x axis – perioperative moment of measuring saturation.

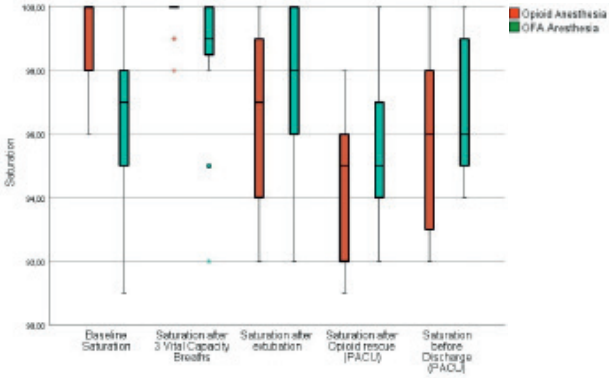

Fig. 2. – Change in saturation from baseline to extubation.

Green – OFA group; Orange – OA group; y axis - Saturation change in percentual points; x axis – perioperative saturation category.

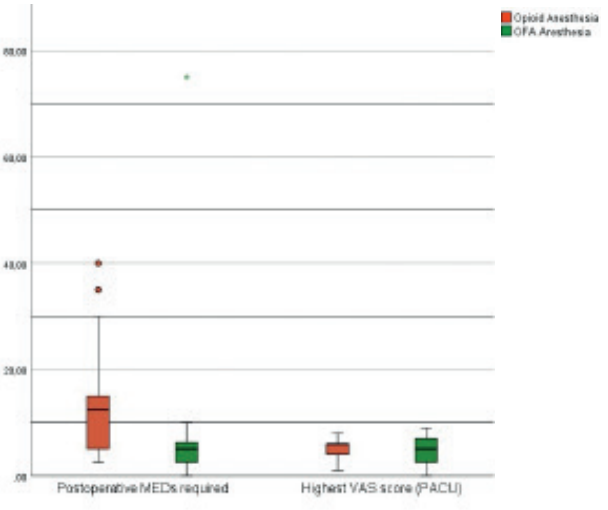

Fig. 3. — Postoperative MEDs required and highest VAS score in OA vs. OFA.

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.

Table 2

Clinical outcome of OA vs OFA

	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 = 0.000** [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 = 0.000** [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 mean+- 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 – Post-Operative Nausea and Vomiting.*

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.

Considering the pre-induction period, one observes that the OA patients presented relatively highersaturation levels. This applied both to baseline and post triple vital capacity breath values. Although groups were 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 0,25 mcg/kg 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 either minimally lower saturation (no lower than 95%) (16). In obese patients, loading doses up to 1 mcg/kg have been reported to effectively reduce plethysmographic saturations up to 25 minutes after loading (17). Thiscontrasts to reported oxygenation improvements in obese patients affected by restrictive lung disease (18). As such, in the absence of alternative causality arguments, one could 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 standardized vital capacity breath exercise.

Further on the perioperative period, and taking into account 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 re-saturation 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, a 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%.

Individual saturations show a large variation between each patient and each moment in both groups even with exclusion of severe OSAS and cardio pulmonary diseases. These differences are however for most patients clinical small and probably not clinical important except when values dropped below 94 % requiring a clinical action like treating the reason and given oxygen under close monitoring and supervision (3, 12).

The intraoperative saturation trends did not necessarily set forth into the PACU, and clear differences were found on the proportion of patients requiring supplemental post-operative oxygen administration. In fact, while 53,3% of OA patients required oxygen 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 post-operative 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 versus 100% OA) despite an absence of evident differences on the highest reported VAS

scores. This might partially be accounted for by a higher cumulative background pain control need in OA patients, a hypothesis supported by the higher MEDs required for effective post- operative 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).

No difference in PONV was found between both groups in the first moments at the PACU before any postoperative opioid was given. Both groups had the same Apfel score. All patients received the same dose of prophylactic antiemetic, being dexamethasone 10 mg to suppress peritoneal inflammation. Previous studies (21, 22, 23) did not find a difference either. After opioid rescue, OA patients exhibited significantly higher PONV complaints.

The present study presents design limitations that should be taken into account when interpreting the presented 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 post-operative respiratory and analgetic results. Given the potential accumulation of potent liposoluble opioids such as sufentanil, a post-operative extension of their effect is thus not excluded, nor are eventual correlations for an idiosyncratic opioid sensitivity, which are practically difficult to account for.

Moreover, a trans-operative analysis where intraoperative saturations are taken into account to set continuity from pre- to postoperative 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 post-operative saturation changes. However, the need for opioid rescue as well as cumulative MEDs are significantly higher in OA patients. This led to a significantly increased need for oxygen administration at PACU in OA patients compared to OFA.

Author contribution

Lieselot Geerts: This author helped design the study, develop and execute the protocol, analyze the results and develop the statistical analysis, get Institutional Review Board approval, analyze the results and develop the manuscript.

Hugo Carvalho: This author helped design the study, analyze the results and develop the statistical analysis, writing methods and editing manuscript.

Eliza Yarahyan: This author helped design the study, develop and execute the protocol, get Institutional Review Board approval and develop the manuscript.

Jan Mulier: This author helped design the study, develop, execute and supervise execution of the protocol, get Institutional Review Board approval, analyze the results and develop the manuscript.

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