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ORIGINAL INVESTIGATION

Comparison of three intraoperative analgesic strategies in laparoscopic bariatric surgery: a retrospective study of immediate postoperative outcomes

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Abstract

Introduction and objectives: Multimodal Analgesia (MMA) has shown promising results in post-operative outcomes across a broad spectrum of surgeries, including bariatric surgery. We compared the analgesic effect immediately after Laparoscopic Bariatric Surgery (LBS) of the combined effect of MMA and methadone against two techniques that were based mainly on the use of high-potency medium-acting opioids.

Methods: Two hundred seventy-one patients were retrospectively reviewed. The primary outcome was postoperative pain score > 3/10 measured by the Verbal Numeric Scale (VNS) during the Postanesthetic Care Unit (PACU) stay. The three protocols of intraoperative analgesia were: (P1) sufentanil at anesthetic induction followed by remifentanil infusion; (P2) sufentanil at induction followed by dexmedetomidine infusion; and (P3) remifentanil at induction followed by MMA including dexmedetomidine, magnesium, lidocaine, and methadone. Only P1 and P2 patients received morphine toward the end of surgery. Poisson regression was used to adjust confounding factors and calculate Prevalence Ratio (PR).

Results: Postoperative VNS > 3 was recorded in 135 (49.81%) patients, of which 93 (68.89%) were subjected to P1, 25 (18.56%) to P2, and 17 (12.59%) to P3. In the final adjusted model, both anesthetic techniques (P3) (PR = 0.10; 95% CI [0.03–0.28]), and (P2) (PR = 0.42; 95% CI [0.20–0.90]) were associated with lower occurrence of VNS > 3, whereas age range 20–29 was associated to higher occurrence of VNS > 3 (PR = 3.21; 95% CI [1.22–8.44]) in PACU. Postoperative Nausea and Vomiting (PONV) was distributed as follows: (P1) 20.3%, (P2) 31.25% and (P3) 6.77%; (P3 < P1, P2; $p < 0.05$). Intraoperative hypotension occurred more often in P3 (39%) compared to P2 (20.31%) and P1 (17.46%) ($p < 0.05$).

Conclusion: MMA + methadone was associated with higher incidence of intraoperative hypotension and lower incidence of moderate/severe pain in PACU after LBS.

Introduction

One of the challenges of general anesthesia is to allow smooth emergence at the end of surgery with relative comfort. Inadequate analgesia in the Postanesthetic Care Unit (PACU) is common[1] and negatively affects hemodynamics, respiration, metabolism, delayed discharges from PACU, and creates dissatisfaction. Poor pain control after emergence from anesthesia negatively impact postoperative outcomes.[2] Obesity may be associated with increased pain perception after surgery and increased risk of developing chronic pain.[3] The additional presence of obstructive sleep apnea, restrictive lung disease, coronary artery disease, metabolic syndrome, etc. make postoperative analgesia particularly crucial and challenging in obese patients.[4] Medium-acting opioids such as morphine and hydromorphone are commonly used during and after surgery to mitigate moderate-to-severe postoperative pain while striving to avoid obstructive sleep apnea and excessive respiratory depression.[4] Perioperative Multimodal Analgesia (MMA) combines medications that act synergistically at different sites and pathways with the ultimate goal of achieving pain relief while minimizing side effects. Under the umbrella term of MMA, practices vary widely.[5] Most strive to maintain consistent superior analgesia without large breakthroughs and reduce dependency on the use of medium-acting opioids such as morphine for analgesia.[5]

Methadone is a strong opioid μ-receptor agonist, N-Methyl-Aspartate (NMDA) receptor antagonist, and serotonin and noradrenaline reuptake inhibitor in the central nervous system. It has a long elimination half-life of 24−36 hours.[6] A recent meta-analysis of Randomized Controlled Trials (RCTs) showed that intraoperative methadone results in reduced pain and reduced morphine (equivalent) requirements in PACU and for 2−3 days postoperative across a spectrum of surgeries.[7] Machado et al. compared intraoperative methadone vs. fentanyl in a RCT involving patients undergoing open bariatric surgery and found that the methadone group had less postoperative pain and less morphine requirements.[8]

The recognition of the advantages of MMA and methadone prompted our group to incorporate them in January 2019 into our enhanced recovery protocol for laparoscopic bariatric surgery. Hence, the objective of the present investigation was to retrospectively review immediate postoperative outcomes (namely pain scores, nausea/vomiting, and occurrence of hypoxemia) as well as incidence of intraoperative hypo/hypertension in patients undergoing laparoscopic bariatric surgery before (up to December 2018) and after (January−December 2019) such protocol had been observed.

Methods

Institutional ethics approval (nº 3.664.935) was obtained to conduct this review at a tertiary hospital in Sao Paulo, Brazil. Patients undergoing laparoscopic bariatric surgery (Roux-en-Y or sleeve gastroplasty) from January 2014 to December 2019 were reviewed. Primary outcome was pain > 3/10 assessed by the Verbal Numeric Scale (VNS) at any time in PACU.

Patients included in the study were registered in a hospital database. Exclusion criteria were open bariatric surgery, chronic opioid use, ASA (American Society of Anesthesiologists) physical status $\geq$ IV, reoperation, allergy to any medication used in the study, drug addiction, combined surgical procedures, general anesthesia combined with neuraxial blockade, administration of other analgesic adjuvants not included in the protocol in force at the time, and other protocol violations.

During the study period, 1447 bariatric surgeries were performed, of which 271 were eligible (Fig. 1). During the study period, three standardized intraoperative protocols related to opioids and opioid-adjuncts/coanalgesics were observed:

P1: Protocol (sufentanil-remifentanil-morphine for analgesia) in force for period Jan 2014−Aug 2017. Sufentanil 1.0 μg.kg^{-1} of Corrected Body Weight (CBW) at anesthetic induction followed by continuous infusion of remifentanil (0.1−0.3 μg.kg^{-1}.min^{-1}). Twenty minutes prior to surgical completion, patients received ondansetron 0.1 mg.kg^{-1} (max. 8 mg) and morphine 100 μg.kg^{-1}.

P2: Protocol (sufentanil-dexmedetomidine-morphine for analgesia) in force for the period Sept 2017−Dec 2018. Sufentanil 0.5−07 μg.kg^{-1} CBW at anesthetic induction followed by dexmedetomidine (initial bolus of 1 μg.kg^{-1} over 10 minutes, followed by maintenance of 0.4−0.7 μg.kg^{-1}.h^{-1}). Twenty minutes prior to surgical completion, patients received morphine 100 μg.kg^{-1}. The antiemetic palonosetron 0.075 mg was administered upon anesthetic induction.

P3: Protocol (MMA incorporating methadone) in force for period Jan−Dec 2019. Target-controlled infusion of remifentanil (initial bolus of 4 ng.mL^{-1} over 5 minutes at anesthetic induction, followed by maintenance with 2−5 ng.mL^{-1}), methadone 0.2 mg.kg^{-1} (real body weight) up to 20 mg, lidocaine 2 mg.kg^{-1}, dexmedetomidine 0.5 μg.kg^{-1} single dose over 1 minute, and magnesium sulphate 40 mg.kg^{-1} after loss of consciousness. Twenty minutes prior to surgical completion, patients received ondansetron 0.1 mg.kg^{-1} (max. 8 mg). No sufentanil or morphine was administered intraoperatively.

In all patients, anesthesia was induced with propofol and rocuronium and maintained with sevoflurane to keep a Bispectral Index (BIS) of 40−60. Prior to surgical incision, all
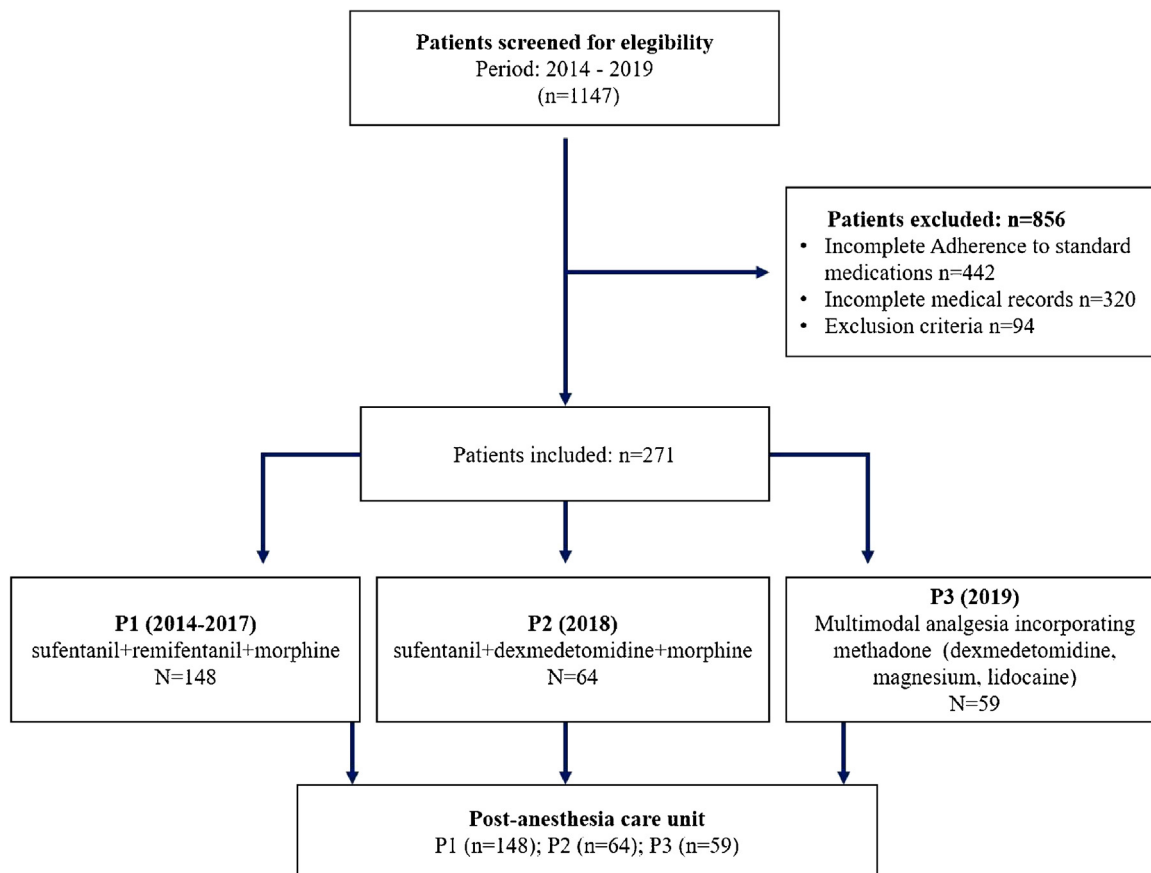
Figure 1 STROBE flow diagram.

patients received parecoxib 40 mg, pantoprazole 40 mg, and dexamethasone 0.1 mg.kg^{-1} (max. 10 mg). Twenty minutes prior to surgical completion, all patients received dipyrone (a non-steroidal anti-inflammatory drug) 2000 mg.

Intraoperative monitoring consisted of Noninvasive Blood Pressure (NIBP), ECG, oximetry (SpO$_2$), capnography, and BIS. Controlled ventilation was performed in a closed circuit with a flow up to 2 L.min^{-1}, tidal volume up to 8 mL.kg^{-1} based on CBW, with a positive end expiratory pressure of 6–8 mmHg, inspired oxygen fraction up to 50% and respiratory rate to maintain end-tidal CO$_2$ 35–40 mmHg. Neuromuscular blockade was maintained at a post-tetanic count < 5 (i.e., deep block). Reversal of neuromuscular blockade was achieved with sugammadex in all patients. All patients received Ringer's lactated solution 10 mL.kg^{-1} before anesthetic induction. Intraoperatively, crystalloid was infused at 5 mL.kg^{-1}.h^{-1}. Nasogastric tubes and surgical drains were not used routinely. Normothermia was maintained by a convective air circulation heating system (Bair Hugger, 3M-Switzerland, Ruschlikon, Swtzerland).

The studied variables included age, gender, body weight, height, Body Mass Index (BMI), Heart Rate (HR), NIBP, SpO$_2$, and anesthetic technique according to the protocol in force. HR, NIBP and SpO$_2$ were recorded prior to anesthetic induction and every 10 minutes thereafter until the end of the procedure. Hypotension and hypertension were defined as > 20% decrease and > 20% increase in mean arterial pressure, respectively, from pre-induction blood pressure, and treated

initially with changes in end-tidal sevoflurane and remifentanil and/or dexmedetomidine infusion rates, followed by ephedrine or hydralazine, respectively, when anesthetic dose adjustment was insufficient to reestablish the target blood pressure.

In PACU, the VNS score (0–10 scale) was assessed every 15 minutes. Postoperative Nausea and Vomiting (PONV) was assessed based on a 0–4 intensity scale (modified from Wengritzky et al.)[9] in which 0 = no nausea, 1 = mild nausea, 2 = moderate nausea, 3 = severe nausea, and 4 = retching/vomiting. Upon arrival to PACU, hypoxemia was defined as a SpO$_2$ < 90%.[10]

Pain was treated with morphine 30–50 μg.kg^{-1} and PONV with dimenhydrinate 30 mg. Discharge from PACU was considered when Aldrete score ≥ 9 and pain score ≤ 3.

Statistical analysis

Histograms and the Shapiro-Wilk test were utilized for verification of data distribution symmetry. Pearson Chi-squared test was employed for categorical variables, and partitioning Chi-Square when $p < 0.05$. Variables with normal distribution were compared with ANOVA (3 groups), followed by the Tukey post-hoc test in case of $p < 0.05$ or two-sample independent t-test, when two groups were compared. The pain scores (VNS) were compared through the median (percentile 25–75%) of each protocol and the Kruskal-Wallis Analysis of Variance was used for multiple

Table 1 Demographic and intraoperative variables.

Variables	Anesthetic technique			p-value
	P1 (n = 148)	P2 (n = 64)	P3 (n = 59)	
Age[a] (years)	36.13 ± 10.08	37.75 ± 12.38	36 ± 10.91	0.67
Gender[b]				0.54
Female	109 (73.65)	45 (70.31)	39 (66.10)	
Male	39 (26.35)	19 (29.69)	20 (33.90)	
Body mass index[a] (kg.m^{-2})	41.13 ± 5.25	40.69 ± 7.31	40.63 ± 5.38	0.43
Smokers[b,c]				0.54
No	126 (94.03)	51 (89.47)	49 (92.45)	
Yes	8 (5.97)	6 (10.73)	4 (7.55)	
Surgery duration[a] (min)	100 ± 43.87	81.25 ± 34.20	[d]77.71 (27.99)	0.002
Type of surgery[b]				0.074
''Roux-en-Y'' bypass	126 (85.13)	57 (89.00)	44 (74.58)	
''Sleeve'' gastroplasty	22 (14.86)	07 (11.00)	15 (25.42)	

VNS, Verbal Numeric Scale.

[a] Values expressed as mean ± standard deviation – Analysis of variance (ANOVA).

[b] Values expressed as n (%) - Chi-Square test. (P1) sufentanil + remifentanil + morphine (2014-2017).

[c] Smokers: incomplete medical records were observed in 9.5% of charts in P1, 11% in P2 and 7% in P3.

[d] Tukey post-hoc test: P3 < P1-P2; (P2) sufentanil + dexmedetomidine + morphine (2018); (P3) Multimodal Analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).

comparisons, followed by the Dunn post-hoc test in case of p-value < 0.05. Prevalence Ratios (PR) were calculated to determine the relationship between independent Variables and Pain Scores (VNS) > 3. Univariate analysis was performed by Poisson regression, with simple robust variance, and estimative of gross Prevalence Ratios (PR) and respective Confidence Intervals (95% CI) to assess the extent of association between variables. Independent variables that were deemed statistically significant (i.e., p < 0.20) in the univariate analysis were considered candidates for the multivariable model, which then retained predictors that remained statistically significant at p < 0.10 by stepwise selection. Statistical analysis was performed using STATA 12.0 software (Stata Corp, College Station, TX). The research data related to this submission has been published in Mendeley Data (doi:10.17632/txzbhmfxc4.1). The files associated with this dataset are licensed under an attribution non-commercial 3.0 Unported license (CC BY NC 3.0).

Results

The final analysis included 271 patients, of whom 71.2% were female (Table 1). The overall mean age was 36.5 ± 10.4 years. The mean duration of surgery was 92 ± 39.61 minutes. The P3 cohort had shorter duration of surgery. Total number of subjects for each cohort was 148 in P1, 64 in P2 and 59 in P3 (Table 1).

Pain > 3 was documented in 49.8% of patients. Severe pain (VNS > 7) was observed in 28.7% (42) in P1, 9.37% (6) in P2, and 8.47% (5) in P3 (P1 > P2–P3; p < 0.05). Figure 2 shows the median (25–75% percentile) of pain scores between anesthetic protocols (p < 0.05). Amongst all patients presenting with pain > 3, 93 (68.89%) were submitted to P1 (sufentanil-remifentanil-morphine analgesia), 25 (18.56%) to P2 (sufentanil-dexmedetomidine-morphine analgesia), and 17 (12.59%) to P3 (MMA + methadone)
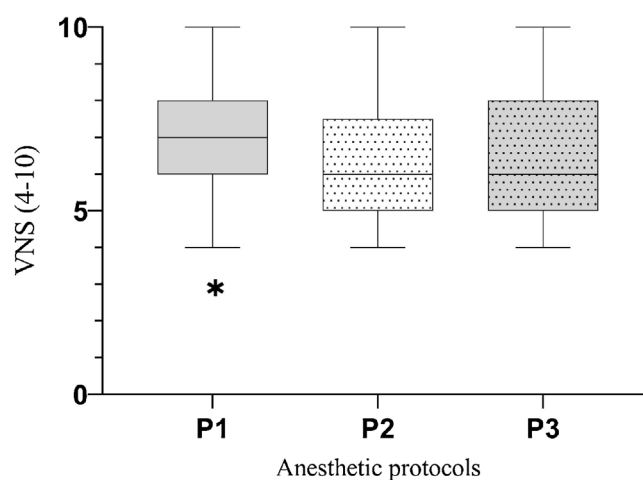

Figure 2 Boxplot: Median (25–75%) of pain scores between anesthetic protocols. (P1) sufentanil + remifentanil + morphine (2014–2017); (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) multimodal analgesia (dexmedetomidine, magnesium, lidocaine) and methadone (2019). VNS, Verbal Numeric Scale; MMA, Multimodal Analgesia – dexmedetomidine + magnesium sulfate + lidocaine. *Analysis of Variance (Kruskal Wallis): p = 0.01; Dunn post-hoc test: P1 > P2–P3.

(Table 2). From the factors potentially related to postoperative pain, anesthetic protocol, surgery duration and age presented statistical significance in the univariate analysis (Table 2). In the final adjusted model, anesthetic protocol P3 (MMA-methadone) (PR = 0.10; 95% CI [0.03–0.28]) and P2 (sufentanil-dexmedetomidine-morphine) (PR = 0.42; 95% CI [0.02–0.90]) were associated with lower occurrence of pain > 3 in PACU when compared to protocol P1 (sufentanil-remifentanyl-morphine). Age range 20–29 years-old was associated with higher postoperative pain scores (PR = 3.21; 95% CI [1.22–8.44]) (Table 3).

Table 2 Univariate analysis of demographic and intraoperative variables related to pain score > 3 in the postanesthetic care unit.

Demographic and intraoperative variables	Pain score > 3 (VNS)		Unadjusted PR (CI)	p-value
	No	Yes		
Age (years)[a]	38.0 ± 10.9	34.2 ± 10.5	0.97 (0.85–0.99)	0.02
Gender[b]				0.11
Female	91 (66.91)	102 (75.56)	1.00	
Male	45 (33.09)	33 (24.44)	2.30 (0.89–3.88)	
Body mass index(kg.m^{-2})[a]	40.76 ± 5.49	41.07 ± 6.14	1.00 (0.96–1.05)	0.66
Surgery duration (min)[a]	85.6 ± 34.56	96.50 ± 33.29	1.008 (1.002–1.01)	0.01
Type of surgery[b]				0.92
''Roux-en-Y'' bypass	111 (81.62)	116 (85.93)	1.00	
''Sleeve'' gastroplasty	25 (18.38)	19 (14.07)	1.03 (0.44–2.40)	
Anesthetic technique[b,c]				< 0.001
(P1) Sufentanil + remifentanil + morphine	55 (40.44)	93 (68.89)	1.00	
(P2) Sufentanil + dexmedetomidine + morphine	39 (28.68)	25 (18.52)	0.48 (0.74–2.95)	
(3 P3) MMA + methadone	42 (30.88)	17 (12.59)	0.14 (0.03–0.64)	

VNS, Verbal Numeric Scale; CI, Confidence Interval; PR, Prevalence Ratio.
[a] Values expressed as mean ± standard deviation – Two-sample independent t-test.
[b] Values expressed as n (%) - Chi-Square test.
[c] Partitioning test: Incidence of pain score > 3 (VNS) in P1 > P2 and P3; Pain in P3 < P2. (P1) sufentanil + remifentanil + morphine (2014-2017); (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) multimodal analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).

Table 3 Adjusted analysis of independent variables associated with pain score > 3 in the postanesthetic care unit.

Demographic and intraoperative variables	Unadjusted PR (CI)	Adjusted PR (CI)	p-value
Age (years)			0.01
20–29	2.54 (1.05–6.64)	3.21 (1.22–8.44)	
Anesthetic technique			< 0.001
(P1) Sufentanil + remifentanil + morphine	1.00	1.00	
(P2) Sufentanil + dexmedetomidine + morphine	0.48 (0.74–2.95)	0.42 (0.20–0.90)	
(3 P3) MMA + methadone	0.14 (0.03–0.64)	0.10 (0.03–0.28)	

The univariate analysis (presented in Table 2) was followed by multivariable analysis using Poisson regression. (P2) sufentanil + dexmedetomdine + morphine (2018); (P3) Multimodal Analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).
VNS, Verbal Numeric Scale; CI, Confidence Interval; PR, Prevalence Ratio.

Incidence of intraoperative hypotension was 17.46% in the P1 cohort, 20.31% in the P2 cohort, and 39% in the P3 cohort (P3 > P1, P2; p < 0.05). Intraoperative arterial hypertension was observed in 5.90% of all patients (P1 = P2 = P3, p > 0.05). PONV was observed in 19.93% from analyzed patients, 20.3% from which in P1, 31.25% in P2, and 6.77% in P3 (P3 < P1, P2; p < 0.05). The incidence of hypoxemia was 21.40%, with no difference observed between the analyzed anesthetic protocols (p > 0.05) (Table 4). Respiratory depression requiring non-invasive ventilatory support occurred in one case in group P1. There was no need for reintubation or other major complications observed in the immediate postoperative period.

Discussion

The main result of this study is that in laparoscopic bariatric surgery, MMA in conjunction with methadone, when compared to techniques based mainly on the intraoperative use of medium-acting and high-potency opioids, significantly reduces the incidence of pain and PONV in PACU. These findings are consistent with similar postoperative pain studies comparing MMA and morphine[7] and studies comparing methadone and morphine[5] in obese and non-obese patients.

The use of methadone in bariatric surgery has shown to be safe and significantly reduce perioperative opioid consumption, postoperative pain (both at rest and with activity), and PONV.[7,8] In the present investigation, intraoperative-high-dose sufentanil (P1) resulted in greater necessity of analgesic rescue in PACU when compared to MMA including methadone. These findings are consistent with previous studies on multimodal opioid-sparing anesthetic techniques, in which methadone was the only opioid used.[8,11] Similarly, perioperative methadone results in lower pain scores in non-obese patients.[12–14]

We also found that age is a risk factor for increased immediate postoperative pain. In Ip et al's literature review, they found correlation between higher postoperative pain and younger age in most, but not all, of the studies.[14]

Table 4 Intraoperative (arterial hypotension and hypertension) and postoperative (PONV and hypoxemia) outcomes in relation to the anesthetic technique employed.

Outcome	Anesthetic technique			p-value
	P1 (n = 148)	P2 (n = 64)	P3 (n = 59)	
Intraoperative				
Arterial hypotension	n (%)	n (%)	n (%)	0.001*
Yes	22 (17.46)	13 (20.31)	23 (39.00)	
No	126 (82.54)	51 (79.69)	36 (61.00)a	
Arterial hypertension				0.18
Yes	8 (5.40)	7(13.00)	2 (3.38)	
No	140 (94.60)	57 (87.00)	57 (96.61)	
Postanesthetic care unit				
PONV				0.003*
Yes	30 (20.3)	20 (31.25)	04 (6.77)	
No	118 (79.7)	44 (68.75)	55 (93.23)b	
Hypoxemia (SpO_2 < 90%)**				0.23
Yes	29 (20.00)	12 (18.75)	17 (28.81)	
No	119 (80.00)	52 (81.25)	39 (71.19)	
Respiratory depressionc				NA
Yes	01 (0.67)	00 (0.00)	00 (0.00)	
No	147 (99.33)	64 (100)	59 (100)	

NA, Not Applicable; (P1); Sufentanil + remifentanil + morphine (2014-2017); (P2) Sufentanil + dexmedetomidine + morphine (2018); (P3), Multimodal-analgesia (MMA) comprising dexmedetomidine + magnesium + lidocaine + methadone (2019).
PONV, Postoperative Nausea/Vomiting.
  * Chi-Square test (p < 0.05) − Partitioning test: (a) P3 > P1 (p < 0.05), P2; (b) P3 < P1, P2 (p < 0.05).
  ** At admission to PACU.
  c Respiratory depression requiring ventilatory support.

We hypothesize that cultural factors, modulating social influences, as well as personality and behavior features of different age groups can influence the individual expectation of pain and ultimately their expression in measurement scales. Nonetheless, this finding highlights the importance of a thorough preoperative consultation during which the clinicians (both anesthesiologist and surgeon) must clarify the patient's uncertainties and set up the perioperative expectations accordingly.

Magnesium is the more abundant divalent intracellular cation, implicated in numerous physiologic processes such as blood pressure regulation through modulation of vascular tone and peripheral vascular resistance. The increase in extracellular concentration of magnesium, therefore, results in arterial vasodilation,[15] which may have contributed to the higher incidence of hypotension (39%) observed in P3 (Table 4). Additionally, magnesium modulates pain through antagonism of the NMDA receptors. In obese patients, intraoperative administration of magnesium sulphate is associated with lower postoperative pain scores and opioid consumption.[15,16] Similarly, the well-known hemodynamic (i.e., bradycardia and hypotension) and analgesic/opioid-sparing effects of dexmedetomidine most likely contributed to the higher incidence of intraoperative hypotension and lower incidence (through an opioid-sparing effect) of PONV in P3 (Table 4). Indeed, in a meta-analysis of RCTs, dexmedetomidine significantly reduced postoperative opioid requirements.[17] This was corroborated in our study by a lower incidence of severe pain in P2 and P3 when compared to P1. Finally, intravenous lidocaine (used in P3) can also result in lower opioid requirements, thereby reducing the incidence of PONV.[18]

Interestingly, despite patients in P3 not being given high-potency medium-acting opioids, the incidence of hypoxemia (SpO_2 < 90%) at admission to PACU was similar between groups (Table 4). Several factors may have contributed to this finding such as (1) the incidence and severity of obstructive sleep apnea (not measured) in each group; (2) the somnolence associated with lidocaine combined with the residual effect of other anesthetic agents, leading to obstructive airway episodes; and (3) the respiratory depression associated with methadone (which has a prolonged effect). Notably, even though the incidence of hypoxemia upon PACU admission in the present investigation was in line with previous published data,[19] this study was underpowered to demonstrate differences in this regard.

Historically, the use of potent opioids, such as sufentanil, had been considered the standard practice to promote good quality postoperative analgesia because of its known prolonged residual analgesic effect.[20] Subsequently, multimodal opioid-sparing techniques came to establish a new paradigm, one which targets multiple pain pathways instead of focusing mostly (or solely) on opioid receptors, thereby reducing side effects and improving/accelerating postoperative recovery.[21] Additionally, MMA allows for a reduction in the amount of hypnotic agents required to maintain unconsciousness and anesthetic depth. Hence, multimodal anesthesia has a rather global concept which implies optimization of all pharmacologic agents available in the anesthesiologist's armamentarium to ensure safety

and comfort to patients, while minimizing complications and shortening hospital stay.[21]

This study has several limitations. Since this is a retrospective before-after study, there is the potential that the cohorts in the three different time periods were not similar. Specifically, not all potentially relevant factors that could impact pain, PONV, and desaturation were necessarily analyzed. Before-after studies are susceptible to other biases.[22] For example, the study period spanned 6 years, during which many aspects of care might have changed (historic bias). Clinicians might have been more diligent, perhaps even anticipating the results would be scrutinized, when the new protocol was introduced (Hawthorne effect). Surgery length was shorter in P3, which is usually associated to higher surgeons' experience and potentially lower postoperative pain. Lastly, although the median VNS = 7 for patients in P1 was statistically higher than P2 and P3 (median VNS = 6) (Fig. 2), one may question the clinical relevance of this finding. However, the overall lower incidence of moderate/severe pain (i.e., VNS > 3) in P3 reflects a better efficacy of the MMA regimen including methadone. It was not possible to evaluate the independent effects of MMA technique and methadone. However, the purpose of our review was to validate our strategy of merging MMA and methadone, both of which have been shown to improve postoperative analgesia in our laparoscopic bariatric surgery program. Finally, we did not look beyond the PACU period. Based on previous studies on methadone, however, its analgesic advantages typically extend up to 2–3 days after surgery.[6–8]

Conclusion

Our results show an association of the newer protocol period (MMA + methadone) and a lower occurrence of pain in PACU. Notably, a higher incidence of intraoperative hypotension was also observed in the newer protocol period.

Conflicts of interest

The authors declare no conflicts of interest.

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