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ORIGINAL RESEARCH

Obstructive Sleep Apnea and Postoperative Hyperalgesia in Bariatric Surgery: A Prospective Observational Cohort Study

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Purpose: Postoperative hyperalgesia (POH) is a common clinical phenomenon that will increase the experience of patients' pain. Previous studies have confirmed that surgical site, opioid analgesics, gender, and age were risk factors of POH. Limited research has been investigated to prove the association between obstructive sleep apnea (OSA) and POH. This study investigated the relationship between severity of OSA and POH in patients undergoing bariatric surgery.

Patients and Methods: We conducted a single-center prospective observational study in the Affiliated Hospital of Xuzhou Medical University from April 2022 to September 2022. Patients were stratified for OSA risk according to their scores of STOP-Bang questionnaire. Postoperative pain was assessed using a 100 mm Visual Analogue Scale (VAS). Mechanical pain threshold was measured with Von Frey filaments in order to determine whether patients developed POH. Characteristic variables were selected by means of least absolute shrinkage and selection operator (LASSO) regression. Multivariate logistic regression was used to identify the independent risk factors associated with POH.

Results: Postoperative hyperalgesia was diagnosed in 69.1% of all patients, and the risk factors for POH were: male(OR, 2.43; 95% CI, 1.04–6.10), age(OR, 2.03;95% CI, 1.28–3.31), BMI≥35 $kg \cdot m^{-2}$(OR, 3.13;95% CI, 1.46–6.83), high risk of moderate to severe OSA (OR, 6.43;95% CI, 2.71–15.52), preoperative mechanical pain thresholds(OR, 4.05;95% CI, 2.35–9.14).

Conclusion: Our study found that patients with high risk of moderate to severe OSA were more likely to have postoperative hyperalgesia than those in the low-risk group, and the hyperalgesia was more severe in patients with high risk of moderate to severe OSA within 24 hours after surgery. These results highlight the need for OSA screening in preoperative assessments to mitigate postoperative hyperalgesia.

Keywords: obstructive sleep apnea, hyperalgesia, bariatric surgery, risk factors

Introduction

Postoperative hyperalgesia (POH) is a common clinical phenomenon, which is mainly defined by reduced nociceptor threshold and excessive nociceptor response to nociceptor stimulation in the incision and the surrounding tissue. On the one hand, hyperalgesia will increase the experience of patients' pain, and may even turn into chronic or neuropathic pain. On the other hand, more pain means that patients experience more mental pressure after surgery, which is not conducive to patients' recovery. The phenomenon of POH is indicative of central nervous system (CNS) sensitization, which can arise from surgical tissue or nerve damage, as well as the effects of narcotic medications.[1,2] Previous studies have demonstrated associations between POH and surgical site, opioid analgesics, gender, and age.[3–5] Additionally, it has been observed that inter-individual factors such as genetic predisposition, prior experiences of both physical and psychological

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pain, as well as psychological factors are also linked to POH.[6,7] Although numerous risk factors have been identified for POH, limited research has been investigated to prove the association between obstructive sleep apnea (OSA) and POH.

OSA is a common type of sleep disorder that causes daytime sleepiness and fatigue, which can negatively affect patients' quality of life, and more and more studies have shown that OSA syndrome is associated with the occurrence of postoperative adverse events.[8,9] According to statistics, 50% to 60% of obese people and people with metabolic syndrome have obstructive sleep apnea.[10,11] The prevalence of OSA in patients undergoing elective surgery is significantly higher than in the general population. The prevalence was approximately 91% in patients undergoing bariatric surgery, 8.4% in orthopedic patients, and 30% in patients undergoing neurosurgery.[12–14]

OSA is characterized by sleep fragmentation and recurrent nocturnal hypoxemia, both of which can affect pain perception in patients.[15] Sleep deprivation and/or sleep disruption can heighten pain sensitivity in humans, while prolonged sleep deprivation stimulates the expression and release of cytokines involved in sleep regulation, including tumor necrosis factor (TNF-α), interleukin-1β, and IL-6, all of which exert pain-sensitive effects in various experimental models.[16–22] Recurrent episodes of apnea-related hypoxia in patients with OSA, similar to hypoxia/reperfusion injury, can induce oxidative stress.[23] This leads to the upregulation of hypoxia-inducible factor-1α (HIF-1α) and increased production of mitochondrial oxygen free radicals, thereby amplifying pain transduction and transmission processes.[24–29]

Currently, there is a limited number of prospective studies investigating the association between OSA and POH, with subjective scale evaluations being the predominant method for assessing POH. Moreover, objective biological quantitative indicators of postoperative hyperalgesia have been largely overlooked. Therefore, further improvement in research conclusions' generalizability is necessary. Given the high incidence of OSA in this cohort, this analysis aims to explore the relationship between the severity of OSA and POH in bariatric surgery patients.

Methods

Ethics Statement

The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2200058637) and approved by the Ethics Committee of The Affiliated Hospital of Xuzhou Medical University (XYFY2022-KL128-01). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all study participants prior to surgery.

Study Participants

This study adopted a prospective observational cohort study design. The study had the following inclusion criteria: (1) patients aged ≥18 years; (2) American Society of Anesthesiologists physical status classification (ASA) grade II-III. (3) patients scheduled to undergo elective bariatric surgery under general anesthesia. Exclusion criteria were serious renal or hepatic insufficiency, severe hearing or vision impairment and are unable to communicate effectively with physicians, unable to understand scale content and patients who reject, diabetic peripheral lesions. Eliminated criteria were being admitted to intensive care unit after surgery, cancelling operation, requiring reoperation, failing to complete the follow-up.

Anesthesia, Surgery and Postoperative Management

The patients were induced with midazolam 0.04mg/kg, etomidate 0.3mg/kg, rocuronium bromide 0.6mg/kg and sufentanil 0.5μg/kg, and maintained with sevoflurane 1–2%, remifentanil 0.1–0.3μg/ (kg ·min) and propofol 2–5mg/ (kg ·h). Dosage is calculated according to ideal body weight.

Ultrasound-guided transversus abdominis plane block was performed after induction of anesthesia. The depth of anesthesia was monitored by bispectral index, which was maintained at 40 to 60 during operation. Muscle release was monitored using train of four stimulation, the intraoperative muscle release dosage was adjusted, and the duration of muscle release antagonism was selected. Ketorolac tromethamine 30 mg was applied 30 min before the end of surgery.

All bariatric surgeries included in this study were performed laparoscopically. Specifically, 209 patients underwent laparoscopic sleeve gastrectomy. For this procedure, the surgical team made multiple small incisions to insert trocars for

instrument access, and a slightly larger incision was sometimes required to remove the resected gastric specimen. In contrast, 92 patients underwent laparoscopic Roux-en-Y gastric bypass, which typically involved the use of 5 trocars to facilitate the creation of the gastrojejunal anastomosis and other necessary connections, without the need for an additional large incision for specimen removal.

After leaving PACU and returning to the ward, 10 mg of opioid analgesics (oxycodone, converted to morphine equivalent) were administered intravenously. When the patient requests rescue analgesia, oxycodone is used for rescue analgesia after being evaluated by a clinical physician. Guidelines issued in 2015 showed that patient-controlled analgesia (PCA) is associated with an increased risk of postoperative respiratory depression in undiagnosed patients with obstructive sleep apnea.[30] Therefore, we did not choose PCA.

Data Collection

We collected demographic characteristics and clinical data include gender, age, height, weight, previous history of hypertension, diabetes and other diseases, medication history, surgical history, family history, allergy history, abnormal examination or test results, polysomnography results, STOP-Bang questionnaire score, anxiety and depression score and preoperative baseline mechanical pain threshold, intraoperative anesthetic drug, operation method, operation time, anesthesia time, other types and doses of perioperative drugs, mechanical pain threshold and VAS score at 1h, 12h, 24h, 48h after surgery. The STOP-Bang questionnaire requires yes/no responses to 8 questions (Appendix 1). Patients can be classified as being at different risk for obstructive sleep apnea syndrome based on their respective scores. Patients with a STOP-Bang score of 0 to 2 can be classified as having a low risk of moderate to severe OSA, while those with a score of 5 to 8 can be classified as having a high risk of moderate to severe OSA. For patients with a STOP-Bang score in the intermediate range (3 or 4), further classification criteria are needed (Appendix 2).[31] The apnea/hypopnea index (AHI) was used to grade the severity of OSA.

Outcomes

The primary outcome of the study was the incidence of POH within 48h in patients undergoing elective bariatric surgery. The mechanical pain threshold was evaluated in the area around the surgical incision using von Frey filament before surgery and 1h, 12h, 24h and 48h after surgery. Considering the measurement error, if the average pain threshold at four time points after surgery was more than 30% lower than the preoperative basic pain threshold, the mechanical pain threshold was considered to be significantly lower, and the patient was defined hyperalgesia.

The secondary outcome was the mechanical pain threshold and VAS score at 1h, 12h, 24h and 48h after operation, the pain threshold of the inner forearm of the non-dominant arm at 1h after surgery.

Assessment of Mechanical Hyperalgesia

Calibrated von Frey filaments (0.6–180 g/mm^2) preoperatively and repeated at 48 hours after surgery was applied to assess the pain threshold for mechanical stimuli (static hyperalgesia) according to the methods of limits.[32] Tactile pain threshold was defined as the smallest force (g/mm^2) that was just perceived as painful. The tactile mechanical pain threshold was measured in an area 2 cm above the abdominal umbilical incision, which was the baseline pain threshold. Quantitative sensory testing was measured with von Frey filaments on the skin 2 cm above abdominal umbilical during this preoperative visit to obtain basal preoperative values. The mechanical pain threshold was measured 2 cm above the paraumbilical incision (Supplementary Figure 1) at 1, 12,24 and 48 hours after operation. We also measured the mechanical pain threshold about 5cm above the fossae of the non-dominant arm before and 1 hour after surgery.

Our researcher would bend the von Frey filament into a "C" or "S" shape on the skin and held it for about 1.5 seconds. von Frey filaments were applied in ascending order of stiffness to the designated point on the skin; the first von Frey used was 0.6 g/mm^2 and the last one was when patient's sensation changes from light touch to tingling for the first time. Then, we would perform another four times according to the following rules. When the patient feels stinging pain, the researcher gradually reduces the target force of the fiber filaments, if the patient does not feel a tingling pain, gradually increase the target force of the fiber filaments. If the patient does not feel a tingling pain, it is marked as "○" on the record sheet; if the patient feels a tingling pain, it is marked as "×" (Supplementary Figure 2). Mechanical

pain threshold (ED_{50}) is calculated using Dixon's up-and-down method.[33] Von Frey filament applications were separated by at least 30 seconds to reduce the likelihood of anticipatory responses, 3 determinations were made at each point, and a mean was calculated. If the mechanical pain threshold is significantly reduced, POH is considered to occur.

Statistical Analyses

All data were analyzed using R software (version 4.4.2) and SPSS version 22.0. The distribution of variables was assessed using the Shapiro–Wilk test. Data were expressed as mean ± standard deviation (SD) for the normal distribution data. Non-normal distribution data are expressed as median and interquartile range. Categorical data were presented as number and percentages. LASSO regression analysis was used to screen the characteristic variables of POH, and multivariate logistic regression analysis was performed based on LASSO regression-selected variables to investigate the independent variables associated with POH in patients undergoing bariatric surgery. In addition, we conducted an exploratory analysis of 65 patients undergoing polysomnographic measures. Apnea/hypopnea index was included as a risk factor in multivariate regression analysis to further confirm the risk factors for POH. Statistical significance was set at $P<0.05$.

Results

Study Patients

A total of 331 patients were collected, there were 12 patients who had surgery canceled, 2 patients who had surgery again due to complications after surgery, 16 patients failed to complete the trial for other reasons, and a total of 301 participants were finally included. The 301 patients were divided into POH group and non-POH group. The baseline characteristics and comparison of the two groups are shown in Table 1.

Table 1 Baseline Characteristics of Patients with Non-POH and POH

Variable	Non-POH(n=93)	POH(n=208)
Male [number (%)]	10 (10.8)	65 (31.3)
Age (years)	29 (24, 33)	32 (27, 37)
BMI [number (%)]		
<35 kg·m^{-2}	41 (44.1)	39 (18.8)
≥35 kg·m^{-2}	52 (55.9)	169 (81.3)
Risk of OSA [number (%)]		
Low	33 (35.5)	14 (6.7)
Moderate	25 (26.9)	15 (7.2)
High	35 (37.6)	179 (86.1)
Hypertension [number (%)]	16 (17.2)	65 (31.3)
Diabetes [number (%)]	12 (12.9)	53 (25.5)
Anxiety disorder [number (%)]	1 (1.1)	2 (1.0)
Depressive disorder [number (%)]	1 (1.1)	2 (1.0)
Hb1Ac (%)	5.6 (5.4, 5.8)	5.8 (5.5, 6.7)
CRP (mg/L)	3.80 (1.90, 6.70)	4.80 (2.35, 9.20)
ACTH (pg/mL)	25.80 (17.40, 40.60)	31.85 (20.35, 49.05)
Cortisol (ug/dL)	12.00 (8.91, 16.60)	13.15 (9.63, 16.15)
White blood cell count(10^9/L)	7.1 (6.2, 8.6)	7.5 (6.2, 8.8)
Neutrophil count(10^9/L)	4.31 (3.42, 5.31)	4.44 (3.60, 5.67)
Lymphocyte count(10^9/L)	2.2 (1.8, 2.7)	2.1 (1.7, 2.7)
Monocyte count(10^9/L)	0.38 (0.30, 0.51)	0.44 (0.34, 0.53)

(*Continued*)

Table 1 (Continued).

Variable	Non-POH(n=93)	POH(n=208)
Modus operandi [number (%)]		
Sleeve gastrectomy	69 (74.2)	140 (67.3)
Gastric bypass	24 (25.8)	68 (32.7)
Duration of Anesthesia (min)	135 (115, 160)	145 (125, 175)
Duration of operation [number (%)]		
≤2h	58 (62.4)	102 (49.0)
>2h	35 (37.6)	106 (51.0)
Sufentanil(ug)	30 (30, 50)	33 (30, 50)
Remifentanil (mg)	2.20 (1.93, 2.53)	2.27 (2.00, 2.80)
Midazolam (mg)	3 (3, 3)	3 (3, 3)
Propofol (mg)	275.00 (241.67, 316.67)	291.67 (258.33, 354.17)
Etomidate (mg)	20 (20, 20)	20 (20, 20)
Rocuronium bromide (mg)	75.0 (60.0, 75.0)	75.0 (63.8, 83.8)
Cisatracurium besylate (mg)	0 (0, 22.5)	0 (0, 16.6)
Sevoflurane (mL)	18.48 (14.40, 24.00)	20.16 (16.20, 26.58)
Postoperative analgesic dosage (mg)	25 (20, 30)	25(20, 30)
Maximum postoperative VAS score	6 (5, 6)	6 (6, 7)
Minimum postoperative VAS score	2 (2, 2)	2 (2, 3)
Total hospital stays (day)	4 (4, 6)	5 (4, 6)
Preoperative basal pain threshold [number (%)]		
≤18.08g	73 (78.5)	77 (37.0)
>18.08g	20 (21.5)	131 (63.0)

Notes: All results were expressed as median (quartile) [M (Q1, Q3)] or number of cases (%), except for the dosage of cisatracurium besylate. The amount of cis-atracurium is expressed as: median (minimum, maximum) [M (min, max)]. Preoperative basal pain threshold was grouped by median.

The incidence of hyperalgesia 48 hours after operation was 69.1%, which was calculated by the difference between the patient's mechanical pain threshold before and after surgery (Table 2). The postoperative pain scores of the patients are shown in Supplementary Table 1.

Risk Factors of Hyperalgesia in Patients Undergoing Bariatric Surgery

Twenty-eight potential risk factors from perioperative clinical indicators were included in the LASSO regression analysis (Figure 1a and b). We selected 6 non-zero characteristic variables including gender, age, BMI, risk of OSA, preoperative mechanical pain thresholds, sufentanil (Table 3).

Then, these 6 variables were included to establish model 1. In the multivariable analysis, male(OR, 2.46; 95% CI, 1.05–6.24), age(OR, 1.95;95% CI, 1.23–3.15), BMI (OR, 3.10;95% CI, 1.47–6.62), high risk of moderate to severe OSA (OR, 6.99;95% CI,

Table 2 Mechanical Pain Thresholds in Non-POH and POH Patients

Mechanical Pain Threshold (g)	Non-POH(n=93)	POH(n=208)
Preoperative basal pain threshold	11.29(7.83,15.11)	22.03(14.30,39.81)
1h postoperative pain threshold	7.11(3.23,10.04)	2.64(1.88,3.85)
Pain threshold 12h after surgery	8.81(5.76,12.50)	7.19(4.72,10.77)
Pain threshold 24h after surgery	11.02(8.49,15.03)	14.00(10.05,19.69)
Pain threshold 48h after surgery	11.91(8.06,15.21)	20.08(13.5733.25)
Preoperative forearm pain threshold	9.92(6.58,12.56)	14.60(10.09,22.02)
Postoperative forearm pain threshold	6.83(4.31,9.64)	7.52(4.72,11.70)

Note: All results are expressed in median (quartile) [M (Q1, Q3)].

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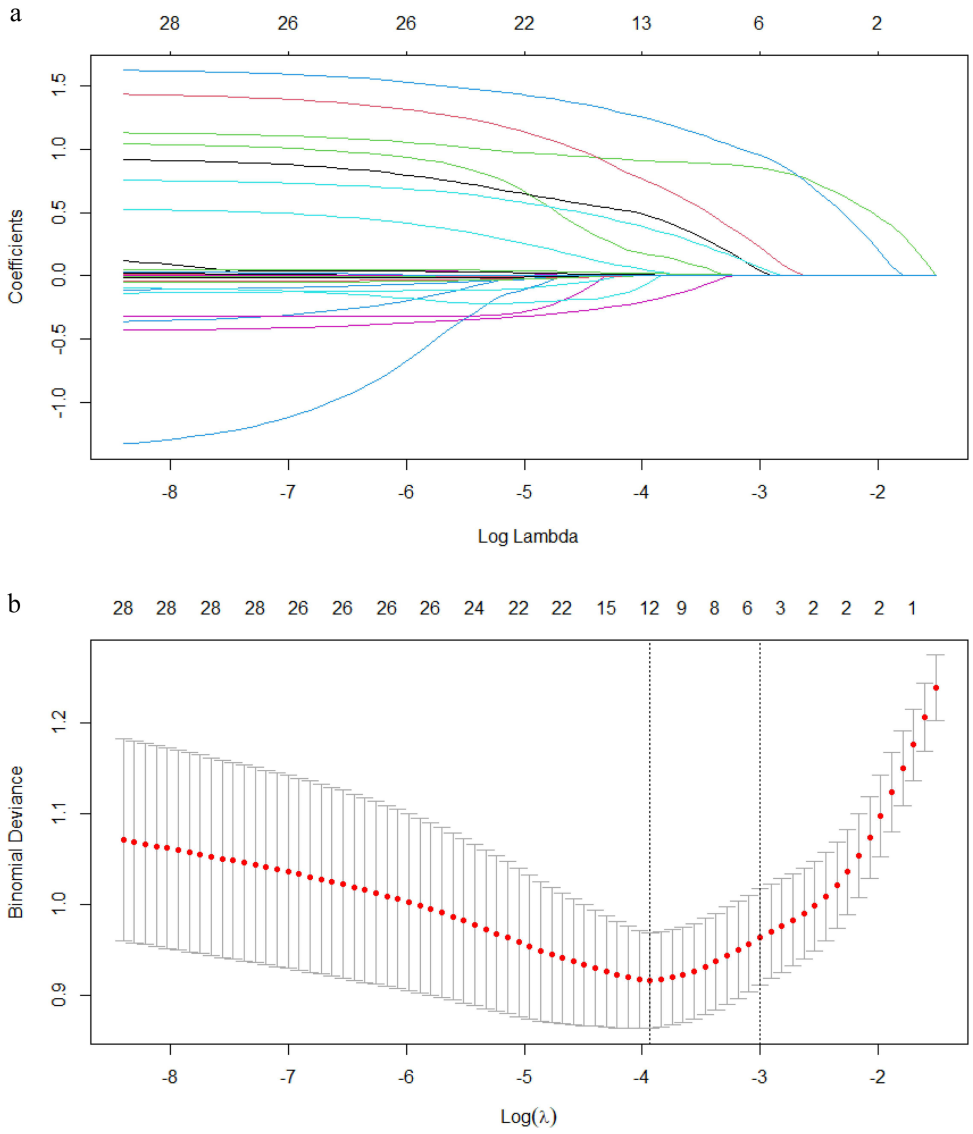

Figure 1 Potential variables associated with POH in patients undergoing bariatric surgery were selected by LASSO regression. (**a**) LASSO coefficients profiles for all variables. A coefficient profiSle was generated based on the log(λ) sequence. Each curve in the figure represents the change trajectory of the coefficient of each independent variable. The vertical axis represents the value of the coefficient, the lower horizontal axis represents log(λ), and the upper horizontal axis represents the number of non-zero coefficients in the model at this time. As the value of λ changes, the variables whose coefficients are compressed to 0 later are more important. (**b**) The selection of the optimal penalization coefficient(λ) in the LASSO model used 10-fold cross-validation with the minimum criteria and 1-SE (standard error) criteria. A curve was plotted to show the relationship between the binomial deviance and log(λ). The vertical axis represents the binomial deviance, the lower horizontal axis represents log(λ), and the upper horizontal axis represents the number of non-zero coefficients in the model at this time. The left dashed line is drawn at the minimum error, representing the model coefficients corresponding to the λ value that minimizes the model deviance. The right dashed line is drawn at 1 standard error of the minimum, representing the model coefficients corresponding to the λ value that yields the simplest model within one variance range of the minimum error.

3.04–16.76), preoperative mechanical pain thresholds (OR, 4.19;95% CI, 2.19–8.28), sufentanil (OR, 1.03;95% CI, 1.00–1.07) were independently associated with POH in patients undergoing bariatric surgery (Table 4). Clinically, we considered that remifentanil and operation time may serve as potential risk factors for POH. Therefore, gender, age, BMI, risk of OSA, preoperative mechanical pain thresholds, sufentanil, remifentanil and duration of the operation were used to establish model 2. In the multivariable analysis, male (OR, 2.43; 95% CI, 1.04–6.10), age (OR, 2.03;95% CI, 1.28–3.31), BMI≥35kg·m^{-2} (OR, 3.13;95% CI, 1.46–6.83), high risk of moderate to severe OSA (OR, 6.43;95% CI, 2.71–15.52), preoperative mechanical pain thresholds (OR, 4.05;95% CI, 2.35–9.14) were independently associated with POH in patients undergoing bariatric surgery (Table 4).

Table 3 Coefficients and Lambda.1se Value of the LASSO Regression

Variable	Coefficients	Lambda.1SE
Gender	0.039419058	0.04972967
Age (years)	0.064839913	
BMI ($kg \cdot m^{-2}$)	0.224097998	
Risk of OSA	0.848975839	
Preoperative mechanical pain thresholds (g)	0.951689107	
Sufentanil (ug)	0.003727921	

Note: The coefficient value for each increase in age of 10 years.

Table 4 Multivariate Logistic Regression Analysis of POH in Patients Undergoing Bariatric Surgery

Variable	model 1			model 2		
	OR (95% CI)	wald	*P*-value	OR (95% CI)	wald	*P*-value
Gender			0.05			0.05
Male	2.46(1.05–6.24)	4		2.43(1.04–6.10)	3.93	
Female	1 [Reference]			1 [Reference]		
Age (years)	1.95(1.23–3.15)	7.93	0.005	2.03(1.28–3.31)	8.6	0.003
BMI			0.003			0.003
<35 $kg \cdot m^{-2}$	1 [Reference]			1 [Reference]		
≥35 $kg \cdot m^{-2}$	3.1(1.47–6.62)	8.77		3.13(1.46–6.83)	8.45	
Risk of OSA			<0.001			<0.001
Low	1 [Reference]			1 [Reference]		
Moderate	1.22(0.43–3.46)	0.14		1.16(0.41–3.33)	0.08	
High	6.99(3.04–16.76)	20.13		6.43(2.71–15.52)	18.11	
Preoperative mechanical pain thresholds			<0.001		19.36	<0.001
≤18.08g	1 [Reference]			1 [Reference]		
>18.08g	4.19(2.19–8.28)	18		4.05(2.35–9.14)		
Sufentanil(ug)	1.03(1.00–1.07)	4.26	0.04	1.03(0.10–1.07)	3.4	0.07
Remifentanil (ug)				0.5(0.17–1.45)	1.63	0.2
Duration of operation (min)					2.85	0.09
<2h				1 [Reference]		
≥2h				1.87(0.91–3.52)		

Note: The coefficient value for each increase in age of 10 years.

Mediation Analysis

We also conducted mediation analysis. The results revealed that OSA risk level partially mediates the impact of gender on POH. Additionally, it was found that OSA risk level also plays a partial mediating role in the relationship between BMI and POH (Supplementary Table 2).

Comparison of Changes in the Percentage of Pain Threshold Reduction in Patients with Different OSA Risk Levels

We also compared the percentage of pain threshold reduction over time after surgery in patients with different OSA risk levels, and a box plot was drawn with the 95th and 5th percentiles as the upper and lower edges (Supplementary Figure 3). At 1h, 12h and 24h after surgery, patients with high risk of OSA had the highest median percentage of pain threshold reduction, while patients with low risk had the lowest median percentage of pain threshold reduction. It can be considered that the patients with higher risk of OSA have a higher percentage of pain threshold reduction within 24h after surgery, that is, the hyperalgesia is severe. With the extension of time, the percentage of pain threshold reduction in each group gradually decreased after surgery, which can be considered as the degree of hyperalgesia gradually reduced with the time. At 48h after operation, the mechanical

Table 5 Results of Multivariate Logistic Regression Analysis of POH in 65 Patients with PSG Data

Variable	OR (95% CI)	*P*-value
AHI		
<46.7 events/h	1 [Reference]	0.043
≥46.7 events/h	13.056(1.090–156.367)	
Preoperative mechanical pain thresholds		
<18.08g	1 [Reference]	0.024
≥18.08g	16.263(1.440–183.734)	
Sevoflurane (mL)	1.145(0.767–1.710)	0.508
Remifentanil (mg)	0.102(0.002–5.755)	0.267
Duration of operation		
<2h	1 [Reference]	0.155
≥2h	42.278(0.242–7395.579)	

pain threshold of each group has basically returned to the preoperative level, but the dispersion of low risk patients is the smallest, and the dispersion of high-risk patients is the largest at this time point. It can be considered that the recovery of hyperalgesia in low risk patients is better.

Exploratory Analysis

We collected polysomnography (PSG) data from 65 patients and classified OSA according to apnea hypoventilation index (AHI). In the multivariable analysis, AHI(OR, 13.056; 95% CI, 1.090–156.367) and preoperative mechanical pain thresholds(OR, 16.263;95% CI, 1.440–183.734) were risk factors for POH(Table 5). This confirms our results from the other side.

We also compared the percentage change of the pain threshold of the patients' non-dominant arm 1h before and after surgery (Supplementary Table 3). Percentage reduction in pain threshold was higher in the POH group compared to the non-POH group[median (interquartile range): 0.45(0.29, 0.58) vs 0.18(0.10, 0.30), P<0.001], it may be due to the simultaneous occurrence of central nociceptive sensitization. However, considering the small number of such patients, the relationship between AHI index and POH still needs further exploration.

Discussion

Our study found that patients with high risk of moderate to severe OSA were more likely to have postoperative hyperalgesia than those in the low-risk group, and the hyperalgesia was more severe in patients with high risk of moderate to severe OSA within 24 hours after surgery. Other risk factors for POH include age, BMI≥35kg·m^{-2}, and preoperative baseline pain threshold.

In our study, among a total of 301 patients, 208 (69.1%) patients developed POH. Some previous studies described the incidence of POH as about 28.5%-41.8%.1,[34] We hypothesize that the differences in incidence may be related to differences in the way POH is assessed and differences in patient characteristics (eg, general patients, cardiac surgery patients, and obese patients).

Studies have shown that under the Predictable Chronic Mild Stress (PCMS) model, the pain sensitivity of mice increases with the increase of sleep disorder.[35] Several studies in healthy people have found that sleep deprivation enhances pain sensitivity in subjects and increases spontaneous pain.[36,37] Chronic intermittent hypoxia can lead to oxidative stress, resulting in upregulated expression of HIF-1α and increased production of mitochondrial oxygen free radicals, thus enhancing the transduction and transmission of pain.[24–29] A study found that the thenar cold pain threshold was reduced in healthy subjects after sleep restriction.[38] Anthony g. Doufas et al found an independent correlation between reduced arterial oxygen saturation at night and pain experience in patients with OSA.[39] Our study also showed that preoperative STOP-Bang score was linearly correlated with postoperative pain severity.

The results of this study showed that the higher the risk of OSA, the higher the percentage of pain threshold reduction within 24h after surgery, that is, the more severe the hyperalgesia. By 48h after operation, the mechanical pain threshold of all groups had basically recovered to the pre-operation level, and the recovery of hyperalgesia in low-risk patients was better. This suggests that we should pay more attention to pain assessment and treatment within 48 hours after surgery for patients with high risk of moderate to severe OSA, as these patients are more likely to develop POH and may be accompanied by central hyperalgesia. Although hyperalgesia in our study cohort resolved within 48 hours, it is essential to recognize that this short - term pain phenomenon may have long - term implications.

In our study, age is a risk factor for POH, and the older the person, the higher the risk of developing POH. Among the patients included in our study, the maximum age was 55 years old. In addition, BMI≥35kg·m^{-2} is another risk factor for POH. In mouse experiments, obesity caused by a high-fat diet increases pain sensitivity by altering the branched-chain amino acid catabolism in the dorsal root ganglion.[40] This is consistent with our conclusions, but we have not found any articles describing whether BMI is a risk factor for hyperalgesia in humans, and further studies are needed on the effect of BMI on POH.

Opioids, such as remifentanil and sufentanil used in our study, have been associated with opioid - induced hyperalgesia (OIH). Dose-controlled case-control studies or large sample studies of multiple surgical types have shown that remifentanil is associated with opioid-induced hyperalgesia in a dose-dependent manner.[41–44] However, in our research, the lack of a significant difference in opioid dosage between POH and non - POH groups suggests that OIH may not be the primary driver of POH in patients with OSA. This is contrary to previous studies demonstrating a dose - dependent relationship between remifentanil and OIH. One possible explanation is that both the non-POH and POH groups were patients undergoing bariatric surgery. The same surgical type led to similar surgical and anesthetic processes, medication duration, and trauma severity, which resulted in no significant difference in remifentanil dosage between the two groups. Consequently, the study results failed to identify remifentanil as a risk factor for POH. Besides, benzodiazepines and barbiturates are central nervous system depressants. Their use can lead to relaxation of the upper airway muscles, increasing the risk of airway obstruction during sleep and thus potentially inducing or worsening OSA. Regarding POH, although these drugs can affect the central nervous system's pain - regulating pathways, the direct link is less clear.

In addition, anxiety, depression, fear and other psychosocial factors may also enhance pain sensitivity,[45–48] but the number of such cases collected in our study was too small, so we did not conclude that anxiety and depression are risk factors for POH, which needs further large-scale and prospective studies to explore.

Moreover, our study found no significant impact of bariatric surgery type on postoperative hyperalgesia, with comparable outcomes observed between laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. This result may be attributed to shared physiological responses triggered by both procedures. Despite different anatomical alterations, both surgeries induce systemic inflammatory responses, releasing cytokines (eg, interleukin-6, tumor necrosis factor-α) that sensitize peripheral and central pain pathways. Additionally, hormonal changes, such as fluctuations in ghrelin and glucagon-like peptide-1, are common to both surgeries, potentially modulating pain perception in a similar manner. However, this null finding may also reflect limitations in our study. The relatively small sample size, particularly for the Roux-en-Y subgroup, may have reduced statistical power to detect subtle differences. A standardized multimodal analgesia protocol may be sufficient for both surgical types, simplifying postoperative pain management and potentially reducing healthcare costs.

Our findings suggest that systematic identification of OSA patients should be included in routine preoperative risk assessment of patients undergoing bariatric surgery. According to current guidelines for Sleep Apnea Disorder (SDB) and perioperative management, all patients should be assessed for SDB risk before surgery.[49,50] Patients with a high probability of SDB pre-detection should be thoroughly screened for SDB before surgery. For patients at high risk of moderate to severe OSA, pain management should be strengthened during perioperative period, multi-mode post-operative analgesia should be adopted. It is believed that strengthening the implementation of effective preventive strategies can provide them with a better perioperative experience. POH should be identified early, and anti-hyperalgesia treatment should be performed immediately after diagnosis of hyperalgesia, so as to inhibit the stress response in the

acute phase and improve the pain in the early postoperative period. Non-steroidal anti-inflammatory drugs and NMDA receptor antagonists (such as ketamine) are commonly used to prevent and treat POH.

Limitations

Due to the limited conditions of the study, only 65 patients received polysomnography monitoring and were not included in the study. Giving that, we had to focus only on patients with and without OSA in this study, and were unable to distinguish between patients with Central Sleep Apnea (CSA) or OSA and those without sleep-disordered breathing. This limited our ability to accurately stratify OSA severity. Future studies should aim to include a larger number of patients with polysomnography data to improve the reliability of OSA severity assessment.

Another limitation is related to the small number of patients with diagnosed anxiety (n=3) and depression (n=3). This low prevalence of psychological comorbidities in our cohort severely restricted our ability to evaluate the potential impact of psychological factors on postoperative hyperalgesia. Previous studies have indicated that anxiety, depression, and pain catastrophizing can contribute to increased pain sensitivity and postoperative hyperalgesia. However, in our study, the insufficient sample size of patients with these psychological conditions precluded us from conducting meaningful statistical analysis. This means that we may have underestimated or overlooked the role of psychological factors in the development of POH, especially in patients with OSA.

In addition, we only studied patients' pain and hyperalgesia within 48 hours after bariatric surgery, and did not study patients' long-term chronic pain.

Conclusions

The study found that patients with high risk of moderate to severe OSA were more likely to have postoperative hyperalgesia, and the hyperalgesia was more severe in patients with high risk of moderate to severe OSA within 24 hours after surgery. Given the robust evidence from our study highlighting the strong association between OSA and postoperative hyperalgesia, we firmly advocate for the routine use of validated screening tools such as the STOP - Bang questionnaire and PSG in the preoperative phase.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available because of patient privacy but are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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