Post-operative sleep-disordered breathing with different anesthesia techniques: an observational study

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Objective: It has been suggested that regional anesthesia may prevent post-operative exacerbation of obstructive sleep apnea. However, clinical evidence is lacking. We have hypothesized that post-operative exacerbation of sleep-disordered breathing is related to the anesthetic technique.
Design: Prospective observational study.
Setting: Orthopedic intensive care unit.
Material and methods: The inclusion criterion was orthopedic surgery requiring anesthesia. Multichannel polygraphy sleep studies were performed one night before and four consecutive nights after surgery. The Kruskal–Wallis test and Friedman's ANOVA were used.
Results: Thirty-five patients completed investigations and were compared according to anesthetic techniques which included 1) general anesthesia (n = 11); 2) subarachnoid anesthesia with intrathecal morphine (n = 11); and 3) subarachnoid anesthesia (without intrathecal morphine) with epidural catheter for opioid-free post-operative analgesia (n = 13). Obstructive sleep apnea was diagnosed pre-operatively in 22 (63%) patients. In the general anesthesia group, hypopnea significantly increased on the third and fourth post-operative nights ($p < 0.05$). In the subarachnoid anesthesia with intrathecal morphine group, hypopnea and oxygen desaturation index decreased significantly on the first post-operative night and increased on the third and fourth post-operative nights as did the apnea–hypopnea index (all $p < 0.05$). In the subarachnoid anesthesia with epidural catheter group, there were no significant changes in sleep-disordered breathing parameters. In the subarachnoid anesthesia with epidural catheter group, the cumulative opioid dose was significantly lower compared to the other two groups.
Conclusion: Compared to pre-operative findings, changes in sleep-disordered breathing events were less pronounced in patients who received subarachnoid anesthesia (without intrathecal morphine) with epidural catheter for opioid-free post-operative epidural analgesia.

Key words: anesthesia, sleep-disordered breathing, post-operative period, surgery.

Pooperační změny poruch dýchání ve spánku v závislosti na použité anesteziologické technice: observační studie

Cíle studie: Regionální anestezie bývá doporučována u pacientů s obstrukční spánkovou apnoe jako prevence pooperační exacerbace. Nicméně klinická data pro toto doporučení chybí. Naší hypotézou bylo, že exacerbace poruchy dýchání ve spánku závisí na použité anesteziologické technice.
Typ studie: Prospektivní observační studie.
Typ pracoviště: JIP fakultní nemocnice.

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Materiál a metoda: Zařazeni byli pacienti s plánovaným ortopedickým výkonem. Vícekanálová polygrafie byla provedena noc před operačním výkonem a první čtyři pooperační noci. Kruskal-Wallisův test a Friedmanova ANOVA byla použita pro analýzu dat.

Výsledky: Celkem bylo zařazeno 35 pacientů, kteří byli rozděleni do skupin na základě použité anesteziologické techniky: celková anestezie (11 pacientů), subarachnoidální anestezie s podáním intratekálního morfinu (11 pacientů), kombinace subarachnoidální anestezie (bez podání intratekálního morfinu) a epidurálního katetru pro pooperační bez-opioidovou analgezii (13 pacientů). Obstrukční spánková apnoe byla diagnostikována u 22 (63 %) pacientů. Ve skupině celkové anestezie došlo k signifikantnímu nárůstu hypopnoe třetí a čtvrtou pooperační noc ($p < 0,05$). Ve skupině subarachnoidální anestezie s intratekálním morfinem došlo nejprve k signifikantnímu poklesu hypopnoe a indexu desaturace první pooperační noc, s následným signifikantním vzestupem obou parametrů společně s apnea-hypopnea indexem třetí a čtvrtou pooperační noc ($p < 0,05$). Ve skupině subarachnoidální anestezie s epidurálním katetrem významné změny parametrů dýchání ve spánku pozorovány nebyly. Kumulativní dávka opioidů byla signifikantně nejnižší ve skupině subarachnoidální anestezie s epidurálním katetrem.

Závěr: Změny dýchání ve spánu byly nejméně vyjádřeny u pacientů podstupujících výkon v kombinaci subarachnoidální anestezie (bez podání intratekálního morfinu) a epidurálního katetru po pooperační bezopioidovou analgezii.

Klíčová slova: anestezie, poruchy dýchání ve spánku, perioperační péče, chirurgie.

Introduction

Obstructive sleep apnea (OSA) is the most frequent type of sleep-disordered breathing (SDB) and is characterized by periodic obstruction of the upper airway [1]. The prevalence of OSA is estimated to be up to 25% in the general population and as high as 41% in surgical patients [1]. In patients with OSA, sleep is characterized by frequent arousals and episodic oxygen desaturations, both of which may lead to increased sympathetic activation, reduced heart rate variability, endothelial dysfunction, and prothrombotic state [2–4] as well as higher concentrations of inflammatory (C-reactive protein, cytokines) and oxidative stress markers [5, 6]. Furthermore, OSA has been shown to be associated with post-operative complications including prolonged hypoxemia and respiratory failure [7], adverse cardiovascular events (arrhythmias, myocardial infarction, pulmonary embolism) [8], and central nervous system dysfunction (cognitive deficits, impaired vigilance, depression, anxiety and delirium [9]). Intermittent recurrent hypoxemia may also cause reduced oxygen tissue supply and, as a result, impaired wound healing [10] and a higher incidence of post-operative infections [11]. It is also important to note that the majority of anesthesiologists and surgeons fail to recognize OSA in the perioperative period [12]. OSA may be exacerbated during the perioperative period [13] and increase the risk for perioperative complications. Indeed, benzodiazepines, anesthetics or opioids promote respiratory depression and greater upper airway collapsibility [1]. Furthermore, residual neuromuscular blockade may also contribute to the development of respiratory complications [14]. Therefore, the use of local or regional anesthesia has been recommended in patients with OSA, whenever possible [15]. However, direct evidence to support this recommendation has not previously been reported [15].

We have hypothesized that SDB is modified post-operatively in surgical patients in relation to the type of anesthesia administered. Accordingly, the aim of this study was to evaluate SDB pre-operatively in surgical patients in comparison with SDB during the first four consecutive nights post-operatively in patients receiving different anesthetic techniques.

Material and methods

Subjects. Consecutive patients scheduled for elective orthopedic surgery were enrolled in this prospective observational study. The inclusion criteria were major surgery (expected surgery time > 120 minutes), age ≥ 18 years, and American Society of Anesthesiologists (ASA) Classification score I-III. The exclusion criteria were known OSA, tracheostomy, and ASA class ≥ IV. The study was conducted over a period of one year (4/2018 to 5/2019), registered at ClinicalTrials.gov (NCT03499132), conducted in accordance with the declaration of Helsinki, and approved by the Ethics Committee of St. Anne's University Hospital in Brno, Czech Republic (3V/2018). All participants provided written informed consent. This manuscript adheres to the applicable STROBE guidelines.

Sleep study. For overnight multichannel polygraphy (PG) recordings, the portable ambulatory device Embletta MPR PG (Natus Medical Inc., San Carlos, CA, USA) was used. Studies were performed on the night before surgery and during the first four post-operative nights. Simultaneous recordings of respiration (nasal airflow sensors and oronasal thermal sensor), thoracic and abdominal inductance plethysmography, arterial oxygen saturation, snoring, three-channel electrocardiogram, and body-position were performed. Sleep studies were scored by board-registered polysomnographic technologists who were blinded as to the type of anesthesia which the patients received. The American Academy of Sleep Medicine criteria were used to score the findings of PG [16, 17].

Apnea was defined as ≥ 90% reduction of airflow for at least 10 seconds and hypopnea as a reduction in nasal pressure ≥ 30% of the baseline for at least 10 seconds associated with oxygen desaturation of at least 3% from the pre-event baseline or with an arousal [17]. Obstructive apnea was characterized by paradoxical rib cage movements with abdominal excursions; central apnea was characterized by an absent inspiratory effort throughout the apnea event; and mixed apnea was characterized by loss of inspiratory effort in the initial part of the event and restoration of inspiratory effort in the later part of the event. The severity of apnea was quantified by the apnea–hypopnea index (AHI)

to allow comparison with previous studies [13, 18] as follows: AHI < 5 no apnea; 5 ≤ AHI < 15 mild apnea; 15 ≤ AHI < 30 moderate apnea; AHI ≥ 30 severe apnea.

Premedication. All patients received standard premedication: alprazolam 0.5 mg (Neurol, Zentiva, Czech Republic) on the night before surgery and alprazolam 0.5 mg with paracetamol 1.0 g (Paralen 500, Sanofi-aventis, Czech Republic) on the day of surgery.

Anesthesia. Anesthesia technique was selected clinically by patient providers and based on health status, medical history, the type of surgery, and patient preference. In our institution, anesthesia management, post-operative pain management and care are standardized and follow the national guidelines [19, 20]. In general, three main anesthesia types are routinely used for major orthopedic surgery in our institution: 1) general anesthesia (GA); 2) subarachnoid anesthesia with intrathecal morphine (SAA+IM); and 3) subarachnoid anesthesia without intrathecal opioid with lumbar epidural catheter for post-operative analgesia (SAA+EPI).

For GA, intravenous induction with a combination of propofol (1-2 mg/kg; 1% MCT/LCT; Fresenius Kabi GmbH; Germany), sufentanil (10-20 mcg; Sufentanil Torrex; Chiesi Pharmaceuticals GmbH; Austria) and atracurium (0.5 mg/kg; Atracurium; AS Kalcex, Latvia) was followed by anesthesia maintenance with sevoflurane (Sevorane; AbbVie; Czech Republic) and additional sufentanil as required. Anesthesia depth was routinely monitored with Entropy (the E-Entropy module integrated into the anesthesiologist device, Datex-Aisys CS2, GE Healthcare, USA) with a target value of 40-60. State Entropy data were measured and recorded during the time of surgery in 5-minute intervals and averaged. Neuromuscular blockade was monitored by the NeuroMuscular Transmission Module (Datex-Ohmeda, Madison, WI) and patients extubated when their train-of-four ratio was > 0.9.

For SAA+IM, intrathecal injection of local anesthetic hyperbaric bupivacaine 10-15 mg (Bupinostrum 0.5% hiperbarica, BLUEMED, Portugal) and morphine 0.2-0.3 mg (Morphin 0.001%, Morphine; FNUSA, Czech Republic) was administered via the lumbar space at L3/L4 with a Quincke spinal needle (Spinocan, B Braun, Melsungen AG, Germany).

For SAA+EPI, the procedure was the same as for SAA, but intrathecal morphine was not administered and, instead, an epidural catheter (Epidural Minipack System 1, Smiths Medical, Czech Republic) was inserted in the same lumbar interspace for post-operative pain management.

Additional peripheral nerve block (single shot/continuous) was permitted as needed for all of the above-mentioned options. Periprocedural sedation with propofol (1% MCT/LCT; Fresenius Kabi GmbH; Germany) infusion was used in all patients with SAA+IM and SAA+EPI. During sedation, entropy was routinely monitored with a target value of 80.

After surgery, all patients were transferred to the post-operative high dependency unit (HDU) as per routine clinical practice. Patients with oxygen saturation < 88-90% were treated with supplemental oxygen [21]. A visual analog scale (VAS) and opioid doses were monitored daily during the study; VAS was monitored every hour and averaged every 24 hours. In order to make opioid doses comparable for the purpose of analysis and comparison, dosages were converted to morphine equivalents as follows: 10 mg of iv morphine equivalent to 10 mcg of iv sufentanil; 0.1 mg intrathecal morphine; 15 mg iv piritramide; and 100 mg of iv tramadol [22, 23]. The anesthesiologist and physicians providing care in the post-operative HDU were blinded to sleep study results.

Statistics. Sample size estimation was done a priori using the G*Power 3.1 [24], with an estimated mean increase of AHI on the fourth post-operative night (12 for GA, 8 for SAA+IM group, and 6 for the SAA+EPI group), with a standard deviation (SD) of 4, power 0.80, and p = 0.05, which yielded a total sample size of 30. We expected a significant drop-out [18] during the four post-operative study nights and planned to enroll 80-100 subjects. To test normality, the Shapiro–Wilk test was used. One-way analysis of variance (ANOVA) or the Kruskal–Wallis test by ranks (for continuous variables with non-normal distribution) followed by the post-hoc Tukey HSD test (for normal distribution) or the Mann–Whitney U test (for non-normal distribution) were used to test for differences among the groups as appropriate. The Chi-square test was used to compare categorical variables. Friedman's ANOVA was used to test for SDB parameter differences among the study nights. The Wilcoxon signed-rank test was used for pairwise comparisons between the nights. Data are presented as median (IQR) or mean ± SD; the statistical significance was defined as p values < 0.05. Statistica 12.0 software (StatSoft Inc., Prague, Czech Republic) was used for analysis.

Results

Eighty patients were enrolled in the study, of which 19 (24%) withdrew consent after the pre-operative night, 9 (11%) withdrew it after the first post-operative night, 12 (15%) after the second post-operative night, and 5 (6%) after the third post-operative night. All of them were excluded from further analysis. Thirty-five subjects completed all four post-operative nights and comprised the study group. The subjects were divided into three groups (GA – 11 patients, SAA+IM – 11 patients, SAA+EPI – 13 patients) for analysis.

Subject characteristics are shown in Table 1. There were no differences in sex, body mass index (BMI), STOP-BANG score (snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference and gender), and Epworth questionnaire. Patients in the GA group were significantly younger compared to both SAA+IM and SAA+EPI groups. Twenty-two (63%) subjects were diagnosed with OSA (AHI ≥ 5) pre-operatively and the distribution of OSA was similar in all groups.

Anesthesia characteristics are shown in Table 2. There was no significant difference in ASA class and anesthesia duration. Compared to SAA+IM, the number of total hip arthroplasties was lower in the SAA+EPI group. Otherwise, there were no differences in the type of surgery between the groups. There were more single-shot peripheral nerve blockades in the GA group compared to SAA+IM and SAA+EPI. The number of continuous peripheral nerve blockades was similar between the groups. Patients in the SAA+IM and SAA+EPI did not receive any intravenous opioids during surgery. Only patients in the SAA+IM group received intrathecal morphine. There was no difference in entropy between the SAA+IM and SAA+EPI groups.

Tab. 1. *Subject characteristics*

Parameter	GA n = 11	SAA+IM n = 11	SAA+EPI n = 13	p
age (years)	57 ± 9	68 ± 10**	68 ± 6**	< 0.01
male No. (%)	7 (64)	4 (36)	8 (62)	0.35
BMI (kg/m2)	27 ± 2	27 ± 4	28 ± 3	0.70
STOP BANG	4 ± 1	3 ± 1	4 ± 2	0.86
ESS	7 ± 4	4 ± 2	5 ± 3	0.31
no apnea No. (%)	2 (18)	3 (27)	2 (15)	0.76
OSA (AHI ≥ 5) No. (%)	8 (73)	7 (64)	7 (54)	0.63
CSA (AHI ≥ 5) No. (%)	1 (9)	1 (9)	4 (31)	0.26

** = p < 0.05 vs. GA; ** = p < 0.01 vs. GA*
& = p < 0.05 vs. SAA+IM; && = p < 0.01 vs. SAA+IM
AHI = apnea–hypopnea index; BMI = body mass index; CSA = central sleep apnea; EPI = epidural catheter; ESS = Epworth Sleepiness Scale; GA = general anesthesia; IM = intrathecal morphine; OSA = obstructive sleep apnea; SAA = subarachnoid anesthesia; STOP BANG = snoring, tiredness, observed apnea, high blood pressure, body mass index, age, neck circumference and gender

Tab. 2. *Anesthesia characteristics*

Parameter	GA n = 11	SAA+IM n = 11	SAA+EPI n = 13	p
ASA I No. (%)	1 (9)	1 (9)	4 (31)	0.26
ASA II No. (%)	9 (82)	8 (73)	6 (46)	0.16
ASA III No. (%)	1 (9)	2 (18)	3 (23)	0.66
THA No. (%)	6 (55)	8 (73)	3 (23)&	0.05
TKA No. (%)	4 (36)	3 (27)	9 (69)	0.09
other surgery No. (%)	1 (9)	0	1 (8)	0.61
anesthesia duration (min)	90 (75;105)	90 (90;120)	100 (80;110)	0.49
sufentanil iv dose (mcg)	35 (30;40)	0 (0;0)**	0 (0;0)**	< 0.01
intrathecal morphine dose (mg)	0	0.3 (0.2;0.3)**	0&&	< 0.01
single peripheral nerve block No. (%)	7 (64)	1 (9)*	1 (8)**	< 0.01
continuous peripheral nerve block No. (%)	3 (27)	1 (9)	1 (8)	0.33
SE	41 (40;45)	81 (79;84)**	82 (81;85)**	< 0.01

** = p < 0.05 vs. GA; ** = p < 0.01 vs. GA*
& = p < 0.05 vs. SAA+IM; && = p < 0.01 vs. SAA+IM
ASA class = American Society of Anesthesiologists Classification; BMI = body mass index; EPI = epidural catheter; GA = general anesthesia; IM = intrathecal morphine; SAA = subarachnoid anesthesia; SE = state entropy; THA = total hip arthroplasty; TKA = total knee arthroplasty

Sleep-disordered breathing parameters are shown in Table 3. In the GA group, compared to the pre-operative night, hypopnea increased significantly on the third and fourth nights. The same changes were observed for AHI, but these changes were not significant compared to the pre-operative night. The proportion of time spent in the supine position increased significantly on the first, second, and third post--operative nights.

In the SAA+IM group, hypopnea and oxygen desaturation index (ODI) decreased significantly on the first post-operative night and then, along with AHI, significantly increased on the third and fourth post-operative nights compared to pre-operative findings. There was also a significant increase in the proportion of time spent in the supine position which increased on the first night and remained significantly increased for the remainder of the study nights.

In the SAA+EPI group, there was an insignificant change towards a higher obstructive apnea index on the first post-operative night. Changes in hypopnea and ODI followed the same pattern as in the SAA+IM group. However, these changes were less pronounced and insignificant compared to the pre-operative night. The proportion of time spent in the supine position increased significantly on the first night and remained high for the remainder of the study nights.

When the three groups were compared, only the proportion of time spent in the supine position on the fourth post-operative night was significantly higher in the SAA+IM group compared to the GA group.

The post-operative VAS and opioid doses are shown in Table 4. In the SAA+EPI group, the opioid dose was significantly lower on the first day and the cumulative dose (over the five days) was also significantly lower compared to both the GA and SAA+IM groups. The opioid dose for the SAA+IM group was significantly lower on the second day compared to the GA group, and corresponded to the lower VAS score observed in the SAA+IM group on the same day compared to the GA and SAA+EPI groups (Table 4).

Discussion

The major finding of this study was that changes in post-operative SDB events were most pronounced in patients with a higher post-operative opioid dose and perioperative intrathecal morphine administration. By contrast, patients who underwent surgery with a combination of

Tab. 3. *Sleep-disordered breathing parameters*

parameter	pre-op night	1st post-op night	2nd post-op night	3rd post-op night	4th post-op night	p
GA						
obstructive (e/h)	2.5 (0.5;4.7)	0.8 (0.1;5.3)	0.7 (0;1.2)	0.4 (0;4.2)	1 (0.5;3)	0.46
central (e/h)	0.1 (0;0.9)	0 (0;0.3)	0 (0;0.1)	0 (0;0.2)	0.2 (0;0.8)	0.21
mix (e/h)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0.74
hypopnea (e/h)	7.6 (3.2;14.3)	3.2 (0.9;6.2)	7.5 (2.9;20)	8.5 (6.5;22)*	12.4 (3.9;23.2)*	0.01
AHI (e/h)	7.9 (5.2;19.5)	5.3 (2.8;11.1)	10.6 (5.6;20.1)	8.5 (6.5;22.5)	15.5 (5.8;26.2)	0.03
ODI (e/h)	9.5 (6.8;19.5)	4.9 (1.2;11.6)	13 (5.9;22.5)	13.2 (9.6;31)	16.9 (6.9;31.3)	0.06
supine %	35 (26;86)	100 (97;100)**	97 (73;100)*	100 (97;100)*	88 (24;93)	< 0.01
SAA						
obstructive (e/h)	1 (0;1.5)	0.8 (0;5.9)	7.1 (0;9.9)	0.1 (0;2.9)	0.4 (0.1;3.5)	0.13
central (e/h)	0.1 (0.1;0.7)	0 (0;0.1)	0 (0;2.5)	0.2 (0;0.9)	0 (0;0.1)	0.05
mix (e/h)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0.96
hypopnea (e/h)	8.7 (4.2;13.4)	1.6 (1;5.7)*	6.8 (2.9;31.4)	21 (9.5;31.3)**	20.6 (3.8;49.4)*	< 0.01
AHI (e/h)	10.5 (4.9;14.7)	2.4 (1.1;15.8)	13.6 (3.1;50)	24.3 (9.6;31.4)*	21.3 (4.1;57)*	< 0.01
ODI (e/h)	13.9 (6.7;15.7)	2.8 (1;13.2)*	7.8 (5.5;56.3)	27.3 (14.9;33.4)**	21.6 (7.2;66.3)*	< 0.01
supine %	45 (20;85)	100 (100;100)*	98 (93;100)**	100 (76;100)**	100 (92;100)**&&	< 0.01
EPI						
obstructive (e/h)	1.1 (0.4;5.7)	3.5 (0.3;14.4)	1.3 (0.1;5.7)	1.2 (0.1;3.7)	0.8 (0.2;2.2)	0.06
central (e/h)	0.3 (0.1;1.7)	0.1 (0;1.3)	0.2 (0;1.5)	0 (0;1.3)	0.2 (0;0.4)	0.81
mix (e/h)	0 (0;0.3)	0 (0;0)	0 (0;0.1)	0 (0;0)	0 (0;0)	0.43
hypopnea (e/h)	7.7 (5.3;12.4)	4.8 (1;10.9)	13.3 (12;25.4)	18.8 (5.3;25.9)	15.8 (9.7;28.3)	0.05
AHI (e/h)	13.5 (7.2;22.4)	14 (2.6;26.4)	17.9 (12.8;36.9)	19.4 (6.3;32.8)	16.5 (10.8;30.5)	0.66
ODI (e/h)	13.7 (7.9;22.5)	7.8 (2.1;25.8)	25.1 (14.8;39.4)	24.9 (18.6;34)	21.2 (14.7;40.8)	0.16
supine %	31 (17;66)	100 (95;100)**	96 (92;100)**	97 (55;100)**	79 (41;96)**	< 0.01

** = p < 0.05 vs. pre-operative night; ** = p < 0.01 vs. pre-operative night*
& = p < 0.05 vs. GA; && = p < 0.01 vs. GA
 # = p < 0.05 vs. SAA+IM; ## = p < 0.01 vs. SAA+IM
AHI = apnea–hypopnea index; CSA = central sleep apnea; EPI = epidural catheter; GA = general anesthesia; ODI = oxygen desaturation index; SAA = subarachnoid anesthesia

Tab. 4. *Peri-operative VAS and opioids (equivalent dose of morphine)*

Parameter	GA n = 11	SAA+IM n = 11	SAA+EPI n = 13	p
VAS day 1	2 (2;2)	2 (2;2)	2 (2;3)	0.14
VAS day 2	2 (2;2)&	2 (1;2)	2 (2;2)&	0.04
VAS day 3	3 (2;3)	2 (2;3)	2 (2;2)	0.22
VAS day 4	2 (2;3)	2 (2;3)	2 (2;3)	0.86
VAS day 5	2 (2;2)	2 (2;3)	2 (2;3)	0.63
opioid dose day 1 (mg)	35 (30;40)	30 (20;30)	0 (0;0)**&&	< 0.01
opioid dose day 2 (mg)	10 (0;20)	0 (0;0)*	10 (0;10)	0.04
opioid dose day 3 (mg)	10 (0;20)	10 (0;20)	10 (0;10)	0.81
opioid dose day 4 (mg)	10 (0;30)	10 (0;20)	0 (0;10)	0.17
opioid dose day 5 (mg)	10 (0;10)	0 (0;10)	0 (0;20)	0.42
opioid cumulative dose (mg)	60 (50;105)	50 (40;70)	25 (10;40) **&	0.01

** = p < 0.05 vs. GA; ** = p < 0.01 vs. GA*
& = p < 0.05 vs. SAA+IM; && = p < 0.01 vs. SAA+IM
EPI = epidural catheter; GA = general anesthesia; IM = intrathecal morphine; SAA = subarachnoid anesthesia; VAS = visual analog scale

subarachnoid anesthesia (without intrathecal morphine) with epidural catheter for post-operative analgesia exhibited only insignificant SDB changes post-operatively. Therefore, an opioid-sparing anesthesia technique may be beneficial for patients with known or suspected OSA.

In our cohort, the frequency of OSA was 63% pre-operatively, which is higher than in the general population [1], but similar to the previous study by Chung et al. [18].

The observed SDB parameter changes were characterized by increased hypopnea on the third and fourth post-operative nights in the GA group and decreased hypopnea and ODI on the first post-operative night followed by an increase in both parameters along with AHI on the third and fourth post-operative nights in the SAA+IM group. These findings are in agreement with the previous study by Chung et al. who also showed a significant decrease in AHI in patients with severe OSA, along with a decrease in AHI during rapid eye movement (REM) sleep and a decrease in ODI in patients with OSA during the first post-operative night [18], followed by an increase in AHI and ODI in both OSA and non-OSA patients with a peak on the third post-operative night [13, 18]. In our study, SDB parameter changes involved mainly hypopnea while changes of the obstructive

and central apnea index were minimal, which is also in agreement with previous reports [18].

In the SAA+EPI group, a pattern of SDB parameter changes similar to that in the SAA+IM group was observed. However, changes in this group were less pronounced and insignificant compared to the pre-operative study night. This observation is in agreement with the previous study by Memtsoudis et al. [25] who showed lower rates of major complications in patients with OSA undergoing surgery with neuraxial anesthesia than in those with GA.

Several factors including perioperative drug use (anesthetics, benzodiazepines, opioids, and neuromuscular blocking agents [1, 14]) and supine position [26] may influence SDB in the post-operative period. Moreover, surgical trauma, post-operative opioids, and environmental factors (noise, light) may lead to sleep disturbances [27], which may also contribute to SDB changes [1].

On the first post-operative night, we speculate that the observed decrease in hypopnea and ODI may have been caused by a decrease in REM sleep, which has been shown to be inversely related to surgical stress [13] and opioid dose [28]. Indeed, in the GA and SAA+IM groups, the opioid dose was highest on the day of surgery. However, the same changes towards lower hypopnea and ODI were observed in the SAA-EPI group, wherein the opioid dose was minimal, suggesting that a surgical stress-induced decrease in REM sleep [13] may have accounted for the observed decrease in hypopnea and ODI on the first post-operative night.

On the third to fourth post-operative nights, the increased hypopnea in the GA group and the increased hypopnea, AHI, and ODI in the SAA+IM group could be explained by the REM sleep rebound phenomenon [1] or by the cumulative opioid dose which has been shown to be associated with an increased post-operative AHI [13]. Indeed, the cumulative opioid dose was significantly higher in both the GA and SAA+IM groups compared to the SAA+EPI group.

Despite no difference in the cumulative opioid dose, SDB changes seemed to be more pronounced in the SAA+IM compared to the GA group. Supine position may lead to a worsening of OSA [26] and, on the fourth post-operative night, the proportion of time spent in the supine position was significantly higher in the SAA+IM group than in the GA group. However, when compared to the SAA+EPI group (where SDB changes were minimal), there was no difference. Another explanation of the observed difference between the SAA+IM and the GA groups could be the administration of intrathecal morphine. Patients with OSA have been shown to have a decreased beta-endorphin-like activity in the cerebrospinal fluid [29]. This finding together with an inverse association between endogenous opioid activity and morphine response [30] may suggest that OSA patients are more sensitive to intrathecal morphine. By contrast, a recent retrospective study has shown that intrathecal morphine had no effect on post-operative pulmonary complications in OSA [31]. However, lower doses of intrathecal morphine were used in the study by Bai et al. (0.1 mg vs. 0.3 mg) and SDB parameters were not monitored [31].

Our observations may have important clinical implications. OSA has been shown to be associated with delirium and myocardial infarction [8, 9]. Notably, the highest incidence of delirium and myocardial infarction is between the second and fifth post-operative nights [32, 33], and may therefore correspond with post-operative exacerbation of OSA. Importantly, on the third post-operative day, patients are usually no longer in the HDU, and may therefore be at an increased risk of adverse effects of OSA exacerbation due to less intensive monitoring. Therefore, using an opioid-sparing anesthesia technique and routine monitoring of vital signs on the third to fourth post-operative days may be a satisfactory approach in patients with known or suspected OSA.

Our study has several limitations. First, it was an observational study; therefore, we cannot comment on causality. Second, our patients were monitored during the night only. We cannot exclude short periods of sleep during the day. Third, 45 patients (56%) withdrew their consent (mostly because of discomfort) before completing all four post-operative study nights and were excluded. Exclusion of these subjects may have introduced bias to our study and limited the generalizability of our findings. However, OSA exacerbation is reported most frequently on the fourth post-operative night [18]; therefore, we believe it was necessary to include only patients who completed all study nights. Moreover, a high drop-out rate seems to be a common problem in similar studies, as an even higher drop-out rate (90%) was observed in the first study by Chung et al. [18]. Fifth, since a portable ambulatory device (i.e. without electroencephalography) was used to conduct sleep studies, we cannot comment on sleep architecture changes. Sixth, patients in the GA group were significantly younger compared to both the SAA+IM and SAA+EPI groups. We speculate that younger patients preferred general anesthesia with a peripheral nerve block to neuraxial techniques.

Conclusions

In conclusion, compared to pre-operative findings, changes in SDB events were less pronounced in patients who received subarachnoid anesthesia (without intrathecal morphine) with epidural catheter for opioid-free post-operative epidural analgesia. Therefore, an opioid-sparing anesthesia technique may be beneficial for patients with known or suspected OSA.

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