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ORIGINAL RESEARCH

The Relationship Between Postoperative Opioid Analgesia and Sleep Apnea Severity in Patients Undergoing Hip Arthroplasty: A Randomized, Controlled, Triple-Blinded Trial

Eric Albrecht[1], Pedro Pereira[1], Virginie Bayon[2], Mathieu Berger[2], Julien Wegrzyn[3], Alexander Antoniadis[3], Raphaël Heinzer[2]

[1]Department of Anesthesia, University Hospital of Lausanne and University of Lausanne, Lausanne, Vaud, Switzerland; [2]Center for Investigation and Research in Sleep, University Hospital of Lausanne and University of Lausanne, Lausanne, Vaud, Switzerland; [3]Department of Orthopedic Surgery, University Hospital of Lausanne and University of Lausanne, Lausanne, Vaud, Switzerland

Correspondence: Eric Albrecht, Department of Anesthesia, University Hospital of Lausanne, Rue du Bugnon 46, Lausanne, 1011, Switzerland, Tel +41 79 556 63 41, Email eric.albrecht@chuv.ch

Purpose: Residual postoperative pain after hip arthroplasty is usually treated with oral opioids. While classic opioids are associated with respiratory depression and worsening of sleep apnea, tramadol has been reported to preserve respiratory function. However, this has not been investigated in a prospective trial using respiratory polygraphy. This randomized controlled triple-blinded trial tested the hypothesis that postoperative treatment with oral opioids such as oxycodone would increase sleep apnea severity, measured with a respiratory polygraphy, compared with oral tramadol.

Patients and Methods: Sixty patients undergoing hip arthroplasty under spinal anesthesia with 15 mg isobaric bupivacaine 0.5% were randomized to receive postoperative pain treatment with either oral oxycodone (controlled-release 10 mg every 12 hours and immediate-release 5 mg every 4 hours as needed) or oral tramadol (controlled-release 100 mg every 8 hours and immediate-release 50 mg every 4 hours as needed). Respiratory polygraphy was performed on the first postoperative night. The primary outcome was the apnea-hypopnea index in the supine position. Secondary outcomes included the oxygen desaturation index, postoperative pain scores and intravenous morphine consumption.

Results: Mean supine apnea-hypopnea index on postoperative night 1 was 11.3 events.h^{-1} (95% confidence interval, 4.8–17.7) in the oxycodone group and 10.7 (4.6–16.8) events.h^{-1} in the tramadol group (p=0.89). There were no significant differences between the oxycodone and tramadol groups with respect to any secondary sleep-related or pain-related outcomes.

Conclusion: Oral oxycodone did not increase sleep apnea severity measured using respiratory polygraphy compared with oral tramadol on the first postoperative night after hip arthroplasty.

Trial Registration Number: Clinicaltrials.gov – NCT03454217 (date of registration: 05/03/2018).

Keywords: sleep apnea, postoperative analgesia, hip arthroplasty, perioperative medicine

Introduction

Following a wide range of surgical procedures, patients with sleep apnea may develop several severe postoperative complications such as acute respiratory failure, desaturation, myocardial infarction, pulmonary embolism, arrhythmia and even cardiac arrest, resulting in increased mortality at 30 postoperative days.[1–3] We have previously investigated whether using short-acting anesthetic agents would reduce the impact of general anesthesia on sleep apnea severity.[4] Likewise, we have also studied the impact of low dose of intrathecal morphine,[5] which is commonly administered in anesthesia to provide effective postoperative analgesia.[6] The administration of short-acting anesthetic agents or low dose intrathecal morphine did not worsen sleep apnea severity.[4,5]

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Intravenous or oral opioids are administered after surgery to treat moderate to severe postoperative pain.[7,8] Independent of the route of administration, opioids are associated with respiratory depression and can worsen sleep apnea,[9,10] to such an extent that severe postoperative respiratory arrests might occur.[11] The mechanisms underlying this effect include a diminished ventilatory response from the brainstem in response to increased carbon dioxide and decreased oxygen, and a blunted respiratory response secondary to an increase in airway resistance.[12]

Although considered to be an opioid, tramadol acts as a weak agonist at μ receptors in the central nervous system, and its analgesic effect also results from an antinociceptive effect in the descending pathway secondary to inhibition of serotonin reuptake.[13] Tramadol is usually prescribed following surgery with mild-to-moderate postoperative pain or in an ambulatory setting. Due to only having weak activity at μ receptors, it has been suggested that it can provide pain relief without associated respiratory depression.[12,14,15] However, these studies only investigated this effect under general anesthesia with spontaneous breathing[14,15] or in the postoperative period in a young female population.[12] In addition, these three studies only measured the primary outcome during the first 30 minutes after drug administration, and the parameters evaluated were end-tidal carbon dioxide concentration[14,15] or oxygen saturation.[12]

While opioids might worsen sleep apnea severity in at-risk patients, tramadol might provide an alternative analgesic option, especially in the setting of a surgery with infiltration of local anesthetics resulting in moderate postoperative pain. However, this has not been investigated in a prospective trial using respiratory polygraphy.

This randomized, controlled, triple-blinded trial tested the hypothesis that postoperative treatment with oral opioids such as oxycodone would increase sleep apnea severity measured with a respiratory polygraphy, compared with oral tramadol in patients undergoing hip arthroplasty.

Materials and Methods

This study (clinicaltrials.gov: NCT03454217; date of registration: 05/03/2018) was conducted at the University Hospital of Lausanne between March 2018 and September 2020. The trial protocol was approved by the local ethics committee (Commission d'Ethique Romande, protocol number CER 2017/01976), and all patients provided written informed consent prior to enrolment. The "Commission d'Ethique Romande" is an institution that is independent from the University Hospital of Lausanne that is in charge of assessing research projects from different Hospitals in the French part of Switzerland. This study complies with the Declaration of Helsinki.

Eligible patients were adults aged 18 to 85 years who were scheduled to undergo hip arthroplasty. Patients who met any of the following exclusion criteria were excluded: use of continuous positive airway pressure (CPAP) for obstructive sleep apnea, presence of severe cardiovascular or respiratory disease, preoperative consumption of a benzodiazepine, chronic opioid usage at a daily dosage of ≥30 mg morphine equivalents, allergy to either of the study treatments, and pregnancy. Patients with an existing diagnosis of sleep apnea who were not using CPAP could be included.

Randomization to either the oxycodone group or the tramadol group was performed on the day of surgery using a computer-generated randomization table (block size of 10). Treatment group allocation information was concealed in a sealed opaque envelope. The sleep physician, sleep technicians evaluating study data, surgeons, the person collecting the data, and the statistician who performed data analysis were all unaware of treatment allocation (triple-blind design).

A portable respiratory polygraphy recorder (ResMed Embletta® system) was used to measure sleep-related respiratory outcomes on postoperative night 1. This device provides non-invasive recording of nasal airflow via a nasal cannula, oxygen saturation (SpO_2) using finger pulse oximetry, respiratory efforts based on thoracic and abdominal belts, and body position.[4,5] A specialized sleep technician scored all recordings, with independent, blinded review by a sleep specialist. Apnea was recorded when a respiratory event consisted of cessation of breathing for ≥10 seconds; hypopnea was scored when there was a >30% reduction in the respiratory flow signal associated with oxygen desaturation of ≥3%. The apnea-hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of recording. The number of oxygen desaturation (≥3%) episodes per hour of sleep was reported as the oxygen desaturation index.

Surgical procedures were performed using routine monitoring under spinal anesthesia with the patient in the lateral position. Sterile skin preparation was undertaken, then a 25-gauge pencil-point needle was inserted at the L3–L4 or L4–L5 level via a 21-gauge introducer needle and 3 mL isobaric bupivacaine (5 $mg.mL^{-1}$) was injected. After a cemented or uncemented prosthesis had been implanted following a posterior approach, the surgical site was infiltrated with 50 mL

ropivacaine 0.2%. Postoperative care included administration of intravenous acetaminophen 1 g and ketorolac 30 mg (for multimodal anesthesia) and intravenous ondansetron 4 mg (for antiemetic prophylaxis), as per routine clinical practice at the study institution.[16,17]

After routine surveillance in Phase I recovery, patients were transferred onto the ward, where they were mobilized early, and usually discharged on postoperative day 2, following an enhanced recovery program after surgery. Common postoperative pain and antiemetic treatments consisted of oral acetaminophen 1000 mg every 6 hours, oral ibuprofen 400 mg every 8 hours, and intravenous ondansetron 4 mg as needed. Study treatment started on the day of surgery, and consisted of controlled-release oral oxycodone 10 mg every 12 hours and immediate-release oral oxycodone 5 mg every 4 hours as needed for residual pain (visual analogue scale [VAS] score ≥4 on a scale from 0–10 where higher scores indicate more pain, or patient request for analgesia), or oral controlled-release tramadol 100 mg every 8 hours and immediate-release tramadol 50 mg every 4 hours if the VAS score was ≥4 or on request. These are considered to be equivalent analgesic doses.[18,19]

The primary endpoint was supine AHI on the first postoperative night. This endpoint was chosen rather than the overall AHI because sleep apnea tends to be worse when patients are in the supine position and because subjects need to sleep in the supine position after hip arthroplasty surgery. Secondary respiratory-related outcomes were overall AHI, obstructive apnea index, central apnea index, hypopnea index, oxygen desaturation index, respiratory rate, percentage of recording time with SpO_2 <90%, and percentage of time spent in the supine position, all recorded on the first postoperative night. When polygraphy recording failed the patient was considered as a drop-out and no data were used. Secondary pain-related outcomes were consumption of oral morphine equivalents, and rest and dynamic pain scores at 2, 24, and 48 hours postoperatively (pain was rated on a VAS from 0–10), postoperative nausea/vomiting and pruritus at 24 and 48 hours after surgery, and satisfaction score (on a VAS from 0–10, where higher scores indicate greater satisfaction). In addition to demographic data, we also evaluated the STOP-Bang[20] and NoSAS scores.[21] The STOP-Bang score includes eight items, and high risk of OSA is defined as a positive response to ≥3 items (Appendix 1).[20] The NoSAS score refers to Neck circumference, Obesity, Snoring, Age and Sex.[21] Points are awarded for each item and a score of ≥8 indicates a high probability of sleep-disordered breathing. More details of both scores are provided in Appendix 1.

It was calculated that a total of 44 patients (22 per group) would be required to detect a between-group difference in supine AHI of 5 events.h^{-1} with 90% power, standard deviation of 5, and alpha of 0.05. To the best of our knowledge, there were no published randomised controlled trials investigating the impact of any anesthetic intervention on sleep apnea and measuring the apnea-hypopnea index as a primary outcome other than our two previous studies.[4,5] In the absence of data, we considered that 5 events.h^{-1} would be a clinically relevant difference in AHI between groups. To allow for a 30% dropout rate due to protocol violation, failed recording or withdrawal of consent, the target sample size was set at 60 patients.

Categorical data are summarized as n (%), and continuous data are presented as means with 95% confidence intervals (CI). Categorical data were compared using the Fisher's exact test or Pearson Chi-square test, as appropriate. Normality of continuous data was checked with the Shapiro–Wilk test. Continuous variables were analyzed using independent *t*-test or Mann–Whitney *U*-test, as appropriate. Statistical analysis was performed using the IBM SPSS Statistics for Mac, Version 26.0 (IBM Corp, Armonk, NY). Statistical significance was defined as a two-sided p-value of <0.05.

Results

Sixty patients were recruited and 45 provided data for evaluation of the primary endpoint (Figure 1). Patient characteristics, including sleep apnea risk scores, were similar in the oxycodone and tramadol groups at baseline (Table 1).

The mean supine AHI on postoperative night 1 was 11.3 events.h^{-1} (95% CI 4.2–18.4) in the oxycodone group and 10.7 events.h^{-1} (4.1–17.2) in the tramadol group (p=0.89). Sleep-related respiratory outcomes were consistently similar between the oxycodone and tramadol groups (Table 2). Postoperative pain-related secondary outcomes were also similar between treatment groups (Table 3).

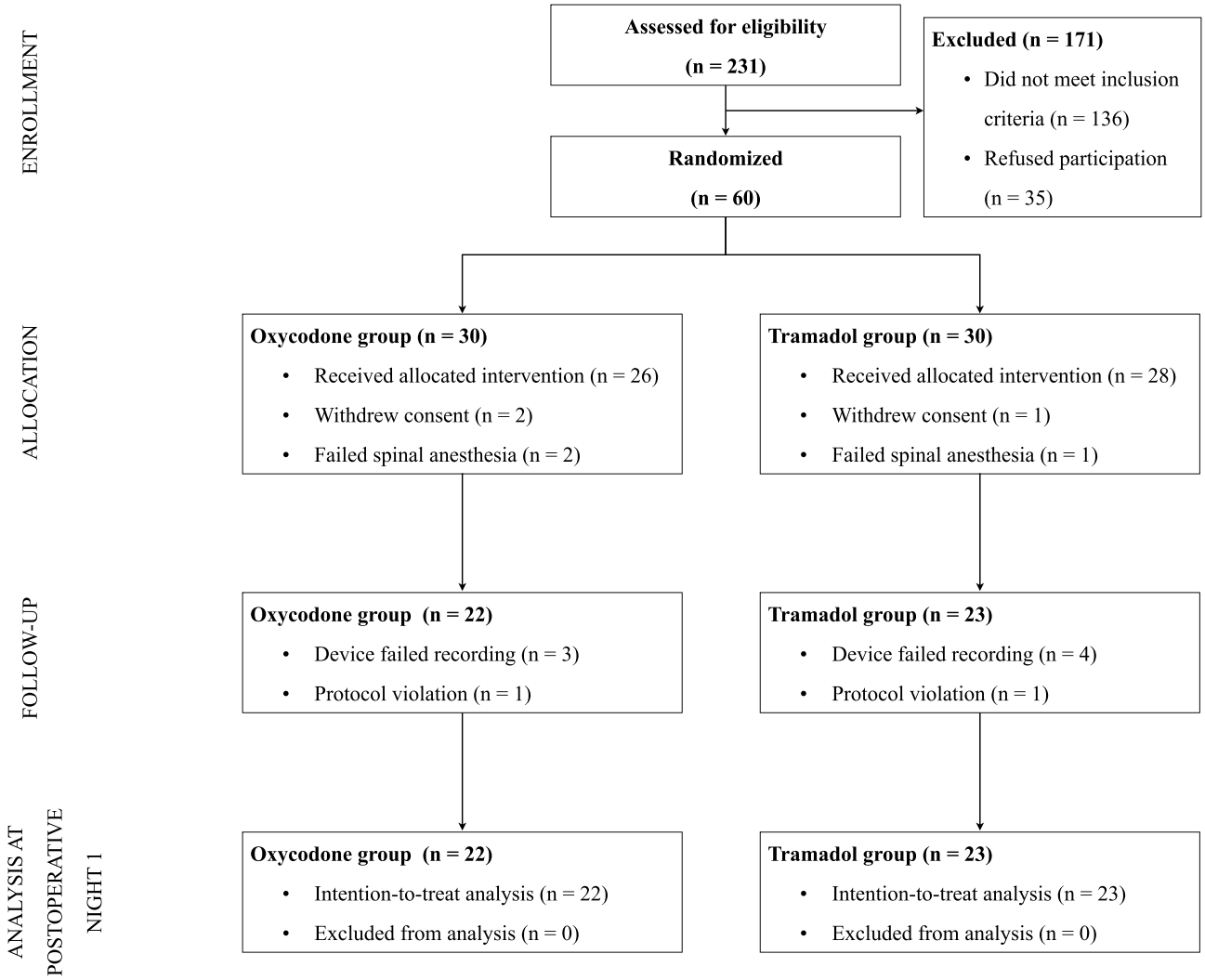

Figure 1 CONSORT diagram of patient recruitment.

Discussion

The results of this randomized, controlled, triple-blind trial showed that oxycodone did not have a negative effect on sleep apnea parameters, including the supine AHI, on the first postoperative night compared with tramadol. Consequently, this study does not confirm the findings of a reduced respiratory depression associated with tramadol, when compared with oxycodone, as previously stated.[15] There were also no between-group differences in postoperative pain outcomes between the two groups. This is unexpected given that patients were treated with either a weak opioid (tramadol) or a strong opioid (oxycodone); the results might reflect a type II error as the trial was not powered for these secondary outcomes. Alternatively, we cannot exclude the possibility that patients undergoing hip arthroplasty with local infiltration analgesia only experience mild-to-moderate postoperative pain and therefore do not require more potent opioids than tramadol. Indeed, rest pain scores were reasonably low during the first 24 postoperative hours, with a mean score of 1.5. Taken together, our results indicate that tramadol might be a reasonable option to treat postoperative pain after hip arthroplasty in the setting of multimodal analgesia, and oxycodone can be reasonably prescribed to patients undergoing surgery who are expected to experience moderate-to-severe postoperative pain without any increased risk of worsening sleep apnea severity.

Although our study population was at high risk of having sleep apnea based on the STOP-BANG[20] and NoSAS scores[21] (predictive rates of 82% and 69%, respectively), only 47% were found to have sleep apnea (AHI >5 events.h^{-1})

Table 1 Patient Demographics and Clinical Characteristics at Baseline for Patients Receiving Oxycodone or Tramadol

	Oxycodone (n=22)	Tramadol (n=23)	p value
Male; n (%)	11 (50%)	12 (52.2%)	0.88
Age; years	62.5 (56.4–68.7)	63.3 (57.9–68.7)	0.85
Weight; kg	76.8 (68.3–85.2)	81.6 (74.4–88.9)	0.28
Height; cm	169 (164–173)	172 (168–176)	0.25
Body mass index; kg/m^2	27.0 (24.1–30.0)	27.8 (25.4–30.1)	0.29
ASA score; n (%)			0.19
I	6 (27.3%)	4 (17.4%)	
II	15 (58.2%)	14 (60.9%)	
III	1 (4.5%)	5 (21.7%)	
Duration of surgery; min	128 (78–178)	114 (92–137)	0.76
Propofol dosage; mg	114 (45–183)	258 (83–432)	0.19
Comorbidities; n (%)			
Coronary artery disease	0 (0%)	4 (17.4%)	0.11
Hypertension	9 (40.9%)	10 (43.5%)	1.00
Renal failure	0	0	–
Diabetes	1 (4.5%)	2 (8.7%)	1.00
Hyperlipidemia	2 (9.1%)	6 (26.1%)	0.24
Sleep apnea scores; n (%)			
NoSAS score* ≥8	14 (63.6%)	17 (73.9%)	0.46
STOP-BANG score** ≥3	16 (72.7%)	21 (91.3%)	0.14

Notes: *Neck circumference, obesity, snoring, age and sex: points are awarded for each item and a score of ≥8 indicates a high probability of sleep-disordered breathing. **This score includes eight items; and high risk of OSA is defined as a positive response to ≥3 out of eight items. Continuous data are presented as means with 95% confidence intervals; categorical data are presented as number of patients (%).
Abbreviation: ASA, American Society of Anesthesiology.

Table 2 Sleep-Related Respiratory Outcomes on Postoperative Night One in Patients Receiving Oxycodone or Tramadol

	Oxycodone (n=22)	Tramadol (n=23)	p value
Apnea-hypopnea index; $events.h^{-1}$	10.9 (3.8–17.9)	10.1 (3.7–16.6)	0.50
Obstructive apnea index; $events.h^{-1}$	2.1 (0–4.8)	0.6 (0.1–1.2)	0.32
Central apnea index; $events.h^{-1}$	0.4 (0.1–0.6)	0.9 (0.1–1.6)	0.62
Mixed apnea index; $events.h^{-1}$	0.1 (0–0.3)	0.1 (0–0.3)	0.72
Hypopnea index; $events.h^{-1}$	8.3 (2.9–13.7)	8.5 (2.7–14.3)	0.51
Oxygen desaturation index; $events.h^{-1}$	12.9 (5.1–20.7)	12.0 (5.1–19.0)	0.59
Mean SpO_2; %	92.1 (90.7–93.5)	92.1 (91.1–93.1)	0.94
Proportion of time with SpO_2 <90%; %	15.0 (2.3–27.8)	14.6 (5.7–23.5)	0.77
Respiratory rate; $breaths.min^{-1}$	15.2 (13.4–17.0)	14.6 (13.4–15.9)	0.73
Proportion of time spent in the supine position; %	92.0 (85.7–98.3)	89.0 (79.8–98.3)	0.89

Note: Data are presented as means with 95% confidence intervals.
Abbreviation: SpO_2, oxygen saturation.

on polygraphy. Furthermore, the mean BMI in our patients was 27.5 $kg.m^{-2}$ and only 24% were obese. Given that the prevalence of obesity in a typical sleep apnea population is usually higher than this,[22,23] we cannot exclude the possibility that the impact of tramadol and oxycodone on postoperative sleep apnea could be different in more obese patients. However, our study suggests that, in an unselected general population undergoing elective hip arthroplasty, there was no major difference in the effects of these two opioids on sleep breathing parameters. Nevertheless, further confirmation is required before robust and definitive conclusions can be drawn. Of note, in a sleep laboratory crossover study, Rowsell et al showed that 40 mg oral controlled-release morphine administered in the late afternoon did not worsen sleep apnea in 60 male patients with obstructive sleep apnea.[24]

Table 3 Postoperative Pain-Related Outcomes in Patients Receiving Oxycodone or Tramadol

	Oxycodone (n=22)	Tramadol (n=23)	p value
2 hours postoperatively			
Oral morphine equivalent consumption, mg	4.6 (1.3–7.8)	3.5 (1.6–5.4)	0.74
Rest pain score (VAS, 0–10)	0.4 (0–0.9)	1.0 (0.3–1.6)	0.06
24 hours postoperatively			
Oral morphine equivalent consumption between 2 and 24 hours, mg	24.3 (18.6–30.0)	17.6 (14.3–21.0)	0.05
Cumulative oral morphine equivalent consumption at 24 hours, mg	28.9 (22.3–35.4)	21.1 (17.8–24.5)	0.06
Rest pain score (VAS, 0–10)	1.7 (0.8–2.5)	1.8 (1.1–2.5)	0.88
Dynamic pain score (VAS, 0–10)	3.1 (2.1–4.2)	3.1 (2.2–4.0)	0.75
Postoperative nausea and vomiting, n (%)	2 (9.1%)	0 (0%)	0.49
Pruritus, n (%)	0 (0%)	1 (4.3%)	1.00
48 hours postoperatively			
Oral morphine equivalent consumption between 24 and 48 hours, mg	32.5 (20.1–44.9)	26.9 (22.2–31.5)	0.45
Cumulative oral morphine equivalent consumption at 48 hours, mg	61.4 (47.1–75.6)	48.0 (41.5–54.5)	0.14
Rest pain score (VAS, 0–10)	1.4 (0.4–2.5)	1.2 (0.5–1.8)	0.98
Dynamic pain score (VAS, 0–10)	3.1 (2.0–4.2)	2.8 (2.2–3.4)	0.86
Postoperative nausea and vomiting, n (%)	2 (10.0%)	1 (4.8%)	0.61
Pruritus, n (%)	0 (0%)	1 (4.8%)	1.00

Notes: VAS, visual analogue scale score (from 0–10), where higher values indicate more pain. Continuous data are presented as means with 95% confidence intervals; categorical data are presented as number of patients (%).

This randomized controlled trial has several weaknesses. First, no sleep exam was performed prior to surgery, and therefore we were unaware of the preoperative sleep status of the patients. However, the similarity in demographic data and sleep apnea scores indicate there was probably no major preoperative difference between groups. While portable respiratory polygraphy is recognized as a diagnostic tool for sleep apnea in clinical practice, it does not provide data on different sleep stages. Use of full polysomnography inclusive of EEG, electrooculogram and electromyogram would have provided a greater level of detail on sleep parameters. On the other hand, the number of different sensors required for full polysomnography could potentially have further disturbed sleep quality in our patients, potentially undermining the study findings. Moreover, it would have been difficult to implement full polysomnography on an orthopedic ward. Regarding the hypopneas, they were not scored into obstructive or central. Although opiates may decrease respiratory drive during sleep and generate hypoventilation with hypercapnia, we could not measure the partial pressure of carbon dioxide overnight for technical reasons. However, since both oxygen saturation and the respiratory rate did not differ significantly between groups, a significant difference in hypercapnia between patients receiving oxycodone or tramadol is unlikely, even if it cannot be excluded. We did not perform any sleep exams on the second or third postoperative night, which are times when opioid consumption was higher than in the first 24 postoperative hours. Caution is warranted when extrapolating the results of this study to other more painful surgeries where higher doses of opioids are required or to patients with untreated severe sleep apnea. Finally, despite a non-negligible drop-out rate, we believe that our results are worth disseminating because sufficient patients were included for analysis of the primary outcome according to the power analysis.

Conclusion

The results of this study showed that oral oxycodone did not increase postoperative sleep apnea severity measured with a respiratory polygraphy compared with oral tramadol in patients undergoing hip arthroplasty.

Abbreviations

AHI, apnea-hypopnea index; CI, confidence interval; SpO_2, oxygen saturation; VAS, visual analogue scale.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The trial protocol was approved by the local ethics committee (Commission d'Ethique Romande, protocol number CER 2017/01976), and all patients provided written informed consent prior to enrolment. The study protocol is performed in accordance with the relevant guidelines.

Consent for Publication

Consent for publication was provided by the local ethics committee and patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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