ANESTHESIOLOGY

Intrathecal Morphine and Pulmonary Complications after Arthroplasty in Patients with Obstructive Sleep Apnea

A Retrospective Cohort Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Intrathecal morphine is commonly and effectively used for analgesia after joint arthroplasty, but has been associated with postoperative pulmonary complications such as delayed respiratory depression
- Patients with obstructive sleep apnea may be at higher risk of these complications, especially if intrathecal morphine is used for analgesia

What This Article Tells Us That Is New

- Low-dose intrathecal morphine, in conjunction with multimodal analgesia, was not associated with increased risk of postoperative pulmonary complications in patients with obstructive sleep apnea

ABSTRACT

Background: Intrathecal morphine is commonly and effectively used for analgesia after joint arthroplasty, but has been associated with delayed respiratory depression. Patients with obstructive sleep apnea may be at higher risk of postoperative pulmonary complications. However, data is limited regarding the safety of intrathecal morphine in this population undergoing arthroplasty.

Methods: This retrospective cohort study aimed to determine the safety of intrathecal morphine in 1,326 patients with documented or suspected obstructive sleep apnea undergoing hip or knee arthroplasty. Chart review was performed to determine clinical characteristics, perioperative events, and postoperative outcomes. All patients received neuraxial anesthesia with low-dose (100 μg) intrathecal morphine (exposure) or without opioids (control). The primary outcome was any postoperative pulmonary complication including: (1) respiratory depression requiring naloxone; (2) pneumonia; (3) acute respiratory event requiring consultation with the critical care response team; (4) respiratory failure requiring intubation/mechanical ventilation; (5) unplanned admission to the intensive care unit for respiratory support; and (6) death from a respiratory cause. The authors hypothesized that intrathecal morphine would be associated with increased postoperative complications.

Results: In 1,326 patients, 1,042 (78.6%) received intrathecal morphine. The mean age of patients was 65 ± 9 yr and body mass index was 34.7 ± 7.0 kg/m^2. Of 1,326 patients, 622 (46.9%) had suspected obstructive sleep apnea (Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender [STOP-Bang] score greater than 3), while 704 of 1,326 (53.1%) had documented polysomnographic diagnosis. Postoperatively, 20 of 1,322 (1.5%) patients experienced pulmonary complications, including 14 of 1,039 (1.3%) in the exposed and 6 of 283 (2.1%) in the control group ($P = 0.345$). Overall, there were 6 of 1 322 (0.5%) cases of respiratory depression, 18 of 1,322 (1.4%) respiratory events requiring critical care team consultation, and 4 of 1,322 (0.3%) unplanned intensive care unit admissions; these rates were similar between both groups. After adjustment for confounding, intrathecal morphine was not significantly associated with postoperative pulmonary complication (adjusted odds ratio, 0.60 [95% CI, 0.24 to 1.67]; $P = 0.308$).

Conclusions: Low-dose intrathecal morphine, in conjunction with multimodal analgesia, was not reliably associated with postoperative pulmonary complications in patients with obstructive sleep apnea undergoing joint arthroplasty.

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Major joint arthroplasty is a common surgical intervention aimed at improving pain and function for patients with advanced arthritis of the hip or knee joint. Intrathecal morphine provides effective analgesia for this operation and is often used as a component of multimodal analgesic regimens to facilitate early ambulation, rehabilitation, and ultimately, improved recovery.[1–3] However, neuraxial opioids are not without risk: apart from possible adverse events of pruritus, nausea, vomiting, and urinary retention, there have been reports of delayed respiratory depression with intrathecal morphine.[4,5] While a meta-analysis of 1,314 patients from 28 studies showed that low-dose intrathecal morphine (300 μg) caused no more episodes of respiratory depression than placebo in a general surgical

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patient population,[6] there is limited evidence of its safety for patients with obstructive sleep apnea, who may be at a higher baseline risk of respiratory events than the general population.

Obstructive sleep apnea is a common sleep disorder caused by repetitive upper airway obstruction during sleep leading to episodic oxygen desaturation and cortical arousals.[7] This condition has been associated with worse perioperative outcomes such as unplanned intensive care unit (ICU) admission and ventilatory support, cardiac events, prolonged hospitalization, and increased mortality.[7–9] Furthermore, patients with obstructive sleep apnea are reportedly more sensitive to opioids administered through oral, parenteral, or neuraxial routes, with a higher risk of perioperative desaturation and apnea.[7,10] It is estimated that between 5 and 9% of patients undergoing total joint arthroplasty have a preexisting diagnosis of obstructive sleep apnea, and that many surgical patients have obstructive sleep apnea which had gone undetected.[8,11,12] A recent systematic review of intrathecal morphine in obstructive sleep apnea identified only five low-quality studies comprising 121 subjects; six major cardiorespiratory events occurred in this small cohort.[13] Given the high prevalence of obstructive sleep apnea in the orthopedic patient population and the scarcity of data on the safety of intrathecal morphine in this susceptible population, we performed this retrospective cohort study with the objective of evaluating the impact of administration of low-dose intrathecal morphine (100 μg) on the incidence of postoperative pulmonary complications in patients with obstructive sleep apnea undergoing total joint arthroplasty. We hypothesized that the use of intrathecal morphine would be associated with an increase in postoperative pulmonary complications in this population.

Materials and Methods

Study Design and Aims

The study protocol was approved by the Research Ethics Board of the University Hospital Network, Toronto, Canada (No. 17-5390), and requirement for informed consent was waived in view of the retrospective nature of the study. This retrospective cohort study is a preplanned, primary analysis of data collected through retrospective chart review. The aim of this retrospective cohort study was to evaluate the association of low-dose intrathecal morphine (100 μg) with a composite outcome of postoperative pulmonary complications in patients with diagnosed or suspected obstructive sleep apnea undergoing total joint arthroplasty. Our secondary outcomes were all-cause mortality, incidence of pulmonary embolus, acute coronary syndrome, and hospital length-of-stay. A well-designed large retrospective cohort study is ideally suited to answer these questions, where the event of interest is relatively rare.[7]

Study Population

This study included patients with diagnosed or suspected obstructive sleep apnea who underwent joint arthroplasty under spinal anesthesia at our hospital between January 1, 2004 and December 31, 2015. Inclusion criteria were: (1) elective total hip or knee arthroplasty under neuraxial anesthesia (spinal or combined spinal–epidural anesthesia); (2) a history of previously diagnosed or suspected obstructive sleep apnea (Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender [STOP-Bang] score greater than 3) [14]; (3) age 18 yr or older; and (4) American Society of Anesthesiologists Physical Status classification I to IV. The STOP-Bang questionnaire has been well-validated to identify obstructive sleep apnea, with a score of 4 or more demonstrating 88% sensitivity in obese patients.[14] Patients who received a dose of intrathecal morphine greater than 100 μg or general anesthesia were excluded.

Data Collection

Data were collected from several sources. Patients who underwent total hip or knee arthroplasty between January 1, 2004 and December 31, 2015 (a 12-yr period) under regional anesthesia were identified from an institutional Regional Anesthesia Database.[15] The database contains basic patient demographics, planned surgery, and neuraxial and regional anesthesia techniques; extraction from this database for patients undergoing joint arthroplasty has been previously described.[15] Postoperative opioid consumption was sought from a local acute pain service database (Networked Online Processing of Acute Pain Information).[16] The database includes data on in-hospital opioid consumption and IV patient-controlled analgesia (PCA) use, and its use has been previously described.[16] After this, a detailed review of each electronic medical record was conducted to identify a history of diagnosed or suspected obstructive sleep apnea, anesthetic information, demographic and other clinical data, and postoperative outcomes. Any documentation of primary and secondary outcomes were reviewed based on definitions proposed in previously published literature, as described in the Outcome Measures section.[9,17–20]

Exposure and Control

The principal exposure was the use of intrathecal morphine (100 μg) as a component of the spinal anesthetic solution. The control group consisted of patients who received spinal anesthesia with local anesthetic only and without intrathecal morphine. The decision not to administer intrathecal morphine at our institute is based on clinician preference; patient characteristics, such as obstructive sleep apnea (with greater severity reducing the likelihood of intrathecal morphine administration); and history of chronic opioid use which may increase the likelihood of administration. As per institutional protocol, both groups received multimodal analgesia including spinal anesthesia, peripheral nerve blocks

(for those undergoing total knee arthroplasty), intraoperative local infiltration of the joint capsule, and postoperative systemic analgesics (round-the-clock acetaminophen and nonsteroidal antiinflammatory drugs, with oral opioids as needed). IV PCA opioids were used if the multimodal oral regimen was insufficient to control postoperative pain.

Outcome Measures

Primary Outcome. The primary outcome of this study was the incidence of postoperative pulmonary complications. Based on definitions from several previous studies,[9,17–20] we defined postoperative pulmonary complications as a composite outcome of one or more of the following postoperative events: (1) respiratory depression (bradypnea or hypoxia) requiring treatment with naloxone; (2) pneumonia, defined as a new infiltrate on chest radiograph, temperature above 38°C, and requirement of antimicrobial therapy; (3) severe acute respiratory event requiring consultation with the critical care response team; (4) respiratory failure requiring unplanned intubation and mechanical ventilation; (5) unplanned admission to the ICU for respiratory support; and (6) death from a primary respiratory cause.

Secondary Outcomes. There were multiple secondary outcomes in this study including: (1) 30-day in-hospital mortality rate (from any cause); (2) incidence of pulmonary embolus at any time during the hospital admission; (3) incidence of acute coronary syndrome (defined as new findings on electrocardiogram and elevated serum troponin level consistent with myocardial ischemia) at any time during the hospital admission; and (4) hospital length-of-stay.

Sample Size

Our sample size estimate was based on the expected incidence of postoperative pulmonary complications as suggested by previous literature.[17–20] Assuming a baseline incidence of the primary outcome of around 4% in the control group, and considering a 50% increase in complications (to 6%) to be clinically important, we estimated that a total of 853 patients would be required to demonstrate this difference with a type 1 error less than 0.05 and power of 0.8.[21] The prevalence of obstructive sleep apnea in patients undergoing joint arthroplasty has been estimated to be between 5.6 and 9%.[8,11,12,20] Assuming a 7.5% incidence of diagnosed (by previous polysomnography) or suspected (STOP-Bang score greater than 3) sleep apnea in our patient population, we estimated that we would need to screen approximately 12,000 patient records. Since approximately 1,000 total joint arthroplasties are performed at the Toronto Western Hospital annually, we obtained approval for this retrospective review over a 12-yr period.

Statistical Analysis

Statistical analysis was performed using SPSS V20 (IBM, USA).[22] All *P*-values are two-tailed, with statistical significance defined at $P < 0.05$. Descriptive characteristics are reported as frequency (%), mean ± SD, or median and inter quartile range if nonnormally distributed. Comparisons between intrathecal morphine and control groups were conducted using two-sample independent *t* test for data with normal distribution, Mann–Whitney U test for data with nonnormal distribution, or chi-square test for categorical data. Standardized differences or unadjusted odds ratios (95% CI) were provided to quantify differences. Primary and secondary outcomes were represented as frequency (%) and compared using the chi-square test between exposure and control subgroups.

Multivariable Firth logistic regression was performed to determine the independent association of intrathecal morphine use with the presence of postoperative pulmonary complication, as a binary dependent variable. Given the expected rare incidence of the outcome, we estimated odds ratios using Firth penalized likelihood approach to reduce small-sample bias, rather than conventional maximal likelihood logistic regression.[23] To adjust for confounding, analysis was performed using clinically relevant, *a priori* selected variables, including: age, sex, higher body mass index, undergoing hip (*vs.* knee) arthroplasty, diagnosed (*vs.* suspected) obstructive sleep apnea, and use of intrathecal morphine. These clinically relevant variables were chosen based on biologic plausibility and are the most consistently reported confounders in cohort and meta-analytic studies on postoperative outcomes in patients with obstructive sleep apnea.[7,8,13] For instance, the profile of an older obese male with diagnosed severe obstructive sleep apnea may conceivably influence the relationship between intrathecal morphine use and postoperative pulmonary complications. Variance inflation factor was used to detect multicollinearity among all predictors.

Two sensitivity analyses were planned to confirm the results of the primary regression. To account for the rare incidence of the primary outcome, Poisson regression with a robust error variance was performed using the number of postoperative pulmonary complication events (up to six) as count data.[24] As a second sensitivity analysis to account for potential baseline differences between exposed and control groups, univariable logistic regressions were performed to determine the association between potential confounding variables and presence of postoperative pulmonary complications. Estimates were obtained using Firth penalized likelihood method. Significant predictors in univariable regression (defined as $P < 0.2$), in addition to intrathecal morphine use, were forced into a multivariable Firth logistic regression to determine the independent association between intrathecal morphine and postoperative pulmonary complications (appendix).

Missing data were assumed to be missing at random, except for postoperative opioid consumption (these data

were available on a subgroup of patients only during the last year of the study cohort). Available-case analysis was used to report patient characteristics while complete-case analysis was used for regression. Patients lacking documentation of obstructive sleep apnea status from chart review were excluded from the study, and patients with missing data on postoperative pulmonary complications were excluded from analysis of the primary outcome and multivariable regressions. Outliers were not excluded from analysis as the primary outcome is a binary variable. Indeed, patients who experienced respiratory depression requiring naloxone treatment—expected to be a rare event—were further reviewed as they would likely provide valuable insight into the effects of intrathecal morphine.

Results

A total of 8,177 patients were identified as having undergone total joint arthroplasty during the study period and underwent electronic chart review. Of this group, 5,820 patients were excluded from the study as they had no obstructive sleep apnea or were missing documentation of obstructive sleep apnea status. After screening for inclusion and exclusion criteria, 1,326 patients were identified as having either diagnosed or suspected obstructive sleep apnea and were included in the study cohort for analysis. Of these, 1,042 patients in this cohort received intrathecal morphine (exposure) and 284 patients had spinal anesthetic without intrathecal morphine (control group; fig. 1). There were no missing data related to the use or absence of intrathecal morphine.

Patient and Clinical Characteristics

Patient characteristics are summarized in table 1. Compared to the control group, the exposed group had a lower proportion of females (391 of 1,042 [37.5%] *vs.* 130 of 284 [45.8%]; $P = 0.012$) and a slightly lower body mass index (34.5 *vs.* 35.7 kg/m^2; $P = 0.018$), although these differences were clinically small. In addition, patients in the intrathecal morphine group had a higher rate of hip arthroplasty (469 of 1,042 [45.0%] *vs.* 93 of 284 [32.7%]; $P < 0.001$) and chronic opioid use (96 of 1,042 [9.2%] *vs.* 11 of 284 [3.9%]; $P = 0.003$) of more than 30 mg of oral morphine equivalents per day. The incidence of smoking, chronic obstructive pulmonary disease, congestive heart failure, diabetes, chronic kidney disease, past myocardial infarction or cardiovascular disease, and cancer were similar in both groups.

Obstructive Sleep Apnea Status and Treatment

Of the 1,326 patients in the cohort, 704 of 1,326 (53.1%) patients had documented medical history of diagnosed obstructive sleep apnea based on previous positive polysomnography and 622 of 1,326 (46.9%) had suspected obstructive sleep apnea (STOP-Bang score greater than 3) (table 1).

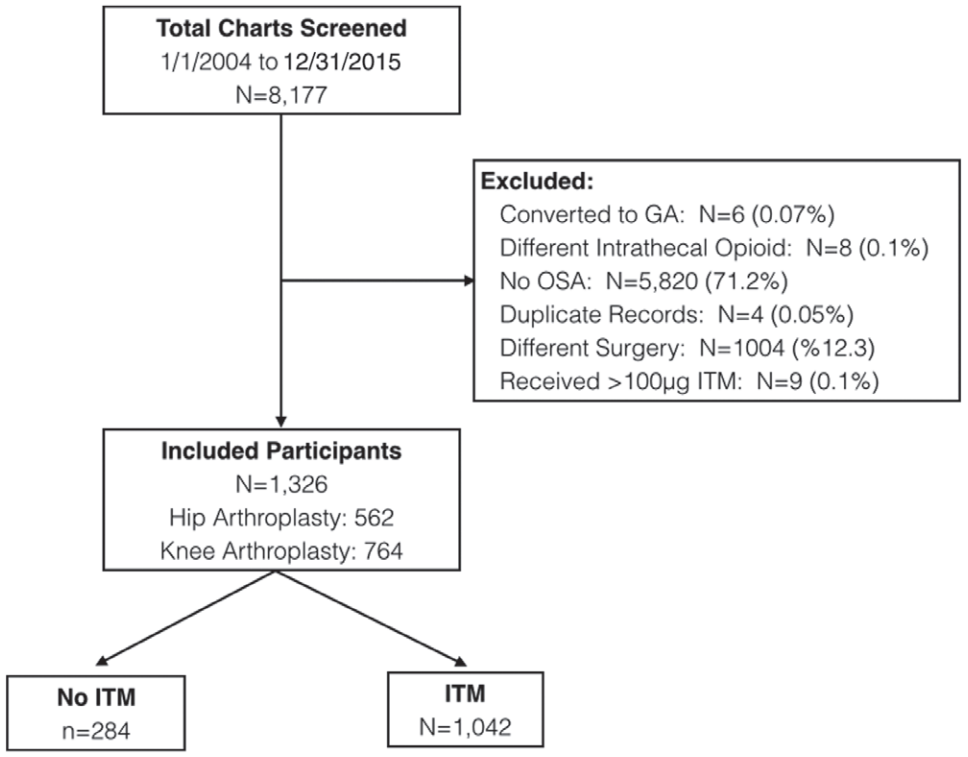

Fig. 1. Study patient flow diagram. GA, general anesthesia; ITM, intrathecal morphine; OSA, obstructive sleep apnea.

Table 1. Demographic and Clinical Data

	All Patients (n = 1,326)	Control (n = 284)	Intrathecal Morphine (n = 1,042)	Standardized Differences	*P* Value
Age (yr)	65 ± 9	65 ± 10	65 ± 9	0.012	0.858
Female sex	521 (39.3%)	130 (45.8%)	391 (37.5%)	–0.169	0.012*
Body mass index (kg/m^2)	34.7 ± 7.0	35.7 ± 8.0	34.5 ± 6.8	–0.175	0.018*
Comorbidities					
Current smoker	691 (52.1%)	137 (48.2%)	554 (53.2%)	0.100	0.141
COPD	99 (7.5%)	22 (7.7%)	77 (7.4%)	–0.011	0.839
Congestive heart failure	46 (3.5%)	12 (4.2%)	34 (3.3%)	–0.047	0.436
Diabetes	353 (26.6%)	78 (27.5%)	275 (26.4%)	–0.025	0.717
Chronic kidney disease	51 (3.8%)	12 (4.2%)	39 (3.7%)	–0.026	0.708
Past MI	111 (8.4%)	21 (7.4%)	90 (8.6%)	0.044	0.695
Cardiovascular disease	1,073 (81.0%)	219 (77.1%)	854 (82.0%)	0.122	0.065
Cancer	96 (7.2%)	19 (6.7%)	77 (7.4%)	0.027	0.687
Chronic opioid use (>30 mg MEQ/day)	107 (8.1%)	11 (3.9%)	96 (9.2%)	0.215	0.003*
ASA Physical Status	III [II, III]	III [III, III]	III [II,III]	–0.231	0.001*
Preoperative serology					
Hb (g/l)	141 ± 16	141 ± 18	142 ± 16	–0.024	0.717
Estimated glomerular filtration rate (ml · min^{-1} · 1.73 m^2)	108 ± 40	111 ± 43	107 ± 38	–0.115	0.118
Surgery performed					
Hip replacement	562 (42.4%)	93 (32.7%)	469 (45.0%)	0.254	< 0.001*
Knee replacement	764 (57.6%)	191 (67.3%)	573 (55.0%)	–0.254	
Obstructive sleep apnea					
Suspected	622 (46.9%)	72 (25.4%)	550 (52.8%)	0.585	< 0.001*
Diagnosed	704 (53.1%)	212 (74.6%)	492 (47.2%)	–0.585	
STOP-Bang score (maximum score 8)†	4 [4,5]	4 [4,5]	4 [4,5]	–0.037	0.721
Mild sleep apnea‡	125 (50.8%)	25 (32.1%)	100 (59.5%)	0.572	< 0.001*
Moderate sleep apnea‡	42 (17.1%)	16 (20.5%)	26 (15.5%)	–0.130	
Severe sleep apnea‡	79 (32.1%)	37 (47.4%)	42 (25.0%)	–0.479	
Sleep apnea therapy in diagnosed patients§					
Home continuous positive airway pressure therapy	453 (64.3%)§	152 (71.7%)‖	301 (61.2%)#	–0.224	0.008*
Home dental appliance	14 (2.0%)§	7 (2.5%)‖	9 (1.8%)#	–0.048	0.057
Postoperative continuous positive airway pressure therapy	375 (53.5%)§	133 (63.0%)‖	242 (49.4%)#	–0.277	0.001*

Data presented as mean ± SD, median [interquartile range], or numbers (%); *P* values between intrathecal morphine and control groups are calculated using Student *t* test, Mann–Whitney U test, or chi-square test depending on variable distribution. Percentages are calculated from available data. Standardized differences are reported for both mean and proportions to compare between exposure and control groups.

*$P < 0.05$ is statistically significant. †STOP-Bang data only available for 620 of 1326 patients. ‡Based on AHI score from documented polysomnography: mild (5 to 14), moderate (15 to 30), severe (greater than 30). Data only available for 246 of 1326 patients. §n = 704. ‖n = 212. #n = 492.

AHI, Apnea Hypopnea Index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; Hb, hemoglobin; MEQ, morphine equivalents; MI, myocardial infarct; STOP-Bang, Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender.

Patients in the control group had a higher rate of formally diagnosed obstructive sleep apnea compared to the intrathecal morphine group (212 of 284 [74.6%] *vs.* 492 of 1,042 [47.2%]; $P < 0.001$), as well as greater proportion of severe obstructive sleep apnea based on available Apnea-Hypopnea Index scores. Consequently, a greater proportion of patients in the control group received preoperative home continuous positive airway pressure treatment (152 of 212 [71.7%] *vs.* 301 of 492 [61.2%]; $P = 0.008$) and postoperative continuous positive airway pressure treatment while in hospital (133 of 212 [63.0%] *vs.* 242 of 492 [49.4%]; $P = 0.001$).

Anesthetic Technique

Anesthetic technique was guided by institutional protocol for anticipated complexity and length of the arthroplasty, where 98.3% of patients received spinal anesthesia while 1.7% received combined spinal–epidural anesthesia. When present, the epidural catheter was removed at the end of surgery. Multimodal analgesia was as per standard institutional practice and included oral acetaminophen 650 to 1,000 mg every 6 h, oral celecoxib 100 to 200 mg twice daily, and low-dose short-acting oral opioids (oral hydromorphone 1 to 2 mg or oxycodone 5 to 10 mg every 2 h) as needed. IV opioids (morphine or hydromorphone) delivered by a patient-controlled pump were used if the oral regimen was insufficient to control postoperative pain. Peripheral nerve blocks were performed for total knee arthroplasty as per standard institutional practice, which evolved over time. Patients received a femoral or combined femoral and sciatic block at the beginning of the study period and adductor canal block combined with local infiltration of the knee intraoperatively toward the end of the study period. The proportion of patients who received any peripheral nerve block was similar between groups (table 2). Patients in

Table 2. Peripheral Nerve Blocks for Patients Undergoing Total Knee Arthroplasty

	All Patients (n = 764)	Control (n = 191)	Intrathecal Morphine (n = 573)	Unadjusted Odds Ratios (95% CI)	*P* Value
Any peripheral nerve block	488 (63.9%)	132 (69.1%)	356 (62.1%)	0.73 (0.52–1.04)	0.082
Adductor canal block and local joint infiltration	334 (43.7%)	102 (53.4%)	232 (40.5%)	0.59 (0.43–0.83)	0.002*
Femoral block only	94 (12.3%)	22 (11.5%)	72 (12.6%)	1.10 (0.66–1.84)	0.755
Femoral and sciatic block	60 (7.9%)	8 (4.2%)	52 (9.1%)	2.28 (1.06–4.90)	0.030*

Data available for 764 patients who underwent total knee arthroplasty. Data presented as numbers (%) and *P* values are calculated using chi-square test. Percentages are calculated from available data. Unadjusted odds ratios (95% CI) calculated using intrathecal morphine use (*vs.* control) as independent variable.

*$P < 0.05$ is statistically significant.

the intrathecal morphine group had a slightly higher rate of combined femoral and sciatic block, and lower rate of adductor canal block and local infiltration analgesia.

Primary and Secondary Outcomes

Primary and secondary outcomes are summarized in table 3. Four patients had missing data on postoperative pulmonary complications and were excluded from analysis of the primary outcome. There were no significant differences in the incidence of postoperative pulmonary complications or secondary outcomes between the exposed and control groups. Postoperative pulmonary complications were experienced by 20 of 1,322 patients (1.5% of the whole cohort), including 6 of 283 (2.1%) in the control group and 14 of 1,039 (1.3%) in the intrathecal morphine group ($P = 0.345$). There were a total of 22 secondary outcome events, with no significant differences between groups.

Data on postoperative systemic opioid consumption was available from the Networked Online Processing of Acute Pain Information database for a subgroup of patients who had surgery between April 27, 2015 to December 15, 2015 (n = 157). The intrathecal morphine group had 9% less IV PCA requirement compared to the control group, although this was not a statistically significant difference (5 of 35 [14.3%] *vs.* 6 of 122 [4.9%]; $P = 0.146$). There was no difference in 24-h opioid consumption (21.9 ± 21.3 mg *vs.* 23.9 ± 19.3 mg of oral morphine equivalents for the control and exposed groups respectively; $P = 0.606$).

Factors Associated with Postoperative Pulmonary Complications

Multivariable logistic regression using Firth penalized likelihood method was performed using the presence of postoperative pulmonary complication as the dependent variable (table 4). This complete case analysis included 1,322 patients, with 4 patients excluded due to incomplete primary outcome data, assumed to be missing at random. Among the *a priori* chosen predictors, older age (adjusted odds ratio, 1.06 [95% CI, 1.01 to 1.12]; $P = 0.016$) and hip (*vs.* knee) (adjusted odds ratio, 3.28 [95% CI, 1.31 to 9.15];

Table 3. Prevalence of Postoperative Pulmonary Complications

	All Patients (n = 1,322)	Control (n = 283)	Intrathecal Morphine (n = 1,039)	Unadjusted Odds Ratios (95% CI)	*P* Value
Primary outcomes					
At least one postoperative pulmonary complication	20 (1.5%)	6 (2.1%)	14 (1.3%)	0.60 (0.25–1.65)	0.345
Respiratory depression requiring naloxone	6 (0.5%)	2 (0.7%)	4 (0.4%)	0.49 (0.11–2.82)	0.475
Pneumonia	0 (0%)	0 (0%)	0 (0%)	—	—
Critical care response team consultation	18 (1.4%)	4 (1.4%)	14 (1.3%)	0.88 (0.33–2.89)	0.932
Intubation and ventilation	0 (0%)	0 (0%)	0 (0%)	—	—
Unplanned intensive care unit admission	4 (0.3%)	2 (0.7%)	2 (0.2%)	0.27 (0.04–1.76)	0.163
Death from respiratory cause	0 (0%)	0 (0%)	0 (0%)	—	—
Secondary outcomes					
30-day mortality	2 (0.2%)	1 (0.4%)	1 (0.1%)	0.27 (0.02–3.35)	0.323
Postoperative pulmonary embolus	9 (0.7%)	4 (1.4%)	5 (0.5%)	0.57 (0.08–1.40)	0.090
Postoperative acute coronary syndrome	11 (0.8%)	1 (0.4%)	10 (1.0%)	1.91 (0.45–17.8)	0.319
Hospital length of stay (days)	3.0 [3.0,4.0]	3.0 [3.0, 4.0]	3.0 [3.0,4.0]	—	0.593

Data presented as numbers (%); *P* values calculated using chi-square test. Unadjusted odds ratios (95% CI) calculated using Firth penalized likelihood method, using intrathecal morphine use (*vs.* control) as independent variable. 1,322 patients included in analysis.

$P < 0.05$ is statistically significant.

Table 4. Results of Multivariable Logistic Regression with Presence of Postoperative Pulmonary Complications as Dependent Variable

Variable	Adjusted Odds Ratios	95% CI	*P* Value
Age (yr)	1.06	1.01–1.12	0.016*
Female sex (*vs.* male)	0.89	0.34–2.21	0.808
Body mass index (kg/m^2)	1.01	0.94–1.08	0.759
Hip (*vs.* knee surgery)	3.28	1.31–9.15	0.010*
Obstructive sleep apnea diagnosed (*vs.* suspected)	1.65	0.67–4.37	0.283
Intrathecal morphine use (*vs.* control)	0.60	0.24–1.67	0.308

Results of multivariable logistic regression using *a priori* selected predictors forced into the model. 1,322 patients included in analysis. Estimates generated using Firth penalized likelihood method.

*$P < 0.05$ is statistically significant.

$P = 0.010$) were independently associated with the presence of postoperative pulmonary complications. The use of intrathecal morphine was not significantly associated with the primary outcome after adjustment for confounding (adjusted odds ratio, 0.60 [95% CI, 0.24 to 1.67; $P = 0.308$). Variance inflation factors for all predictors in multivariable regression were close to 1.0, supporting a lack of collinearity in the model.

As a sensitivity analysis with the same predictors previously discussed, Poisson regression with robust error variance confirmed that intrathecal morphine use was not independently associated with postoperative pulmonary complications (adjusted rate ratio, 1.45 [95% CI, 0.49 to 4.28]; $P = 0.506$). In the second sensitivity analysis using Firth penalized likelihood method, variables associated with postoperative pulmonary complications in univariable regression were forced into a multivariable regression. In the multivariable model, only older age and hip (*vs.* knee) surgery were independently associated with the primary outcome (appendix). Intrathecal morphine was not significantly associated with postoperative pulmonary complications in either univariable or multivariable logistic regression (adjusted odds ratio, 0.59 [95% CI, 0.23 to 1.68]; $P = 0.310$). This supports the results of our primary analysis.

Of the six patients who experienced respiratory depression requiring naloxone therapy, it is unclear whether intrathecal morphine may have been the culprit (table 5). Five out of six patients were obese and three were previously diagnosed with obstructive sleep apnea by polysomnography. The events occurred at various times during the first 3 postoperative days and two of the six patients did not receive intrathecal morphine. The four patients who received intrathecal morphine and later developed respiratory depression presented other possible precipitating factors, such as worsening heart failure, morbid obesity, and use of systemic opioids.

Discussion

In our analysis of 1,326 patients with diagnosed or suspected obstructive sleep apnea undergoing total joint arthroplasty under neuraxial anesthesia, we found a very low incidence of postoperative pulmonary complications which was similar for the intrathecal morphine and control groups. Furthermore, we did not find an association between the use of low-dose intrathecal morphine (100 μg) and increased rates of postoperative pulmonary complications or other major life-threatening complications. This suggests that 100 μg of intrathecal morphine may be a safe intervention in this patient population. Although practice guidelines for perioperative management of obstructive sleep apnea exist, these are largely based on retrospective studies and the consensus of expert opinion.[10,25] This study will add to the literature by evaluating a large number of patients with obstructive sleep apnea undergoing major joint arthroplasty at a large academic center, using data spanning more than 12 yr.

Composite variables are often used to study pulmonary or respiratory complications in the perioperative literature. Although there is no single accepted definition of postoperative pulmonary complication, respiratory failure, mechanical ventilation requiring ICU admission, postoperative pneumonia, and mortality from respiratory causes are commonly included in such composite outcomes.[9,17–20] A meta-analysis of patients with obstructive sleep apnea undergoing various operations estimated a 1.96% incidence of acute respiratory failure, 0.92% reintubation, 5.09% ICU admission, and 10.71% oxygen desaturation; these rates were higher than in those with no obstructive sleep apnea patients.[7] Memtsoudis *et al.* showed that patients with obstructive sleep apnea undergoing joint arthroplasty had 1.86 higher odds of pulmonary complications.[20] More akin to our study population, Thompson *et al.* studied respiratory outcomes in patients with obstructive sleep apnea receiving intrathecal morphine for major joint arthroplasty, though the intrathecal doses were not reported. The rate of complications (desaturation, bradypnea, naloxone use, advanced level of care) was 2% in patients with formally diagnosed obstructive sleep apnea, 2% in those with STOP-Bang score 3 to 4, and 4% with patients with STOP-Bang score 5 to 8.[26] Similarly, a systematic review of 121 patients with obstructive sleep apnea receiving neuraxial opioids

Table 5. Clinical Data on Six Participants Who Had Postoperative Respiratory Depression Requiring Naloxone Treatment

Age/ Sex	BMI	Obstructive Sleep Apnea Status	Comorbidities	Surgery	Regional Anesthesia	Event Timing	Naloxone Used	Respiratory Depression Details	Other Complications	Relationship to Intrathecal Morphine
76/M	24	Diagnosed home bilevel positive airway pressure advised (poorly compliant)	Irritable bowel syndrome, glaucoma, benign prostatic hyperplasia	Unilateral knee, primary	Spinal with no intrathecal morphine, femoral and sciatic block	Postoperative day 0	1 dose	Unresponsive after given hydromorphone 1 mg IV postoperatively; treated with naloxone and overnight intensive care unit admission	Respiratory event requiring critical care response team consult, unplanned intensive care unit admission	No intrathecal morphine used. Patient reported increased sensitivity to opioids, and inadvertently received IV opioid on the ward.
55/F	44	Suspected STOP-Bang 4	Hypertension, acid reflux, diabetes, anemia, hypothyroidism, angina, schizoaffective disorder, chronic pain	Unilateral knee, primary	Spinal with 100 mcg intrathecal morphine, no nerve block	Postoperative day 2	2 doses	Decreased level of consciousness with low oxygen saturation, improved with naloxone administration	Respiratory event requiring critical care response team consult	Not certain. Patient required high doses of opioids with IV PCA, including long-acting opioids.
79/M	35.5	Diagnosed non compliant to home continuous positive airway pressure therapy	Congestive heart failure, previous pulmonary embolus, gastric ulcer, renal calculi, past poliomyelitis, diabetes, thalassemia, acid reflux	Unilateral knee, primary	Spinal with 100 mcg intrathecal morphine, adductor canal block	Postoperative day 2	1 dose	Decreased level of consciousness with low oxygen saturation. Required overnight intensive care unit stay and bilevel positive airway pressure; multifactorial cause from opioid use, heart failure exacerbation, and untreated sleep apnea.	Respiratory event requiring critical care response team consult, unplanned intensive care unit admission	Not certain. Patient was placed on systemic opioids and had other contributing illness.
64/M	29.6	Diagnosed no continuous positive airway pressure therapy	Hypertension, smoker, inflammatory bowel disease	Unilateral knee, primary	Spinal with 100 mcg intrathecal morphine, femoral nerve block catheter and sciatic block	Postoperative day 2	3 doses	Developed respiratory depression and became obtunded; placed on overnight continuous oxygen monitoring	Respiratory event requiring critical care response team consult	Not certain. Patient placed on long-acting systemic opioids and gabapentin. Femoral catheter had been removed.
74/F	36.6	Suspected STOP-Bang 4	Hypertension, acid reflux, anemia, hypothyroidism	Unilateral knee, primary	Spinal with 100 mcg intrathecal morphine, femoral nerve block catheter	Postoperative day 3	1 dose	Respiratory events confounded by posttransfusion pulmonary edema and wheezing which preceded the event and naloxone use.	Respiratory event requiring critical care response team consult	Not certain. Long-acting systemic opioids used, and other contributory respiratory illness.
71/M	36.2	Suspected STOP-Bang 4	Hypertension, peripheral vascular disease, smoker	Unilateral knee, primary	Spinal with no intrathecal morphine, adductor canal block	Postoperative day 1	2 doses	Respiratory depression requiring two doses of naloxone 0.2 mg IV	—	No intrathecal morphine used.

Data presented for each individual patient who experienced respiratory depression requiring naloxone therapy. Events occurred between postoperative days 0 to 3. 4/6 received intrathecal morphine. There were no data available on postoperative opioid or IV PCA consumption from the Networked Online Processing of Acute Pain Information database for these patients. The use of intrathecal morphine was not clearly implicated in any of the cases as there were other contributory factors. BMI, body mass index; F, female; IV, intravenous; M, male; PCA, patient-controlled analgesia; STOP-Bang, Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender.

reported a 4.1% rate of serious cardiorespiratory complications (death, cardiorespiratory arrest, severe respiratory depression).[13] The incidence of pulmonary complications in our cohort was slightly lower than previous estimates (1.5%) and no different for those receiving intrathecal morphine *versus* the control group.

Our study has several limitations. First, the use of a retrospective study can only suggest association rather than causality between intrathecal morphine use and postoperative complications. Furthermore, the lack of finding an association between intrathecal morphine and complications does not necessarily mean there is no association, especially given the uncertainty associated with a wide CI of the multivariable regression estimate (95% CI, 0.24 to 1.67). Second, retrospective studies are at risk of patient selection bias, which was demonstrated by higher rates of formally diagnosed and severe obstructive sleep apnea in the control group. Furthermore, the greater severity of obstructive sleep apnea in the control group may have influenced the outcome, thereby masking any true effects of intrathecal morphine. To reduce the effect of selection bias and account for these baseline differences, we used multivariable regression to determine the independent association between the exposure and outcome. In addition, the overall incidence of complications was very low in our cohort, which supports the safety of intrathecal morphine in this population. Nonetheless, conclusions should be drawn cautiously given this risk of bias. Third, a retrospective study design is also at risk of measurement bias, as obstructive sleep apnea remains a largely underdiagnosed condition in the perioperative setting.[12] Moreover, baseline oxygenation, presence of hypoventilation syndrome, or compliance with continuous positive airway pressure treatment were also not known. We addressed this issue by including patients with documented obstructive sleep apnea diagnosis, as well as those at a high risk or suspected obstructive sleep apnea (as per the STOP-Bang questionnaire). Fourth, institutional practices and peripheral nerve block preferences evolved over the duration of the study period. For example, patients received femoral or combined femoral and sciatic block at the beginning and adductor canal block and intraoperative local infiltration of the knee toward the end of the study period. However, it is known that these regional anesthesia options provide similar magnitude of analgesia within a multimodal regimen, so these small differences are unlikely to be of any clinical importance. The dose of intrathecal morphine remained stable throughout the study period. Lastly, as this is a single center study using low-dose intrathecal morphine (100 μg), the external validity of our findings is limited to similar patient populations, perioperative care pathways, and drug dosing used in this study.

Conclusion

Our study found that the use of low-dose intrathecal morphine, in conjunction with multimodal analgesia, was not reliably associated with higher incidence of postoperative pulmonary complications in patients with suspected or diagnosed obstructive sleep apnea undergoing joint arthroplasty under neuraxial anesthesia. Future studies should aim to use a well-powered prospective design to overcome and control for the limitation of selection bias. Important topics to explore include the impact of intrathecal morphine dose on treated and untreated patients with obstructive sleep apnea, and the use of intrathecal morphine in other high-risk populations such as those on chronic opioid therapy with central sleep apnea.[27]

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Competing Interests

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Appendix: Results of Univariable Firth Logistic Regression and Multivariable Firth Logistic Regression of Variables Associated with Postoperative Pulmonary Complications

	Univariable Firth Logistic Regression			Multivariable Firth Logistic Regression (N = 1,310 included)		
Variable	Unadjusted Odds Ratio	95% CI	*P* Value	Adjusted Odds Ratio	95% CI	*P* Value
Age (yr)	1.06	1.01–1.12	0.016*	1.06	1.00–1.12	0.026†
Female (*vs.* male)	0.86	0.33–2.06	0.735			
Body mass index (per kg/m^2)	0.97	0.91–1.03	0.367			
ASA Status (out of 6)	1.95	0.80–4.99	0.145*	1.48	0.57–4.14	0.432
STOP-Bang score	0.66	0.09–2.08	0.548			
Diagnosed sleep apnea (*vs.* suspected)	1.62	0.68–4.20	0.283			
Home continuous positive airway pressure therapy	1.94	0.81–4.65	0.136*	1.60	0.62–4.03	0.322
Smoker	0.76	0.31–1.80	0.525			
COPD	2.50	0.65–7.19	0.163*	1.82	0.45–5.59	0.364
Congestive heart failure	3.82	0.75–12.57	0.097*	2.08	0.39–7.46	0.348
Chronic kidney disease	1.91	0.21–7.72	0.490			
Cardiovascular disease	0.66	0.26–1.95	0.430			
Chronic opioid use (>30 mg MEQ/day)	2.29	0.60–6.58	0.202			
Hip surgery (*vs.* knee surgery)	3.08	1.26–8.40	0.013*	3.63	1.41–10.8	0.007†
Intrathecal morphine use (*vs.* control)	0.60	0.25–1.65	0.306	0.59	0.23–1.68	0.310

Results of sensitivity analysis using Firth logistic regressions and presence of postoperative pulmonary complication as the outcome. Significant variables from univariable screening were moved to multivariable regression, estimates obtained using Firth penalized likelihood method. Intrathecal morphine was forced into the multivariable logistic regression. Intrathecal morphine use was not independently associated with postoperative pulmonary complication.

*$P < 0.20$ in univariable regression used for inclusion in multivariable regression. †$P < 0.05$ is statistically significant.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; MEQ, morphine equivalents; STOP-Bang, Snoring, Tired, Observed, Pressure, Body Mass Index, Age, Neck size, Gender.