Obstructive Sleep Apnea and Incidence of Postoperative Delirium after Elective Knee Replacement in the Nondemented Elderly

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ABSTRACT

Background: Postoperative delirium, a common complication in the elderly, can occur following any type of surgery and is associated with increased morbidity and mortality; it may also be associated with subsequent cognitive problems. Effective therapy for postoperative delirium remains elusive because the causative factors of delirium are likely multiple and varied.

Methods: Patients 65 yr or older undergoing elective knee arthroplasty were prospectively evaluated for postoperative Diagnostic and Statistical Manual of Mental Disorders-IV delirium. Exclusion criteria included dementia, mini-mental state exam score less than 24, delirium, clinically significant central nervous system/neurologic disorder, current alcoholism, or any serious psychiatric disorder. Delirium was assessed on postoperative days 2 and 3 using standardized scales. Patients' preexisting medical conditions were obtained from medical charts. The occurrence of obstructive sleep apnea was confirmed by contacting patients to check their polysomnography records. Data were analyzed using Pearson chi-square or Wilcoxon rank sum tests and multiple logistic regressions adjusted for effects of covariates.

Results: Of 106 enrolled patients, 27 (25%) developed postoperative delirium. Of the 15 patients with obstructive sleep apnea, eight (53%) experienced postoperative delirium, compared with 19 (20%) of the patients without obstructive sleep apnea ($P = 0.0123$, odds ratio: 4.3). Obstructive sleep apnea was the only statistically significant predictor of postoperative delirium in multivariate analyses.

Conclusions: This is the first prospective study employing validated measures of delirium to identify an association between preexisting obstructive sleep apnea and postoperative delirium.

What We Already Know about This Topic

- The causes of postoperative delirium are not yet known

What This Article Tells Us That Is New

- In a small group of patients undergoing total knee replacement, postoperative delirium was associated with sleep apnea
- Because the study is limited, further evaluation is needed; nevertheless, the association of postoperative delirium and sleep apnea if verified will be of significant clinical importance

P OSTOPERATIVE delirium, a common complication in the elderly, is associated with increased morbidity and mortality[1,2] and has recently been associated with long-term cognitive and functional decline.[3,4] Effective therapies

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for postoperative delirium remain elusive because we do not understand the biology of delirium.[5] Recent data indicate that the incidence of postoperative delirium in elderly patients undergoing major surgeries is quite variable, ranging from 5–15% in patients undergoing general anesthesia[6] to as high as 62% in hip fracture patients[7] and 73% in elderly cardiac surgery patients.[8] In surgeries requiring postoperative intensive care, the incidence of postoperative delirium was found to be 44%.[9] Finally, in the case of elective orthopedic surgery, a recent study reports an incidence of 22% in hip replacement patients and 32% in knee replacement patients.[10]

Given the high incidence and clinically significant sequelae of postoperative delirium in the elderly, it is crucial to better understand the risk factors for and pathophysiology of delirium. Studies have identified several clinical risk factors for postoperative delirium, including preexisting subtle cognitive impairment, dementia, low mini-mental state exam (MMSE) score, active depressive symptoms, preoperative psychotropic drug use, alcohol abuse, functional impairment, and intraoperative procedural issues such as oxygen desaturation.[11–15]

Total knee arthroplasty is a routine procedure in the elderly population and has been shown to restore functional status and improve patient pain.[16,17] Although total knee arthroplasty does increase the risk of morbidity and mortality, there is strong evidence to support its use in elderly patients,[18–20] and recent changes in treatment strategies have improved the safety of the procedure.[16] In patients undergoing the procedure in the United States, osteoarthritis is present 95% of the time.[21] Patients tend to be female (62%) and obese (56%), with an average body mass index (BMI) of 31; their average age is 69.[21] Knee arthroplasty was chosen as a procedure for our study based on the volume of patients seen at our institution, the average age of patients undergoing surgery, and the elective nature of the procedure, allowing for the examination of a delirium in a healthy elderly population.

The present study was undertaken to explore the molecular markers of postoperative delirium by prospectively recruiting a cohort of elderly patients undergoing elective knee replacement surgery. Although our molecular studies are ongoing, we examined whether any of the preexisting medical conditions found in our patients contribute to postoperative delirium. We report here that in elderly patients undergoing elective knee replacement surgery, there is an association between preexisting obstructive sleep apnea and postoperative delirium.

Materials and Methods

Subjects

After obtaining approval from our Institutional Review Board (Duke University, Durham, North Carolina), we prospectively recruited 106 elderly persons aged 65 or older scheduled to undergo elective single knee replacement surgery at Duke University Medical Center or the Durham Veterans Association Medical Center. Informed consent was obtained from all patients. Because we sought to examine the development of new-onset postoperative delirium, patients with preexisting delirium were excluded. Other exclusion criteria included alcohol abuse or dependence within last 3 months, active psychosis within the last 3 months, current depression, dementia, MMSE less than 24, and/or clinically significant neurologic disorder.

Approximately 400 total knee replacements per year were done in our hospital system during the study period. Of these, approximately 80% of the patients were older than 65. This study included patients undergoing knee replacement surgery by any of three surgeons at our institution. The initial goal was to recruit enough patients so that we would have 25–50 delirious patients, an empirical number needed for gene expression analysis; no *a priori* power calculation was conducted for the specific association with sleep apnea. Patient recruitment was based on the availability of our staff nurse. Of the 149 patients originally consented, 106 completed the study. Sixteen patients were excluded after consent was obtained, six patients canceled their surgery, seven patients refused blood work or otherwise did not complete the study, four were excluded because of alcohol abuse noted upon further evaluation, two patients died before their surgery date, and eight patients were excluded for other reasons.

Subjects were recruited and evaluated by two study nurses who have training in psychiatry and received training in the study assessment methods. In cases where there were questions in terms of a patient's diagnosis or eligibility, the study psychiatrist adjudicated using all available information, including chart review. The study psychiatrist reviewed each chart, including all testing by the study nurses.

Dementia was evaluated in all patients by review of the medical record, administration of the MMSE,[22] and structured interview questions to assess for any limitations in independent activities of daily living. Subjects with a diagnosis of dementia or a MMSE score less than 24 were excluded. MMSE scores were adjusted for age and education level.[23] If the MMSE was 24 or more, yet limitations in independent activities of daily living were noted, further questions to assess for dementia using Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)[24] criteria were used; patients meeting criteria for dementia were excluded.

The CAGE questionnaire[25] was used to screen for alcohol abuse; subjects with a score of 2 or more, or with a history of active alcohol abuse or dependence, were excluded. The Geriatric Depression Scale[26] was used to evaluate patients for current depression, and subjects scoring 4 or more were excluded. Patients with a documented or reported diagnosis of a psychiatric disorder and/or receiving psychiatric medications were included, provided they did not screen positive on the scales above nor meet the criteria for a current mood episode nor psychosis at or within 3 months of preoperative evaluation.

Patients were evaluated before surgery and on postoperative days 2 and 3 unless discharged before those time points. There were three subjects who were discharged before the postopera-

tive day 3 assessment. Postoperative day 1 was not included in order to minimize the role of residual anesthesia effects. Observations were limited to postoperative days 2 and 3 because the vast majority of patients were discharged on postoperative day 3, and prior studies have shown that most postoperative delirium occurs on postoperative days 2 and 3.[27]

Patients were screened for baseline delirium using the Confusion Assessment Method (CAM)[28] and the Delirium Rating Scale-Revised-98 (DRS-R-98). The CAM is a four-item screening tool based on criteria for delirium from the Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., revised. The CAM requires the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or an altered level of consciousness to suggest a diagnosis of delirium. The 16-item DRS-R-98 is a delirium symptom rating scale with anchored severity ratings for a broad range of symptoms, which has been validated to discriminate between dementia and other neuropsychiatric conditions.[29] The DRS-R-98 provides a numerical value for delirium severity, with a 39-point maximum for the severity score and a 46-point maximum for the total score. Patients who screened positive for delirium by the CAM before surgery were excluded from the study. Subjects who had a baseline DRS-R-98 score more than 0 were reviewed by the study psychiatrist; they were excluded from the study if they met DSM-IV criteria for delirium.

Assessments for delirium on postoperative days 2 and 3 were performed in the mornings, though not at a standard time. The period of inquiry for the DRS-R-98 includes the 24 h before the assessment, although the CAM is cross-sectional. Because the CAM is only a screening tool, it may only suggest a diagnosis of delirium, and cases may be missed at the time of assessment, particularly because of the fluctuating nature of delirium. Thus, delirium was diagnosed using the DSM-IV criteria and all available data, including that from the CAM, DRS-R-98, and chart documentation (nursing, physical therapy, and physician notes), by the study psychiatrist. Specifically, charts were examined for evidence of: 1) disturbance of consciousness, with reduced ability to focus, sustain, or shift attention; 2) change in cognition or the development of a new perceptual disturbance not accounted for by a preexisting, established, or evolving dementia; 3) development of the disturbance over a short period of time (usually hours to days) and a tendency to fluctuate during the course of the day; and 4) a likely medical etiology.

There were four subjects who had a negative screening for delirium by the CAM but DRS-R-98 scores more than 0 on postoperative day 2. These four subjects' charts were reviewed by the study psychiatrist and a diagnosis of delirium was made using DSM-IV criteria in each case. The mean DRS-R-98 severity score for these subjects was 8.25 and the total severity score was 13.5. There was one subject on postoperative day 3 who screened negative for delirium by CAM at the time of the assessment, but had a DRS-R-98 severity score of 17 and total score of 24 and met DSM-IV criteria for delirium in the past 24 h.

Baseline medical diagnoses and pulse oximetry were obtained from the admission note and preoperative anesthesia evaluation. Any conditions occurring in at least 10% of cases were tested for association with postoperative delirium. These were benign prostatic hyperplasia, coronary artery disease, diabetes, gastroesophageal reflux disorder, hypertension, hyperlipidemia, incontinence, and obstructive sleep apnea.

The presence of a major neurologic disorder was determined through interview and review of the patient's medical records. Patients with neurologic disorders with clinically significant sequelae that might interfere with assessment of delirium, such as prior stroke or head trauma with deficits such as aphasia or agnosia, were excluded. Patients with a history of transient ischemic attack without clinically significant sequelae were included.

Procedures

All patients underwent elective total knee arthroplasty or revision of a total knee arthroplasty. The choice of anesthesia was at the discretion of the anesthesiologist and included both general and regional anesthesia. Preoperative oxygen saturation and hemoglobin data were obtained from medical charts. BMI was calculated using weight and height data from preoperative admission evaluation. Postoperative oxygen saturation data were not included because of the lack of continuous or standardized data collection.

Following their operations, patients were assessed for postoperative delirium using the CAM and the DRS-R-98. The diagnosis of delirium was made by the study psychiatrist using the DSM-IV criteria, information gathered in the DRS-R-98, CAM, and nursing notes. Patients were tested for delirium on postoperative day 2 and postoperative day 3 by study staff.

From medical records, 16 patients were initially identified as having obstructive sleep apnea. In 15 of the 16 cases, verification of obstructive sleep apnea was obtained. For 12 out of 15 patients, we were able to obtain polysomnography reports. Polysomnography reports were reviewed by one of our research team (ADK), a board-certified physician in sleep medicine, to confirm the presence of obstructive sleep apnea. This review included the diagnostic criterion of the presence of five or more apneic events per hour as determined by polysomnography.[30,31] For two of the three patients without polysomnography reports, the use of continuous positive airway pressure was employed as a surrogate confirmation of obstructive sleep apnea diagnosis. The third patient who did not have polysomnography records had undergone uvulopalatoplasty surgery 10 yr earlier but had returned to his presurgical obstructive sleep apnea symptoms at the time of his participation in our study, and the medical team ordered continuous positive airway pressure during his hospital stay. Given the possibility of uvulopalatoplasty failure[32] and the

Table 1. Clinical Characteristics of Knee Arthroplasty Patients

Characteristic	Nondelirious (n = 79)	Delirious (n = 27)	P Value*
Age ± SD	73.7 ± 5.1	72.9 ± 4.9	0.4832
Female sex, n (%)	41 (51.9)	18 (66.7)	0.1824
Caucasian, n (%)	73 (92.4)	23 (85.2)	0.2679
ASA score = 3 (*vs.* 2), n (%)	48 (60.8)	15 (55.6)	0.6345
Mini-mental state examination ± SD	29.2 ± 1.4	29.1 ± 1.1	0.2601
Education (years) ± SD	14.9 ± 3.2	14.5 ± 3	0.6194
Received general anesthesia, n (%)	32 (40.5)	7 (25.9)	0.1750
Procedure on left knee, n (%)	43 (54.4)	13 (48.1)	0.5724
Total knee arthroplasty revision procedure, n (%)	7 (8.9)	1 (3.7)	0.3812
Body mass index ± SD	31.1 ± 7.3	31.9 ± 7.2	0.5281
Preop hemoglobin (g/dl) ± SD	13.4 ± 0.2	12.8 ± 0.3	0.0476
Preop oxygen saturation ± SD	96.9 ± 1.6	97 ± 1.6	0.4173
Number of preop comorbidities ± SD	3 ± 1.7	3.1 ± 1.4	0.5424
Coronary artery disease, n (%)	12 (15.2)	6 (22.2)	0.4008
Diabetes, n (%)	9 (11.4)	5 (18.5)	0.3451
Hypertension, n (%)	58 (73.4)	23 (85.2)	0.2137
Hyperlipidemia, n (%)	35 (44.3)	12 (44.4)	0.9899
Sleep apnea, n (%)	7 (8.9)	8 (29.6)	0.0123
Benign prostatic hyperplasia, n (%)	15 (19)	2 (7.4)	0.1570
Incontinence, n (%)	9 (11.4)	6 (22.2)	0.1634
Gastroesophageal reflux disorder, n (%)	26 (32.9)	11 (40.7)	0.4612
Higher DRS-R-98 total, postoperative days 2, 3 ± SD	3.7 ± 3.6	16.1 ± 5.6	<0.0001
Higher DRS-R-98 severity score, postoperative days 2, 3 ± SD	2.1 ± 2	10.7 ± 5	<0.0001

* P value from Pearson chi-square or Wilcoxon rank-sum test of association between comorbidity and any postoperative delirium.
ASA = American Society of Anesthesiologists; DRS-R-98 = Delirium Rating Scale-Revised-98.

return of baseline symptoms, this patient was coded as an obstructive sleep apnea patient.

The home usage of continuous positive airway pressure by obstructive sleep apnea patients was ascertained through preoperative anesthesia interviews. The use of continuous positive airway pressure administration in the hospital after the surgical procedure was determined using nursing records, physician orders, and progress notes.

Statistical Analysis

Patients who did not develop delirium were compared with those who became delirious on postoperative day 2 and/or 3. Categorical variables were analyzed using two-tailed Pearson chi-square tests with exact tests for small cell counts. Continuous demographic variables were compared with Wilcoxon rank-sum tests (two-sided independent sample tests). The effect of obstructive sleep apnea on postoperative delirium and their potential interactions were further assessed with separate logistic regression models adjusting for covariates. Covariates tested included age, sex, race (Caucasian *vs.* other), BMI, preoperative oxygen saturation, preoperative hemoglobin concentration, anesthesia type (general *vs.* other), MMSE, educational level, and baseline medical diagnoses. Because of the low incidence of delirium, only one covariate at a time could be tested reliably. Follow-up testing was performed to determine the effect of home and in-hospital continuous positive airway pressure use on the development of postoperative delirium. Statistical significance for all

tests was determined as $P < 0.05$ without adjustment. Descriptive statistics are presented as mean ± SD (SD) for numeric measures and as count (percent) for categorical variables. Statistical analysis was completed using SAS version 9.2, SAS Institute Inc., Cary, NC.

Results

Incidence and Characteristics of Postoperative Delirium

Twenty-seven of the 106 patients developed postoperative delirium, for an incidence of 25.5% (95% CI, 17.5–34.9%). Twenty-four (89% of those with delirium) became delirious on postoperative day 2, and nine of these were delirious on both postoperative day 2 and postoperative day 3 (8.5% of all patients, 95% CI, 4.0–15.5%). Mean postoperative DRS-R-98 total was 16 ± 6 and severity was 11 ± 5 in the delirium group, as compared with DRS-R-98 total 3.7 ± 3.6 and severity 2.1 ± 2.0 in the nondelirium group. There was no statistically significant sex difference for delirium incidence (30% of females *vs.* 19% of males, $P = 0.182$). There were no statistically significant differences between the delirium and nondelirium groups for age, race, education, baseline MMSE, BMI, preoperative oxygen saturation, or American Society of Anesthesiologists score (table 1). No difference was found between patients who received general *versus* regional anesthesia ($P = 0.1750$). A small amount of data were unavailable for some of the secondary analysis variables (17 data points were unavailable out of the 4,028 collected, 0.4%).

Table 2. Clinical Characteristics of Knee Arthroplasty Patients with and without Sleep Apnea

Characteristic	No Sleep Apnea (n = 91)	Sleep Apnea (n = 15)	P Value*
Age ± SD	74 ± 5.1	70.3 ± 3.3	0.0111
Female sex, n (%)	52 (57.1)	7 (46.7)	0.5768
Caucasian, n (%)	83 (91.2)	13 (88.7)	0.6309
ASA score = 3 (vs. 2), n (%)	52 (57.1)	11 (73.3)	0.2715
Mini-mental state examination ± SD	29.1 ± 1.4	29.4 ± 0.8	0.5244
Education (years) ± SD	14.8 ± 3.2	14.9 ± 2.5	0.7717
Received general anesthesia, n (%)	33 (36.2)	6 (40)	0.9999
Procedure on left knee, n (%)	46 (50.6)	10 (66.7)	0.2780
Total knee arthroplasty revision procedure, n (%)	6 (6.6)	2 (13.3)	0.3156
Body mass index (kg/m^2) ± SD	30.5 ± 6.8	36.1 ± 7.9	0.0047
Preop hemoglobin (g/dl) ± SD	13.2 ± 1.5	13.6 ± 1.8	0.3717
Preop oxygen saturation (%) ± SD	96.9 ± 1.7	96.9 ± 1	0.7648
Number of preop comorbidities ± SD	2.9 ± 1.6	3.9 ± 2.5	0.0074
Coronary artery disease, n (%)	15 (16.5)	3 (20)	0.9999
Diabetes, n (%)	11 (12.1)	3 (20)	0.4146
Hypertension, n (%)	67 (73.6)	14 (93.3)	0.1137
Hyperlipidemia, n (%)	38 (41.8)	9 (60)	0.2627
Benign prostatic hyperplasia, n (%)	16 (17.6)	1 (6.7)	0.4561
Incontinence, n (%)	14 (15.4)	1 (6.7)	0.4681
Gastroesophageal reflux disorder, n (%)	30 (33)	7 (46.7)	0.3824

* P value from Wilcoxon rank-sum test comparing sleep apnea groups.
ASA = American Society of Anesthesiologists.

Postoperative Delirium and Preexisting Comorbidities

The incidence of postoperative delirium was higher in patients with obstructive sleep apnea. Among patients with obstructive sleep apnea, 53.3% (8/15) experienced postoperative delirium, compared with 20.9% of patients without obstructive sleep apnea (19/91) (exact $P = 0.0123$, odds ratio = 4.3, exact 95% CI, 1.2–15.8) (see table 1). No statistically significant association was found between postoperative delirium and other baseline medical conditions, listed in table 1. In the adjusted multiple logistic tests, obstructive sleep apnea was consistently a statistically significant independent predictor of delirium (largest $P = 0.0237$), whereas none of the covariates or their interactions were significant. Also, although we found no difference between the delirium and nondelirium groups in presurgery oxygen saturation levels ($P = 0.4173$), those who developed delirium had significantly lower mean preoperative hemoglobin levels compared with the nondelirium group (12.8 g/dL $vs.$ 13.4 g/dL, $P = 0.0476$; table 1). However, this difference did not hold up as being significant in multivariate analyses; only obstructive sleep apnea remained a statistically significant predictor of delirium.

Postoperative Delirium and Obstructive Sleep Apnea

Because obstructive sleep apnea is associated with obesity and may lead to lower oxygen saturation, we examined whether BMI and preoperative oxygen saturation were associated with postoperative delirium. We found that the mean BMI of patients with obstructive sleep apnea was 5.6 kg/m^2 higher than that of patients without obstructive sleep apnea ($P = 0.0047$) (table 2), but we found no statistically significant association between postoperative delirium and BMI ($P =$

0.5281). No difference was seen between patients with and without obstructive sleep apnea in preoperative oxygen saturation ($P = 0.7648$) or hemoglobin levels ($P = 0.3717$). Table 2 compares the demographic profiles of 15 patients with obstructive sleep apnea and 91 patients without obstructive sleep apnea. In addition to developing postoperative delirium more frequently, the obstructive sleep apnea group was significantly younger (70.3 ± 3.3 $vs.$ 74 ± 5.1, $P = 0.0111$) and had more medical comorbidities (3.9 ± 2.5 $vs.$ 2.9 ± 1.6, $P = 0.0074$).

We also examined the use of continuous positive airway pressure by obstructive sleep apnea patients and the incidence of postoperative delirium. As table 3 shows, the home use of continuous positive airway pressure by obstructive sleep apnea patients who became delirious (4/8) and who did not (4/7) was similar. However, the use of continuous positive airway pressure in hospital was higher in obstructive sleep apnea patients who did not become delirious (4/7) than those who became delirious (2/8), but the difference in usage was not statistically significant in this small sample.

Table 3. Continuous Positive Airway Pressure Treatment Profile of Sleep Apnea Patients

CPAP Usage	Delirious (n = 8)	Nondelirious (n = 7)	P Value*
Home use, n (%)	4 (50)	4 (57)	0.9999
Hospital use, n (%)	2 (25)	4 (57)	0.3147

* P value from Pearson chi-square test.
CPAP = continuous positive airway pressure.

Discussion

Using sensitive measures of delirium, our prospective study found a 25.5% incidence of postoperative delirium in relatively healthy nondemented elderly patients undergoing elective knee replacement surgery. Interestingly, despite our stringent exclusion criteria, our study still found an incidence of postoperative delirium that is comparable to that reported in recent studies that did not specifically exclude patients with dementia, which is a major risk factor for delirium in older persons.[10,12,33] The most notable clinical finding of this study is the identification of a possible association between postoperative delirium and preexisting obstructive sleep apnea. Given the exploratory nature of our investigation, we present this finding as hypothesis-generating and recognize that a more definitive study of the association is needed.

Postoperative delirium was most frequent on postoperative day 2, consistent with previous reports.[27,34] The postoperative delirium seen in our patient population was of mild severity as measured by the DRS-R-98 scale. The majority (66%) of patients who were delirious on postoperative day 2 had recovered by postoperative day 3. We did not assess postoperative delirium on postoperative day 4 because most of the patients had been discharged by that time.

Inadequate oxygenation is a well known cause of delirium, and the impact of hemoglobin on the development of delirium has been reported in previous studies.[35–40] Patients in our study who developed delirium had significantly lower preoperative hemoglobin levels than those who did not develop delirium, but this difference did not remain statistically significant in multivariate models. In fact, only obstructive sleep apnea was significantly associated with postoperative delirium in our study, but obstructive sleep apnea has not been evaluated in other postoperative delirium reports. The interplay between hemoglobin, obstructive sleep apnea, and delirium is less clear. In a study of delirium predictors in 101 intensive care unit patients, investigators found an association between lower premorbid hemoglobin levels and development of delirium.[38] Anemia has also been shown to be an independent predictor of delirium in the acutely ill elderly population.[36] Furthermore, several studies have shown an association between lower postoperative hemoglobin levels and postoperative delirium in multiple surgery populations.[35,37,39,40] One study of 44 intensive care unit patients failed to find an association between lower premorbid hemoglobin levels and delirium, but this study may have been underpowered.[41]

In our sample, obstructive sleep apnea was associated with a more-than-fourfold increased risk for incident postoperative delirium and was the only baseline clinical factor associated with postoperative delirium in multivariate models. Although delirium occurred even in those who used their continuous positive airway pressure in the hospital, the use of continuous positive airway pressure appears to have benefit in obstructive sleep apnea patients, though our numbers are small and deserve replication in a larger sample. Although an association between obstructive sleep apnea and postoperative delirium has been identified in a case report[42] and a prior retrospective study,[43] this is, to our knowledge, the first prospective study employing validated measures of postoperative delirium that identifies obstructive sleep apnea as a potential risk factor for postoperative delirium. In fact, previous studies examining multiple risk factors for postoperative delirium have not evaluated the potential impact of preexisting obstructive sleep apnea.[9,11–13]

An association of obstructive sleep apnea and postoperative delirium represents a significant public health problem, given the prevalence and under-diagnosis of obstructive sleep apnea, particularly in the elderly, and its frequent misdiagnosis as insomnia. Obstructive sleep apnea is highly prevalent in the adult population and is estimated to affect 3.9% to 4% of men and 1.2–2% of women in the United States,[44–46] rising to more than 20% of the population older than 65.[47] Furthermore, it has been estimated that about 80% of men and 93% of women with moderate to severe obstructive sleep apnea are undiagnosed.[48,49] In the surgical population, a recent prospective study using portable sleep testing found that 82% of a group of previously undiagnosed surgical patients who screened as high risk for obstructive sleep apnea in fact had the diagnosis.[50] Thus, the results of this study suggest that a large number of patients undergoing surgery appear to be at risk for both postoperative delirium and the associated adverse consequences of undetected obstructive sleep apnea.

Our study provides preliminary evidence to support better presurgical screening for obstructive sleep apnea and institution of effective therapy for obstructive sleep apnea as means to reduce this risk. This is consistent with recent recommendations to screen for and treat obstructive sleep apnea to decrease adverse perioperative respiratory and cardiovascular outcomes associated with obstructive sleep apnea.[51] Further studies will be needed to identify whether home continuous positive airway pressure, the mainstay of obstructive sleep apnea therapy, or other available obstructive sleep apnea treatments mitigate the risks for postoperative delirium associated with obstructive sleep apnea. We found a preliminary trend suggesting a decreased chance of delirium among hospital continuous positive airway pressure-treated patients, consistent with case reports in which delirium was resolved using positive airway pressure for both obstructive sleep apnea and central sleep apnea.[52–54]

The mechanism by which obstructive sleep apnea increases the risk for postoperative delirium remains unknown, though there is reason to believe that the reduced oxygen metabolism that occurs with obstructive sleep apnea might be playing a role. Obstructive sleep apnea is a sleep disorder characterized by the recurrent collapse of the pharynx, causing upper airway obstruction and leading to recurrent arousals during sleep and episodes of oxygen desaturation,[31,55] and hypoxia is a known cause of delirium.[56] Consistent with

this etiology, a previous study reported that all of its enrolled patients who became delirious after thoracotomy for pulmonary malignancy had inadequate arterial oxygen saturation; delirium in these patients was resolved by administration of supplemental oxygen.[57] However, oxygen desaturation has not been consistently shown to predict the development of delirium in either the medical or the postoperative setting,[38,58] and in our study, no association was found between preoperative oxygen saturation levels and postoperative delirium or obstructive sleep apnea. Further, one study found that infrared spectroscopy measurement of prefrontal cortex oxygen desaturation during coronary artery bypass graft surgery predicted postoperative delirium even when peripheral oxygen desaturation was not noted,[15] suggesting that transient brain oxygenation deficits are important and may not be reflected with conventional monitoring methods.

It is also possible that hypoxemia may have occurred postoperatively. Given that mitochondrial defects consistent with oxidative stress are common with increased age,[59] chronic nocturnal oxygen desaturation associated with obstructive sleep apnea could conceivably exacerbate delirium risk by reducing adenosine triphosphate and synthesis of acetylcholine precursors (and hence cholinergic function).[60–62] Extensive research supports a hypocholinergic state underlying delirium.[6,63] Although all patients in this study underwent routine spot checking of their oxygen saturation, saturation was not recorded continuously, and we cannot exclude the possibility that obstructive sleep apnea patients may have experienced periods of desaturation.

Other possible mechanisms linking obstructive sleep apnea and delirium might include an increase in proinflammatory cytokines caused by obstructive sleep apnea or by subacute or chronic oxidative stress.[64,65] The increase in inflammatory cytokines is thought to be related to repeated cycles of apneic oxygen desaturation and restoration.[44,66–70] Obstructive sleep apnea has been shown to be an inflammatory process, associated with increased levels of systemic interleukin-2, interleukin-6, C-reactive protein, and tumor necrosis factor-α.[66,67,69,71–74] There is a growing body of literature supporting the role of inflammatory cytokines in delirium, yet there is no consensus at this time.[7,75–82]

Future prospective studies that employ polysomnography and measure the impact of continuous positive airway pressure therapy are needed to confirm the obstructive sleep apnea-postoperative delirium association and establish the mechanism by which obstructive sleep apnea might increase the risk of postoperative delirium. A limitation of our research is the possible role of undiagnosed obstructive sleep apnea. However, such false negatives would tend to dampen the observed effect of obstructive sleep apnea that we found, so it is possible that the effect of obstructive sleep apnea on postoperative delirium is actually more substantial than our data indicate. Whether obstructive sleep apnea is a risk factor for postoperative delirium in patients undergoing other types of surgeries, such as coronary artery bypass graft, deserves study.

In summary, using multivariate regression, we identified preexisting obstructive sleep apnea as the predominant predictive risk factor for incident postoperative delirium in elderly patients undergoing elective knee arthroplasty. A key limitation of our study is the small number of patients with obstructive sleep apnea and the small number of patients with delirium. As with any observational finding, the importance of obstructive sleep apnea in precipitating delirium needs rigorous examination in a hypothesis-directed study using a larger number of patients. Another limitation of our study is that a relationship between obstructive sleep apnea and postoperative delirium is confounded by the fact that our patients with obstructive sleep apnea had significantly more comorbidities that could increase the risk for postoperative delirium in obstructive sleep apnea patients. In our study, obstructive sleep apnea patients had a higher likelihood of having diabetes, hypertension, hyperlipidemia, coronary artery disease, and obesity, but we did not find a relationship between these individual conditions and postoperative delirium. Future studies may be able to further characterize the relationship between various comorbidities and postoperative delirium in the obstructive sleep apnea population. Another weakness of our study is that we did not collect information on certain predisposing factors, such as history of stroke, and precipitating factors, such as electrolyte disturbances, known to be associated with delirium, and omission of these risk factors might confound our findings.[83]

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