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Impact of Obstructive Sleep Apnea in Transsphenoidal Pituitary Surgery: An Analysis of Inpatient Data

Sei Y. Chung, MD; Michael J. Sylvester, MD; Varesh R. Patel, BA; Michael Zaki, MD; Soly Baredes, MD, FACS; James K. Liu, MD, FACS; Jean Anderson Eloy, MD, FACS

Objectives/Hypothesis: Although previous studies have reported increased perioperative complications among obstructive sleep apnea (OSA) patients undergoing any surgery requiring general anesthesia, there is a paucity of literature addressing the impact of OSA on postoperative transsphenoidal surgery (TSS) complications. The aim of this study was to analyze postoperative outcomes in transsphenoidal pituitary surgery patients with OSA. Secondarily, we examined patient characteristics and comorbidities.

Study Design: Retrospective analysis.

Methods: The 2002 to 2013 National Inpatient Sample was queried for patients undergoing TSS for pituitary neoplasm. Patients with an additional diagnosis of OSA were identified, and compared to a non-OSA cohort.

Results: There were 17,777 patients identified; 5.0% (N = 889) had an additional diagnosis of OSA. The OSA cohort had more comorbidities including diabetes mellitus, congestive heart failure, chronic pulmonary disease, coagulopathy, hypertension, hypothyroidism, liver disease, obesity, peripheral vascular disease, renal failure, acromegaly, and Cushing’s syndrome. Postoperatively, OSA was independently associated with increased risks of tracheostomy (P = .015) and hypoxemia (P < .001), and decreased risk of cardiac complications (P = .034). OSA patients did not have increased rates of cerebrospinal fluid rhinorrhea, diabetes insipidus, reintubation, aspiration pneumonia, infectious pneumonia, thromboembolic complications, or urinary/renal complications. In-hospital mortality rates did not vary between the two cohorts.

Conclusions: In patients who underwent transsphenoidal pituitary surgery, OSA was associated with higher rates of certain pulmonary and airway complications. OSA was not associated with increased non–pulmonary/airway complications or inpatient mortality, despite older average age and higher comorbidity rates.

Key Words: Pituitary, obstructive sleep apnea, transphenoidal, National Inpatient Sample.

Level of Evidence: 2C.

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INTRODUCTION

The treatment of pituitary neoplasms has seen many advancements, including the emergence of transsphenoidal surgery (TSS) for surgical intervention initially developed in the early 1900s. This technique became the standard of care in the initial treatment of pituitary neoplasms after proving to be less invasive and associated with lower morbidity and mortality than the historically used transcranial surgical route.1–3

More recently, endoscopic techniques have gained popularity compared to microscopic techniques, due to better intraoperative visualization and tumor resection.2,4 TSS complications have been previously characterized in various patient populations, such as those with acromegaly, Cushing’s disease, and pituitary malignancies.5–7 However, the impact of obstructive sleep apnea (OSA) on TSS outcomes is a relevant concern that has not been well examined. OSA is a sleeping disorder characterized by upper airway collapse, with an incidence of 3% to 7% in the general population.8,9 Furthermore, airway complications secondary to OSA could potentially worsen following TSS due to increased nasal and oral airway edema, as well as placement of nasal packing or catheters. OSA is thus an important diagnosis to study specifically among TSS patients.10 OSA is typically managed with continuous positive airway pressure (CPAP), which remains the most effective treatment to decrease postoperative respiratory complications.9,10 However, this intervention is relatively contraindicated following TSS due to the risk of developing pneumocephalus and meningitis.10 Although some have demonstrated increased total perioperative complications and pulmonary-specific complications among OSA patients undergoing any surgery requiring general anesthesia, there is a paucity of literature addressing the impact of OSA on TSS outcomes.11–14
We aim to elucidate this topic by utilizing the largest database of inpatient discharge data in the United States, the National Inpatient Sample (NIS).

**MATERIALS AND METHODS**

This retrospective cross-sectional analysis was performed utilizing data from the 2008 to 2011 and the 2012 to 2013 NIS. The NIS is the largest all-payer inpatient database in the United States and is part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality. The database represents a sample of approximately 20% of all hospital discharges in the United States, excluding rehabilitation and long-term acute care hospitals. Prior to 2012, the NIS data sampling included 100% of discharges from 20% of HCUP hospitals. Since 2012, however, the sampling method was reconfigured to include 20% of discharges from 100% of HCUP hospitals to facilitate more accurate national estimates.

Each case in the NIS represents one hospitalization, from admission to discharge. Henceforth, we will refer to an NIS case as a “patient.” The Rutgers New Jersey Medical School Institutional Review Board (IRB) does not consider the use of deidentified data from the NIS to meet the regulatory definition of human subjects research provided in 45 CFR 45.102. IRB approval was, therefore, not required for the present study.

Inclusion criteria for the present analysis included all patients with a primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) diagnosis code for pituitary neoplasm (194.3, 227.3) and a primary ICD-9 procedure code for TSS pituitary surgery (07.14, 07.62, 07.65). Cases were further stratified based on the presence or absence of OSA (327.23). Table I lists relevant ICD-9 diagnosis and procedure codes. Variables were derived to determine presence of functioning adenoma, including acromegaly/gigantism (253.0), Cushing’s syndrome (255.0), and other and unspecified anterior pituitary hyperfunction (253.1). Patient characteristics and in-hospital outcomes were compared between patients with and without OSA. Data collection and analysis were completed in June 2016. Unweighted data are reported and were used for all statistical analyses.

**Statistical Analysis**

Two-tailed t tests, Pearson’s χ², and Fisher exact test were used where appropriate. SPSS version 22 (IBM, Armonk, NY) was used for all statistical analyses, with threshold for significance set at P < .05. Univariate and multivariate logistic regression analyses, correcting for the effects of age, gender, race, and all comorbidities, were performed to determine the effects of OSA status on complications that were found to differ significantly between the non-OSA and OSA groups. Variables with missing data for 10% or more of cases were recoded with dummy variables to represent the missing data in the regression analysis.

**RESULTS**

In total, 17,777 transsphenoidal pituitary surgery patients were identified in the NIS. Five percent of these had a diagnosis of OSA (N = 889).

Patient characteristics of TSS pituitary patients with and without OSA are listed in Table II. OSA patients were older (53.4 years vs. 51.5 years; P < .001), and more commonly male (59.4% vs. 48.6%; P < .001). With respect to race, OSA patients were more commonly white (68.7% vs. 62.0%; P < .001) and less commonly Hispanic (7.7% vs. 13.0%; P < .001) or Asian/Pacific Islander (1.9% vs. 3.9%; P = .007), relative to non-OSA patients. On average, OSA patients stayed in the hospital for fewer days (3.9 days vs. 4.4 days; P = .001), but they incurred higher average hospital charges ($56,495 vs. $51,193; P < .001).

Table III lists comorbidity frequencies in patients with and without OSA. All comorbidities were significantly more common in OSA patients. The most common comorbidities in the OSA cohort were hypertension (64.8% vs. 44.2%; P < .001), obesity (36.3% vs. 10.1%; P < .001), and diabetes mellitus (DM) (36.1% vs. 16.6%; P < .001). The OSA cohort also had significantly higher rates of functioning adenomas, specifically acromegaly (17.1% vs.
6.4%; \( P < .001 \) and Cushing’s syndrome (11.5% vs. 6.8%; \( P < .001 \)).

Table IV lists in-hospital complications. The most common complication was diabetes insipidus, followed by fluid/electrolyte complications and neurological complications. The OSA group had higher rates of tracheostomy (0.2% vs. 0.7%; \( P = .017 \)) and hypoxemia (1.6% vs. 0.4%; \( P < .001 \)). Cardiac complications were less likely in the OSA group (0.1% vs. 0.9%; \( P = .007 \)). There was no significant difference in in-hospital mortality between the two cohorts (0.1% vs. 0.4%; \( P = .052 \)).

To determine which complications may be independently related to the presence of OSA, multivariate logistic regression analysis was performed. It demonstrated that patients with OSA were at significantly greater risk of postoperative tracheostomy (\( P = .015 \)) and hypoxemia (\( P < .001 \)), and at lower risk of cardiac complications (\( P = .034 \)), when adjusted for age, gender, race, and all comorbidities (Table V).

### DISCUSSION
The OSA cohort was significantly older and more commonly male than the non-OSA cohort. OSA has been generally known to be more prevalent among elderly males.\(^8\) The OSA group suffered from significantly more comorbidities, such as chronic pulmonary disease, congestive heart failure, hypertension, peripheral vascular disease, chronic kidney disease, and liver disease, in accord with prior studies that have noted these particular comorbidities to occur commonly among OSA patients.\(^9,15–18\)

These conditions are likely secondary to chronic intermittent hypoxic stress placed on vital organs due to interrupted breathing. As expected, OSA patients were

### TABLE II.
Characteristics of Transsphenoidal Pituitary Surgery Patients With and Without OSA.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>No.</th>
<th>Non-OSA</th>
<th>OSA</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, mean ( \pm ) SD</td>
<td>17,676</td>
<td>51.5 ( \pm ) 16.6</td>
<td>53.4 ( \pm ) 12.8</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Race, %</td>
<td>14,305</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>62.0</td>
<td>62.3</td>
<td>68.7</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Black</td>
<td>16.8</td>
<td>17.4</td>
<td>17.4</td>
<td>.639</td>
</tr>
<tr>
<td>Hispanic</td>
<td>13.0</td>
<td>13.9</td>
<td>7.7</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>3.9</td>
<td>1.9</td>
<td>1.9</td>
<td>.007*</td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
<td>4.3</td>
<td>4.3</td>
<td>.963</td>
</tr>
<tr>
<td>Gender, %</td>
<td>17,517</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48.6</td>
<td>48.6</td>
<td>59.4</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Female</td>
<td>51.4</td>
<td>51.4</td>
<td>40.6</td>
<td></td>
</tr>
<tr>
<td>Length of stay, d, mean ( \pm ) SD</td>
<td>17,776</td>
<td>4.4 ( \pm ) 5.5</td>
<td>3.9 ( \pm ) 3.7</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hospital charges, $, mean ( \pm ) SD</td>
<td>17,221</td>
<td>51,193 ( \pm ) 53,201</td>
<td>56,495 ( \pm ) 37,468</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

*Significant at \( P < .05 \).
†Analysis among groups of a given variable.

OSA = obstructive sleep apnea; SD = standard deviation.

### TABLE III.
Comorbidities of Transsphenoidal Pituitary Surgery Patients With and Without OSA.

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>No.</th>
<th>Non-OSA, (%)</th>
<th>OSA, (%)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>17,645</td>
<td>16.6</td>
<td>36.1</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>17,645</td>
<td>1.3</td>
<td>3.1</td>
<td>.001*</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>17,645</td>
<td>4.4</td>
<td>14.4</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>17,645</td>
<td>0.9</td>
<td>1.6</td>
<td>.045*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17,645</td>
<td>44.2</td>
<td>64.8</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>17,645</td>
<td>13.3</td>
<td>22.8</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Liver disease</td>
<td>17,645</td>
<td>1.0</td>
<td>1.9</td>
<td>.003*</td>
</tr>
<tr>
<td>Obesity</td>
<td>17,645</td>
<td>10.1</td>
<td>36.3</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>17,645</td>
<td>0.9</td>
<td>1.7</td>
<td>.027*</td>
</tr>
<tr>
<td>Renal failure</td>
<td>17,645</td>
<td>1.7</td>
<td>3.6</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Acromegaly</td>
<td>17,645</td>
<td>6.4</td>
<td>17.1</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Cushing's</td>
<td>17,645</td>
<td>6.8</td>
<td>11.5</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Other/unspecified anterior pituitary hyperfunction</td>
<td>17,645</td>
<td>1.7</td>
<td>1.5</td>
<td>.787</td>
</tr>
</tbody>
</table>

*Significant at \( P < .05 \).
TABLE IV.
In-hospital Complications in Transsphenoidal Pituitary Surgery Patients With and Without OSA.

<table>
<thead>
<tr>
<th>Complications (%)</th>
<th>No.</th>
<th>Non-OSA</th>
<th>OSA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintubation</td>
<td>17,777</td>
<td>0.9</td>
<td>1.0</td>
<td>.735</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>17,777</td>
<td>0.2</td>
<td>0.7</td>
<td>.017*</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>17,777</td>
<td>0.4</td>
<td>1.6</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
<td>17,777</td>
<td>0.3</td>
<td>0.5</td>
<td>.335</td>
</tr>
<tr>
<td>Infectious pneumonia</td>
<td>17,777</td>
<td>0.2</td>
<td>0.3</td>
<td>.431</td>
</tr>
<tr>
<td>Cardiac</td>
<td>17,777</td>
<td>0.9</td>
<td>0.1</td>
<td>.007*</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>17,777</td>
<td>0.4</td>
<td>0.3</td>
<td>1.000</td>
</tr>
<tr>
<td>Neurological</td>
<td>17,777</td>
<td>6.7</td>
<td>7.9</td>
<td>.179</td>
</tr>
<tr>
<td>Urinary/renal</td>
<td>17,777</td>
<td>1.1</td>
<td>1.5</td>
<td>.304</td>
</tr>
<tr>
<td>Hemorrhage/hematoma</td>
<td>17,777</td>
<td>1.3</td>
<td>0.7</td>
<td>.201</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>17,777</td>
<td>11.0</td>
<td>11.2</td>
<td>.808</td>
</tr>
<tr>
<td>Fluid/electrolyte</td>
<td>17,777</td>
<td>9.8</td>
<td>9.8</td>
<td>1.000</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td>17,777</td>
<td>1.8</td>
<td>1.4</td>
<td>.637</td>
</tr>
<tr>
<td>Iatrogenic pituitary</td>
<td>17,777</td>
<td>1.0</td>
<td>0.3</td>
<td>.346</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>17,767</td>
<td>0.4</td>
<td>0.1</td>
<td>.052</td>
</tr>
</tbody>
</table>

*Significant at $P < .05$. OSA = obstructive sleep apnea.

significantly more likely to be obese, as obesity is a common cause of OSA.\(^8\) In addition, sleep deprivation endured by OSA patients exacerbate and perpetuate their condition by causing weight gain.\(^8,19\) The present study established that OSA patients had greater rates of comorbid coagulopathy, DM, and hypothyroidism, which have also been demonstrated in previous publications.\(^19–21\)

Although OSA patients were older and exhibited more cardiopulmonary and coagulopathic comorbidities, they were not found to experience greater postoperative rates of cardiac, aspiration or infectious pneumonia, or thromboembolic events. These findings contrast other studies that have demonstrated increased rates of these postoperative complications among OSA patients in various surgical fields.\(^8,9,21–26\) These contradictions may highlight the less invasive nature of TSS, and may indicate that certain inpatient complications depend on the specific surgical procedure and location. Furthermore, the presence of OSA did not significantly alter rates of postoperative cerebrospinal fluid (CSF) rhinorrhea, diabetes insipidus, fluid or electrolyte imbalances, and iatrogenic pituitary disorders, which are common complications of TSS.\(^1\)

When examining specific pituitary tumor types, the OSA cohort had significantly higher rates of acromegaly and Cushings syndrome, as expected. Studies have reported a high prevalence of OSA and central sleep apnea in acromegaly patients.\(^10,27–29\) Proposed explanations have included elevated growth hormone and insulin-like growth factor-I levels that dysregulate the central respiratory drive, and anatomical changes such as increased mandibular and maxillary growth, tongue hypertrophy, and greater oropharyngeal soft-tissue thickening.\(^30–32\) The prevalence of OSA is also increased in Chugings syndrome patients, with hypercortisolism being an independent risk factor for developing OSA.\(^33\) Obesity, DM, and increased adipose tissue in the subcutaneous tissues of the neck have been attributed to developing OSA in Chugings syndrome patients.\(^32–34\)

It is well-documented that OSA patients experience increased rates of airway compromise, especially in the early postoperative period following various elective surgeries.\(^35\) One institutional review has reported higher rates of postoperative hypoxemia in OSA patients who underwent TSS.\(^10\) Although CPAP is the mainstay treatment for OSA and could reduce respiratory compromise, its use following TSS has been associated with pneumocephalus, in which a one-way valve between the intracranial contents and nasopharynx develops, resulting in CSF leaks or shunts that decrease intracranial pressure.\(^36–38\) CPAP could also potentially insufflate air into the cranial cavity, causing tension pneumocephalus.\(^39,40\)

In our investigation, OSA was independently associated with more than a threefold increased risk of postoperative hypoxemia and tracheostomy in patients undergoing TSS surgery. These findings may be attributed to the lack of CPAP therapy, which has been associated with better respiratory outcomes after other surgeries.\(^41\)

The exact timing of initiation of CPAP therapy after TSS is largely unknown. Our results underscore the challenge in predicting and weighing the risks of apnea and hypoxia against the risks of CSF leak, pneumocephalus, or meningitis in each patient. Most agree that the time-line to start CPAP should be flexible and adjusted depending on the patient's OSA severity, history of radiotherapy, size of the skull base defect, and the material used for repair. Certain institutions have demonstrated safely using CPAP, delayed until the third postoperative day after TSS.\(^10\) Animal models have shown that fascial dural repair develops a fibrous ingrowth as early as 2 weeks, and thus some institutions have recommended waiting 6 weeks after dural repair for CPAP use.\(^37\) Other institutions have used CPAP both immediately and 2 to 4 weeks after TSS in OSA patients and reported no correlation with pneumocephalus.\(^42\) To begin to develop a more

TABLE V.
Multivariate Logistic Regression of Complications for OSA Versus Non-OSA Transsphenoidal Pituitary Surgery Patients.*

<table>
<thead>
<tr>
<th>Complications</th>
<th>Unadjusted OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P</th>
<th>Adjusted OR</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracheostomy</td>
<td>3.190</td>
<td>1.343</td>
<td>7.578</td>
<td>.009†</td>
<td>3.205</td>
<td>1.249</td>
<td>8.219</td>
<td>.015†</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>4.550</td>
<td>2.535</td>
<td>8.167</td>
<td>&lt;.001†</td>
<td>3.157</td>
<td>1.674</td>
<td>5.952</td>
<td>&lt;.001†</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.126</td>
<td>0.018</td>
<td>0.902</td>
<td>.039†</td>
<td>0.117</td>
<td>0.016</td>
<td>0.847</td>
<td>.034†</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, race, and comorbidities.
†Significant at $P < .05$.
CI = confidence interval; OR = odds ratio; OSA = obstructive sleep apnea.
standardized algorithm in CPAP management of OSA patients after TSS, prospective trials evaluating the safety of early versus delayed CPAP use are required. 

Prior studies have demonstrated increased length of stay in postoperative OSA patients, even when adjusted for age, sex, and body mass index.12,35,43,44 When Rahimi et al. compared OSA and non-OSA patients undergoing TSS for endocrine disease, no differences in length of stay were found.10 Despite OSA patients having greater comorbidities and postoperative airway complications, which would have required more treatments, interventions, and higher levels of management and care, and thus may have accounted for the considerably higher hospital charges this group incurred (P < .001), OSA patients had significantly shorter hospital stays than the non-OSA patients. This discrepancy in our study may be due to the greater rate of cardiac complications observed in the non-OSA group that may have required longer lengths of management and observation.

The influence of OSA on postoperative mortality across various surgical fields has been inconsistent and debated in the literature. Most studies report no difference in mortality, whereas others report increased or decreased mortality in OSA patients.13 In our analysis, it is reasonable to anticipate higher postoperative mortality for OSA patients, given their older age and greater number of comorbidities and complications. However, we demonstrated no significant differences in postoperative in-hospital mortality rates following TSS for pituitary neoplasms.

Although this analysis provides a comprehensive and nationally representative illustration of inpatient outcomes in OSA versus non-OSA patients undergoing TSS for pituitary neoplasms, there are several limitations. Inherent in performing any database study, the accuracy and standardization of how OSA was defined in our patients are dependent on the coders. The authors also hoped to utilize a homogeneous patient population and limit potential confounders by examining patients undergoing TSS specifically for pituitary neoplasms. However, by excluding other indications for TSS, we may be introducing a source of selection bias. Furthermore, the NIS does not provide information regarding whether CPAP was used perioperatively. This is important because some studies have shown that preoperative use of CPAP in OSA patients decreases the risk of postoperative complications and results in a shorter length of stay, which could have helped explain some of our findings.22,41 Furthermore, NIS does not contain information on surgical technique, and outpatient or readmission data. The database also lacks tumor-specific information such as the classification, size, local involvement, or extension of each patient’s pituitary neoplasm. Nevertheless, the NIS provides a large sample size distributed across the United States, allowing us to generalize our conclusions regarding outcomes with sufficient external validity.

CONCLUSION

This analysis of the National Inpatient Sample database suggests that obstructive sleep apnea may be a significant risk factor for developing postoperative pulmonary/airway complications in transsphenoidal surgery patients. In particular, the presence of OSA was an independent predictor of greater rates of postoperative tracheostomy and hypoxemia. The OSA cohort also incurred significantly greater total costs of care. OSA was not associated with increased nonairway complications or inpatient mortality, despite being an older patient population with substantially more comorbidities.

BIBLIOGRAPHY


Chung et al.: OSA and Transsphenoidal Surgery


