Risk Factors and Incidence of Postoperative Delirium in Patients Undergoing Laryngectomy

Yiru Wang, MD1,*, Huiqian Yu, MD2,*, Hui Qiao, MD1, Chan Li, MD1, Kaizheng Chen, MD1, and Xia Shen, MD1

Abstract

Objective. To explore the risk factors and incidence of postoperative delirium (POD) in patients undergoing laryngectomy for laryngeal cancer.

Study Design. Prospective cohort study.

Setting. Shanghai Eye, Ear, Nose, and Throat Hospital, Fudan University.

Subjects and Methods. A total of 323 patients underwent laryngectomy from April 4, 2018, to December 28, 2018. Perioperative data were collected. The primary outcome was the presence of POD as defined by the Confusion Assessment Method diagnostic algorithm. Univariate and multivariable logistic regression analyses were used to identify risk factors associated with POD.

Results. Of the patients who underwent laryngectomy during the study period, 99.1% were male, with a mean age of 60.0 years. Of these patients, 28 developed POD, with most episodes (88.1%) occurring during the first 3 postoperative days. The type of POD was hyperactive in 7 cases and hypoactive in 21 cases. The mean duration of POD was 1 day. The mean Delirium Rating Scale-Revised-98 score (a measure of POD severity) was 11.5. For the multivariable analysis, risk factors associated with POD included advanced cancer stage, lower educational level, higher American Society of Anesthesiologists classification, and intraoperative hypotension lasting at least 30 minutes. Intraoperative dexmedetomidine use was protective against POD.

Conclusion. This study identified risk factors associated with POD, providing a target population for quality improvement initiatives. Furthermore, intraoperative dexmedetomidine use can reduce POD.

Keywords
head and neck cancer, laryngeal cancer, postoperative delirium, outcome

Delirium is characterized by an acute disturbance of consciousness and cognition that fluctuates over time. The overall incidence of postoperative delirium (POD) ranges from 11% to 42% among medical inpatients, and the incidence rises with increasing age. In addition, POD is associated with poor outcomes, such as increased length of hospital stay, long-term cognitive impairment, and increased costs.

The etiology of POD is not well known. Its development involves the complex interrelationship between multiple predisposing factors (eg, preoperative cognitive impairment, functional impairment, alcohol abuse, and advanced age) and precipitating factors (eg, polypharmacy, psychoactive medication use, physical restraints, and abnormal laboratory values) in vulnerable patients. While no specific pathophysiologic mechanism has been identified for POD, leading hypotheses include neuronal aging, neuroinflammation, neurotransmitter deficiency, neuroendocrine activation, and changes in brain network connectivity.

Active and deliberate strategies to prevent POD appear to be more important and beneficial than its treatments. Successful preventive strategies include multidisciplinary approaches that target known risk factors. However, risk factors can vary widely, depending on the type of intervention and the particular patient groups affected. While specific risk factors, such as increasing age, smoking, length of surgery, and cerebral hypotension, have been examined in

1Department of Anesthesiology, Shanghai Eye, Ear, Nose, and Throat Hospital, Fudan University, Shanghai, China
2Department of Otorhinolaryngology, Shanghai Eye, Ear, Nose, and Throat Hospital, Fudan University, Shanghai, China

*These authors contributed equally to this article.

Corresponding Author:
Xia Shen, MD, Department of Anesthesiology, Shanghai Eye, Ear, Nose and Throat Hospital, Fudan University, 83 Fenyang Road, Shanghai, China.
Email: zlsx@yahoo.com
the context of cardiovascular and orthopedic procedures, limited studies have been performed in patients with head and neck cancer. Patients with head and neck cancer are at a high risk of POD owing to the significant dysfunction, disfigurement, and psychosocial problems related to surgical treatment. Although some studies have been carried out to outline the risk factors of POD in this population, the weaknesses of these studies include a retrospective study design, meta analysis, or lack of validated instrument for identification of POD. Consequently, it is necessary to investigate POD in patients with head and neck cancer. This observational cohort study aimed to assess the incidence and severity of POD in patients undergoing partial or total laryngectomy to identify perioperative risk factors associated with the development of POD in this specific setting.

Methods

Design of the Study

This protocol was approved by the institutional review board of the Shanghai Eye, Ear, Nose, and Throat Hospital affiliated with Fudan University. All procedures were followed in accordance with the Declaration of Helsinki.

A total of 402 consecutive patients scheduled for laryngectomy were admitted to the otorhinolaryngology ward, screened, and asked to participate in the study. Inclusion criteria were as follows: total laryngectomy, partial laryngectomy, total laryngectomy plus neck dissection, and total laryngectomy with neck dissection and pectoralis major myocutaneous flap. Exclusion criteria included failure of the patient to perform cognitive and psychometric tests for any reason, including sensory impairment, disorders of language, and previous diagnosis of dementia or delirium. Patients who underwent transoral partial laryngectomy were also excluded. This observational cohort study documented a range of pre-, intra-, and postoperative risk factors to which the patients were exposed. Patient recruitment began on April 4, 2018, and was completed on December 28, 2018. All participants provided written informed consent prior to being enrolled in the study. The primary measurement was the incidence of POD. Secondary measurements were length of hospital stay and complications after surgery (eg, pharyngocutaneous fistula and wound infection).

Pre- and Perioperative Measures

Preoperative data included age, sex, American Society of Anesthesiologists (ASA) classification, smoking and alcohol status, diabetes mellitus, cerebrovascular disease, chronic obstructive pulmonary disease, psychological distress, cognitive impairment, and impaired functional autonomy, because these factors are known to increase the risk of POD. Cognitive status was measured with the Mini-Mental State Examination (MMSE), and a score of 27 was utilized as a cutoff to recognize the patients with cognition impairment. The Cumulative Illness Rating Scale (CIRS) was used to assess comorbidity in each patient. The CIRS score is derived from impairment ratings of 14 organ systems, with each item being scored for severity on a Likert scale (0, no problem; 1, current mild or past significant problem; 2, moderate disability requiring first-line treatment; 3, uncontrollable chronic problems or significant disability; 4, end organ failure requiring immediate treatment). Within each category, when 2 diseases were present, only the disease with the higher score was counted. The CIRS cutoff score of 8 was applied to assess the severity of comorbidity. Psychological distress was assessed with the Hospital Anxiety and Depression Scale (HADS), a 14-item scale with 2 subscales (7 items for anxiety and 7 for depression). A score of 8 was used to recognize the patients with anxiety or depression preoperatively. HADS and MMSE were carried out in the afternoon of the day before surgery.

Intraoperative variables included the type of surgical procedure, duration of surgery, presence and duration of hypotension, and use of dexmedetomidine. Intraoperative hypotension was defined as a blood pressure <70% of baseline and lasting at least 30 minutes. Postoperative factors included an O2 saturation of <90%, poor sleep quality, a white blood cell count >12,000/mm3, postoperative fever (>37.0°C), hemoglobin levels <10.0 mg/dL, sodium ion levels <130 mEq/L, potassium ion levels <3.0 mEq/L, albumin levels <3.0 g/dL, and overall hospital stay. These variables were chosen because previous studies showed them to be risk factors of POD. Wound infection, skin necrosis, and pharyngocutaneous fistula were also noted. Self-reported sleep quality was assessed with 5 dichotomous questions: (1) “Did you sleep well?” (2) “Did you sleep better than expected?” (3) “Did you sleep better than at home?” (4) “Were you awake for a long time before falling asleep?” (5) “Do you feel sufficiently rested?” The score on question 4 was reversed. A higher total score on the 5 questions showed a better sleep perception. A score <2 was categorized as bad sleep.

POD Screening

Since symptoms of POD are often worse at night, patients were interviewed once daily between 4 PM and 6 PM for 6 days. Clinical investigators with medical or psychological training conducted all assessments. The presence of delirium was assessed with the Confusion Assessment Method (CAM) diagnostic algorithm. Accurate detection of delirium with the CAM requires evaluation of 4 features: acute onset with a fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Patient charts were not reviewed for episodes of delirium. The severity of POD was assessed with the Delirium Rating Scale-Revised-98. If the delirium persisted, the follow-up continued until the symptoms disappeared. In addition, patients with delirium underwent a comprehensive physical examination with additional laboratory testing to identify a possible underlying cause (eg, sepsis, electrolyte imbalance) for the delirium and were treated when necessary until delirium was resolved.

Statistical Analysis

Continuous variables (age, HADS, MMSE, CIRS, dexmedetomidine use, and surgery duration) are described as mean
medetomidine use significantly differed between groups. Since the number of female patients was few, sex was not considered for the multivariable analysis. Factors that were statistically significant predictors of POD in the multivariable analysis are listed in Table 3.

We did not observe postoperative desaturation or abnormal laboratory findings during the first 6 postoperative days. Median length of hospital stay for patients with POD was longer than for the control group: 18 days (range, 10-35 days) versus 16 days (range, 5-64 days) (P = .044). There was no significant relationship between the development of POD and postoperative complications, such as wound infection (17 patients in the POD group vs 2 patients in the control group, P = .675), skin necrosis (1 in POD vs none in control, P > .99), and pharyngocutaneous fistula (3 in POD vs 1 in control, P = .305).

Discussion

In this study, the incidence of POD after laryngectomy was 8.7% (28 of 323 patients): 25.0% with hyperactive delirium and 75.0% with hypoactive delirium. The risk factors were advanced cancer stage, lower educational level, higher ASA classification, and perioperative hypotension lasting at least 30 minutes. The intraoperative use of dexmedetomidine was related to a lower incidence of POD.

Table 1. Surgical Procedures Performed in the Study Patients.*

<table>
<thead>
<tr>
<th>Surgical Procedures</th>
<th>POD (n = 28)</th>
<th>No POD (n = 295)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PL</td>
<td>8 (28.6)</td>
<td>119 (40.3)</td>
</tr>
<tr>
<td>PL + ND</td>
<td>4 (14.3)</td>
<td>64 (21.7)</td>
</tr>
<tr>
<td>TL only</td>
<td>5 (17.9)</td>
<td>51 (17.3)</td>
</tr>
<tr>
<td>TL + ND</td>
<td>7 (25)</td>
<td>40 (13.6)</td>
</tr>
<tr>
<td>Total laryngopharyngectomy</td>
<td>2 (7.1)</td>
<td>13 (4.4)</td>
</tr>
<tr>
<td>+ ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total laryngopharyngectomy + ND</td>
<td>2 (7.1)</td>
<td>8 (2.7)</td>
</tr>
</tbody>
</table>

*Data are presented as n (%).

Abbreviations: ND, neck dissection; PL, partial laryngectomy; PMMC, pectoralis major myocutaneous flap; POD, postoperative delirium; TL, total laryngectomy.

Figure 1. Diagram of trial recruitment with exclusion and inclusion criteria. MMSE, Mini-Mental State Examination.
Delirium, characterized as the acute disruption of attention and cognition, is a common clinical syndrome in patients with cancer. Recently, Wada et al reported an incidence of POD as high as 39.1% in patients with cancer. Previous prospective studies reported that the prevalence of POD ranged from 11.5% to 17% in patients with head and neck cancer. In the present study, the average POD incidence was 8.6%, with a POD incidence of 4.6% in patients <65 years of age and 15.1% in patients ≥65 years. This rate is lower than that in the study of Weed et al, in which POD developed in 24 of 138 patients (17%). The underlying reasons for this difference include diagnostic criteria (CAM vs the lack of a screening tool), sex (99.1% vs 41.3% male patients), and type of surgical procedure (laryngeal cancer vs multiple cancer types).

Findings of 75% hypoactive delirium and only 25% hyperactive delirium in the current study stress the importance of proactively screening all patients for delirium. Without screening, it is very likely that the patients with hypoactive delirium would not have been identified because they were not causing “problems” for staff, unlike the patients with hyperactive delirium, who tended to cause a fair number of “problems” for staff. There is a global issue with missing hypoactive delirium in patients in general.

**Table 2. Perioperative Variables Related to the Development of Postoperative Delirium.**

<table>
<thead>
<tr>
<th>Factors</th>
<th>POD (n = 28)</th>
<th>No POD (n = 295)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>65.5 ± 6.4</td>
<td>61.7 ± 8.8</td>
<td>.006</td>
</tr>
<tr>
<td>Male</td>
<td>26 (92.9)</td>
<td>294 (99.7)</td>
<td>.021^b</td>
</tr>
<tr>
<td>ASA</td>
<td></td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (10.7)</td>
<td>60 (20.3)</td>
<td>.017^b</td>
</tr>
<tr>
<td>II</td>
<td>19 (67.9)</td>
<td>223 (75.6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6 (21.4)</td>
<td>12 (4.1)</td>
<td></td>
</tr>
<tr>
<td>Previous cerebral stroke</td>
<td>5 (17.9)</td>
<td>14 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (32.1)</td>
<td>102 (34.6)</td>
<td>.796</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (7.1)</td>
<td>32 (10.8)</td>
<td>.752</td>
</tr>
<tr>
<td>Poor sleep quality</td>
<td>5 (17.9)</td>
<td>60 (20.3)</td>
<td>.754</td>
</tr>
<tr>
<td>Family history of dementia</td>
<td>2 (7.1)</td>
<td>19 (6.4)</td>
<td>.701</td>
</tr>
<tr>
<td>Alcohol consumption (&gt;2 drinks per day)</td>
<td>3 (10.7)</td>
<td>27 (9.2)</td>
<td>.734</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td>.002</td>
</tr>
<tr>
<td>I</td>
<td>3 (10.7)</td>
<td>82 (27.8)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (21.4)</td>
<td>119 (40.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>11 (39.3)</td>
<td>59 (20.0)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>8 (28.6)</td>
<td>35 (11.9)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td>.011</td>
</tr>
<tr>
<td>High (greater than high school degree)</td>
<td>24 (85.7)</td>
<td>181 (61.4)</td>
<td></td>
</tr>
<tr>
<td>Low (less than high school degree)</td>
<td>4 (14.3)</td>
<td>114 (38.6)</td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total, mean ± SD</td>
<td>6.9 ± 4.7</td>
<td>7.0 ± 5.0</td>
<td>.888</td>
</tr>
<tr>
<td>Anxiety, mean ± SD</td>
<td>4.0 ± 2.9</td>
<td>3.8 ± 3.0</td>
<td>.682</td>
</tr>
<tr>
<td>Anxiety ≥8</td>
<td>3 (10.7)</td>
<td>31 (10.5)</td>
<td>.973^b</td>
</tr>
<tr>
<td>Depression, mean ± SD</td>
<td>3.1 ± 2.2</td>
<td>3.3 ± 2.8</td>
<td>.769</td>
</tr>
<tr>
<td>Depression ≥8</td>
<td>1 (3.6)</td>
<td>21 (7.1)</td>
<td>.749^b</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>26.2 ± 2.9</td>
<td>26.1 ± 3.2</td>
<td>.796</td>
</tr>
<tr>
<td>MMSE &lt;27</td>
<td>16 (57.1)</td>
<td>133 (45.1)</td>
<td>.221</td>
</tr>
<tr>
<td>CIRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.4 ± 3.9</td>
<td>5.5 ± 2.7</td>
<td>.844</td>
</tr>
<tr>
<td>CIRS ≥8</td>
<td>6 (21.4)</td>
<td>63 (21.4)</td>
<td>.993</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td>17 (60.7)</td>
<td>117 (39.7)</td>
<td>.031</td>
</tr>
<tr>
<td>Surgery duration, min, median (IQR)</td>
<td>141.5 (114.5-233)</td>
<td>143 (95-246)</td>
<td>.314</td>
</tr>
<tr>
<td>Intraoperative dexmedetomidine use, µg, median (IQR)</td>
<td>0 (0-20)</td>
<td>20 (0-30)</td>
<td>.015</td>
</tr>
</tbody>
</table>

**Abbreviations:** ASA, American Society of Anesthesiologists; CIRS, Cumulative Illness Rating Scale; HADS, Hospital Anxiety and Depression Scale; IQR, interquartile range; MMSE, Mini-Mental State Examination; POD, postoperative delirium.

*Data are presented as n (%) unless noted otherwise.

^bFisher’s exact test.
which is why the CAM and other screening measures exist and why many hospital protocols have nursing staff completing the CAM or other observational screeners at various points during the day to identify all delirium.

The risk factors for POD are both predisposing and precipitating. The risk factors for POD reported in previous studies include the preoperative factors of age, educational level, ASA classification, and cancer stage, and these were included in the univariate analysis. Age in the multivariable model was no longer associated with POD, because they have more contact with the patients. Third, the screening for delirium was performed only once daily. Although symptoms of delirium tend to be at their worst in late afternoon (ie, at the time of screening), its incidence may still have been underestimated given its fluctuating nature. Furthermore, note that the CAM instrument is completed, not by surgeons or physicians, but rather by nurse staff because they have more contact with the patients. Third, although blood pressure variations were not found to affect POD, they have been reported to be an independent predictor of POD. Finally, psychological distress with HADS was assessed preoperatively. Postoperative distress may be associated with the development of delirium in the more immediate term. Further study is warranted to confirm this hypothesis.

Conclusions

The findings of the present study reveal an 8.7% overall incidence of POD. The risk factors associated with the development of POD after laryngectomy include advanced cancer stage, lower educational level, increased ASA classification, and intraoperative hypotension lasting at least 30 minutes. Intraoperative hypotension to lower the incidence of POD.6 However, some researchers have argued that intraoperative hypotension does not correlate with the development of delirium.8-10 More studies are warranted to confirm the relationship between intraoperative hypotension and POD.

Patients with head and neck cancer have high levels of psychosocial distress due to the critical roles of the head and neck in body functions, body image, and socialization.1 A recent study showed that preoperative anxiety could predict POD in patients with cancer.27 Smith et al found that preoperative depression was associated with increased risk of POD in patients after noncardiac surgery.42 In the present study, neither the HADS anxiety nor the HADS depression subscale was associated with POD. It is possible that the 17 patients who declined to participate were more distressed than the other patients who participated. Exclusion of these patients may have underestimated the role of the HADS in the prediction of POD. In addition, the number of patients who perioperatively received dexmedetomidine, which modulates the systemic stress response via the hypothalamic-pituitary-adrenal axis,43 could have confounded the role of the HADS to predict POD. Some studies reported that the perioperative use of dexmedetomidine effectively reduces POD.41,44,45 The underlying mechanism proposed by Wang et al is that dexmedetomidine prevents excessive γ-aminobutyric acid type A receptor function after anesthesia.46 However, Deiner et al found that the administration of dexmedetomidine during surgery does not prevent POD.47 The findings of the present study suggest that the intraoperative use of dexmedetomidine can prevent POD.

The strengths of this study include use of the CAM diagnostic algorithm, a validated instrument, to screen for POD in a large homogeneous population (ie, patients enrolled were diagnosed with laryngeal cancer). The present study has several limitations. First, patients were assessed for delirium only on days 1 to 6 after surgery because delirium usually occurs within 2 to 3 days after surgery and declines rapidly thereafter.1 However, POD could have occurred at a later time, and the true incidence of delirium could therefore be underestimated. Second, the screening for delirium was performed only once daily. Although symptoms of delirium tend to be at their worst in late afternoon (ie, at the time of screening), its incidence may still have been underestimated given its fluctuating nature. Furthermore, note that the CAM instrument is completed, not by surgeons or physicians, but rather by nurse staff because they have more contact with the patients. Third, although blood pressure variations were not found to affect POD, they have been reported to be an independent predictor of POD.37 Finally, psychological distress with HADS was assessed preoperatively. Postoperative distress may be associated with the development of delirium in the more immediate term. Further study is warranted to test this hypothesis.
minutes. However, intraoperative use of dexmedetomidine was associated with a reduced risk of POD and should be examined further in this patient population. Since intraoperative hypotension and dexmedetomidine use are modifiable risk factors, the avoidance of intraoperative hypotension by the progressive use of dexmedetomidine is encouraged during anesthesia management. Health care providers should closely monitor high-risk patients during the perioperative period. Additionally, a multidisciplinary collaboration with anesthesiologists, surgeons, and internists is needed to create a standardized risk reduction protocol for these patients.

Acknowledgments

The authors express special gratitude to the physicians and nurses of the departments that cooperated with this study.

Author Contributions

Yiru Wang. Study concept and design. Acquisition, analysis, and interpretation of data. Drafting and revision of the manuscript. Final approval of the version to be published and agreement to be accountable for all aspects of the work; Huiqian Yu. Study concept and design. Acquisition, analysis, and interpretation of data. Administrative, technical, and material support. Drafting and revision of the manuscript. Final approval of the version to be published and agreement to be accountable for all aspects of the work; Hui Qiao. Acquisition, analysis, and interpretation of data. Administrative, technical, and material support. Drafting of the manuscript. Final approval of the version to be published and agreement to be accountable for all aspects of the work; Kaizheng Chen. Acquisition, analysis, and interpretation of data. Administrative, technical, and material support. Drafting and revision of the manuscript. Final approval of the version to be published and agreement to be accountable for all aspects of the work; Xia Shen. Study concept and design. Critical revision of the manuscript for important intellectual content. Study supervision. Final approval of the version to be published and agreement to be accountable for all aspects of the work.

Disclosures

Competing interests: None.

Sponsorships: None.

Funding source: This work was supported by the National Natural Science Foundation of China, 81671045.

References