Preservation of olfactory function following endoscopic single nostril transseptal transsphenoidal surgery

Running head: Preservation of olfactory function following TSS

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Abstract

Objective: Olfactory dysfunction is a significant postoperative complication related to endoscopic transsphenoidal surgery (TSS). This study aimed to determine the impact of endoscopic TSS on olfactory function.

Methods: We conducted a prospective study of 32 patients with sellar or parasellar tumors who were treated with endoscopic TSS between December 2013 and October 2016. TSS was performed via a right transseptal approach. We performed the Toyota and Takagi (T&T) olfactometer test and the venous olfaction test for the evaluation of olfactory function preoperatively and at one and three months postoperatively.

Results: The results of the T&T test showed that olfactory function deteriorated in four out of 32 (12.5%) patients one month postoperatively and improved to preoperative baseline levels in all patients three months after the procedure. Olfactory function deteriorated in one of 31 (3.2%) patients three months after the procedure. The venous olfaction test revealed no response in one of 31 (3.2%) patients one month postoperatively, with no improvement three months after the procedure.

Conclusions: Endoscopic single nostril transseptal TSS for sellar or parasellar tumor resection has minimal impact on olfactory function.

Introduction

Endoscopic transsphenoidal surgery (TSS) has been the first-line treatment for the management of several pituitary tumors.[1,2] Recent advances in technology and surgical techniques have led to TSS becoming a common approach used not only for the resection of pituitary adenomas, but also for the resection of other sellar or parasellar tumors.[3,4] Olfactory dysfunction is a common postoperative complication related to TSS,[5,6,7,8,] and it results in a significant decrease in patient quality of life.[9] However, the impact of TSS on olfactory function in patients with sellar or parasellar tumors has not been adequately evaluated through prospective studies.[8,10] This study aims to evaluate preoperative and postoperative olfactory function and prospectively investigate the impact of TSS on olfactory function.

Materials and Methods

Patients and selection criteria

Patients with sellar or parasellar tumors who were candidates for TSS at Nagoya University Hospital from December 2013 to October 2016 were included in this prospective study. Written informed consent was obtained from all study participants. The exclusion criteria were: (a) recurrence cases, (b) existing sinus disease, and (c) anosmia diagnosed based on preoperative olfactory function testing. The study was approved by the institutional review board of Nagoya University.

Olfactory function testing

We conducted the Toyota and Takagi (T&T) olfactometer test and the venous olfaction test to evaluate olfactory outcomes at three time-points: (a) preoperatively, (b) one month after TSS, and (c) three months after TSS. These tests were performed using the method described below, as in a previous study.[11]

The T&T olfactometer test comprised testing responses to five kinds of standard odorants. Each odorant was diluted 10-fold and then evaluated at eight grades, with -2 and 5 being the minimum and maximum concentrations, respectively. The lowest odor concentration which a patient was able to detect was termed the detection threshold. The lowest odor concentration at which a patient was able to identify the odor was termed the recognition threshold. Olfactory assessment involved calculation of the average recognition threshold for each of the five kinds of odorants. Olfactory function was considered to have changed if there was a deterioration or improvement of more than 1 point in the average recognition threshold compared to the preoperative baseline.

The venous olfaction test comprised the injection of prosultiamine (10 mg over 20 s) in the cubital vein. Patients who were not able to detect the odor of prosultiamine within 120 s of injection were considered to show no response.

Nasal cavity assessment

Results from rhinomanometry and nasal endoscopy performed by an otorhinolaryngologist were used to evaluate patients' nasal conditions preoperatively as well as one and three months postoperatively.

Nasal patency was calculated at a pressure of 100 Pa by bilateral resistance. Nasal patency was considered to have changed if there was a postoperative deterioration or improvement of more than 0.10 $Pa/cm^3/s$.

The nasal condition was observed preoperatively and postoperatively using nasal endoscopy. Any crusts or nasal discharges on the nasal mucosa were irrigated or removed under endoscopic guidance postoperatively, if needed.

Surgical method

All transsphenoidal procedures were performed by neurosurgeons under complete endoscopic guidance. After administration of general anesthesia, the patient's upper body was elevated by 15°. Next, the patient's head was rotated to the operator's side by 10-20° and fixed in a Sugita four-point head holder® (Mizuho Medical Innovation, Tokyo, Japan). The single nostril transseptal approach was used in all cases. We did not use a nasal speculum or retractor during the surgery. A vertical incision was made in the nasal septal mucosa from the right nostril and dissected between the periosteum and the septal bones. After removing the septal bones, we reached the anterior wall of the sphenoidal bone. We preserved the contralateral mucosa and did not resect any turbinate on either side. We removed the sphenoidal bone and the septum wall widely. Next, we widely opened the sellar floor to expose the dura rostrally to the tuberculum sellae and the cavernous sinuses bilaterally. Depending on the shape of the tumor, we removed the tuberculum sellae and planum sphenoidale (extended TSS). We cut the dura based on the location of the tumor and resected the tumor. The sellar floor was reconstructed by suturing the dura using abdominal fat or fascia and spraying it with fibrin glue. Our methods for sellar floor reconstruction have been reported previously.[12,13]

Results

Patient characteristics and surgical methods

Thirty-two patients (number of women: 18; age at time of operation: mean, 56.5 years; standard deviation, 11 years) were enrolled in this study. The clinical diagnoses of the patients included non-functioning pituitary adenoma (n=19), acromegaly (n=4), craniopharyngioma (n=2), Rathke's cleft cyst (n=2), tuberculum sellae meningioma (n=2), Cushing disease (n=1), metastatic tumor (n=1), and suprasellar arachnoid cyst (n=1). The average diameter of tumors was 24.9 mm; standard deviation, 11 mm. We performed conventional TSS in 25 (78.1%) patients and extended TSS in seven (21.9%) patients. We used a pedicle septal flap in one

(3.1%) patient with tuberculum sellae meningioma. The demographic information of patients and the surgical methods employed are presented in Table 1.

Olfactory outcomes

We performed the T&T olfactometer test on all 32 patients preoperatively and one month postoperatively; one patient did not participate in the test conducted three months after the operation. Average olfactory function slightly deteriorated from the preoperative baseline of 1.39 ± 1.14 to 1.52 ± 1.38 at the one-month postoperative evaluation but improved to 1.08 ± 0.85 at the three-month postoperative evaluation. We found that olfactory function deteriorated in four (12.5%) patients one month postoperatively and improved to preoperative baseline function in all four cases three months after the operation. Olfactory function was observed to have deteriorated in one (3.2%) patient three months after the procedure. Results of the T&T test in this patient were 0.6 at the preoperative baseline, 1.4 at the one-month postoperative evaluation, and 1.8 at the three-month postoperative evaluation. However, this patient did not show any symptoms related to olfactory dysfunction. Moreover, the results from the venous olfaction test and rhinomanometry did not show deterioration. There was no adhesion on olfactory mucosa via nasal endoscopy in this patient. Hence, we could not detect any cause for olfactory dysfunction in this patient. Conversely, we found an improvement in olfactory function in one (3.1%) patient one month postoperatively and in five (16.1%) patients three months postoperatively.

We performed the venous olfaction test on 31 patients preoperatively and one month postoperatively; three patients did not participate in the test conducted three months after the operation. We observed no response in one (3.2%) patient one month postoperatively, with no improvement three months after the operation; however, this patient did not show any symptoms related to olfactory dysfunction. Moreover, this patient showed deteriorated

olfactory function (T&T olfactometer test) one month postoperatively, which then improved to preoperative baseline levels three months after the operation. Thus, we found a discrepancy between the results of the T&T olfactometer test and the venous olfaction test. All other patients showed responses to the venous olfaction test one and three months after the operation. The results of the T&T olfactometer test and the venous olfaction test at each time-point are detailed in Table 2.

Rhinomanometry and nasal endoscopy findings

Rhinomanometry was performed in 27 patients preoperatively, in 24 patients one month postoperatively, and in 14 patients three months postoperatively. The average total airway resistance improved from the preoperative baseline of 0.28 ± 0.17 to 0.21 ± 0.18 at the one-month postoperative evaluation. The average total airway resistance was 0.23 ± 0.19 at the three-month postoperative evaluation. We observed a deterioration in nasal patency in two (8.3%) patients one month postoperatively and in one (7.1%) patient three months postoperatively. Nasal patency had not deteriorated in the five patients who showed deteriorated olfactory function based on the T&T olfactometer test. Conversely, 11 (45.8%) patients showed improved nasal patency one month postoperatively, while three (21.4%) patients showed an improvement three months postoperatively.

Nasal endoscopy was performed in 31 cases preoperatively, in 25 cases one month postoperatively, and in 19 cases three months postoperatively. Distinct infection and nasal obstruction were not detected in any of the patients, including the patient who showed deteriorated olfactory function based on the T&T olfactometer and venous olfaction tests. We did not find evidence of postoperative cerebrospinal fluid leakage in any of the patients.

Discussion

Olfactory dysfunction following TSS

The olfactory cleft is located between the superior turbinate and the nasal septum. The olfactory organ exists in the olfactory cleft, which is covered by the olfactory mucosa. The axons of olfactory receptor cells extend directly into the olfactory bulb. The afferent nerves from the olfactory bulb transmit signals to the piriform cortex via the lateral olfactory tract. Olfactory information is processed in the piriform cortex and transmitted to the hippocampus, amygdala, medial dorsal nucleus of the thalamus, and the orbitofrontal cortex in the ventral portion of the frontal lobe; information is further processed in each of the above regions. TSS might result in changes in the normal nasal structures, which may lead to postoperative olfactory dysfunction. Olfactory dysfunction can be classified into three groups based on pathology: (a) conductive impairment from the obstruction of nasal passages, (b) sensorineural impairment resulting from damage to the olfactory mucosa, and (c) central olfactory impairment resulting from damage to the olfactory bulb or the olfactory area. Olfactory dysfunction following TSS performed for the resection of sellar or parasellar tumors is considered to be a case of (a) conductive impairment as the smell is not delivered to the olfactory cleft because of obstruction related to the crust or adhesions from the nasal mucosa to the olfactory mucosa, and/or (b) sensorineural impairment related to damage to the olfactory mucosa located in the olfactory cleft between the superior turbinate and septum.

Impact of TSS on olfactory function

While the venous olfaction test can detect anosmia, it cannot detect the threshold or the degree of impairment of olfactory function. In order to overcome this limitation, we performed the T&T olfactometer test to appropriately assess the impact of TSS on olfactory function.

We found a deterioration in olfactory function in five patients, with the deterioration being transient in four out of five the patients. Transient decline in olfactory function after TSS followed by a subsequent improvement to preoperative baseline levels within a few months has

been reported previously.[9] The authors suggested that patients could recover from the damage to the nasal cavity following TSS in due course. Thus, we considered that if the operation-related damage to the nasal mucosa was not significant and did not involve direct injury to the olfactory mucosa, olfactory function could improve within a few months. We did not observe deterioration in nasal patency on rhinomanometry or any evidence of occlusion in nasal endoscopy performed in the five patients who showed deteriorated olfactory function. Thus, we concluded that the underlying cause of olfactory dysfunction observed in this study was not related to nasal obstruction.

We found that one out of four patients with transient olfactory decline showed no response on the venous olfaction test three months postoperatively, in disagreement with the results of the T&T olfactometer test. This difference in olfactory response in patients with olfactory dysfunction was considered to be due to variations in the number of olfactory receptors for specific odors within olfactory cells or differential responses to different odor molecule types.[14]

Conversely, we found an improvement in olfactory function in five patients, three of whom were diagnosed with acromegaly. Previous reports have indicated that olfactory function in patients with acromegaly was significantly improved after TSS.[15,16] This finding may result from the normalization of the hypertrophy of the nasal mucosa three months after TSS. Postoperative nasal endoscopy has been shown to be beneficial because nasal endoscopy can cure the occlusion resulting from the crusts in the nasal cavity.[8] Nasal endoscopic observation and treatment for nasal cavity occlusion can allow recovery of the mucosa, thereby preventing olfactory dysfunction. Thus, treatment together with consultation with an otorhinolaryngologist is important for the maintenance of olfactory function after TSS.

Correlation between surgical method and olfactory dysfunction

Olfactory dysfunction after TSS performed for the resection of sellar or parasellar tumors is not rare. For example, severe hyposmia and anosmia, as determined using T&T olfactometry, have been reported in 12% of patients who undergo Hardy surgery.[10] Wang et al. performed a prospective study based on T&T olfactometry to investigate olfactory function following a microscopic transseptal transsphenoidal procedure and reported severe hyposmia and anosmia in 25% of patients.[8] Kahilogullari et al. used the Small Diskettes Olfaction Test to compare olfactory outcomes between patients who underwent endoscopic surgery and those who underwent microscopic surgery.[17] Olfactory dysfunction was detected in 8% of the patients in the endoscopic surgery group and in 20% of the patients in the microscopic surgery group. The authors concluded that olfactory dysfunction was more prevalent in the microscopic surgery group because of the compression of and/or damage to the nasal mucosa by inserting the specula. Hong et al. reported a decline in olfactory function measured with the Cross-Cultural Smell Identification Test in 3.9% of patients with pituitary adenomas who underwent endoscopic transsphenoidal surgery.[5] While the olfactory outcomes were good, the degree of olfactory dysfunction was not mentioned in detail in their study.

Our study found a postoperative olfactory dysfunction prevalence of only 3.2% (n=1); therefore, the impact of TSS on olfactory function was considered to be minimum. This result demonstrates an improved outcome relative to previous studies that have employed T&T olfactometry. We used an endoscopic single nostril transseptal approach for resection of sellar or parasellar tumors in order to preserve the nasal and olfactory mucosa as much as possible. Endoscopic single nostril transseptal TSS can preserve the contralateral nasal mucosa and structure. Therefore, this approach is considered to be less invasive to the nasal mucosa than the bilateral nostril approach.[18] Moreover, the use of this approach reduces the risk of damage to the nasal cavity while moving the instruments in and out of the surgical field. Furthermore, as we prefer not to remove any turbinate, this approach also helps in the preservation of normal

nasal structure. However, most neurosurgeons usually use the bilateral nostril approach to resect sellar or parasellar tumors. The following guidelines may help to restrict injury to olfactory structures when using the bilateral nostril approach. First, the vertical incision in the mucosa in front of the sphenoidal sinus should be minimal; while this incision leaves the olfactory mucosa intact, it can provide a surgical corridor for sellar or parasellar lesions. Second, insertion and removal of surgical instruments should be performed under endoscopic guidance to minimize the risk of injury to the nasal mucosa.

Conversely, the creation of a septal flap for sellar floor reconstruction has been reported to cause significant olfactory dysfunction.[7] We sutured the dura with abdominal fat or fascia and performed dural closure without a septal flap. This may be another reason for the preservation of olfactory function following TSS.

Limitations

It is important to note several limitations of this study. First, this study was a single-institution non-randomized trial with a small sample size. Second, we were unable to perform olfactory function testing in all patients at each timepoint. Third, we did not compare olfactory outcomes following endoscopic single nostril transseptal TSS for sellar or parasellar tumors with those following any other surgical approach such as bilateral nostril approach. We also did not compare olfactory function between the group receiving the nasoseptal flap and the group without the nasoseptal flap. Moreover, we know that single nostril transseptal TSS is not suitable for all sellar or parasellar tumors. Finally, further studies are required to directly investigate the relationship between olfactory function following TSS and the quality of life of patients.

Conclusions

Endoscopic single nostril transseptal TSS for sellar or parasellar tumors did not result in permanent olfactory dysfunction in a majority of the patients in this study, as this approach is less invasive to olfactory function.

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Declarations of Conflicts of Interest

None

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Table 1. Demographic information of patients and surgical procedures

Characteristics	Value
Age [mean (SD*)]	56.50 ± 11.28
Men/women	14/18
Diagnosis	
Non-functioning pituitary adenoma [no (%)]	19 (59.4%)
Acromegaly [no (%)]	4 (12.5%)
Craniopharyngioma [no (%)]	2 (6.3%)
Rathke's cleft cyst [no (%)]	2 (6.3%)
Tuberculum sellae meningioma [no (%)]	2 (6.3%)
Cushing disease [no (%)]	1 (3.1%)
Metastatic tumor [no (%)]	1 (3.1%)
Suprasellar arachnoid cyst [no (%)]	1 (3.1%)
Tumor diameter [mean (SD*)]	24.88 ± 11.31
Surgical procedure	
Conventional TSS†	25 (78.1%)
Extended TSS	7 (21.9%)
Pedicled nasoseptal flap	1 (3.1%)

*SD, standard deviation. †TSS, transsphenoidal surgery.

Table 2. Impact of endoscopic transsphenoidal surgery on the olfaction test

	Postop. 1 month	Postop. 3 months
T&T* olfactometer	n = 32	n = 31
Deteriorated [no (%)]	4 (12.5%)	1 (3.2%)
Unchanged [no (%)]	27 (84.4%)	25 (80.6%)
Improved [no (%)]	1 (3.1%)	5 (16.1%)
Venous olfaction test	n = 31	n = 29
No response [no (%)]	1 (3.2%)	1 (3.4%)
Response [no (%)]	30 (96.8%)	28 (96.6%)

*T&T, Toyota and Takagi.