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뇌하수체 선종에 대한 내시경 경접형동 수술 후 발생하는 심한 두통의 원인 분석에 대한 연구

Affecting factors to postoperative severe headache after endoscopic transsphenoidal surgery for pituitary adenoma

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의 학 과

문 은 지

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이 논문을 의학석사 학위 논문으로 제출함

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Korean Abastract

뇌하수체 선종에 대한 내시경적 경접형동 제거 수술 이후, 대다수의 두통은 호전되는 것으로 알려졌다. 그러나 생각보다 많은 환자들이 수술 후 두통을 심하게 호소하여, 이에 대해 내시경적 경접형동 뇌하수체 종양 제거술 후 심한 두통을 일으키는 원인 인자를 분석하고자 이 연구를 시행하였다. 이를 통해 원인인자를 밝혀내어 이를 교정함으로써 수술 경과를 호전시키고, 수술 후 환자들의 삶의 질 향상을 향상시키고자 한다.

본원에서 2016년 3월부터 2020년 12월까지 뇌하수체 선종에 대해 내시경적 경접형동 수술을 시행한 총 172명의 환자를의 후향적 데이터 분석을 시행하였다. 평균 연령은 51세, 남성이 74명, 43%였으며, 이중 35명(20%)의 환자가 진단 당시 두통을 호소하였다. 또 51%의 환자들이 수술 후 NRS 5점 이상의 심한 두통을 호소하였고, 이 환자 군을 수술 후 두통 그룹으로 정의하여 인구통계학적, 혈액 검사 및 영상 검사, 수술 소견 등의 요인을 대조군과 비교하였다.

분석 결과 성별, 비만도, 고혈압 및 진단 당시 증상은 수술 후 두통과 연관이 없었다. 일변량 분석에서 45세 미만의 젊은 나이, 수술 후 혈청 나트륨 수치의 큰 변동, 종양 크기 및 수술 전후 종양의 위상 변화가 클수록 수술 후 심한 두통과 유의하게 연관있었다. (p= 0.02, p <0.01, p = 0.01, p = 0.01) 또 수술 전 백혈구 수치 증가 및 수술 후 증가된 CRP 수치, 수술 중 터키안장을 보완하기 위해 인공물질을 사용한 경우 수술 후 심한 두통을 호소하는 것으로 나타났다. (p =0.03, p <0.01, p= 0.02) 반면 수술 중 뇌척수액 누출 혹은 수술 후 뇌출혈을 포함한 합병증 여부 또 해면동 침범 여부는 수술 후 두통과 연관성이 없었다.

뇌하수체 선종에 대해 내시경적 경접형동 수술 이후의 두통에 대한 연구는 거의 없었다. 본 연구에서 수술 후 두통과 연관 있는 인자로 젊은 나이, 큰 종양 크기 및 수술 전후 종양의 위상변화, 증가된 수술 전 백혈구 수치 및 수술 후 CRP 증가소견, 그리고 수술 중 인공물질 사용 여부가 밝혀졌다. 이를 토대로 수술 후 두통을 완화를 위해 수술 전후로 비스테로이드성 소염제를 사용하거나, 수술 중 인공물질 사용의 지양을 고려해 볼 수 있겠다.

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Introduction

Pituitary adenoma (PA) is the most common benign brain tumor in the sellar region, approximately 10-15% of all intracranial tumor.[1] Headache is a common symptom regardless of the tumor size, reported in 33-72% of patients with pituitary adenoma.[2-4] The exact pathophysiology of headache in pituitary adenoma is unclear; whether structural or functional consequence of pituitary disease.[3,5-8] Structural factors including the tumor size increasing intrasellar pressure, sellar destruction, optic chiasm compression and cavernous sinus invasion had been widely accepted as the mechanism of pituitary-related headache.[9] Also, Gondim et al found that biochemical-neuroendocrine factor can be important to pituitary-related headache, especially in growth-hormone- or prolactin-producing pituitary adenoma, and in these cases, medical endocrinologic treatment can improve headache. The primary treatment of pituitary tumor is surgical resection except functioning pituitary adenoma.[10] With development of endoscopic techniques and devices, endoscopic endonasal transsphenoidal approach (ETSA) for pituitary adenoma has become the most preferred surgical methods in worldwide. The efficacy and advantages of ETSA are represented as the minimal invasiveness; providing direct surgical corridor for midline skull base lesion and minimal invasive technique that reduces bleeding, postoperative pain and length of hospital stay (LOS).[11-15] In this context, pituitary-related headache can be relieved after ETSA. There are many studies that have reported significantly improved headache after ETSA in patients with pituitary adenoma, supporting this hypothesis.[5,9,16,17]

However, some patients complain of severe postoperative headache after ETSA for pituitary adenoma. Prolonged or severe postoperative headache can debase the patient's satisfaction and quality of life. As such, identifying the factors with severe postoperative headache may provide the clue of the mechanism of headache in pituitary adenoma and contribute to improve the postoperative care of ETSA. The aim of our study is to explore the association factors of postoperative severe headache in pituitary adenoma treated by ETSA. Moreover, we expect to reveal the clue of the mechanism of pituitary-related headache in this study.

Methods

Patient demographics

We retrospectively reviewed the hospital charts of patient with sellar lesion who underwent ETSA between March 2016 and December 2020 at the Asan Medical Center in Seoul. All surgeries were performed by one neurosurgeon. Eligible patients for this study inclusion are over 18 years of age who underwent ETSA for the first time and diagnosed as pituitary adenoma. Exclusion criteria are as follows: 1) other etiologies such as craniopharyngioma, Rathke's cleft cyst, meningioma, metastatic head and neck cancer or CSF leakage; 2) pre-existing sinusitis which requires surgical treatment; 3) previous transsphenoidal surgical history of pituitary adenoma. Additionally, one case was excluded; postoperative subarachnoid hemorrhage and intracerebral hemorrhage with ruptured pseudoaneurysm at left A1-2 junction. The minimum follow-up period required for inclusion was 6 months.

Patients' demographic data were verified by electronic medical records (EMR), including general information; sex, age, past medical history of hypertension, diabetes mellitus, sinusitis, and history of alcohol or smoking. Also, initial symptom at the time of diagnosis, the presence and severity of headache, pre-, post-operative laboratory values were reviewed.

Imaging evaluation

All patients underwent paranasal CT and pre-, post-operative MRI of the sellar area, followed standard pituitary protocol with coronal and sagittal T1- and T2-weighted spin echo sequences with maximum slice thickness of 3 mm before and after gadolinium-based contrast. The sinusitis location and severity were identified using paranasal CT scan. The size of tumor, the component of tumor (cystic or solid), the severity of optic nerve, cavernous sinus invasion (not or invasion to encasing intracranial artery) and the length of suprasellar extension were determined on the basis of the radiological appearance in preoperative MRI and measured by one neurosurgeon and several neuro-radiologists.

The degree of optic nerve compression was classified as touch and mild to severe compression which evaluate the thickness and the degree of convex curve of optic chiasm in coronal view of T2- weighted MRI images. The presence or absence of cavernous sinus invasion was verified in coronal view of T1-weighted contrast enhanced MRI. (Figure 1) Postoperative MRI were checked within 48 hours after the operation and follow-up MRI at 3 to 6 months to evaluate the extent of resection. Extent of resection was evaluated with the first postoperative MRI, within 48 hours. Gross total resection (GTR) was defined as no evidence of residual tumor. Near total resection (NTR) indicates as above 90% reduction in tumor volume while subtotal resection (STR) indicates <90% volumetric resection.

For assessment to dynamic changes of the tumor volume, we measured pre-and post-operative the length of suprasellar extension of tumor capsule. We hypothesized that the greater difference between pre- and post-operative tumor capsule levels, the more severe postoperative headache induced by diaphragm dura stretching. The length of suprasellar extension was determined in T1-enhance sagittal images, based on an imaginary line between anterior cranial fossa and dorsum sella. (Figure 2)

Operation procedure

Endoscopic endonasal transsphenoidal approach was routinely performed by one neurosurgeon with assist from otolaryngologists in the evacuation of paranasal space. First, posterior nasal septectomy using binostril access and entering to the sphenoid sinus was done by the otolaryngologist. After then, the neurosurgeon drilled out the sphenoid wall and explosed sellar floor. Then the dura was incised as cruciate fashion and tumor was resected gently using suction and curETSAge devices. After removal of the tumor and meticulous hemostasis, opened dura and sellar floor were repaired in a layered fashion, several combinations of Tachosil, glue, Gelfoam; dura matrix overlay; autologous bone graft or abdominal fat; cadevaric fascia lata graft, megaderm or hydroset layering; and a pedicled nasoseptal flap. The layering combination of reconstruction material were changed the degree of intraoperative CSF leakage. Sometimes lumbar drain insertion for CSF drainage was done whether the degrees of CSF leakage after reconstruction. Nasal packing with gelfoam, silastic sheath or merocel was performed by otolaryngologists and removed day after the surgery under nasal examination.

At our institution, patients who underwent ETSA were managed by the routine protocol. Postoperative hormonal status and nasal examination was done after the two days of the operation. If there was no problem in this routine check, most of the patients were discharged at 3-4 days after the operation. After discharge, they underwent otolaryngologic examination within 1 weeks to evaluate the healing of paranasal mucosa and leaks of cerebrospinal fluid, and to remove residual nasal packing. All patients had been followed up for at least 6 months in outpatient clinic and checked postoperative MRI at 3 to 6 months after the operation.

Postoperative outcomes and clinical course

After the operation, the patients' clinical status and the aspect of headache were identified in the EMR. The characteristics of headache were collected every day after surgery; site, quality of pain, duration, and severity in Numeric rating scale (NRS). Postoperative hormonal replacement, the length of hospital stay and complications including CSF leakage, postoperative intracranial hemorrhage, CNS infection, hormonal deficiency, and other medical problems were analyzed.

Statistical analysis

All statistical analysis was performed using SPSS® software version 28.0.0.0 for Windows (IBM Corp.). The association between two categorical variables was examined by the chi-square test. Risk factors for postoperative headache were evaluated with multiple logistic regression. All statistical analysis was performed with a 5% level of significance, and a P value < 0.05 and 95% confidence intervals of odds ratio that did not include 1 were considered statistically significant.

This retrospective study was approved by the institutional review board of our medical center. Patient's consent did not require due to the retrospective design of the study.

Results

Patient demographics

A total of 305 patients received ETSA for pituitary tumor during the study period. Of those, 172 patients were enrolled in this study, 74 were male (43%) and 98 were female (57%). The mean age was 50.8 (range 16-78) years. The most common symptom at clinical presentation was visual disturbance (n = 60, 34.9%), followed by incidental finding (n = 43, 25%) and headache was reported as the third most common symptom (n = 35, 20%). Most of tumor was diagnosed as non-functional pituitary adenoma (n = 136, 70.1%), followed by growth hormone secreting pituitary adenoma (n = 22, 61.1%), adrenocorticotrophic hormone-secreting pituitary adenoma (n = 12, 3.3%) and prolactinoma (n = 2, 5.6%).

The prevalence of moderate to severe postoperative headache during hospitalization, above 4 points in NRS was 65.5% (114 of 172 patients). The median of postoperative headache during hospitalization was NRS 5 points (range 2-10 points), and the incidence was 51.2 % (88 patients of 172). We defined as these patients as postoperative headache group. (PH)

Demographic comparison between the PH group and the control group are shown in table 1. The PH group consisted of 88 patients (56.8 % women, mean aged 48.8 ± 13.9 years), and the control group comprised of 84 patients (57.1% women, mean aged 52.9 ± 12.0 years). Obesity, hypertension, sinusitis, and smoking history were not shown to be significantly different.

In laboratory data, preoperative WBC count in the PH group was higher than the control group. (13.5% vs 3.6 %, p value = 0.019). There were no significant differences between the PH group and the control group in preoperative hemoglobin, the serum level of sodium and C-reactive protein.

Tumor characteristics

For the whole group, the mean size of tumor was 2.51 ± 0.98 mm. In the PH group, tumor size was larger than the control group (2.58 ± 1.00 mm vs 2.44 ± 0.96 mm). The percentage of tumor size above 2.51 mm was significantly difference (51.1% of postoperative headache group vs 32.1% of control group, p value = 0.012). Also, optic nerve compression shown significant higher in the PH group (52 cases of 88, 59.1 % vs 37 cases of 84, 44%, p value = 0.048). However, there was no significant difference in the percentage of patients with cavernous sinus invasion (65.9% vs 61.9%, p value = 0.585) and solid tumor (51.1 % vs 52.4 %, p =0.87).

Operation detail, postoperative outcomes and clinical course

The details of the operation were given in table 2, as well as the outcomes in table 3. The mean of operation time was significantly longer in the postoperative headache group than the control group (178.03 ± 55.70 min vs 170.83 ± 71.22 min, p value = 0.04). The most common approach was trans-sellar approach (91.3 % of total) and trans-septal approach (87.8% of total). The percentage of usage of artificial graft for sellar floor reconstruction, such as fascia lata graft, duragen or dura matrix onlay, megaderm, or hydroset was significantly higher in the PH group (22.7 % vs 9.5 % in the control group, p value =0.019). The use of nasoseptal graft and autologous bone grafts did not differ substantially (21.6 % vs 14.3 %, p value = 0.075; 56.8 % vs 65.5 %, p value = 0.244). Unexpectedly, intraoperative CSF leakage, lumbar drainage insertion, and postoperative cerebral hemorrhage had no effect on postoperative headache. (46.6% vs 36.9%, p value = 0.421; 3.4 % vs 2.4 %, p value = 0.688; 9.1% vs 6.0%, p value = 0.436).

In the postoperative headache group, the rate of postoperative CRP above 2 mg/dl was higher than the control group (42.1% vs 15.9%, p value = 0.001). The variation of postoperative sodium level was larger in the postoperative group than in the control group, the percentage of the postoperative sodium level gap above 5 mmol/L was respectively 63.0 % of the postoperative headache group, 35.7% of the control group (p value = 0.003).

The rate of gross total resection (GTR), evaluated by postoperative MRI within 48 hours was similar between the groups (72.7% vs 69%, p value = 0.3). The variation of suprasella extension between pre- and post-operative MRI was much larger in the postoperative headache group (9.43 ± 9.26 mm vs 7.88 ± 7.31 mm). The rate of the variation of suprasellar extension above 20 mm had significantly difference (n=13, 14.8% vs n=2, 2.4% of the control group, p value = 0.004).

The median length of stay was 4 days (rage 2 to 438 days) in total patients. There was graph for postoperative headache trend. (Figure 3) Most of headache relieved at the postoperative 3 days. The mean severity of headache at the day of discharge were respectively 1.26 ± 1.28 NRS in the postoperative headache group, and 0.75 ± 0.93 NRS point in the control group. The percentage of hormonal replacement after the operation was higher in the postoperative headache group, but had no significant difference between the group (46.6 % vs 36.9%, p value = 0.198). In detail, corticosteroid replacement was 38 cases, 43.2 % in the postoperative headache group versus 26 cases, 31.0 % in the control group (p value = 0.097). The rate of thyroid hormone was 4.5 % versus 4.8 % (p value 0.946) and the rate of desmopressin was 21.6 % versus 20.2 % without statistically significant (p value =0.827).

There were no significant differences in complication rate between the groups (20.5 % vs 10.7 %, p value = 0.079). In the PH group, there were three cases of CSF leak without CNS infection compared to five in the control group (3.4 % vs 6.0 %, p value =). CNS infection (5 cases, 5.7 % versus 1 case, 1.2 % of the control group) and postoperative cerebral hemorrhage (4 cases, 4.5 % versus not occurred in the control group) were more common in the PH group. The postoperative headache group had significantly higher revision operations (4 cases, 4.5 % vs 0 case, p value = 0.048).

Characteristics of postoperative headache associated pituitary adenoma

We observed a positive association between increased inflammation reaction, represented as elevated postoperative CRP level and the postoperative severe headache. (OR =2.46; 95% CI 1.02 – 5.97, p value = 0.05) (table 3). In addition, tumor size and the variation of postoperative tumor capsule height have significant correlations to postoperative headache. (OR 2.30; 95% CI 1.04 – 5.11, p value = 0.041; OR 8.81; 95% CI 1.02 – 76.40, p value = 0.048) in multivariable regression models. In univariate regression model, the variation of postoperative serum sodium level and the use of artificial grafts for sellar reconstructions demonstrated correlations to postoperative headache.

Discussion

The present retrospective study of 172 patients treated with EETA for pituitary adenoma identifies the risk factors associated with the postoperative severe headache. To the best of our knowledge, this study is the largest series to investigate the association factors of postoperative headache in pituitary adenoma. Like prior studies, larger tumor size, concordant with optic chiasm compression and the destruction of sellar structure are acceptable factors in pituitary-related headache. Indeed, these effects postoperative headache. We propose that the variation of pre- and post-operative tumor capsule level as a dynamic mechanical action to dura mater evoked afferent fibers innervating the dura maters, producing the pain. This hypothesis is critical for understanding the mechanism for headache in pituitary adenoma. In previous study, traction and displacement of nociceptive structures such as dura mater, cranial nerve or vessels was thought to be reason for headache from brain tumor.[9,18,19] The explanation for dural traction is that the expansion of pituitary tumor within the sella turcica stimulates afferent fibers innervating the dura mater, which are certainly known to be pain producing. This is concordant to the findings in our study.

Additionally, other factors that increased postoperative C-reactive protein and the use of artificial graft in sellar reconstruction also affect postoperative severe headache with ETSA for pituitary adenoma. This was thought that inflammatory reaction has relationship to postoperative headache, like the neurogenic inflammation is relevant to migraine. Moskowits et al, proposed the concept of sterile inflammation of cranial blood vessels during migraine attacks, about 30 years ago.[20-22] The level of CRP reduced in both interventional studies, which was associated with a reduction in migraine symptoms. Based on this concept, triptan or non-steroidal anti-inflammatory drugs (NSAIDs) are the foundation of the current therapy for migraine, which act through peripheral blockade of small fiber C or alpha, delta-dependent neurogenic inflammation within the dura. Preoperative leukocytosis and higher postoperative CRP were found to have substantial association to postoperative severe headache in our study. These findings are the only adjustable factors to intervene the postoperative headache. Postoperatively, preemptive use of NSAIDs may be useful in controlling headache in the patients with pituitary adenoma. Also, trying to lesser use of artificial grafts for sellar reconstructions are one of the points to reduce postoperative headache.

There were certain limitations to our research. First, the results of this study were presented retrospectively. Second the methods and examiners for postoperative headache evaluation were not uniform. Therefore, there may be some errors between the individual. Third infectious conditions were not totally completely excluded.

Conclusion

Younger age, tumor size, postoperatively dural stretching, and inflammatory reaction are associated factors to postoperative severe headache after endoscopic endonasal trans-sphenodial approach for pituitary tumor. These findings are concordant and support to previous hypothesis related to mechanical factors; tumor size and dural stretch. Preemptively use of NSAIDs maybe one strategy to improve surgical outcomes and quality of life by reducing headache.

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Table 1. Basal patient's characteristics comparison between postoperative headache group and control group.

	Total	Postoperative headache group	Control group	P-value
No.	172	88 (51%)	84 (49%)	
Demographic				
Age (years)	51 ± 13	49 ± 14	53 ± 12	
- Age < 45 yrs	57 (33%)	38 (43%)	19 (23%)	0.02
Sex, female	98 (57%)	50 (57%)	48 (57%)	0.97
BMI (kg/m^2)	25.8	26.1	25.3	0.24
HTN	54 (31%)	33 (38%)	21 (25%)	0.08
DM	30 (17%)	17 (19%)	13 (16%)	0.51
Sinusitis	74 (43%)	34 (39%)	40 (48%)	0.23
Initial symptom				
Headache	35 (20%)	19 (22%)	16 (19%)	0.68
Laboratory data				
Preop				
WBC (x 10^3/μL)	6.9 ± 2.5	7.4 ± 2.8	6.4 ± 2.1	
Hb (g/dL)	13.1 ± 1.4	13.2 ± 1.6	12.9 ± 1.3	
Serum Na (mmol/L)	140.6 ± 2.1	141.0 ± 1.9	140.2 ± 2.3	
CRP (mg/dL)	0.2 ± 0.4	0.3 ± 0.5	0.2 ± 0.2	
Postop				
WBC (x 10^3/μL)	11.9 ± 4.1	12.4 ± 4.3	11.3 ± 3.8	
Hb (g/dL)	11.6 ± 1.5	11.5 ± 1.6	11.6 ± 1.4	
Serum Na, max (mmol/L)	145.4 ± 2.8	145.7 ± 3.2	145.1 ± 2.4	
Serum Na, mini (mmol/L)	139.2 ± 3.0	138.8 ± 3.2	139.6 ± 2.8	
CRP (mg/dL)	2.7 ± 5.3	4.0 ± 6.9	1.3 ± 1.5	
- CRP > 2 mg/dL	56 (33%)	35 (40%)	21 (25%)	0.04
Pre-postop change				
WBC (x 10^3/μL)	5.0 ± 0.3	5.1 ± 0.4	4.9 ± 0.3	0.98
Hb (g/dL)	1.5 ± 0.1	1.7 ± 0.1	1.3 ± 0.1	0.12
Pre-postoperative change of Serum Na (mmol/L)	4.8 ± 0.2	4.7 ± 0.3	4.9 ± 0.3	0.88
Postoperative change of serum Na (mmol/L)	6.2 ± 0.3	6.9 ± 0.4	5.5 ± 0.3	<0.01
CRP (mg/dL)	2.5 ± 0.4	3.7 ± 0.8	1.1 ± 0.2	0.04

Table 2. Tumor characteristics in two groups.

	Total	Postoperative headache group	Control group	P-value
Tumor type				
NFPA	136 (79%)	60 (44%)	67 (49%)	0.82
PRL-producing PA	2 (1%)	1 (1%)	1 (1%)	
GH-producing PA	22 (13%)	11 (13%)	11 (13%)	
ACTH-producing PA	12 (7%)	7 (8%)	5 (6%)	
Radiological findings				
Maximum size (cm)	2.5 ± 1.0	2.6 ± 1.0	2.4 ± 1.0	
- Size > 2.5 cm	72 (42%)	45 (51%)	27 (32%)	0.01
Optic chiasm compression	89 (52%)	52 (59%)	37 (44%)	0.05
Cavernous sinus invasion	110 (64%)	58 (66%)	52 (62%)	0.41
Pure solid nature of tumor	89 (52%)	45 (51%)	44 (52 %)	0.36
Preop capsule upward level (cm)	7.7 ± 8.3	8.6 ± 8.6	6.8 ± 7.8	
Postop capsule length (cm)	-1.0 ± 7.3	-1.0 ± 7.7	-1.1v± 6.9	
Pre-postop capsule level variation	8.7 ± 8.4	9.4 ± 9.3	7.9 ± 7.3	
- changes > 10 mm	70 (41%)	38 (43%)	32 (38%)	0.50
- changes > 15 mm	34 (20%)	21 (24%)	13 (16%)	0.17
- changes > 20 mm	15 (9%)	13 (15%)	2 (2%)	<0.01

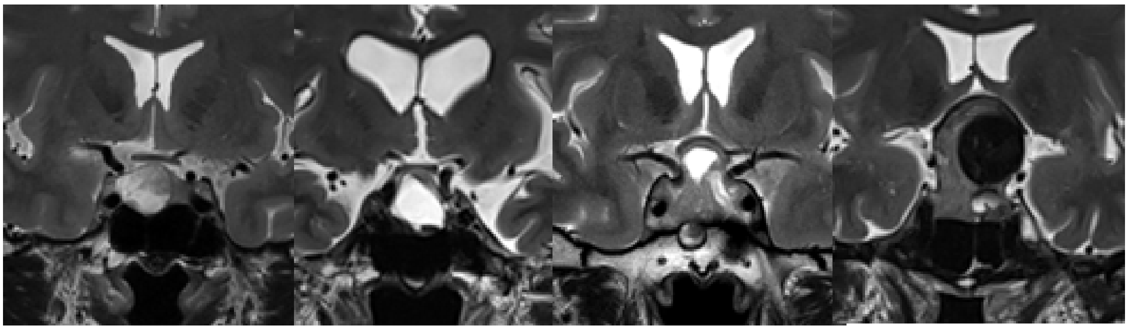
Table 3. Surgical methods, details and postoperative outcomes in two groups.

	Total	Postoperative headache group	Control group	P-value
OP time (minutes)	174 ± 64	178 ± 56	171 ± 71	0.28
Approach				0.40
Trans-sellar	157 (91%)	78 (89%)	79 (94%)	
Trans-tuberculum, planum	13 (8%)	9 (10%)	4 (5%)	
Trans-clival	2 (1%)	1 (1%)	1 (1%)	
Sellar floor reconstruction				
Artificial graft	28 (16%)	20 (23%)	8 (10%)	0.02
Nasoseptal flap	31 (18%)	19 (22%)	12 (14%)	0.21
Autologous bone graft	105 (61%)	50 (57%)	55 (66%)	0.24
Merocel packing	19 (11%)	12 (14%)	7 (8%)	0.27
Intraop CSF leak				
Moderate to severe	18 (11%)	12 (14%)	6 (7%)	0.16
Intraop lumbar drain	5 (3%)	3 (3%)	2 (2%)	0.69
Extent of resection				
GTR	122 (71%)	64 (73%)	58 (69%)	0.6
Complications	27 (16%)	18 (11%)	9 (11%)	0.08
CSF leakage	8 (5%)	3 (3%)	5 (6%)	
Postop hemorrhage	4 (2%)	4 (5%)	0	
Cranial nerve paresis	1 (1%)	1 (1%)	0	
CNS infection	6 (4%)	5 (6%)	1 (1%)	
Other infection	1 (1%)	1 (1%)	0	
Endocrine dysfunction	7 (4%)	1 (1%)	6 (7%)	
Revision operation	4 (2%)	4 (5%)	0	0.05

Table 4. Risk factors of postoperative severe headache in the patient with pituitary adenoma after endoscopic endonasal transsphenoidal approach.

	Univariable	Mutlivariable	
	P value	P value	Odds ratio (95% CI)
Demographics			
Age < 45 years	0.02	0.002	3.617 (1.622 – 8.068)
Sex, Female	0.97		
BMI	0.24		
Hypertension	0.08		
Initial headache	0.51		
Preop WBC count >10.0 x 10^3/μL	0.03	0.115	
Postop Sodium level variation > 5.0 mmol/L	< 0.01	0.456	
Postop CRP level > 2.0 mg/dL	< 0.01	0.046	2.463 (1.016 - 5.969)
Tumor characteristics			
Size > 2.5 cm	0.01	0.041	2.299 (1.035 - 5.107)
Optic chiasm compression	0.05		
Cavernous sinus invasion	0.59		
Preoperative capsule level > 20mm	0.82		
Pre-postop capsule level variation > 20mm	0.01	0.048	8.811 (1.016 - 76.404)
Operation related factors			
Op time	0.29		
Artificial graft for sellar reconstruction	0.02	0.360	
Extent of resection	0.60		
Introperative CSF leakage	0.17		
Complications	0.08		

Figure 1. (a) Coronal-section of MRI with T2-WI for showing optic chiasm compression.



(b) Coronal section of MRI with T1-WI shows the cavernous sinus invasion by the tumor. The left side MRI showed no involvement of cavernous sinus. In the right MRI scan, right side of cavernous sinus was involved by the tumor.

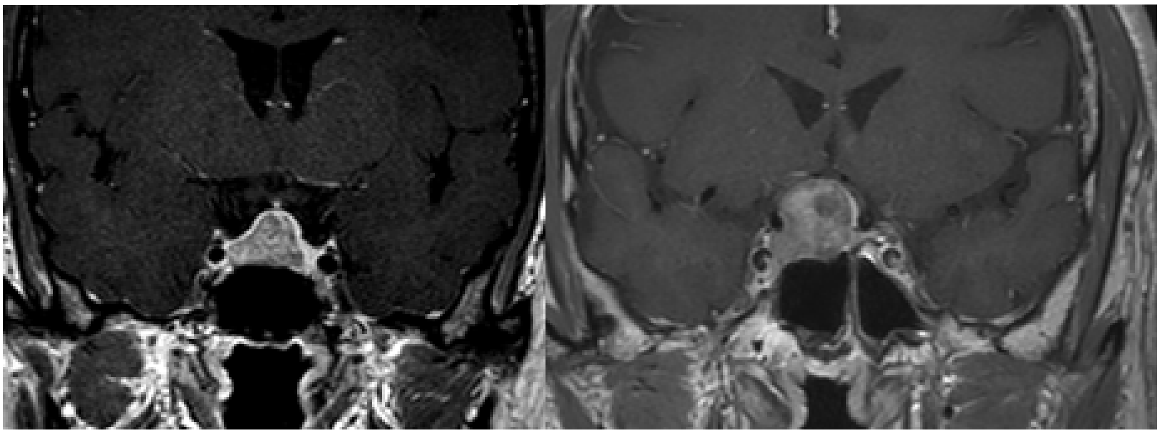


Figure 2. Sagittal section of magnetic resonance images (MRI) with contrast agent and T1 weighted-image show the pituitary adenomas. The length of suprasellar extension is measured from the imaginary line of the tumor in sagittal plane, between anterior cranial fossa to dorsum sellae. (a) Pre-등급operative, (b) post-operative MRI scan for the suprasellar extension in same patients. The gap of tumor capsule was 0.82 mm in this case. (c), (d) showed larger gap of tumor capsule, as 23.30mm.

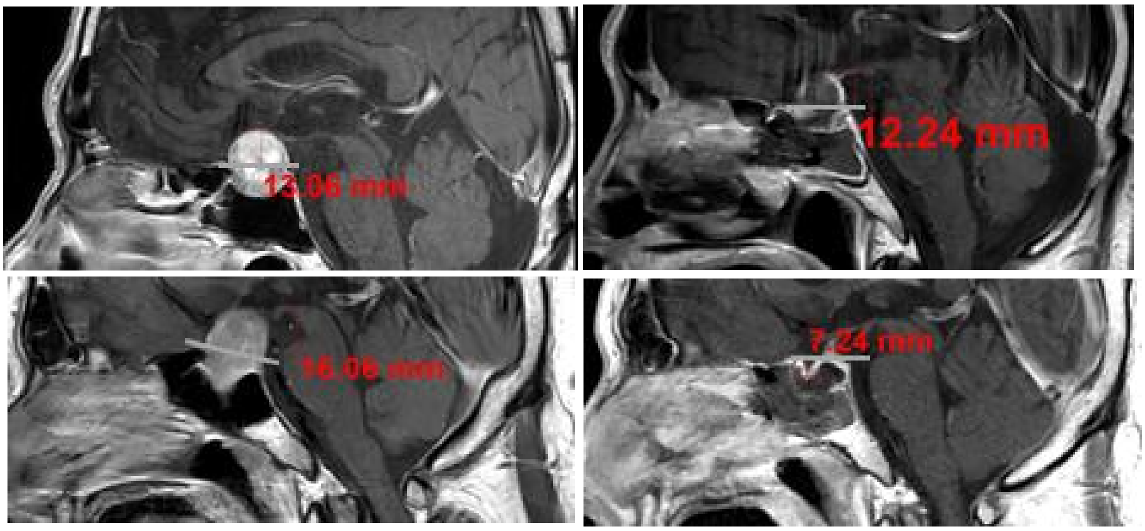
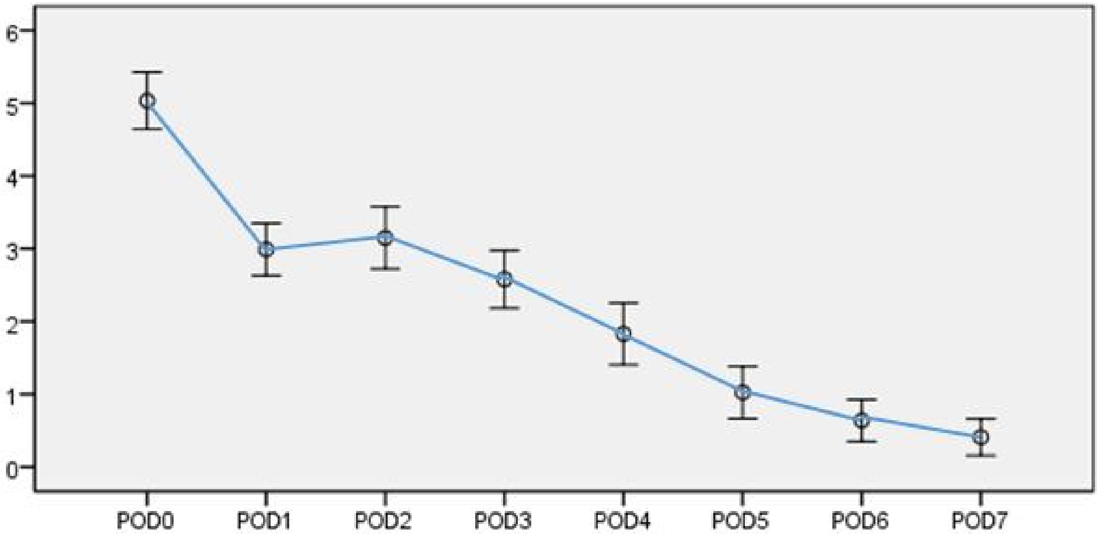


Figure 3. The severity trend of postoperative headache (NRS in scale) in the postoperative headache group (n=88). Postoperative headache was the most severe on the day of surgery. Then, postoperative headache became relief mainly at postoperative day 2 to 3.



Abstract

Introduction

Mostly, postoperative headache has been relieved after endoscopic endonasal transsphenoidal approach (ETSA) for pituitary adenoma However, there were many cases with severe postoperative headache after ETSA. The aim of this study is to investigate the association factors of postoperative severe headache after ETSA for increasing patient's satisfaction and improve quality of life after the operation.

Methods

In this study, we retrospectively reviewed 172 patients (mean age 51 years, male;74, 43%) underwent ETSA, primarily for pituitary adenoma in single institution, between March 2016 to December 2020. Of them, 35 patients (20%) had headache at the time of diagnosis. About half of them (88 patients, 51%) had complaint of severe postoperative headache; over the NRS 5 points. Most severe headaches occurred immediately after surgery, and also reported on the second and third days after surgery. We compared demographic, laboratory, imaging and operation factors in the postoperative headache group which defined as complaining of postoperative headache above NRS 5 points with control group.

Results

Most of them had been diagnosed as non-functioning pituitary adenoma (n = 136, 79%). There were no significant differences in sex, obesity (BMI > 25 kg/m^2), hypertension, initial symptoms. In univariate analysis, younger age under 45 years, increased postoperative sodium level variation, greater tumor size, and larger variation of pre- and post-operative tumor capsule level have significant relationships to severe postoperative headache. ($p= 0.02$, $p < 0.01$, $p = 0.01$, $p = 0.01$, respectively) Also, increased preoperative WBC count, postoperative C-reactive protein (CRP)

level and usage of artificial grafts for sellar reconstruction showed significant correlation with postoperative headache. ($p = 0.03$, $p < 0.01$, $p = 0.02$, respectively). In multivariate study, younger age, increased postoperative CRP level, greater tumor size and larger variation of pre- and post-operative tumor capsule level have significant impact for postoperative headache. On the other hand, there was no correlation between CSF leakage, cavernous sinus invasion, postoperative cerebral hemorrhage and other complications and postoperative headache.

Conclusion

There was lack of study about postoperative headache in pituitary adenoma, treated by ETSA. In this study, younger age, structural factors including larger tumor size and bigger variation of pre- and post-operative tumor capsule level, and inflammatory factors including increased preoperative WBC counts, postoperative CRP level, and the usage of artificial graft for sellar reconstruction are significantly correlate to postoperative severe headache. To relieve postoperative headache, use of NSAIDs before and after surgery and less use of artificial graft for sellar reconstruction should be considered.