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OUR EXPERIENCE OF ENDOSCOPIC TRANSSPHENOIDAL SURGERY FOR CUSHING'S DISEASE: OUTCOMES AND COMPLICATION RATES IN 48 PATIENTS

CUSHİNG HASTALIĞINDA ENDOSKOPİK TRANSSFENOİDAL CERRAHİ DENEYİMLERİMİZ: 48 HASTADA SONUÇLARIMIZ VE KOMPLİKASYON ORANLARIMIZ

Tuğrul Cem ÜNAL[1], Metehan ÖZTÜRK[1], İlyas DOLAŞ[1], Musa Samet ÖZATA[1], Duygu DÖLEN[1], Ümmü MUTLU[2], Ayşe Merve OK[2], Nurdan GÜL[2], Özlem Soyluk SELÇUKBİRİCİK[2], Ayşe Kubat ÜZÜM[2], Sema YARMAN[2], Pulat Akın SABANCI[1], Yavuz ARAS[1], Altay SENCER[1], Aydın AYDOSELİ[1]

[1]Istanbul University, Istanbul Faculty of Medicine, Department of Neurosurgery, Istanbul, Turkiye
[2]Istanbul University, Istanbul Faculty of Medicine, Department of Internal Medical Sciences, Division of Endocrinology, Istanbul, Turkiye

ORCID IDs of the authors: T.C.Ü. 0000-0001-6228-1379; M.Ö. 0000-0002-7772-6331; İ.D. 0000-0002-3425-3220; M.S.Ö. 0000-0003-4401-5741; D.D. 0000-0002-6929-4401; Ü.M. 0000-0002-5259-7326; A.M.O. 0000-0002-1074-1801; N.G. 0000-0002-1187-944X; Ö.S.S. 0000-0003-0732-4764; A.K.Ü. 0000-0003-0478-1193; S.Y. 0000-0002-5938-9618; P.A.S. 0000-0002-0283-0927; Y.A. 0000-0001-8418-2291; A.S 0000-0001-9925-5422; A.A. 0000-0002-4695-8295

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ABSTRACT

Objective: This study aimed to analyze the results of patients who underwent the transsphenoidal endoscopic approach for Cushing's disease in our department and to determine the surgical outcomes, recurrence and complication rates.

Materials and Methods: A single-center retrospective study was performed on 48 patients who underwent endoscopic transsphenoidal surgery for Cushing's disease in our department between January 2005 and January 2019. Patients who underwent endoscopic transsphenoidal surgery received perioperative supraphysiological glucocorticoid therapy. Patients were evaluated for clinical features and basal cortisol levels without medication use in the last 24 hours when glucocorticoid therapy was reduced to a physiological dose. Patients were also evaluated with steroid replacement durations; the 3rd month, the first year and the last examination blood cortisol levels, 1mg dexametazon suppression test; MRI imaging post-operative in the first 24 hours, the 3rd month and the first year.

Results: A total of 48 patients underwent transsphenoidal endoscopic approach. Moreover, 38 patients (79.1%) had biochemical remission 1 year postoperatively. The mean follow-up of duration was 72 months. An additional recurrence of Cushing's disease was detected in 11 patients (22.9%). Consequent-

ÖZET

Amaç: Çalışmamızın amacı kliniğimizde endoskopik transsfenoidal cerrahi (ETC) yöntemle opere edilen Cushing hastalarının cerrahi sonuçları, nüks ve remisyon oranları ile komplikasyon oranlarını değerlendirmektir.

Gereç ve Yöntemler: Kliniğimizde Ocak 2005 – Ocak 2019 tarihleri arasında, ETC yöntemle opere edilen ve histopatolojik olarak ACTH salgılayan hipofiz adenomu tespit edilen olgular retrospektif olarak incelendi ve 48 hasta çalışmamıza dahil edildi. Steroid şemsiyesi altında opere edilen hastaların glukokortikoid replasmanı fizyolojik doza inildiğinde 24 saat ilaçsız iken bazal kortizol seviyesi ve klinik bulguları değerlendirildi. Hastalar steroid replasman süreleri, ilk 3. ay, 1. yıl ve son kontroldeki serum sabah kortizol ölçümleri ve 1 mg deksametazon supresyon testleri; ilk 24 saat içinde, 3. ay, 1. yıl kontrollerinde kontrastlı Manyetik Rezonans görüntülemeleri ile değerlendirildi.

Bulgular: Toplamda 48 hasta kliniğimizde ETC ile opere edilmiş olup bu hastaların 38'inde (%79,1) post-operatif ilk 12 aylık dönemde remisyon sağlandığı görüldü. Ortalama olarak 72 ay süreyle takip ettiğimiz bu hastalardan 11 (%22,9) tanesinde Cushing hastalığının nüks ettiği saptandı. Sonuç olarak uzun dönem takiplerimizde remisyonda kalan hasta sayısının 27 (%56,3) olduğu gözlenmiştir.

Corresponding author/İletişim kurulacak yazar: Metehan ÖZTÜRK – ozturkmete@hotmail.com.tr

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ly, in our long-term results 27 patients (56.3%) remained in remission.

Conclusions: The mortality and morbidity rates of Cushing's disease are significantly decreased with treatment. Surgery is the first line treatment method for Cushing's disease. Transsphenoidal endoscopic surgery is a safe and effective treatment method for Cushing's disease with benefits such as better visualization, providing the opportunity to access parasellar regions, and lower complication rates.

Keywords: Cushing, surgery, endoscopic, transsphenoidal

Sonuç: Cushing hastalığı tedavi edildiği takdirde morbidite ve mortalite riski belirgin azalmaktadır. Cushing hastalığının seçkin tedavisi cerrahidir. Daha iyi bir görüş açısı ve parasellar bölgelere ulaşabilme imkânı sağlaması, daha az komplikasyon oranlarına sahip olması gibi nedenlerden dolayı ETC Cushing hastalığı tedavisinde etkin ve güvenli bir yöntemdir.

Anahtar Kelimeler: Cushing, cerrahi, endoskopik, transsfenoidal

INTRODUCTION

Cushing's disease was first described by Harvey Cushing in 1932, as a clinical condition caused by oversecretion of glucocorticoids due to an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma (1). The annual incidence rates are between 0.7 and 2.4 per million population, and it has a poor prognosis when not treated (2). In Harvey Cushing's case series, the average survival of patients is 4.6 years and cardiovascular diseases are the most common cause of increased mortality rates (1). Moreover, high blood cortisol levels lead to the developement of morbidities such as sarcopenia, osteopenia, central obesity, metabolic disease (dyslipidemia, diabetes mellitus etc.) and arterial hypertension. Previous studies have shown that these risks can be reduced if biochemical treatment is provided (3).

Endoscopic transsphenoidal surgery (ETS) is preferred as the first line treatment of Cushing's disease (4–8). However, survey results of approximately 30 centers within the borders of the USA has shown, that remission rates of these centers are highly variable and are between 10% and 90-100% (9). The major reasons for this variability are the centers' experience with ETS and surgical techniques.

This study aimed to analyze the results of patients who underwent ETS for Cushing's disease in our department and determine the surgical outcomes, recurrence and complication rates.

MATERIALS AND METHOD

The authors present a single-center (a third level reference hospital Istanbul University Faculty of Medicine, Department of Neurosurgery) retrospective review of 48 patients who underwent ETS for Cushing's syndrome. In our clinic, a council of specialists (neurosurgeon-neuroradiologist-endocrinologist) decide on the surgical treatment of pituitary adenomas. If a patient is diagnosed with Cushing's syndrome, but still have some inconsistencies regarding the clinical and radiological features; inferior petrosal sinus sampling (IPSS) is performed. Patients undergoing ETS received perioperative supraphysiological glucocorticoid therapy. In our clinic 69 patients underwent ETS between January 2005 and January 2019. Of these patients 48 who underwent preoperative detailed biochemical evaluations, pre- and postoperative magnetic resonance imaging (MRI), had histopathological diagnosis of ACTH-secreting pituitary adenoma, and were followed-up for at least 12 months postoperatively included our study. This study was approved by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 31.05.2022, No: 09).

Biochemical diagnosis and remission criteria

In the initial testing for Cushing syndrome, the 1-mg overnight dexamethasone suppression test (DST) was performed, and 24-h urine free cortisol (UFC) levels, late-night salivary cortisol levels and 23:00 serum cortisol levels were obtained. After the 1-mg overnight DST after an 08:00 serum cortisol level >1.8 µg/dL (50 nmol/L), 24-h UFC level more than the normal range, late-night salivary cortisol level>145 ng/dL (4 nmol/L) and 23:00 serum cortisol level>7.5 µg/dL (207 nmol/L) were accepted as indicators of endogenous cause (10,11). As a verification test, we used the 48h 2mg/day DST. After the DST, if the following 08:00 serum cortisol level was >1.8 µg/dL (50 nmol/L), Cushing's syndrome was confirmed. After the verification of Cushing's syndrome, morning plasma ACTH level was determined. If the plasma ACTH level was >20 pg/mL, the patient was diagnosed with ACTH-dependent Cushing's syndrome. For differential diagnosis, pituitary imaging and an 8 mg DST were determined. After the 8 mg DST, if the serum cortisol levels reduced by >50% of the baseline level, the patient was evaluated for pituitary Cushing's disease. In cases without an adenoma larger than 6 mm in pituitary MRI, inferior petrosal sinus sampling (IPSS) performed (12). IPSS was accompanied by corticotrophin-releasing hormone level determination (100 µg), if the ratio of the third-minute central and peripheral ACTH level is >3, the condition is diagnosed as Cushing's disease, while if it is <2, it is diagnosed as Cushing's syndrome.

Patients were evaluated for clinical features and basal cortisol levels without medication in the last 24h when

glucocorticoid therapy was reduced to the physiological dose. Patients were also evaluated with steroid replacement durations; the 3rd month, the first year and the last examination blood cortisol levels, and 1 mg DST. Basal cortisol levels without medication in the last 24h<1.8 µg/dL (50 nmol/L); the third month, the first year and the last examination of blood basal cortisol levels after the 1-mg DST<1.8 µg/dl (50 nmol/L); the clinical regression of Cushing's disease symptoms and the patient's continuing need for steroid replacement are accepted as surgical cure criteria.

Radiologic evaluation

All patients underwent sellar magnetic resonance imaging (MRI) preoperatively, which was performed at 1.5 T in the sagittal and coronal planes with a 2.5-mm slice thickness, without an interslice gap. T1-weighted spin-echo images were obtained with a TR of 611 ms and TE of 8.9 ms, both before and after the administration of 10 mL of gadolinium contrast. T1-weighted images with gadolinium contrast were used to classify the tumors as microadenoma (<10 mm) and macroadenoma (≥10 mm). Follow-up MRI scans were performed on the first post-operative day and then at three months and one year post-operatively.

Surgical procedure

All patients were surgically treated using the pure endoscopic endonasal transsphenoidal approach. Most patients underwent surgery with uninostril technique. Although some patients had larger adenomas, a binostril and extended approach was preferred according to the surgeon's preference. Under general anesthesia, the patient was placed in the supine position, with routine rigid fixation of the head for fixed neuronavigational reference. Xylometazoline spray was administered on the nasal mucosa preoperatively. After adequate sterilization, cotton pieces soaked with adrenalin were applied. All surgeries were performed with a 0° rigid endoscope (Storz, Germany). The middle turbinate was lateralized to increase the surgical corridor, and the sphenoid sinus ostium was recognized. After gentle mobilization of the posterior wall of the nasal septum, the anterior wall of the sphenoid sinus was removed with a high-speed drill and rongeurs. The septum in the sphenoid sinus was removed cautiously if necessary, and then the sella was exposed. The anterior wall of the sella was removed using drill and rongeurs. The opening of the superior part of the wall was usually avoided to prevent an unnecessary risk of intraoperative cerebrospinal fluid (CSF) fistula.

The dura was opened with a horizontal incision, and the tumor was resected in fragments using forceps, ring curettes and an aspirator. For macroadenomas growing in the parasellar region, angled scopes (30° and 45°) were used additionally for gross-total resection. After the resection, the autologous grafts, fascia and fat tissue that were harvested from the abdominal wall and a fibrin sealant were used for duraplasty in each patient. A lumbar drain was placed postoperatively if the arachnoid membrane was opened during resection to prevent a CSF leak.

RESULTS

There were 12 male (25%) and 36 female patients (75%), and the mean age was 37.7±1.8 years (range, 17-68 years). Patients were followed for an average of 72 months (interquartile range 82.5; range 12-264 months) postoperatively. Twenty eight (58.3%) patients presented with weight gain; seven (15%) presented with partial vision loss; seven (15%) patients presented with irregular or absent menstrual periods and six (12.5%) presented with headaches. Of these patients 29 (60.1%) had a Cushingoid appearance (weight gain and fatty tissue deposits, particularly around the midsection and upper back, in the face (moon face), and between the shoulders (buffalo hump). A total of 15 (31%) macroadenomas (>10mm) and 27 (56.2%) microadenomas (<10mm) were detected in MRI. The MRI of 6 patients (12.5%) did not show any adenoma. Cavernous sinus invasion was detected in 32 (43.83%) of 73 patients. Twelve (24%) of these patients who had inconsistency between clinical and radiological features underwent IPSS preoperatively.

Twenty-two (45.8%) of 48 patients attained biochemical remission at the early postoperative period, and 13 additional patients (27%) were in remission based on their 12-month postoperative hormone levels. In the early postoperative MRI findings, 3 (6.2%) patients had residue adenoma. In their follow-up, 7 of the 13 patients who were not in remission after postoperatively, underwent a second surgery. Subsequently, two of these seven patients underwent remission. One patient who was not in remission after the first surgery, developed pituitary insufficiency and had remission while planning for a second surgery. Eight (16.7%) patients who were not in remission, received radiotherapy post-operatively and two of them were then in remission. Two patients who were not in remission postoperatively, underwent a bilateral adrenalectomy. One of these patients developed Nelson's syndrome, and underwent a second ETS, and the pituitary adenoma was totally resected. One patient who was not in remission underwent surgery for left adrenal adenoma two years after ETS, and had remission.

A total of 38 patients (79.1%) attained biochemical remission in the first 12-months post-operatively. There were 11 (22.9%) cases of reccurrence in the long-term follow-up. Consequently, in our long-term follow-up 27 patients (56.3%) had remission after surgery. The remission rates of patients are summarized in Table 1.

Table 1: Patient characteristics and remission-recurrence rates

Age at surgery, years	
Mean (range)	37.7 (17-68)
Gender, n (%)	
Female	36 (75%)
Male	12 (25%)
Follow up, (months)	
Mean (range)	72 (12-264)
Tumor type, n (%)	
Macroadenoma (>10mm)	15 (31%)
Microadenoma (<10mm)	33 (69%)
Remission-recurrence rates, n (%)	
Short-term (<12 months) remission	38 (79.2%)
Recurrence	11 (22.2%)
Long-term (>12 months) remission	27 (56.3%)

Of 48 patients who were included our study, 10 (20.8%) had arachnoid membrane lacerated. A lumbar drainage system was placed to these patients postoperatively and followed as immobile to prevent a CSF leak. Of the 10 patients with a lumbar drainage system, one developed rhinorrhea. This patient underwent endoscopic repair surgery for a CSF leak. In the follow-up of the same patient, meningitis and hydrocephalus developed. After appropriate antibiotic therapy, a ventriculoperitoneal shunt placed in this patient. Thirteen (27%) patients had transient diabetes insipidus post-operative. One (2%) patient had hyponatremia, one (2%) patient had hypopituitarism and appropriate replacement therapy was administered. One (2%) patient developed a postoperative hemorrhage in the operative area and was treated conservatively (Table 2).

Table 2: Complication rates in our study

Complication rates	**n (%)**
CSF fistula	10 (20.8)
Diabetes Insipidus	13 (27.1)
Hyponatremia	1 (2.1)
Hypopituitarism	1 (2.1)
Hemorrhage	1 (2.1)

CSF: Cerebrospinal fluid

DISCUSSION

Since being initially described by Harvey Cushing, Cushing's disease is more common in female patients, and previous studies showed the male/female ratio as between 1:2 and 1:15 (2,3). Although the exact cause of Cushing's disease predominance in female patients is unknown, some studies suggest that corticotropic adenoma tissue is more sensitive to estrogen (11,12). In our study, in line with previous studies Cushing disease is more common in female patients and the female/male patient ratio is 2.7.

In our study, the short-term (≦12 months) remission rate of patients was 79.1% , and the recurrence rate of patients was 22.9%. Additionally, our long-term (>12 months) remission rate was 56.3%. The remission and recurrence rates in our study were found to be similar to those of previous studies (9).

When meta-analyses are examined, microscopic transsphenoidal surgery and ETS have similar remission rates, approximately 80%. Both surgical techniques have similar recurrence rates (10%) and short-term mortality rates (<0.5%). Patients who underwent ETS have higher CSF fistula rate (12.9% vs 4.0%) and lower rates of transient diabetes insipidus (11.3% vs 21.7%) post-operatively. Especially in macroadenomas, ETS has better remission rates (76.3% vs 59.9%) and a lower recurrence rate (1.5% vs 17%) compared to microscopic transsphenoidal surgery (13). In our clinic, we are using ETS for Cushing's disease, because of its better remission rate (especially for patients with macroadenoma), better and wider surgical visualization, the opportunity to access the parasellar regions, a lower risk of nasal trauma peroperatively, greater comfort for patients and lower complication rates.

The most common complications of ETS in our study are transient diabetes insipidus (27%) and arachnoid membrane laceration (20.8%). If arachnoid membrane laceration occurs during surgery, a lumbar drainage system was placed postoperatively, and patients are followed as immobile to prevent a CSF leak. With this procedure, a CSF leak was prevented in nine of ten with an intraoperative arachnoid membrane rupture. One (2%) patient had hyponatremia, one (2%) had hypopituitarism and appropriate replacement therapy was administered.

The limitations of this retrospective study, are the inability to measure the early postoperative basal cortisol level because of perioperative supraphysiological glucocorticoid therapy, and the absence of the 24h UFC test of most patients because of not being routinely checked in our clinic. For this reason, remission in patients who underwent surgery was evaluated in the early postoperative period with clinical features and basal cortisol levels without medication use in the last 24 hour when glucocorticoid therapy was reduced to a physiological dose. It is also reported that there is no correlation between the short and long term remission rates in the literature (13).

CONCLUSION

Surgery is the first-line treatment in Cushing's disease. Nowadays ETS is increasingly used as the first surgical option in the treatment of Cushing's disease due to its effectiveness and safety.

Ethics Committee Approval: This study was approved by Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 31.05.2022, No: 09).

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