Comparison of endoscopic and microscopic transsphenoidal pituitary surgery for managing growth hormone-secreting adenomas

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ABSTRACT
Pituitary adenomas are benign tumors with various biological behaviors, including hormonal secretion, cavernous sinus invasion and others. This study aimed to assess the advantages and disadvantages of the endoscopic endonasal transsphenoidal (EET) approach for managing growth hormone-secreting adenomas in achieving clinical remission compared to the microscopic endonasal transsphenoidal (MET) approach. From 2017 to 2020, a series of 29 patients with growth hormone-secreting adenomas (GH) underwent the surgical treatment via MET (n = 13) and EET (n = 16) approach. Preoperatively and postoperatively endocrinological, neuro-ophthalmological and magnetic resonance imaging (MRI) examinations were performed. According to the Knosp classification for cavernous sinus, 34.4% of all adenomas were accessed as invasive. The mean follow-up was 21.6 ± 12.2 months. The endocrinological remission in the whole group was 68.9%. The microscopic group had lower levels of remission in comparison to the endoscopic group (61.53% vs. 75%). However, no significant difference was observed (p > 0.05). Postoperative diabetes insipidus and cerebrospinal fluid (CSF) leaks rates had a similar occurrence in both groups. No other significant complications were recognized. The use of endoscopic approaches provides a couple of advantages, such as wider field of view, superior illumination and better maneuverability compared to conventional microsurgery. A longer follow-up is still needed for further evaluation of our results.

Introduction
Pituitary adenomas are a benign group of tumors with diverse biological behavior. Asymptomatic incidental pituitary adenomas are found in around 16% of the population in autopsy and magnetic resonance imaging (MRI) studies. The incidence rate of symptomatic adenomas is from 76 to 116 per 100,000 population [1]. Acromegaly incidence is distributed equally among males and females, and the average age ranges from 40 to 50 years [2]. They are considered to be 7%–17% of all intracranial neoplasms. Pituitary adenomas arise from the adenohypophysis in the anterior pituitary, and despite their benign nature, they may enlarge and invade surrounding structures [2]. Anterior adenohypophysal cells are highly differentiated, and pituitary adenomas may secrete different hormones excessively, leading to different diseases, including acromegaly. In most cases of acromegaly, overproduction of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) is a result of somatotroph cell tumors [3].

The clinical features of acromegaly can be divided into effects of an expanding pituitary mass and excessive secretion of GH and IGF-1, leading to systemic complications. Manifestations can range from acral overgrowth, soft-tissue swelling, arthralgias, jaw prognathism, mild hyperglycemia, menstrual disturbances, erectile dysfunction, and hyperhydrosis to facial and skeletal disfigurement, florid osteoarthitis, severe headache, sleep apnea, severe hypertension, diabetic ketoacidosis and respiratory and cardiac failure [3].

Acromegaly patients showed an average 10-year reduction in life expectancy in retrospective studies, owing to a range of comorbidities affecting the cardiovascular, cerebrovascular, metabolic and respiratory system [4]. Post-treatment growth hormone levels of less than 2.5 μg/L are associated with regular life expectancy [5].

The treatment options for acromegaly include surgical treatment, stereotactic radiotherapy and somatostatin receptor ligands.

Hardy [6] implemented the operating microscope in transsphenoidal surgery for managing pituitary adenomas. The microscopic transsphenoidal surgery via a sublabial or endonasal approach became the ‘gold
standard’ for surgical treatment of pituitary adenomas [6]. Jankowski published in 1992 a successful endonasal endoscopic adenomectomy in three patients [7]. Jho and Carrau [8] presented in 1997 the first subsequent series of 50 patients who underwent a pure endoscopic transsphenoidal approach for adenomas without a microscope. Since then, many neurosurgeons have transitioned to this technique to manage pituitary adenomas [8].

The microscopic endonasal transsphenoidal approach has been the most commonly used for resecting pituitary tumors over the last five decades. Since the 90s the endoscopic transsphenoidal surgery for pituitary adenomas has been evolving with the introduction of new techniques. Both microscopic and endoscopic transsphenoidal approaches offer satisfactory surgical results.

The study aimed to access the advantages and disadvantages of the endoscopic endonasal transsphenoidal (EET) approach for managing growth hormone-secreting adenomas in achieving endocrinological remission compared to the microscopic endonasal transsphenoidal (MET) approach.

Subjects and methods

Ethics statement

All patients gave informed written consent prior to participation in the study.

Subjects

During the period 2017–2020, a series of 29 patients with growth hormone-secreting adenomas were operated on via microscopic (n = 13) and endoscopic (n = 16) approaches by the same surgical team.

This retrospective study enrolled 29 patients with growth hormone-secreting adenomas: 17 males and 12 females at an average age of 44.9 ± 13.3 (22–68) years, referred to the tertiary clinic for pituitary surgery of neurosurgery between 2017 and 2020.

Patients from both groups were further subdivided according to tumor invasiveness and size (microadenoma and macroadenoma). Five patients had a previous operation of the pituitary adenoma.

Magnetic resonance imaging was performed on all patients before surgery. Hormonal data including serum prolactin, GH levels, IGF-1 levels, free or bioavailable testosterone levels, thyroxine levels and TSH levels. The definition of remission for acromegaly was defined by the 2010 consensus criteria for remission, including normal IGF-1 level and minimum GH to less than 0.4 ng/mL during oral glucose tolerance test or random GH of less than 1.0 ng/mL.

Magnetic resonance imaging was performed on all patients before surgery. Patients underwent a complete ophthalmic examination before the surgery and postoperatively at the third and 12th month. The mean time of follow-up was 21.62 ± 12.25 months.

Surgical methods

Direct microscopic endonasal transsphenoidal approach

The direct endonasal approach is achieved with no septal dissection. After subluxation of the septum and exposing the sphenoid’s anterior wall, the nasal speculum is introduced into the right nasal passage. After the anterior sphenoidotomy, the incision of the dura is done, the adenomectomy is performed with the help of suction, pituitary rongeurs and various angled ring curettes [9].

Endoscopic endonasal approach

Decongestion of the nasal mucosa is performed by packing the nasal cavity with cotonoids soaked in a mixture of lidocaine 1% and epinephrine (1:100,000). After adequate inspection of the nasal cavity, the middle turbinate is lateralized, and the sphenoid ostia are located. The posterior nasal mucosa is dissected, and a mucosal vascularized nasoseptal flap is harvested when needed. A sphenoidotomy is performed. If a biportal approach is preferred, further mucosal dissection of the posterior nasal mucosa is carried out in the other nostril. At this point, the operation can be performed by using a two-hand technique (one surgeon) or a four-hand technique using the biportal approach. After the opening of the sellar floor, the adenoma is resected. After the resection, an endoscopic inspection of the tumor cavity is performed to visualize out of sight compartments. The dural opening is patched with autologous fat graft, hemostatic cellulose polymer, dural sealant, fibrin glue or nasoseptal flap if needed [9].

Statistical analysis

The statistical analysis was done on SPSS for Windows, Version 23.0. (SPSS, Inc., Chicago, IL, USA). The following statistical methods were used: descriptive statistics for tabular and graphical presentation of results, Chi-square test and Fisher exact test. Differences were assessed as statistically significant in threshold level of significance of $p < 0.05$. 
Results

There were 13 patients (eight female and five male) in the MET group and 16 patients (nine female and seven male) in the EET group. The average age was 46.23 ± 16.18 and 43.87 ± 10.95 years, and the mean tumor size was 1750.66 ± 2134.358 mm$^3$ and 2580.29 ± 2829.749 mm$^3$ in MET and EET group, respectively. No statistical difference was identified between the two groups, particularly concerning tumor size and cavernous sinus invasion ($p > 0.05$).

An overall remission of 61.53% was achieved in the microsurgical group. The remission rates in the subgroups of patients with microadenomas ($n = 7$) and macroadenomas ($n = 6$) were 71.42% and 50%, respectively (Table 1).

The endoscopic group had an overall remission of 75%. The remission rates in the subgroups of patients with microadenomas ($n = 5$) and macroadenomas ($n = 11$) were 80% and 72.27%, respectively (Table 1).

Comparison between MET and EET group

There was no statistical difference between the remission rates in both groups and between microadenomas and macroadenomas ($p > 0.05$). Further breakdown of the data in terms of invasive pituitary adenomas (Knosp scale above 0) suggested that there were better remission rates in the group treated trough endoscopic endonasal transsphenoidal approach ($p < 0.05$).

Complications

CSF leak rates were similar in both groups. One patient (7.69%) in the MET group and two patients (12.5%) in the EET group had postoperative CSF leakage (Table 2). Meningitis, diabetes insipidus, postoperative hypopituitarism had similar occurrences and showed no statistical difference between both groups ($p > 0.05$).

Discussion

In the last decade, there has been an ongoing discussion about whether the endoscopic transsphenoidal approach is a superior surgical method to the microscopic approach. There is no clear answer if one of these surgical methods is superior.

A couple of meta-analyses and retrospective series suggest that endoscopic techniques are associated with better rates of gross total removal in pituitary tumors, especially when pituitary adenomas are not just limited to the sella [10–14]. A meta-analysis by Almutairi et al. [12] including over 8000 patients showed evidence for higher gross total resection in patients operated endoscopically. Endoscopic surgery for non-functioning pituitary adenomas also is associated with higher rates of gross total resection. The meta-analysis proved no evidence that functioning pituitary adenomas benefit from the endoscopic approach, as there is no statistical difference between the two surgical methods [12].

Phan et al. [13] compared remission rates between MET and EET approach in the surgical treatment of somatotropinomas in a meta-analysis from 2017. The study reported that the endoscopic group achieved remission in patients with non-invasive macroadenomas at the high rate of 83.3% (80.6–87.1), which was significantly higher than that in the microscopic group (66.9% [60.2%–73.6%], $p < .001$) [13]. Our study also showed better remission rates in this group, but there was no statistical difference.

Endoscopic surgery had significantly higher rates of intraoperative but not postoperative CSF leak with lower rates of meningitis. No difference was found for other complications, including permanent and temporary diabetes insipidus, epistaxis, postoperative CSF leak, hypocortisolemia, hypothyroidism, hypogonadism and visual defect. The rates of postoperative complications in our study are comparable with previous reports [13,15]. Invasive growth hormone tumors are

| Table 1. Remission rates in patients in microsurgical (MET) and endoscopic (EET) groups. |
|---------------------------------|----------------|----------------|----------------|----------------|
| MET remission (n) | MET remission (%) | EET remission (n) | EET remission (%) |
| Somatotropinomas | 8/13 | 61.53% | 12/16 | 75% |
| Microadenomas | 5/7 | 71.42% | 4/5 | 80% |
| Macroadenomas | 3/6 | 50% | 8/11 | 72.27% |

| Table 2. Postoperative complications in MET and EET group. |
|---------------------------------|----------------|----------------|----------------|----------------|
| MET (n) | MET (%) | EET (n) | EET (%) |
| CSF | 1 | 7.69% | 2 | 12.5% |
| Epistaxis | – | – | 1 | 6.25% |
| Transitory diabetes insipidus | 2 | 15.38% | 3 | 18.75% |
| Permanent diabetes insipidus | – | – | – | – |
| Meningitis | – | – | – | – |
| Death | – | – | – | – |
associated with poorer surgical outcomes compared with non-invasive ones [16].

Conclusions
The results of our study support the safety and effectiveness of endoscopic transsphenoidal surgery for growth-secreting pituitary adenomas. Our study supports that the endoscopic approach is linked to higher remission rates in macroadenomas. The endoscopic endonasal transsphenoidal approach is also associated with better remission rates in the surgical treatment of invasive pituitary adenomas. Both surgical methods offer a similar safety profile in terms of operative and postoperative complications.

Conflicts of interest
The authors have no conflicts of interest to declare.

Data availability statement
The data that support the findings of this study are available from the corresponding author (DP) upon reasonable request.

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