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Superiority of endoscopic transsphenoidal pituitary surgery to microscopic transseptal pituitary surgery for treatment of Cushing's disease

Ting Zhang[1], Baozhong Zhang[1], Lei Yuan[1], Yan Song[1], Fei Wang[1]*

SUMMARY

OBJECTIVE: This study aims to compare the efficacy and safety of endoscopic transsphenoidal pituitary surgery and microscopic transseptal pituitary surgery in the treatment of Cushing's disease (CD).

METHODS: A total of 46 patients with CD were randomized into endoscopic group and microscopic group, with 23 cases in each group. The endoscopic group received the endoscopic transsphenoidal pituitary surgery, and the microscopic group received the microscopic transseptal pituitary surgery. The retrospective data, surgical outcomes, surgical cure rates, and complications in two groups were compared.

RESULTS: Compared with microscopic group, the operative time was significantly shorter ($p<0.05$), the estimated blood loss was significantly less ($p<0.05$), and the hospital stay was significantly shorter ($p<0.05$) in endoscopic group. The surgical cure rate in endoscopic and microscopic groups was 69.56% and 60.86%, respectively, with no significant difference between the two groups ($p>0.05$). The incidence of complications in endoscopic group was significantly lower than that in microscopic group ($p<0.01$).

CONCLUSIONS: For the treatment of CD, the efficacy of endoscopic transsphenoidal pituitary surgery is basically the same as that of traditional microscopic transseptal pituitary surgery. However, the endoscopic surgery can further shorten the operative time, reduce the estimated blood loss, shorten the hospital stay, and reduce the complications.

KEYWORDS: Cushing's disease. Pituitary adenomas. Trans-sphenoidal. Endoscopic. Microscopic.

INTRODUCTION

Adrenocorticotropic hormone (ACTH)-secreting adenoma is a particularly challenging subtype for solid tumors. Incomplete tumor resection can lead to late postoperative recurrence and surgical failure. Persisting Cushing's disease (CD) after unsuccessful operation is associated with a four- to five-fold increased standardized mortality rate and a larger number of morbidity[1]. Therefore, successful surgical treatment of CD is critical. Since Hardy[2] used the microscopic approach to selectively excise ACTH-secreting pituitary adenomas through the transsphenoidal route in 1960s, transsphenoidal surgery has become a standard treatment method for CD. Over the decades, there have been many reports about the results of microscopic transsphenoidal surgery in cases with CD[3]. It is demonstrated that, even by the hands of experienced neurosurgeons, the effectiveness is not always satisfactory with a microscopic technique[4]. Besides, remission rates are lower in patients with recurrent tumors and magnetic resonance imaging (MRI) negative CD[5]. In addition, the lateral extensions of mass may be beyond the surgical

[1]PLA Rocket Force Characteristic Medical Center, Department of Neurosurgery – Beijing, China.
*Corresponding author: bjwangf1@163.com
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field achievable with the microscopic approach, which may make it hard to achieve complete resection. Consequently, it has been noted that transsphenoidal surgery is the optimal primary treatment for a specific subset of individuals with CD[6]. Thus, further treatment procedures should be applied to achieve the remission of CD. In the 1990s, Gamea et al.[7] started using the pure endoscopic technique of transsphenoidal surgery to replace the traditional microscopic technique. The main advantage of endoscopic technique is that it adds panoramic illumination and ensures a visual field of the pituitary region and related structures. This study compared the efficacy and safety of endoscopic transnasal transsphenoidal pituitary surgery and traditional microscopic transseptal pituitary surgery for patients with CD.

METHODS

Patients

Forty-six patients undergoing pituitary adenomas excision for CD in The Characteristic Medical Center of PLA Rocket Force from January 2017 to July 2020 were enrolled in this study. They were randomly divided into endoscopic group and microscopic group, with 23 cases in each group. The endoscopic group received the endoscopic transsphenoidal pituitary surgery, and the microscopic group received the microscopic transseptal pituitary surgery. This study was approved by the Ethics Committee of the Characteristic Medical Center of PLA Rocket Force. Consent form was obtained from all patients.

Diagnosis of Cushing's disease

At presentation, all cases had symptoms and signs of active hypercortisolism. The clinical diagnosis of CD was made by two specialists based on a combination of the presence of detectable plasma ACTH concentrations in patients with elevated 24 h free cortisol excretion in urine, loss of circadian plasma cortisol pattern, and failure to suppress plasma cortisol secretion with low-dose (1 mg) dexamethasone overnight.

Pituitary imaging and tumor grading

All preoperative MRI scans were reviewed by two independent neurosurgeons. To evaluate these results, the adenomas were divided into four grades as follows: grade I: microadenomas without cavernous sinus invasion (≤10 mm); grade II: non-invasive macroadenomas (≥10 mm); grade III: local tumor invasion; and grade IV: diffuse tumor invasion. Invasion in the cavernous sinus space was subclassified according to the criteria proposed by Knosp et al.[8]

Perioperative treatment

Seventy-eight percent of all subjects underwent cortisol-lowering treatment (metyrapone in 14 patients, ketoconazole in 18 patients, and a combination of both drugs in 4 patients) before transsphenoidal surgery for 3.1±1.2 months. One hour before surgery, operators started controlling the level of glucocorticoids (prednisolone, 25 mg intravenously every 8 h), then after operation the dose was tapered rapidly.

Endoscopic transsphenoidal pituitary surgery

After infiltration of the posterior septum, middle turbinate, and the area of the sphenopalatine artery foramen with a local anesthetic, a vertical incision was made in the right side. Then, the surgeons elevated the septal perichondrium toward the maxilla inferiorly, the skull base superiorly, and the sphenoid sinus in the anterior wall posteriorly. During this procedure, endoscopic septoplasty can be conducted to widen the exposed area, if septal deviation was seen. After elevating the right side mucoperichondrium, an incision was made anterior to the perpendicular plate. Then, the perichondrium of the left side was elevated toward the anterior sphenoid sinus wall. During elevation of the sphenoid sinus ostium, the mucosa was carefully elevated and the sphenoid sinus ostium was enlarged on both sides. The sphenoid sinus mucosa was elevated laterally; thus, it can be used as a flap at the end of procedure. Next, the anterior wall of the sphenoid sinus was excised so that the sella base was revealed. The surgeon excised the sella base and performed dural incision. Then, resection of the pituitary adenoma was achieved using the routine procedure. Finally, operators excised the tumor, closed the dural with the sphenoid sinus mucosa, and performed transseptal suturation and/or nasal packing to prevent the formation of septal hematomas.

Microscopic transseptal pituitary surgery

The transseptal approach was carried out through a standard sublabial or hemitransfixion incision. The septum was removed with care to preserve the mucosa, and a wide sphenoidotomy was created. Then, the surgeon resected the mass using an operating microscope. After removing the mass, the sella was reconstructed and wounds were closed. Finally, the surgeon used a through-and-through quilting stitch to approximate the septal mucosa and closed the incision with absorbable suture. Both nostrils were compressed with a nasal packing for 3–5 days.

Criteria of remission and recurrence

Remission of clinical symptoms was defined as disappearance of hypercortisolism, with basal plasma cortisol level ≤50 nmol/l after discontinuation of glucocorticoid withdrawal for 24–48 h

and/or suppression of plasma cortisol level ≤50 nmol/l after a 1 mg overnight drug sensitivity test within the first 3 months after surgery[9]. Recurrence after initial remission was defined as a lack of inhibition of plasma cortisol levels after a 1 mg overnight drug sensitivity test (>50 nmol/l) accompanied by an elevated midnight salivary cortisol level and/or elevated 24-h UFC levels[10].

Statistical analysis

Continuous variables were represented by mean and range, and categorical variables were represented by frequency. Analyses were carried out using SPSS version 11.0. Independent-group t test was used for statistics of means and the Mann-Whitney U test was used to analyze nominal variables. Statistical analyses of categorical variables were conducted by χ^2 and Fisher's exact tests. A p-value<0.05 was considered statistically significant.

RESULTS

Comparison of demographics data between the two groups

The demographics data of patients in two groups are provided in Table 1. There was no significant difference in terms of age, gender, tumor shape, tumor size, or invasion site between the two groups (p>0.05).

Table 1. Demographics data of patients in two groups.

Variable	Endoscopic group	Microscopic group	p
n	23	23	
Age (years)	26–58 (55.6)	23–60 (53.2)	>0.05
Gender, n (%)			
Male	13 (57)	12 (52)	>0.05
Female	10 (43)	11 (48)	
Tumor shape, n (%)			
Macroadenomas	4 (17)	5 (22)	>0.05
Microadenomas	19 (83)	18 (78)	
Tumor size (cm)	0.5–2.5 (0.82)	0.4–2.8 (0.89)	>0.05
Invasion site, n (%)			
Cavernous sinus invasion	2 (9)	2 (9)	>0.05
Suprasellar invasion	2 (9)	2 (7)	
Sphenoidal invasion	1 (4)	1 (4)	

Comparison of surgical outcomes between the two groups

The surgical outcomes in two groups are presented in Table 2. Compared with microscopic group, the operative time was significantly shorter (p<0.05), the estimated blood loss was significantly less (p<0.05), and the hospital stay was significantly shorter (p<0.05) in endoscopic group.

Comparison of surgical cure rates between the two groups

The surgical cure rates in two groups are presented in Table 3. The surgical cure rate in endoscopic group and microscopic

Table 2. Surgical outcomes in two groups.

Variable	Endoscopic group	Microscopic group	p
n	23	23	
Operative time (h)	1–3.2 (1.8)	1.6–4.3 (2.9)	<0.05
Estimated blood loss (mL)	64–100 (95)	120–173 (159)	<0.05
Incomplete resection, n (%)	2 (9)	3 (13)	>0.05
Hospital stay (days)	2–5 (2.8)	4–8 (5.1)	<0.05
Visual field improvement, n (%)	2/3 (67)	3/4 (75)	>0.05
Remission, n (%)	16 (70)	14 (61)	>0.05
Complications, n (%)	3 (13)	8 (35)	<0.01

Table 3. Surgical cure rates in two groups.

	Endoscopic group	Microscopic group	p
n	23	23	
Grade I (n)	12/14	8/12	>0.05
Grade II (n)	3/4	5/6	>0.05
Grade III (n)	1/2	1/2	>0.05
Grade IV (n)	0/3	0/3	>0.05
Cure (n)	16/23	14/23	>0.05
Cure rate (%)	69.56	60.86	>0.05

group was 69.56% and 60.86%, respectively, with no significant between the two groups (p>0.05).

Comparison of complications between the two groups

In endoscopic group, there were two cases of sinusitis and one case of massive nasal bleeding. In microscopic group, there were two cases of sinusitis, two cases hypopituitarism, one nasal septum perforation, one wound disruption, one cerebrospinal fluid (CSF) rhinorrhea, and one case of massive nasal bleeding. The incidence of complications was 13.04% (3/23) in microscopic group, which was significantly lower than 34.78% (8/23) in endoscopic group (p<0.01).

DISCUSSION

Endoscopy has been advocated to be a promising treatment for pituitary adenomas on the basis of its panoramic improved visualization and mobility[11]. Rather than tunnel vision, the endoscope is positioned directly in the sphenoid sinus, only 1–2 cm away from the surgical region. A better field of view is favorable in resecting tumor and preserving normal structures. Conversely, for endocrine-active tumors, such as growth hormone or ACTH-secreting adenomas, endoscopic examination facilitates wider resection and higher hormonal remission rates. Our study compared the efficacy of endoscopic transsphenoidal pituitary surgery and microscopic transseptal pituitary surgery in the treatment of CD. Results showed that 69.56% of patients returned to normal plasma cortisol levels in the endoscopic group and 60.86% of patients in the microscopic group. This indicates that the endoscopic technique appears to improve the remission than microscopic, but the surgical cure rate has no statistically significant difference between the two groups.

Patients' comfort is another significant factor in determining the value of a given surgical operation. The rapid spread of endoscopy in clinical surgery was largely due to its ability to achieve the same surgical outcomes and improve patients' wound healing and postoperative comfort simultaneously. Endoscopy-based endonasal pituitary procedure shows similar results. Because this approach does not use a submucosal excision of nasal tissues, subjects generally suffer less pain, bruising, and postoperative rhinological dysfunction than microscopic procedures In a study by Koren et al.[12], the endoscopic procedure allowed a shorter operative time (by about 40 min), and half shorter hospitalization time than the microscopic approach. Consistently, Sheehan et al.[13] showed that endoscopic approach provided a markedly shorter operative time (2.7 h in endoscopic group vs. 3.4 h in microsurgery group) without compromising the extent of tumor removal. In our study, the endoscopic procedure also reduced the operative time and hospital stay. This may be due to the fewer intraoperative and postoperative complications and the fewer need for wound management.

The use of endoscopes can also improve patient safety. The most common complications of pituitary procedure include CSF leak, pituitary hormone dysfunction, diabetes insipidus, and critical artery injury. Koren et al.[12] showed that there was no recurrence of epistaxis or denture problems, and the incidence of septal perforation, synechia, and crust formation was decreased by the endoscopic technique. In a study by Cooke and Jones[14], only 5.8% of patients exhibited major postoperative complications. There was no long-term nasal, septal, or dental complication. In our study, the complications of endoscopic procedure were significantly fewer compared to microscopic approach. The reason may be that, once operators are familiar with the wide view of the surgical region, they quickly learn how to use the improved degree of visualization to completely and safely excise tumors and visualize the structures to be preserved. Therefore, there is less wound trauma by applying endoscopic technique.

CONCLUSIONS

For the treatment of CD, the efficacy of endoscopic transsphenoidal pituitary surgery is basically the same as traditional microscopic transseptal pituitary surgery. However, the endoscopic surgery can further shorten the operative time, reduce the estimated blood loss, shorten the hospital stay, and reduce the complications. This approach seems to be a good choice for minimally invasive surgery for patients with CD.

AUTHORS' CONTRIBUTIONS

TZ: Conceptualization, Writing – review & editing. **BZ:** Data curation, Writing – original draft. **LY:** Formal analysis, Writing – review & editing. **YS:** Data curation. **FW:** Formal analysis, Writing – review & editing.

REFERENCES

1. Pivonello R, Martino MC, Leo M, Simeoli C, Colao A. Cushing's disease: the burden of illness. Endocrine. 2017;56(1):10-8. https://doi.org/10.1007/s12020-016-0984-8

2. Hardy J. Transphenoidal microsurgery of the normal and pathological pituitary. Clin Neurosurg. 1969;16:185-217. https://doi.org/10.1093/neurosurgery/16.cn_suppl_1.185

3. Hassan-Smith ZK, Sherlock M, Reulen RC, Arlt W, Ayuk J, Toogood AA, et al. Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years. J Clin Endocrinol Metab. 2012;97(4):1194-201. https://doi.org/10.1210/jc.2011-2957
4. Honegger J, Schmalisch K, Beuschlein F, Kaufmann S, Schnauder G, Naegele T, et al. Contemporary microsurgical concept for the treatment of Cushing's disease: endocrine outcome in 83 consecutive patients. Clin Endocrinol (Oxf). 2012;76(4):560-7. https://doi.org/10.1111/j.1365-2265.2011.04268.x
5. Prevedello DM, Pouratian N, Sherman J, Jane Jr JA, Vance ML, Lopes MB, et al. Management of Cushing's disease: outcome in patients with microadenoma detected on pituitary magnetic resonance imaging. J Neurosurg. 2008;109(4):751-9. https://doi.org/10.3171/JNS/2008/109/10/0751
6. Albani A, Theodoropoulou M. Persistent Cushing's disease after transsphenoidal surgery: challenges and solutions. Exp Clin Endocrinol Diabetes. 2021;129(3):208-15. https://doi.org/10.1055/a-1220-6056
7. Gamea A, Fathi M, el-Guindy A. The use of the rigid endoscope in trans-sphenoidal pituitary surgery. J Laryngol Otol. 1994;108(1):19-22. https://doi.org/10.1017/s0022215100125721
8. Knosp E, Steiner E, Kitz K, Matula C. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. Neurosurgery. 1993;33(4):610-7; discussion 617-8. https://doi.org/10.1227/00006123-199310000-00008
9. Feng M, Liu Z, Liu X, Bao X, Yao Y, Deng K, et al. Diagnosis and outcomes of 341 patients with Cushing's disease following transsphenoid surgery: a single-center experience. World Neurosurg. 2018;19:e75-e80. https://doi.org/10.1016/j.wneu.2017.09.105
10. Cebula H, Baussart B, Villa C, Assié G, Boulin A, Foubert L, et al. Efficacy of endoscopic endonasal transsphenoidal surgery for Cushing's disease in 230 patients with positive and negative MRI. Acta Neurochir (Wien). 2017;159(7):1227-36. https://doi.org/10.1007/s00701-017-3140-1
11. Gondim JA, Albuquerque LAF, Almeida JP, Bulcao T, Gomes E, Schops M, et al. Endoscopic endonasal surgery for treatment of pituitary apoplexy: 16 years of experience in a specialized pituitary center. World Neurosurg. 2017;108:137-42. https://doi.org/10.1016/j.wneu.2017.08.131
12. Koren I, Hadar T, Rappaport ZH, Yaniv E. Endoscopic transnasal transsphenoidal microsurgery versus the sublabial approach for the treatment of pituitary tumors: endonasal complications. Laryngoscope. 1999;109(11):1838-40. https://doi.org/10.1097/00005537-199911000-00022
13. Sheehan MT, Atkinson JL, Kasperbauer JL, Erickson BJ, Nippoldt TB. Preliminary comparison of the endoscopic transnasal vs the sublabial transseptal approach for clinically nonfunctioning pituitary macroadenomas. Mayo Clin Proc. 1999;74(7):661-70. https://doi.org/10.4065/74.7.661
14. Cooke RS, Jones RA. Experience with the direct transnasal transsphenoidal approach to the pituitary fossa. Br J Neurosurg. 1994;8(2):193-6. https://doi.org/10.3109/02688699409027966