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Original Article

Comparison of microscopic transsphenoidal surgery and neuroendoscopic transsphenoidal surgery in pituitary adenoma resection and the risk factors of postoperative cerebrospinal fluid leakage

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Abstract: Objective: To compare microscopic transsphenoidal surgery (MTS) and neuroendoscopic transsphenoidal surgery (NTS) in pituitary adenoma (PA) resection and analyze the risk factors of postoperative cerebrospinal fluid leakage (CFL). Methods: The clinical data of 127 patients with PA treated in Xi'an International Medical Center Hospital from January 2019 to January 2021 were analyzed retrospectively. Among them, 54 patients treated by MTS for PA resection were assigned to the control group, while the rest of the 73 patients treated by NTS for PA resection were assigned to the study group. The total tumor resection rate, decrease of hormone levels after operation, alleviation of primary symptoms and complications were compared between the two groups. Logistics regression analysis was conducted to analyze the risk factors of CFL. Results: The control group experienced a shorter operation time than the study group (P<0.001). The resection rates of the control and study groups were comparable, but the study group showed a lower incidence of postoperative complications than the control group (P = 0.004). In addition, the study group showed better alleviation of primary symptoms than the control group (P = 0.013). After surgery, the two groups presented decreased levels of prolactin and growth hormone (P<0.001), and also showed decreased average adrenocorticotropic hormone (P<0.001). Moreover, the two groups were not significantly different in the levels of prolactin, growth hormone and adrenocorticotropic hormone after surgery (P>0.05). According to multivariate logistics regression analysis, body mass index (BMI) (P = 0.003, OR = 8.791, 95% CI: 2.050-37.693), intraoperative CFL (P = 0.002, OR = 21.614, 95% CI: 0.305-153.162) and therapeutic regimen (P = 0.011, OR = 7.060, 95% CI: 1.554-32.076) were independent risk factors for postoperative CFL. Conclusion: Compared with MTS, endoscopic transsphenoidal surgery requires a notably longer time, but it can strongly improve the total resection rate of patients and reduce the incidence of postoperative complications. Endoscopic surgery is a protective factor of postoperative CFL.

Keywords: Microscopic transsphenoidal surgery, neuroendoscopic transsphenoidal surgery, pituitary adenoma, postoperative cerebrospinal fluid leakage, risk factors

Introduction

With the change of people's life style and the annual improvement of people's living standards, the aging of the population is becoming more and more significant, resulting in an annual increase in the incidence of brain diseases [1]. Pituitary adenoma (PA) is an endocrine tumor that occurs in the anterior lobe and posterior lobe of the pituitary gland and residual cells of the craniopharyngioma epithelium. Prior epidemiological statistics show that its incidence is approximately 1/100,000, which is second only to glioma and meningioma [2, 3]. PA will disrupt the secretion of growth hormone and thyrotropin in the body and will compress the optic nerve, finally compromising vision. Moreover, tissue damage during surgery will trigger stress responses and delay the prognosis [4].

Surgery is the main treatment for PA. According to different approaches, it can be classified into craniotomy and transsphenoidal surgery

[5]. Large tumors and tumors growing above and on both sides of the saddle are more suitable for craniotomy approach. While if the tumor is confined to the sella or protrudes into the sphenoid sinus, patients with good sphenoid sinus gasification are more suitable for the transsphenoid approach [6]. After more than a hundred years of development, transsphenoidal surgery has the best approach through the nasal cavity-sphenoid sinus-Sellar region [7]. Clinically, PAs are primarily treated by surgery, and common surgeries include microscopic transsphenoidal surgery (MTS) and neuroendoscopic transsphenoidal surgery (NTS), which are minimally invasive operations that can effectively reduce injury to patients during the operation and ensure complete tumor resection [8]. Although both methods are extensively applied in clinical practice, there is no definite conclusion about their operation and curative effect. Neuroendoscope enables the observation of the residual tumor from multiple angles and close range, but the viewing lens can be easily occluded by blood. a microscope enables simple hemostasis and provides a strong stereoscopic impression [9].

Skull base tumors refer to benign and malignant tumors originating from the skull base and involving the skull base inside and outside. PA is a kind of skull base tumor. Because of its deep location and close association with important surrounding blood vessels and nerves, surgery is more difficult and it has more postoperative complications, especially when the tumour involves the cavernous sinus, dorsal sellar region, petrous region and brainstem [10, 11]. Cerebrospinal fluid leakage (CFL) is a common complication. When a skull base tumor is resected through the enlarged nasal approach, the operation is often accompanied by the opening of the third ventricle and/or cisterna cerebri during the operation, resulting in medium-high flow CFL, and the incidence of CFL increases after the operation [12]. Severe CFL will trigger a series of complications, including meningitis, intracranial pneumatosis and reoperation, which will prolong the length of hospitalization and increase medical expenses [13].

This study analyzed the influence of MTS and NTS on PA resection rate and analyzed the risk factors of postoperative CFL, with the purpose of providing reference for surgical options.

Materials and methods

Clinical data

A total of 289 patients with PA who received treatment in Xi'an International Medical Center Hospital from January 2019 to January 2021 were enrolled retrospectively. Finally, the clinical data of 127 patients who met the following criteria were analyzed. Among them, 54 patients treated by MTS for PA resection were assigned to the control group, while the rest of the 73 patients treated by NTS for PA resection were assigned to the study group. This study was approved by the Medical Ethics Committee of Xi'an International Medical Center Hospital.

Inclusion criteria: Patients confirmed with PA through imaging examination [14]; patients confirmed to have PA and have undergone either microscopic transsphenoidal surgery (MTS) or neuroendoscopic transsphenoidal surgery; patients who were admitted to hospital for surgical treatment within 2 days of onset; patients whose skull base tumor was resected in the same treatment group; and those with detailed clinical data. Exclusion criteria: Patients with recurred mixed adenoma or PA; patients with PA apoplexy; patients with diseases of blood system or immune system; patients with other malignant tumors or serious diseases in important organs; patients with infection of nasal sinus or nasal cavity; or patients who were advised to receive one of these operations by a doctor subjectively.

Therapeutic regimen

Therapeutic regimen in the control group: The control group was treated with MTS. The patient was placed in a supine position, and given general anesthesia and disinfection, followed by conventional towel placing, and disinfection of the nasal cavity. Subsequently, the sphenoid sinus opening was explored through the microscope, and the surface mucosa was peeled off to fully expose the sphenoid sinus opening and the anterior wall of sphenoid sinus. Then the saddle bottom was cut and punctured with No. 7 needle. The meninges of the saddle bottom were cut open to identify the tumor tissue and pituitary tissue through the microscope. Afterwards, the tumor was removed by suction device, curette, etc. while avoiding damage to the sellar diaphragm, and the removed tumor tissue was sent for pathological examination.

Therapeutic regimen in the study group: The study group was treated with NTS. The patient was placed in a supine position, and given general anesthesia and disinfection, followed by conventional towel placing, and disinfection of nasal cavity. Subsequently, under the guidance of a neuroendoscope, an aspirator was placed in the right nasal cavity to suck secretions. The surgical passage was between the middle turbinate and the nasal septum. Adrenaline saline was injected in the direction of the sphenoid recess, which was beneficial to the expansion of the surgical passage. Then, the sphenoid sinus opening was explored along the turbinate, and the nasal mucosa was cut with a straight sickle-shaped knife. After that, the junction of nasal mucosa and sphenoid sinus mucosa was separated, and the anterior wall of sphenoid sinus was ground off, so that the diameter of bone window was 15-20 cm. After fully exposing the dura mater of the Sellar floor, the 7 # needle was punctured into the Sellar, and the tumor tissue and pituitary tissue were distinguished through endoscope. Meantime, the tumor tissue was resected and sent for pathological examination.

During resection of the tumor tissues in the two groups, the resection direction was the anterior-lower tangential direction in the order of back-up to the front-up, so as to ensure the maximum removal of the tumor and avoid damage to the surrounding tissue. After hemostasis, the nasal septum cartilage and mucosa were reset, and the nasal cavity was filled with gauze strips to ensure the unobstructed nostrils.

Enzyme-linked immuno-sorbent assay (ELISA)

Peripheral blood (5 mL) was extracted from each patient before surgery and at 3 days after surgery and centrifuged (1500 g, 10 min) after standing for 30 min. Then growth hormone (GH, Shanghai, beyotime, PG411), prolactin (PRL, Shanghai, mlbio, ml058210) and adrenocorticotropic hormone (ACTH, Shanghai, beyotime, PA009) in the serum were quantified via ELISA kits via the kit instructions.

Clinical data collection

From the electronic medical record system of the hospital, the data of patients including gender, age, body mass index (kg/m^2), tumor diameter, pathological type, past surgery history, diabetes mellitus, hypertension, total tumor resection rate, GH, PRL, ACTH, operation time, postoperative blood loss, postoperative hospital stay and postoperative complications, were collected.

Outcome measures

Primary outcome measures: The total tumor resection rate was compared between the two groups after operation. The levels of ACTH, PRL and GH were compared between the two groups before and after the treatment.

Secondary outcome measures: The clinical data of the two groups were compared. The general data of the two groups were compared, including operation time, blood loss during operation and postoperative hospitalization time. The alleviation of primary symptoms and complications were also compared between the two groups. Logistics regression analysis was performed for analyzing the risk factors of CFL.

Statistical analyses

SPSS22.0 software was used for statistical analyses, and GraphPad 8 for data visualization. The measurement data were described by (Mean ± SD), and their inter-group comparison and intro-group comparison were conducted using the independent-samples t test and paired t test, respectively. Counting data were described by % and analyzed using the chi-square test. Logistics regression analysis was carried out to analyze the independent risk factors impacting patients' CFL. $P<0.05$ suggested a notable difference.

Results

Comparison of clinical data

According to inter-group comparison of baseline data, the study and control groups were comparable in clinical data (all $P>0.05$, **Table 1**).

Comparison of total tumor resection rate

According to inter-group comparison of total tumor resection rate, the two groups were not greatly different in total tumor resection rate ($P = 0.260$, **Table 2**).

Table 1. Comparison of baseline data

Factor	Control group (n = 54)	Study group (n = 73)	χ^2 value	*P* value
Gender			0.087	0.767
Male	20	30		
Female	32	43		
Age			0.142	0.705
>55 years old	30	43		
≤55 years old	24	30		
BMI (kg/m^2)			0.339	0.560
≥25	18	28		
<25	36	45		
Tumor diameter			2.251	0.324
<10 mm (microadenoma)	8	15		
10-30 mm (macroadenoma)	36	39		
>30 mm (giant adenoma)	10	19		
Pathological type			1.403	0.924
FSH adenoma	17	25		
Nonfunctional adenoma	11	15		
ACTH adenoma	7	12		
GH adenoma	5	8		
PRL adenoma	8	7		
Other	6	6		
Past surgery history			0.031	0.858
Yes	8	10		
No	46	63		
Diabetes mellitus			0.062	0.802
Yes	13	19		
No	41	54		
Hypertension			0.543	0.461
Yes	10	10		
No	44	63		

Notes: BMI: Body Mass Index; PRL: Prolactin; GH adenoma: Growth Hormone adenoma; ACTH: Adrenocorticotropic hormone; FSH: Follicle stimulating hormone.

Table 2. Comparison of total tumor resection rate

Group	Total resection	Subtotal resection	χ^2 value	*P* value
Control group (n = 54)	56 (87.50%)	8 (12.50%)	1.268	0.260
Study group (n = 73)	68 (93.15%)	5 (6.85%)		

Changes of hormone indexes before and after treatment

According to quantification results of ACTH, PRL and GH in the two groups before and after treatment, the two groups were similar in ACTH, PRL and GH levels before therapy (all P>0.05, **Figure 1**), while after the therapy, the levels decreased notably in both groups (all P<0.001, **Figure 1**); however, there was no apparent difference between the two groups after the treatment (all P>0.05, **Figure 1**).

Improvement of patients' primary symptoms

According to the statistics of the occurrence of primary symptoms in the two groups, the study group had much better alleviation of primary symptoms than the control group (P = 0.013, **Table 3**).

Comparison of general indexes of patients

The operation time, intraoperative blood loss and postoperative hospitalization time were compared between the two groups. According to the results, the control group and study group were not quite different in intraoperative blood loss and postoperative hospitalization time (all P>0.05, **Figure 2**), but the control group experienced a significantly shorter hospitalization time than the study group (P< 0.001, **Figure 2**).

Comparison of complications between two groups

According to the comparison of complications in the two groups, the control group showed a significantly higher incidence of complications than the study group (P = 0.004, **Table 4**).

Analysis of risk factors for CFL

According to the occurrence of postoperative CFL, the patients were divided into two groups: leakage group (n = 16) and non-leakage group (n = 111). Univariate analysis showed that BMI,

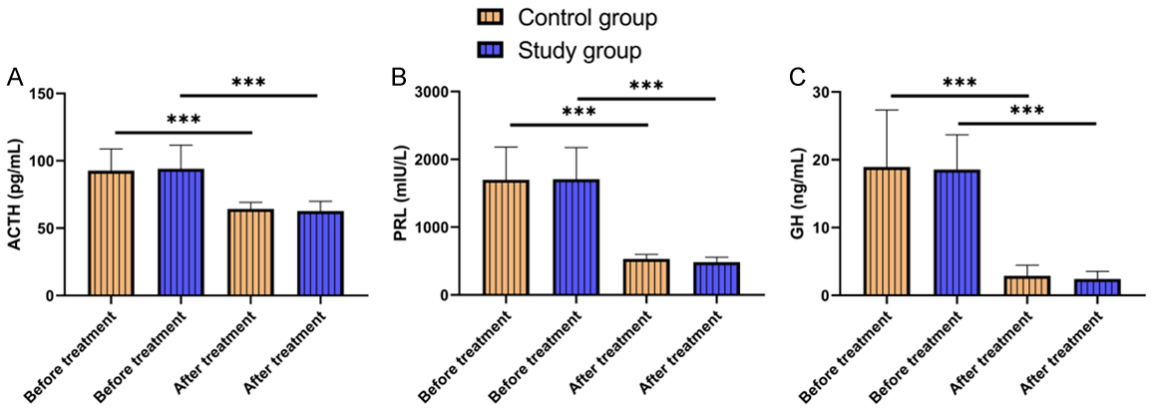

Figure 1. Changes of hormones in patients before and after treatment. A. Comparison of the changes in ACTH between the two groups before and after therapy. B. Comparison of the changes in PRL between the two groups before and after therapy. C. Comparison of the changes in GH between the two groups before and after therapy. Notes: GH: Growth hormone; PRL: Prolactin; ACTH: Adrenocorticotropic hormone. ***P<0.001.

Table 3. The alleviation of primary needle in patients

Group	Improved	Not improved	χ^2 value	*P* value
Control group (n = 54)	41 (75.93%)	13 (24.07%)	6.133	0.013
Study group (n = 73)	67 (91.78%)	6 (8.22%)		

tumor diameter, intraoperative CFL and treatment regimen were the risk factors of postoperative CFL (all P<0.01, **Table 5**). Then the significant indexes were assigned (**Table 6**). The backward LR scheme was adopted to analyze the significant factors with multivariate logistics regression analysis. According to the results, BMI (P = 0.003, OR = 8.791, 95% CI: 2.050-37.693), intraoperative CFL (P = 0.002, OR = 21.614, 95% CI: 0.305-153.162) and therapeutic regimen (P = 0.011, OR = 7.060, 95% CI: 1.554-32.076) were independent risk factors for postoperative CFL (P<0.01, **Table 7**).

Conclusion

Pituitary adenoma (PA) is a common nervous system tumor in clinical practice, which mainly occurs in the anterior and posterior lobes of the pituitary gland and craniopharyngioma epithelium. It is mainly manifested as dizziness, headache, decreased vision, pain in the waist and joints of the spine, swelling of hands and feet, and endocrine abnormalities. Without timely treatment, the continuous progress of the tumor will compromise the patient's visual field and growth, and even endanger the patient's life [15, 16].

Surgery is the primary clinical therapeutic regimen for PA. Commonly used surgical methods include transsphenoidal resection of PA, transoral transsphenoidal surgery, conventional craniotomy and minimally invasive surgery [17]. With the continuous development of minimally invasive technology, minimally invasive resection of PAs via single nostril transsphenoidal approach under the microscope or neuroendoscope has the advantages of rapid recovery, less trauma and fewer complications [18]. Although both the neuroendoscope and microscope can help accurately locate the boundary and position of the tumor, reduce the trauma and improve the treatment effect; the two methods have different effects in practical application. Therefore, MTS and NTS were compared in PA resection rate in this study. In this study, the effects of the two means were not quite different, and the total resection rate and hormone reduction rate of the two were comparable, but NTS greatly lowered the incidence of complications after operation and contributed to better alleviation of primary symptoms. Although NTS has a slightly longer operation time than MTS, the prolonged operation often increases the risk of postoperative infection. Research by Zhang et al. [19] has revealed that endoscopic transsphenoidal pituitary surgery is basically the same as microscopic transsphenoidal pituitary surgery for Cushing's disease, but endoscopic transsphenoidal pituitary surgery can lower the incidence

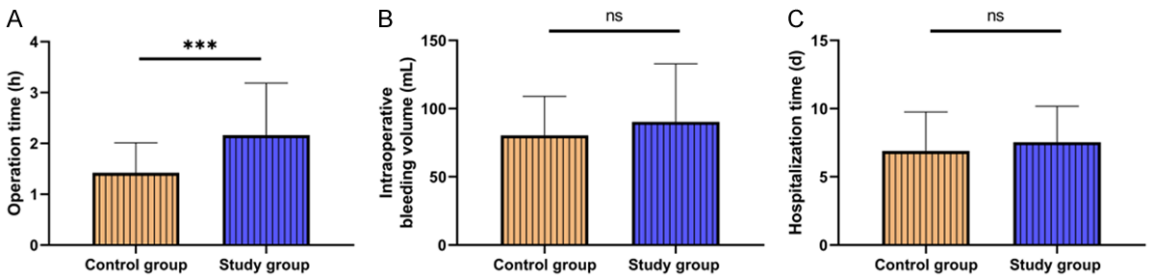

Figure 2. Comparison of general indexes. A. Comparison of operation time between the two groups. B. Comparison of intraoperative blood loss between the two groups. C. Comparison of hospitalization time between the two groups. Note: ***, P<0.001; ns, P>0.05.

Table 4. Statistics of complication rate

Group	Cerebrospinal fluid leakage	Diabetes insipidus	Intracranial infection	Total incidence rate
Control group (n = 54)	12 (22.22%)	3 (5.56%)	2 (3.70%)	17 (31.48%)
Study group (n = 73)	4 (5.47%)	2 (2.73%)	2 (2.73%)	8 (10.93%)
χ^2 value		8.269		
P value		0.004		

of postoperative complications. However, Razak et al. [20] have revealed that endoscopic transsphenoidal surgery is more effective in tumor resection than MTS, which is inconsistent with the results of the present study. We think this may be due to the small number of samples.

Currently, with the maturation in technology, the endoscopic transsphenoidal approach is more extensively used. However, with the gradual expansion of the exposure range of the skull base, the range of skull base defects caused by the surgical process also increases, and the incidence of postoperative complications such as CFL, intracranial infection and encephalocele increases accordingly [21]. Among various complications, CFL is the main complication after endoscopic transsphenoidal surgery [22]. A survey showed that the incidence of CFL after standard endoscopic transsphenoidal approach was 0.5%-15%, while that after extended endoscopic transsphenoidal approach was as high as 21% [23, 24]. Postoperative CFL slows the healing of incision, and may also cause intracranial retrograde infection, leading to meningitis. If too much cerebrospinal fluid is lost, low intracranial pressure, and tension pneumocephalus, etc. may occur, which may be life-threatening in severe cases [25]. In this study, the risk factors of CFL after operation were analyzed. According to results, BMI, intraoperative CFL and therapeutic regimen were the risk factors for postoperative CFL. Obesity is strongly associated with spontaneous and non-iatrogenic CFL. The pathophysiology is still uncertain, but the association between BMI increase and spontaneous CFL and also that between obesity and intracranial hypertension may have similar pathogenesis. Therefore, the increase of BMI leads to increased intracranial pressure, and persistent intracranial pressure increases the risk of postoperative CFL [26, 27]. Dlouhy et al. [28] have revealed notably higher average BMI in the group with CFL after operation than that in the group without CFL (39.2 kg/m^2 vs. 32.9 kg/m^2). When the tumor is large or grows on the saddle, the structure of the arachnoid membrane will be destroyed during the tumor resection, resulting in intraoperative CFL.

When CFL was found during the operation, more active skull base reconstruction was adopted. However, due to large skull defect, long operation time, postoperative necrosis of pedicled nasal mucosa flap and fat liquefaction, the repair failed, and then CFL occurred after the operation [22]. Duntze et al. [29] have found that the incidence of postoperative CFL in patients with intraoperative CFL was 11.5%, while that in patients without intraoperative CFL was 1.5%. The present study found for the first time that therapeutic regimen was a risk

Table 5. Univariate analysis

Factor	Leakage group (n = 16)	Non-leakage group (n = 111)	χ^2 value	*P* value
Gender			1.773	0.183
Male	9	43		
Female	7	68		
Age			0.011	0.915
>55 years old	9	64		
≤55 years old	7	47		
BMI (kg/m^2)			11.917	0.001
≥25	12	34		
<25	4	77		
Tumor diameter			10.714	0.004
<10 mm (microadenoma)	2	21		
10-30 mm (macroadenoma)	4	71		
>30 mm (giant adenoma)	8	21		
Pathological type			1.371	0.927
FSH adenoma	4	38		
Nonfunctional adenoma	4	22		
ACTH adenoma	2	17		
GH adenoma	2	11		
PRL adenoma	1	14		
Other	2	10		
Past surgery history			1.764	0.184
Yes	4	14		
No	12	97		
Diabetes mellitus			1.470	0.225
Yes	6	26		
No	10	85		
Hypertension			3.315	0.068
Yes	5	15		
No	11	96		
Intraoperative cerebrospinal fluid leakage			16.408	<0.001
Yes	5	4		
No	11	108		
Therapeutic regimen			7.901	0.004
Microscopic	12	42		
Neuroendoscopic	4	69		

Note: BMI: Body Mass Index; PRL: Prolactin; GH adenoma: growth hormone adenoma; ACTH: adrenocorticotropic hormone; FSH: Follicle stimulating hormone.

Table 6. Assignment

Factors	Assignment
BMI	≥25 (kg/m^2) = 1, <25 (kg/m^2) = 0
Tumor diameter	≥25 (kg/m^2) = 1, <25 (kg/m^2) = 0
Intraoperative CFL	<10 mm = 0, 10-30 mm = 1, >30 mm = 2
Therapeutic regimen	Control group = 1, Study group (n = 73) = 0
Occurrence of CFL	Yes = 1, No = 0

Note: BMI: Body Mass Index; CFL: Cerebrospinal Fluid Leakage.

factor for postoperative CFL. We believe that this is due to the fact that although the microscope has a better three-dimensional effect and less nasal injury, the light source and lens of the endoscope can be closer to the lesion and provide a more satisfactory visual field, thus reducing the risk of CFL during the operation.

Table 7. Multivariate logistics regression analysis

Factor	β value	Standard error	χ^2 value	*P* value	OR value	95% C.I.	
						Lower limit	Upper limit
BMI	2.174	0.743	8.565	0.003	8.791	2.050	37.693
Tumor diameter	0.852	0.500	2.900	0.089	2.345	0.879	6.252
Intraoperative cerebrospinal fluid leakage	3.073	0.999	9.463	0.002	21.614	3.050	153.16
Therapeutic regimen	1.954	0.772	6.405	0.011	7.060	1.554	32.076

As a result, the risk of postoperative CFL is reduced.

This study determined that MTS and NTS do noe effect the resection rate of PAs, but NTS can reduce the incidence of postoperative complications and it is a protective factor for postoperative CFL. However, this study still has some limitations. First of all, we do not have the results of long-term follow-up, so whether the therapeutic regimen affects the patients' long-term prognosis needs further study. Secondly, the study is a single-center retrospective study, and incomplete or inaccurate information have been eliminated during case collection, which might result in certain sampling bias. We hope to carry out more clinical studies in the future to improve the research conclusions.

To sum up, compared with MTS, endoscopic transsphenoidal surgery requires a notably longer time, but it can substantially reduce the incidence of postoperative complications, and endoscopic surgery is the protective factor of postoperative CFL.

Disclosure of conflict of interest

None.

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