Clinical study of pituitary tumors with EEA resection and its influence on the expression of tumor necrosis factor-α, interleukin-6, and interleukin-12 in patients

Wentao Wang,1 Dequan Zhong,1 Hua Cheng,2 Chengfu Ji,3 Zhouming Shen2 and Yangming Mao2

Abstract
The aim of this study is to investigate the efficacy of expanded endonasal approaches (EEAs) in the treatment of pituitary adenoma, and the effects of serum levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12) in patients were further analyzed. A total of 80 cases of patients with pituitary adenoma admitted to our hospital from January 2013 to May 2015 were randomly divided into the observation group and control group, with 40 cases in each group. The observation group was treated with EEA technique, while the control group was treated with transcranial microsurgery. The prolactin (PRL), growth hormone (GH) and other endocrine hormone indexes, as well as inflammatory factors such as TNF-α, IL-6, and IL-12 were compared before and 1 week after the operation between the two groups. Moreover, the scores of Karnofsky performance status (KPS) and Mini-Mental State Examination (MMSE) at preoperative and postoperative were also compared between the two groups. The operation time, hospitalization time, and postoperative complications were compared between the two groups. And the patients were followed up for 2 years to observe the recurrence rate. The operation time and hospital stay in the observation group were 62.8 ± 9.3 min and 12.5 ± 2.1 days, respectively, while the operation time and length of stay in the control group were 105.6 ± 15.7 min and 18.2 ± 3.4 days, respectively. The operation time and hospitalization time were shorter than those in the control group, and the differences were statistically significant (P < 0.05). Before surgery, there was no significant difference in serum levels of PRL and GH between the two groups (P > 0.05). At 1 week after surgery, the levels of PRL and GH in the two groups were significantly lower than those before surgery (P < 0.05). And the serum levels of PRL and GH in the observation group were significantly lower than those in the observation group at 1 week after the operation (P < 0.05). Before operation, there was no significant difference between the two groups of KPS and MMSE scores (P > 0.05). At 1 week after operation, the scores of KPS and MMSE in both groups were significantly higher than those before the operation (P < 0.05), and the scores of KPS and MMSE in the observation group were significantly higher than those in the control group (P < 0.05). Furthermore, there was no significant difference in the serum levels of IL-6, IL-12, and TNF-α between the two groups before operation (P > 0.05). At 1 week after surgery, the serum levels of IL-6, IL-12, and TNF-α in the two groups were significantly lower than those before surgery (P < 0.05), while the serum levels of IL-6, IL-12, and TNF-α in the observation group were evidently lower than those in the control group at 1 week after the operation. Besides, the incidence of postoperative complications in the observation group was 7.5%, which was significantly lower than that in the control group (17.5%) (P < 0.05). All the patients in the two groups were followed up for 2 years. And there was no recurrence in the observation group and one case in the control group. The therapeutic effect of EEAs on pituitary adenoma is better. It can improve the level of high endocrine hormone in patients with pituitary adenoma, improve the functional status of the patients, reduce the serum level of inflammatory factors, and shorten the hospital stay. Meanwhile, it also has the characteristics of fewer complications and low recurrence rate, so it can be popularized in clinical practice.

1Department of Neurosurgery, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, PR China
2Department of Neurosurgery, Fu’ning People’s Hospital, Fu’ning, Jiangsu, P.R. China
3Department of Hematology, Fu’ning People’s Hospital, Fu’ning, Jiangsu, P.R. China

Corresponding author:
Dequan Zhong, Department of Neurosurgery, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, P.R. China
Email: ce22671@163.com
Pituitary tumor belongs to the category of intracranial tumors. It is a common benign tumor. The incidence of intracranial tumors in the population was only lower than that of gliomas and meningiomas, accounting for about 10% of intracranial tumors. Pituitary adenoma is a group of tumors that occur in the anterior lobe of the pituitary and the posterior lobe of the pituitary, as well as the residual cells of the craniohypophyseal epithelium. And it is the most common sellar region tumor. It not only has the characteristics of space-occupying lesions but also is an endocrine gland tumor, which can affect the body’s metabolism and trigger a variety of endocrine diseases. With the development of detection methods, it was shown in recent reports that the detection rate is about 15%–20%. At present, surgical treatment is the main treatment for pituitary tumor, mainly including craniotomy via frontal and temporal approach and transsphenoidal surgery. With the application of surgical microscopes and the development of neuroendoscopy, transsphenoidal surgery has evolved from mouth-nasal-butterfly to today’s expanded endonasal approaches (EEAs). The EEA method is simple and convenient, which can greatly shorten the operation time and reduce the side injury. At the same time, under the nasal endoscope, the conditions of carotid artery canal, the optic canal, and the cavernous sinus can be identified through different angles, and the dead angle can be eliminated, thereby the tumor can be completely removed under the guidance of it. Meanwhile, whether there is the residual tumor can be observed. In addition, the surgical closure method is simple, there is no need for suture removal after operation, and the recovery is fast enough to achieve minimally invasive surgery. At present, there are few reports about the impact of EEAS on tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-12 (IL-12) in patients with pituitary adenoma. In view of this, research has been carried out in this field and the report is as follows.

**Materials and methods**

**General data**

A total of 80 patients with pituitary adenoma admitted to our hospital from January 2013 to May 2015 were selected as the research subjects, including 47 males and 33 females, aged from 24 to 68 years, with an average onset age of 46.7 ± 2.1 years. All patients underwent magnetic resonance imaging (MRI) and computed tomography (CT) examinations. The results showed that the space-occupying lesions in sella region were tumors with a diameter of 5–35 mm. And the postoperative pathological examinations were confirmed as pituitary tumors. All patients were conscious at admission and had varying degrees of headache. Among them, there were 45 cases of patients with varying degrees of vision loss and visual field defects, 5 cases of acromegaly, 14 cases of amenorrhea, and 6 cases of sexual dysfunction. Then a total of 80 cases of patients with pituitary adenoma were randomly divided into observation group and control group, with 40 cases in each group. There was no significant difference in general data between the two groups (P > 0.05), therefore they were comparable.

**Methods**

The observation group was treated with EEAs. After tracheal intubation with general anesthesia, the patient was placed in a supine position, head tilted 30°, and the pillow was placed under the shoulder to make the head 15° higher than the heart plane. All patients were treated by right nasal approach, while three cases were incised 0.5–1 cm obliquely along the nasal vestibule base of the right nasal cavity as the nasal cavity was too small. The patient was placed at 0° or 30° to look for sphenoid sinus orifice by the nasal endoscope. For patients with no deviated nasal septum or wide nasal cavity, the recessus sphenoidal can be found.
directly from the posterior segment of middle turbinate. If the middle turbinate affects the approach, the posterior lower part can be squeezed outwards with a blunt dissector to displace the fracture, thereby finding the recessus sphenoidalis. After the recessus sphenoidalis was determined using a curved suction tube, 1 mL of 0.5% procaine (with a small amount of epinephrine) was injected submucosally into the septum approximately 1–1.5 cm from the sphenoid sinus, and then approached the bone surface to incise it vertically with a nasal septum. The upper boundary does not exceed the horizontal extension line of the upper boundary of the sphenoid sinus opening, and the lower boundary was 1 cm above the posterior nostril. The lateral bone was laterally detached to fully expose the sphenoid sinus opening. In the posterior segment of the nasal septum, the posterior segment of the nasal septum was fractured by a lateral compression, and the lateral mucosa was separated slightly. Under direct vision, the dilator was inserted between the two sides of the mucous membrane, and the two leaves rode on the sphenoidal crest. While tightening and expanding the dilator, the dilator was pushed to the contralateral side of the sacral vertical plate and the septal cartilage to the contralateral side, revealing bilateral sphenoid sinus openings. Under the nasal endoscope, the right side of the opening was extended downward and inward with the sphenoid sinus rongeur, and the upper edge of the sphenoidal sinus did not exceed the edge of the sphenoid sinus, so as to avoid the low level of the horizontal plate of the ethmoid bone, thereby resulting in the fracture to cause cerebrospinal fluid leakage. At the same time, the sphenoidal crest was removed, the left side of the sphenoid sinus was enlarged, and the anterior wall of bilateral sphenoid sinus was completely opened. A part of the remnants of the sphenoidal crest is regarded as a qualitative marker of midline. If sphenoid sinus septum deviates from midline, the remaining sphenoidal crest is the only midline marker. The width of the anterior tibial window was about 1–1.5 cm and height 1.5–2 cm. After the tumor was excised, it was seen that the sella septum was sunk and hemostasis was completely stopped, then the cavity of the operation was flushed, EC gelatin sponge filling was put into the cavity, of which two cases were prevented from cerebrospinal fluid leakage, and the abdominal fat was stained with EC glue to fill the sphenoid sinus cavity. The dilator was removed, the narrow nasal pressure plate was inserted into the left nasal cavity and the septum was pressed to the right to compress it, and then the rubber was placed in the bilateral nasal cavity into the Vaseline gauze. When the outer nose was notched, a No. 0 silk suture was used to remove the pharynx. The fill gauze and the operation were over. Systemic antibiotics and hormones were applied to the patients. Forty-eight hours after surgery, the Vaseline gauze was removed from both sides of the nasal cavity.

The control group was treated with transcranial microsurgery: the pterional or inferior frontal approach was selected for craniotomy. The lateral fissure, optic chiasmatic pool, and internal carotid artery pool were opened, and cerebrospinal fluid was fully released, so that the optic nerve, internal carotid artery, and tumor were fully exposed. Then the tumor was punctured and aspirated. The aneurysm was excluded and the tumor was resected. Meanwhile, the systemic antibiotics and hormones were also applied to these patients.

**Observed indicator**

1. The serum levels of prolactin (PRL), growth hormone (GH), and other endocrine hormones were compared between the two groups before and 1 week after operation. Meanwhile, the serum levels of PRL and GH were measured by radioimmunoassay. Reference range for normal values is PRL: 0.01–1.13 nmol/L and GH: <0.746 nmol/L.

2. The serum levels of TNF-α, IL-6, IL-12, and other inflammatory factors were compared between the two groups before and 1 week after operation. The serum levels of TNF-α, IL-6, and IL-12 were measured by enzyme-linked immunosorbent assay. The kits were purchased from Shenzhen Jing Mei Biological Engineering Co., Ltd.

3. The Karnofsky performance status (KPS) and Mini-Mental State Examination (MMSE) scores were compared between the two groups before and 1 week after operation. The KPS scale is the most commonly used tool to assess the functional status of patients, and is the criteria for evaluating the quality of life of cancer patients. The scale was divided into 11 grades (100 = normal function, 0 = death), which was evaluated by the medical staff according to
the patient’s functional status within the range of 0–100 points. The higher the score, the better the functional status of the patient. The MMSE scale includes the following seven aspects: temporal orientation, location orientation, immediate memory, attention and calculation, delayed memory, language, and visual space. A total of 30 topics were scored correctly for each point. The score was considered normal in the range of 27–30 points, and the score <27 points was regarded as cognitive dysfunction.

4. The operation time and hospitalization time of patients were observed and compared between the two groups.

5. The postoperative complications of the patients were observed. Patients were followed up for 2 years and were regularly examined by nasal endoscopy, CT, and MRI to observe the recurrence. The criteria for recurrence diagnosis: Patients with effective surgery reappeared with clinical symptoms or exacerbations, with elevated levels of endocrine hormones, and the imaging examination revealed the emergence of new organisms or the increased volume of tumor.

Statistical method

SPSS 21.0 software was used for statistical analysis. The measurement data were detected by t-test and represented by mean ± standard deviation. And the counting data were determined by chi-square test and expressed by percentage. P < 0.05 means a significant difference.

Results

Comparison of operation time and length of stay between two groups

The operation time and hospital stay in the observation group were 62.8 ± 9.3 min and 12.5 ± 2.1 days, respectively, while the operation time and length of stay in the control group were 105.6 ± 15.7 min and 18.2 ± 3.4 days, respectively. The operation time and hospitalization time were shorter than those in the control group, and the differences were statistically significant (P < 0.05), as depicted in Table 1.

Comparison of endocrine hormone indexes between two groups of patients

Before surgery, there was no significant difference in serum levels of PRL and GH between the two groups (P > 0.05). At 1 week after surgery, the levels of PRL and GH in the two groups were significantly lower than those before surgery (P < 0.05). And the serum levels of PRL and GH in the observation group were significantly lower than those in the observation group at 1 week after the operation (P < 0.05), as demonstrated in Table 2.

Comparison of KPS and MMSE scores between two groups of patients

Before operation, there was no significant difference between the two groups of KPS and MMSE scores (P > 0.05). At 1 week after operation, the scores of KPS and MMSE in both groups were significantly higher than those before the operation (P < 0.05), and the scores of KPS and MMSE in the observation group were significantly higher than those in the control group (P < 0.05), as shown in Table 3.

Comparison of serum inflammatory factors between two groups of patients

There was no significant difference in the serum levels of IL-6, IL-12, and TNF-α between the two groups before operation (P > 0.05). At 1 week after surgery, the serum levels of IL-6, IL-12, and TNF-α in the two groups were significantly lower than those before surgery (P < 0.05), while the serum levels of IL-6, IL-12, and TNF-α in the observation group were evidently lower than those

| Groups        | n  | Operation time (min) | Hospital stay (days) |
|---------------|----|----------------------|----------------------|
| Control group | 40 | 105.6 ± 15.7         | 18.2 ± 3.4           |
| Observation group | 40 | 62.8 ± 9.3          | 12.5 ± 2.1           |
| t             | 6.093 |                     | 7.145                |
| P             | 0.029 |                     | 0.023                |
in the control group at 1 week after the operation \((P < 0.05)\), as displayed in Table 4.

**Comparison of postoperative complications and recurrence between two groups of patients**

The incidence of postoperative complications in the observation group was 7.5\%, which was significantly lower than that in the control group (17.5\%) \((P < 0.05)\). All the patients in the two groups were followed up for 2 years. And there was no recurrence in the observation group (as shown in Figure 1) and one case in the control group (Table 5).

**Summary**. The operation time and hospital stay in the observation group were 62.8 ± 9.3 min and 12.5 ± 2.1 days, respectively, while the operation time and length of stay in the control group were 105.6 ± 15.7 min and 18.2 ± 3.4 days, respectively. The operation time and hospitalization time were shorter than those in the control group, and the differences were statistically significant \((P < 0.05)\). Before surgery, there was no significant difference in serum levels of PRL and GH between the two groups \((P > 0.05)\). At 1 week after surgery, the levels of PRL and GH in the two groups were significantly lower than those before surgery \((P < 0.05)\). And the serum levels of PRL and GH in the observation group were significantly lower than those in the observation group at 1 week after the operation \((P < 0.05)\). Before operation, there was no significant difference between the two groups of KPS and MMSE scores \((P > 0.05)\). At 1 week after operation, the scores of KPS and MMSE in both groups were significantly higher than those before the operation \((P < 0.05)\), and the scores of KPS and

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**Table 2.** Comparison of endocrine hormone indexes between two groups of patients.

| Groups          | n  | PRL (nmol/L) Preoperative | I week after surgery | GH (nmol/L) Preoperative | I week after surgery |
|-----------------|----|---------------------------|----------------------|---------------------------|----------------------|
| Control group   | 40 | 5.13 ± 0.68               | 0.85 ± 0.12          | 3.76 ± 0.35               | 0.72 ± 0.16          |
| Observation group| 40 | 5.14 ± 0.75               | 3.29 ± 0.56          | 3.74 ± 0.42               | 2.01 ± 0.72          |
| \(t\)           |    | 0.904                     | 8.312                | 1.071                     | 7.446                |
| \(P\)           |    | 0.316                     | 0.021                | 0.294                     | 0.028                |

GH: growth hormone; PRL: prolactin.

**Table 3.** Comparison of KPS and MMSE scores between two groups of patients.

| Groups          | n  | KPS (points) Preoperative | I week after surgery | MMSE (points) Preoperative | I week after surgery |
|-----------------|----|---------------------------|----------------------|---------------------------|----------------------|
| Control group   | 40 | 61.62 ± 7.32              | 70.78 ± 6.13         | 10.48 ± 1.97              | 13.73 ± 1.08         |
| Observation group| 40 | 60.54 ± 6.28              | 80.25 ± 5.97         | 10.39 ± 1.86              | 15.04 ± 1.19         |
| \(t\)           |    | 1.005                     | 7.009                | 1.413                     | 8.703                |
| \(P\)           |    | 0.209                     | 0.024                | 0.165                     | 0.017                |

KPS: Karnofsky performance status; MMSE: Mini-Mental State Examination.

**Table 4.** Comparison of serum inflammatory factors between two groups of patients (ng/mL).

| Groups          | n  | IL-6 Preoperative | I week after surgery | IL-12 Preoperative | I week after surgery | TNF-\(\alpha\) Preoperative | I week after surgery |
|-----------------|----|-------------------|----------------------|-------------------|----------------------|-----------------------------|----------------------|
| Control group   | 40 | 1.39 ± 0.57       | 0.81 ± 0.17          | 0.72 ± 0.17       | 0.49 ± 0.08          | 1.51 ± 0.47                 | 0.61 ± 0.24          |
| Observation group| 40 | 1.38 ± 0.43       | 0.52 ± 0.13          | 0.71 ± 0.15       | 0.35 ± 0.06          | 1.49 ± 0.52                 | 0.43 ± 0.11          |
| \(t\)           |    | 0.762             | 7.591                | 0.618             | 6.044                | 0.805                       | 6.167                |
| \(P\)           |    | 0.315             | 0.024                | 0.416             | 0.032                | 0.683                       | 0.031                |

IL-6: interleukin-6; IL-12: interleukin-12; TNF-\(\alpha\): tumor necrosis factor-\(\alpha\).
MMSE in the observation group were significantly higher than those in the control group ($P < 0.05$). Furthermore, there was no significant difference in the serum levels of IL-6, IL-12, and TNF-α between the two groups before operation ($P > 0.05$). At 1 week after surgery, the serum levels of IL-6, IL-12, and TNF-α in the two groups were significantly lower than those before surgery ($P < 0.05$), while the serum levels of IL-6, IL-12, and TNF-α in the observation group were evidently lower than those in the control group at 1 week after the operation. Besides, the incidence of postoperative complications in the observation group was 7.5%, which was significantly lower than that in the control group (17.5%) ($P < 0.05$). All the patients in the two groups were followed up for 2 years. And there was no recurrence in the observation group and one case in the control group. Tips: The therapeutic effect of EEA on pituitary adenoma is better. It can improve the level of high endocrine hormone in patients with pituitary adenoma, improve the functional status of the patients, reduce the serum level of inflammatory factors, and shorten the hospital stay. Meanwhile, it also has the characteristics of fewer complications and low recurrence rate, so it can be popularized in clinical practice.

**Discussion**

Pituitary adenoma is usually located in the anterior pituitary of the brain, and the large adenoma can cause the disturbances in endocrine. At the same time, it can damage the optic nerve and related cerebral nerve functions of patients, and reduce the quality of life of patients.5,6 The main method for clinical treatment of pituitary adenoma is surgery. Surgery on these pituitary adenomas can improve the endocrine dysfunction, protect the function of the pituitary gland, release the oppressed nerves, and restore their function.7,8 However, because the location of the pituitary adenoma is a saddle region and the surrounding structure is complex, there is no sufficient operation space. At the same time, the pituitary itself has more complicated functions, thereby increasing the difficulty of surgical treatment. The main treatment method in clinic is transcranial approach microsurgery. This treatment method has a clearer view of the operation, but it...
will cause greater trauma to the patient and increase the amount of bleeding. The postoperative patient will produce a series of complications. At the same time, this treatment method is prone to cause hypothalamic and pituitary damage, and poses a serious threat to the patient’s life safety.9,10

With the progress of endoscopic sinus surgery, many scholars11,12 have adopted EEA resection for the treatment of pituitary adenoma. This method has short path, small damage, simple operation, faster postoperative recovery, good illumination and magnification, clear image and multiple perspectives, as well as a good panoramic view of the suprasellar and saddle region. Anatomical studies13 have demonstrated that nasal endoscopes are superior to surgical microscopes in exposing the operative field, which overcome the shortcomings of the lateral wall of the sphenoid sinus which cannot be observed under microscope. The results of this study showed that the operative time and length of stay in the observation group were shorter than those in the control group \(P<0.05\). Furthermore, the incidence of postoperative complications in the observation group was 7.5%, which was significantly lower than that in the control group (17.5%) \(P<0.05\). All the patients in the two groups were followed up for 2 years. And there was no recurrence in the observation group and one case in the control group. These results suggest that EEA resection for pituitary adenoma has few complications and low recurrence rates.

The clinical symptoms of pituitary tumors mainly include headaches, hypoplasia, and changes in visual field and other symptoms of intracranial neurological dysfunction, endocrine dysfunction, and cognitive dysfunction. The results of this study showed that the serum levels of PRL and GH in the observation group were significantly lower than those of the control group \(P<0.05\) at 1 week after operation \(P<0.05\), while the scores of KPS and MMSE in the observation group were significantly higher than those of the control group at 1 week after the operation \(P<0.05\). Therefore, it can be seen that EEA resection can improve endocrine dysfunction, functional status, and quality of life in patients with pituitary adenoma.

Related data14 show that TNF-\(\alpha\) can promote the adhesion of tumor cells and endothelial cells, make tumor cells more easily adhere to the extracellular matrix, significantly enhance the invasion ability of pituitary tumor cells, and promote the occurrence and development of pituitary adenoma disease. IL-6 and IL-12, as common inflammatory factors in the body, play an important role in cell proliferation and regulation of blood cell differentiation. Several studies have pointed out that IL-6 and IL-12 are associated with the occurrence, development, invasion, and metastasis of tumors.15 Pituitary adenoma promotes the regulation of IL-6 level, promotes neovascularization of tumor, and causes invasive growth of pituitary tumor. The reason is that IL-6 can activate the JAK-STAT signaling pathway in cell by combining with its receptor. IL-12, as a type of cytokine synthesized by antigen-presenting cells, can promote the production of TH1 in helper T cells and lead to the emergence of cellular immune responses, which can be used as a potent antitumor factor. When its level rises, it can be seen that the inflammatory response in vivo is more pronounced. The results of this study showed that the serum levels of IL-6, IL-12, and TNF-\(\alpha\) in the observation group were significantly lower than those in the control group at 1 week after surgery \(P<0.05\). It is suggested that EEA resection can effectively reduce serum levels of TNF-\(\alpha\), IL-6, and IL-12 and relieve clinical symptoms.

To sum up, the therapeutic effect of EEAs on pituitary adenoma is better. It can improve the state of high endocrine hormone levels in patients with pituitary adenomas, at the same time, it can also improve the functional status of patients, reduce the serum levels of inflammatory factors in patients, thereby shortening the length of stay, and it also has the characteristics of less complications and low recurrence rate. Therefore, it can be promoted in clinical practice.

**Declaration of conflicting interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Ethical approval**
Written informed consent was obtained from all patients and the present study was approved by the Ethics Committee of Funing People’s Hospital, Jiangsu, P.R. China (No. Ethics Institute 20130147). The present study was performed in conformity with the Declaration of Helsinki and all the patients and their families were informed and they signed informed consent.
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ORCID iD
Yangming Mao https://orcid.org/0000-0001-7314-2497

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