

Endoscopic transsphenoidal treatment of hormonally active pituitary adenomas

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Abstract

AIM OF THE STUDY: The paper presents endoscopic surgical technique used in the treatment of hormonally active pituitary adenomas and assessment of the method in terms of its effectiveness and safety.

MATERIAL AND METHODS: In 217 cases the surgery was performed due to pituitary adenomas applying the technique developed by Jho and Carrau, with our own modifications. 70 patients were treated for hormonally active adenomas. The group consisted of 36 somatotrophic adenomas, 21 prolactinomas and 13 corticotrophic adenomas. There were 51 females and 19 males with mean age of 42.6 years (range 11–77 years). The follow-up period was between 7 and 56 months (mean - 34 months). The effectiveness and occurrence of complications were confirmed on the basis of neurosurgical, laryngological, endocrinological, ophthalmological examinations and neuroimaging.

RESULTS: Biochemical and neurosurgical criteria for complete resection were obtained in 21 (58.3%) of 36 patients with all somatotrophic adenomas. In the group of prolactinomas complete resection was achieved in 17 (80.9%) of 21 patients. Of the 13 patients with Cushing's disease 11 (84.6%) were cured. In the studied group there were no deaths. In the postoperative course only 2 (2.8%) patients suffered liquorrhoeas and new anterior lobe pituitary insufficiency was noted in 8 (11.4%) cases. Meningitis was noted in 1 (1.4%) case and another 1 (1.4%) patient had epistaxis which required repeated endoscopic surgery.

CONCLUSIONS: Endoscopic technique is an effective method of treatment of hormonally active pituitary adenomas. It is characterised as being minimal invasive and has a low severe complication rate.

INTRODUCTION

Tumours of the sella turcica region were a serious challenge for surgeons in the early 20th century. However, it was then that the two basic surgical approaches to the pituitary developed: transcranial and transsphenoidal ones, whose improved variants are in use until the present day. Since the 1960s, microsurgical transsphenoidal approach has been a recognised and safe standard in the treatment of pituitary adenomas [20]. At present it is believed that over 95% of pathological states of the sella region that can be treated surgically qualify for using the endonasal transsphenoidal surgical approach [7]. The dynamic development of diagnostic techniques, improvement of surgical equipment, more widespread access to new optical systems and methods of digital transmission of images allowed for the development of minimum invasive neurosurgical methods in pituitary surgery [1,4,15,18,21,24]. In 1996 and 1997 Jho and Carrau described the technique of purely endoscopic transsphenoidal procedures, which determined the basic principles of the new microinvasive method of treatment of pathologies of the sella turcica region [8,26]. The aim of the paper is to present the endoscopic surgical technique used in the treatment of hormonally active pituitary adenomas, and to assess the method in terms of effectiveness and safety.

MATERIAL AND METHODS

In the Department of Neurosurgery of the Silesian Medical University in Katowice, Poland the one and only method of transsphenoidal surgeries performed in the case of sella region pathologies since 2001 has been the endoscopic technique based on the experiences of Jho and Carrau, with our own modifications [31]. Between October 2001 and June 2006, 286 endoscopic explorations of sella turcica were performed. In 217 cases the surgery was performed due to pituitary adenomas, of which 70 were hormonally active adenomas. In that group 36 somatotrophic adenomas, 21 prolactinomas and 13 corticotrophic adenomas were operated upon. Of all the 70 endoscopic surgeries 7 were repair procedures after transsphenoidal transeptal procedures. The repeated procedures applied to the following adenomas: 4 - somatotrophinoma, 2 - prolactinoma and 1 - corticotrophinoma. The patients who underwent surgery due to somatotrophic adenomas were 23 females and 13 males. The youngest patient was 24, the oldest - 77. The average age in that group of patients was 50.4 years of age. In the group of patients with prolactinomas there were 17 women and 4 men. The youngest patient was 16 years of age, the oldest - 64. The average age in that group of patients was 34.7. Among the patients with corticotrophinoma there were 11 women and 2 men. The youngest patient was 11 years of age, the oldest - 58. The average age in that group was 42.8. Before the surgery, all the patients underwent magnetic resonance imaging

(MRI) examination of the pituitary. Most of the examinations were performed using the apparatus General Electric Signa 1.5 T in frontal and sagittal scans in the T1 - weighted sequences, before and after intravenous administration of paramagnetic contrast medium, in layers of 3 mm in thickness. On the basis of the MRI examination, adenomas were classified as microadenomas or macroadenomas. Macroadenomas were divided into intrasellar as well as intra- and suprasellar ones. The intra- and suprasellar adenomas reached above the line connecting tuberculum of the sella with posterior clinoid processes in the clival (midline) plane, and above the line passing through upper margins of intracavitary sections of both internal carotid arteries in frontal plane. The proportion of adenoma to cavernous sinuses was assessed in the five-degree Knosp's scale. The characteristics of the adenomas operated upon, depending upon the size, suprasellar growth, Knosp's scale and results of treatment are presented in Table 1 and Table 2. All the patients had been carefully examined and prepared for the surgery in endocrinological clinics. In the case of patients with somatotrophinoma before the procedure analogues of somatotrophin inhibiting factor with prolonged activity were always used. Most patients with Cushing's disease were treated with blockers of steroidogenesis. Two days (48 hours) before the surgical procedure, application of neomycin in aerosol to both nasal passages started, along

Table 1. Characteristics of operated adenomas (type of tumor, grading in Knosp scale, treatment results).

Type of tumor	Grade according to Knosp scale	Number of patients	Number of successfully treated	Percentage of successfully treated
GH secreting adenomas	0	6	6	100
	I	13	11	84.6
	II	5	3	60
	III	6	1	16.7
	IV	6	0	0
	Total	36	21	58.3
PRL secreting adenomas	0	9	9	100
	I	8	7	87.5
	II	1	1	100
	III	1	0	0
	IV	2	0	0
	Total	21	17	80.9
ACTH secreting adenomas	0	10	9	90
	I	2	7	50
	II	1	1	100
	III	0	0	0
	IV	0	0	0
	Total	13	11	84.6

with intravenous administration of *hydrocortisonum hemisuccinatum*, in the case of patients with corticotrophic adenomas in a dose of 400 mg/day, while in other patients in a dose of 200 mg/day. The anaesthesia procedure resulted from systemic disturbances, due to generalised dishormonose, and the fact that in the first phase of the procedure anaemisation of mucous membrane of the nasal cavity was carried out, applying adrenaline solution. Anaesthesia was induced by means of thiopental, phentanyl and cisatracurium. Rocurorium was used for endotracheal intubation of patients with acromegaly. In supporting anaesthesia, sevoflurane was applied in air mixture with oxygen. In patients with arterial hypertension, who constituted the majority of patients with acromegaly and Cushing's disease, remiphenylyl was applied in order to prevent violent increase of arterial pressure and tachycardia after nasal administration of adrenaline solution.

Table 2. Characteristics of operated adenomas (tumor type according to MRI classification, size of the tumor and treatment results).

Type of tumor	Tumor size	Number of patients	Number of successfully treated	Percentage of successfully treated
GH secreting adenomas	microadenoma	6	6	100
	intrasellar macroadenoma	12	4	33.3
	suprasellar and intrasellar macroadenoma	18	11	61.1
	Total	36	21	58.3
PRL secreting adenomas	microadenoma	7	7	100
	intrasellar macroadenoma	4	3	75
	suprasellar and intrasellar macroadenoma	10	7	70
	Total	21	17	80.9
ACTH secreting adenomas	microadenoma	10	9	90
	intrasellar macroadenoma	2	1	50
	suprasellar and intrasellar macroadenoma	1	1	100
	Total	13	11	84.6

For the surgical procedure, a stiff neuroendoscope was used, having the diameter of 4 mm and 0° and 30° angle optics, by Storz. The sphenoid sinus was approached always via the right nasal passage. Having identified the right nasal opening of the sphenoid sinus, frontal sphenoidotomy was performed, diameter about 25 mm. Sella turcica was opened from the tuberculum of the sella from the front to the clivus at the back, and to both prominences of internal carotid arteries, laterally. After incision of the pachymeninx, and localisation of the adenoma, it was removed by means of aspirating nozzle, pituitary curettes, and suitable micropunch. The application of 30° angular optics contributed to thorough inspection of lateral parts of the sella and suprasellar region. After removal of the adenoma, for performance of thorough haemostasis, the surgeons proceeded to reconstruct the anatomic structures of open sella turcica. For that purpose, only synthetic materials were used. The site of adenoma was filled with haemostatic sponge (Spongostan, Curaspon). The sella wall was reconstructed by means of fibrin tissue glue Tissucol and artificial meninx. In the last two years the two-component absorbed haemostatic preparation Tachocomb was used. Having performed the sella reconstruction, the endoscope was removed and in the right nasal passage a thin layer of haemostatic foam was retained. The left nasal passage was left totally unobstructed and patent. Neither stiff nasal dilator nor postoperative tamponage of both nasal passages after the operation were applied. All endoscopic explorations of the sella were carried out by a permanent team, composed of two neurosurgeons, a laryngologist and an anaesthesiologist. After the surgery, obligatory antibiotic protection was initially applied. At present, a postoperative therapy with antibiotics is applied only in patients with liquorrhoea occurring during the procedure. On the first day after the operation the patients were observed for diabetes insipidus and postoperative liquorrhoea. The next day after the operation patients were mobilised and fully selfdependent. They stayed in the hospital for 3–6 after the operation. 4–6 weeks after the operation the patients underwent endocrine and ophthalmological examinations, while 3 months after the operation the MRI follow-up examination of the pituitary was performed. The follow-up period after surgery was between 7 and 56 months, 34 months on average. The removed adenomas underwent classical histopathological examination by staining with eosin and hematoxylin. In order to differentiate pituitary cells, selective p.a.S. and orange G staining was performed. In order to differentiate adenoma, its capsule, and unchanged pituitary, Masson's trichrome was used. Functional profile of pituitary adenomas was determined by means of immunohistochemical reactions. Antibodies: ACTH, hGH, LH, FSH and PRL by DAKO Cytomation were used, as well as antibodies TSH by NOVOCASTRA. The occurrence of complications was confirmed on the basis of surgery protocols and follow-ups in: laryngology, endocrinology, ophthalmology, magnetic resonance

tomography. The following recovery criteria for pituitary adenomas were assumed: in the case of somatotrophic tumor the level of GH <2.5 ng/ml, the level of GH in OGTT <1 ng/ml, the level of IGF-I - norm suitable to sex and age. For prolactinomas the recovery criterion was the level of PRL <15 ng/ml in men and <20 ng/ml in women. In the case of Cushing's disease the success of therapy was based upon normal indications of free cortisol level in 24-hour urine collection - <135 nmol/24 h, and normal level of cortisol - <20 µg/dl in the morning and ACTH - <60 pg/ml in serum.

RESULTS

Of the 36 patients with somatotrophic adenomas, in 21 (58.3%) the tumour was removed completely and the existing biochemical criteria for withdrawal were complied with. The correct level of GH and IGF-I was obtained in 22 patients (61.1%). In the case of somatotrophic microadenomas (6 patients) there was 100% recovery rate. For macrosomatotropinoma the recovery rate was 50%. When considering noninvasive macroadenomas (0°, I°, and II° in Knosp's scale) the recovery criteria were complied with in 77.8% of surgically treated patients, while in the case of macroadenomas infiltrating cavernous sinuses (III° and IV° in Knosp's scale) only 8.3% of patients after surgeries recovered. Of the 21 patients with prolactinomas the total recovery rate was achieved in 17 (80.9%). All seven patients with microprolactinomas were cured. In the case of macroprolactinomas the recovery rate was 71.4%, while for noninvasive macroadenomas it was 88.9%. None of the prolactine macroadenomas which infiltrated cavernous sinuses was completely treated. Of the 13 patients with Cushing's disease who underwent surgery, 11 (84.6%) were cured. The recovery rate in the case of corticotrophic microadenomas was 90%, for macroadenomas - 66.7%. None of the corticotrophic infiltrated cavernous sinuses. Of the 7 cases of repeated surgical procedures, recovery was achieved in 3 cases (42.8%). In 2 cases of repeated procedure, prolactine

macroadenoma and recurrent corticotrophic macroadenoma were completely removed. None of the 4 somatotrophic adenomas was removed totally in the course of repeated procedure. All the recurrent somatotropinomas infiltrated cavernous sinuses. In the group of 70 patients who underwent surgery, no death occurred. There were no rhinological complications. In the course of surgical procedures, 12 (17.1%) liquorrhoeas were noted during the operation, but only 2 (2.8%) after the operation. In one case the liquorrhoea occurred on the second day after the surgery, in the other 2 weeks after discharge from the hospital. In both cases the liquorrhoea was arrested by lumbar drainage of the cerebrospinal fluid. A new postoperative anterior lobe pituitary insufficiency was noted in 8 (11.4%) patients. In 4 (5.7%) patients revealed transient diabetes insipidus, lasting for a few days and requiring treatment. No patient revealed lasting diabetes insipidus. Cerebrospinal meningitis, effectively cured with antibiotics, was noted in 1 (1.4%) case. 1 (1.4%) patient had massive epistaxis, 17 days after the surgery, which required immediate nasal packing, followed by endoscopic exploration of the surgically treated area. The reason for the epistaxis was the recanalised right sphenopalatine artery, which was repeatedly coagulated in the course of repeated endoscopic surgery. Table 3. shows the complications noted in the patients who underwent endoscopic surgical procedures. All the patients, especially those who had previously undergone surgical procedures by transsphenoidal, transeptal method, valued most the possibility of "normal" breathing through the nose, provided immediately after the procedure. The same patients after repeated surgical procedures reported less profound pain sensation after endoscopic procedure.

DISCUSSION

The use of endoscope in transsphenoidal surgery of the pituitary has become almost standard, yet pure endoscopic endonasal approach is still practised only in a few centres. First reports concerning the endoscopic treatment methods of sella pathologies stressed its minimum level of invasiveness, first of all [5,8,26]. At present, on the basis of numerous reports based on bigger groups of patients who underwent endoscopic surgery, one can attempt to compare the effectiveness of transeptal method of treatment with the use of microscope with 'pure' endoscopic method [9,14,27]. The present recovery criteria are based upon the consensus statement published in the year 2000 [16]. The percentage of full recovery after surgery of somatotropinoma depends upon the size of the adenoma, and - for the "classical" method with the use of microscope - varies between 20 and 95%. Shimon *et al.* [32], for the 98 surgically treated patients with acromegaly, achieved 84% recovery for microadenomas, 73% for macroadenomas having a diameter of 11-20 mm, and merely 20% for bigger tumours, exceeding 20 mm in diameter. De *et al.* [11], when analysing the postoperative course in 90 patients with somatotropinomas,

Table 3. Complications in operated group of patients.

Type of complication	Number of patients	Percentage
Postoperative CSF leakage	2	2.8%
Anterior pituitary insufficiency	8	11.4%
Diabetes insipidus - permanent	0	0%
Diabetes insipidus - transient	4	5.4%
Meningitis	1	1.4%
Rhinological complications	0	0%
Epistaxis	1	1.4%
Mortality	0	0%

noted therapeutic success in 79% of cases of microadenomas, and 56% of macroadenomas. Beaugregard *et al.* [2], who operated on 103 patients with acromegaly, obtained 82% recovery rate for microadenomas and 60% for macroadenomas, but only 24% in adenomas with invasion to cavernous sinuses. Trepp *et al.* [33], for the 94 patients surgically treated for somatotrophic adenomas, achieved recovery criteria in 80% of patients with microadenomas, 65% in the group of mesoadenomas, and 27% in macroadenomas having a diameter of over 2 cm. In our own material, the percentage of recoveries for somatotrophic microadenomas was 100%, while for macrosomatotropinomas it was 50%. De Divitiis *et al.* [12], in a group of 46 patients with acromegaly treated by means of endoscopic method, reported: for microadenomas - 90% recovery, for macroadenomas - 63.9% recovery. Cappabianca *et al.* [6], in another series of 36 patients, achieved 83.3% and 61.8%, respectively. Frank *et al.* [14], of 83 patients with acromegaly treated by means of endoscopic method, had 83% recovery rate for somatotrophic microadenomas and 64.5% for macrosomatotropinomas. Since the time of introducing dopamine agonists to

prolactinoma therapy, the percentage of prolactin adenomas qualified for surgical treatment dropped some 10–15%. In our material, prolactinomas constituted 9.7% of all surgically treated pituitary adenomas. At present patients qualified for surgical treatment reveal extreme intolerance of dopamine-mimetic agents, as well as adenoma cases resistant to pharmacological treatment. As the latest literature information indicates, the percentage of recoveries in the case of applying classical transsphenoidal and transeptal method in the case of macroprolactinomas varied between 30–56%, whereas in prolactin microadenomas it reaches even 91% [19,29,30]. In our own material, where endoscopic method was applied, we reached 100% recovery rate for microadenomas and 71.4% for macroadenomas. Similar results of treatment were reached by de Divitiis *et al.* [12] and Cappabianca *et al.* [6] who, for prolactin macroadenomas found 54.5% and 57.1% remission rates, respectively. Frank *et al.* [14], who studied 66 endoscopically treated patients, obtained 85.7% recovery rate for microprolactinoma and 68.5% for macroprolactinoma. Similar to the case of acromegaly, the treatment method of choice in the case of

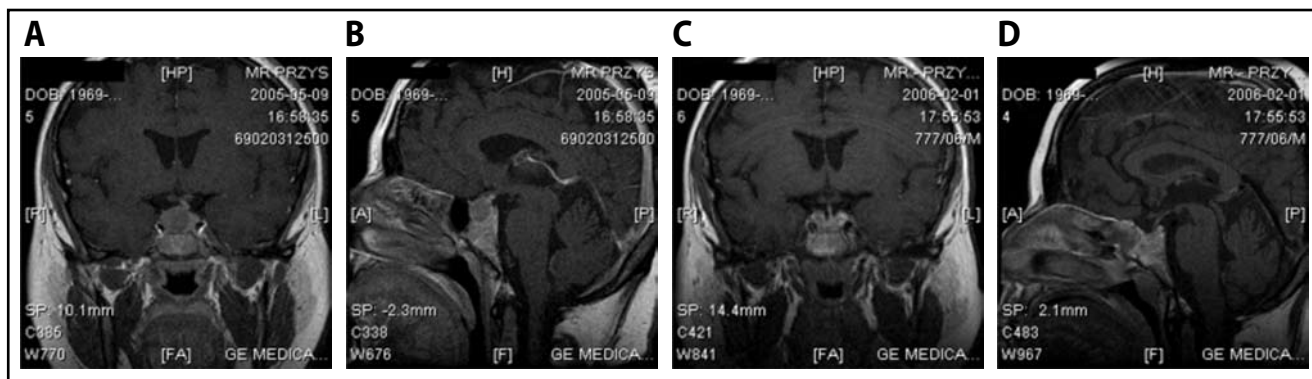


Figure 1. 36-year-old woman with intrasellar macroadenoma hypophysis, grade I according to Knosp scale. Histopathological examination revealed macroprolactinoma. **a)** frontal sections of T1 weighted MR image after contrast administrations (*MRI before removal of the tumor*); **b)** sagittal sections of T1 weighted MR image after contrast administrations (*MRI before removal of the tumor*); **c)** frontal sections of T1 weighted MR image after contrast administrations (*MRI after total removal of the tumor*); **d)** sagittal sections of T1 weighted MR image after contrast administrations (*MRI after total removal of the tumor*).

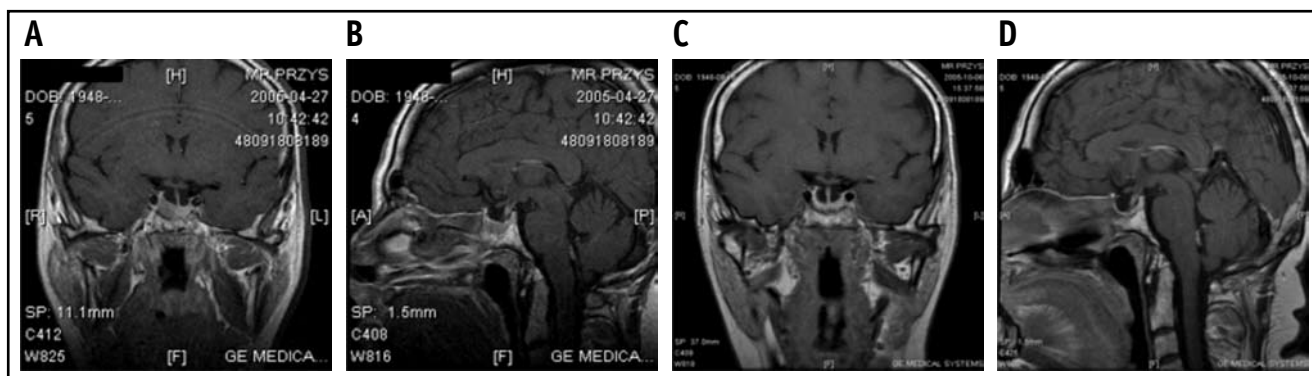


Figure 2. 57-year-old woman with intrasellar microadenoma hypophysis, grade 0 according to Knosp scale. Histopathological examination revealed somatotropinoma. **a)** frontal sections of T1 weighted MR image after contrast administrations (*MRI before removal of the tumor*); **b)** sagittal sections of T1 weighted MR image after contrast administrations (*MRI before removal of the tumor*); **c)** frontal sections of T1 weighted MR image after contrast administrations (*MRI after total removal of the tumor*); **d)** sagittal sections of T1 weighted MR image after contrast administrations (*MRI after total removal of the tumor*).

Cushing's disease is selective transsphenoidal adenectomy. In the microsurgical transsphenoidal method, the percentage of complete recoveries for macrocorticotropinoma oscillated between 40–50%, and in microadenomas it reached even 80–90% [13,22,23]. In our group of endoscopically treated patients we had the recovery rate of 90% for corticotrophic microadenomas, and 66.7% for macroadenomas. De Divitiis *et al.* [12], in his group of patients treated by means of endoscopic method had 78.6% recovery rate for microcorticotropinomas and 100% for macrocorticotropinomas. Cappabianca *et al.* [6], respectively, had 77.8% and 75% of full remissions. Frank *et al.* [14], in a group of 56 patients with corticotrophic adenomas treated by means of endoscopic methods, noted similar recovery rates for micro- and macroadenomas, 67.8% and 68%, respectively. Classical microsurgical approach to the sphenoid sinus is connected with development of a working duct under the mucous membrane of the oral vestibule or nasal vestibule, along the nasal septum, as far as the sphenoid sinus wall, and installation of a stiff nasal dilator. In order to avoid the submucous path, in 1987 Griffith and Veerapen [17] proposed a direct approach to sphenoid sinus. They underlined the advantages of their technique, being the absence of laryngologic complications and shorter access time to sphenoid sinus. Besides giving up the development of a working duct under the mucous membrane of, those surgical procedures did not differ from Hardy's standard. The use of neuroendoscope in traditional transeptal method allowed for better visualisation of lateral parts of the sella and the suprasellar region [7,21]. Endoscope method revealed, however, true advantages in its pure form, without dilator limiting manipulation possibilities for instruments, without a microscope, but with the possibility of applying a range of angular optics possibilities: 30°, 45°, and even 70°. The use of natural approach to sphenoid sinus, giving up stiff nasal dilator, and more convenient use made of suitable surgical instruments, excellent visualisation thanks to panoramic image provided by angular optics, no necessity of using nasal packing of nasal passages, shortening the time of procedure and hospitalisation after the surgery – all these are indisputable advantages of the endoscopic method. Endoscopic technique is as safe as classical transeptal microscopic method. It is superior to it, however, in absence of rhinologic and oral complications, or their only incidental occurrence, as well as lower percentage of more grave complications, for example lasting diabetes insipidus or complications related to infections. Patients after endoscopic surgeries stress the comfort experienced thanks to the possibility of breathing freely through the nose after the procedure, while those who had previously been operated using the classical transeptal method emphasise experiencing less profound pain sensation in the nose and its surrounding after endoscopic procedure [6,9,12,25,31]. In our group of patients we found no difficulty in reaching the pituitary adenomas, although in some reports authors indicate difficul-

ties in reaching the sphenoid sinus in patients with acromegaly. Thanks to the application of rocuronium and remipentanyl, agents recommended for patients undergoing endoscopic surgery procedures, suffering from acromegaly or Cushing's disease, no difficulties occurred in intubation of patients, nor were the complications in the form of increased arterial blood pressure and tachycardia after epinephrine administration to the nose. Our patients, except for one case of epistaxis, revealed no rhinologic complications, which in transeptal surgeries concern 0.3–8.5% of surgically treated patients [3,10]. Two postoperative cases of nasal liquorrhoea were treated successfully by lumbar drainage. The percentage rate of complications in the form of lasting diabetes insipidus in patients after classical surgeries varies between 0.5 and 19%. The appearance of a new postoperative anterior lobe pituitary insufficiency after transeptal procedure is, according to Ciric *et al.*, noted in 7.2–20.6% of patients [10]. In our group, lasting diabetes insipidus did not occur, while new anterior lobe pituitary insufficiency was observed in 11.4% of the patients. Infection-related complications after transsphenoid surgeries are rare. Cerebrospinal meningitis in the Ciric *et al.* study affected 0.8% of patients. In our group of patients that complication occurred in 1 (1.4%) patient with acromegaly. We should mention here a complication which affected one of our patients and required a repeated endoscopic surgery. That was a massive bleeding from the nose, from the trunk of sphenopalatine artery, on the 17th day after surgery. It seems that this complication, which has not been observed in classical transsphenoid approaches, may be characteristic for the endoscopic method. Similar complications were reported by other authors [6, 14, 25]. On the basis of ever more numerous groups of patients treated by the endoscopic method, one may assume that it is a technique with at least comparable treatment effectiveness with that achieved applying the microscopic method. In some studies, authors clearly stress a higher efficiency of the endoscopic technique [27]. In our opinion, the treatment results obtained so far do not allow to state it evidently yet. Results of surgeries by endoscopic method, with its minimum level of invasiveness definitely indicate that it is a technique that can be advised, and has legitimate right to compete with – so far still more popular – traditional transsphenoidal approaches.

CONCLUSIONS

1. The endoscopic technique is an effective method of treatment of hormonally active pituitary adenomas.
2. The endoscopic method is characterised as being microinvasive and having a low percentage of complications.
3. The possibility of applying angular optics, giving up nasal dilators, the possibility of efficient use of surgical instruments, as well as no necessity of using nasal packing after the surgery are indisputable advantages of the endoscopic method.

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