Endoscopic endonasal transsphenoidal approach for pituitary adenomas invading the cavernous sinus

Clinical article

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Object. In this report, the authors describe their experience with surgical access to the cavernous sinus via a fully transnasal endoscopic approach in 20 cases. Clinical and endocrinological follow-up are discussed.

Methods. The authors used an endoscopic transsphenoidal approach in 192 patients with pituitary adenomas between September 1997 and January 2008, adding a cavernous sinus approach in 20 patients with invasive tumors during the last 5 years of this period. Parasellar extension of the tumor was measured according to the Knosp Scale. Radical tumor removal was achieved in 13 (65%) of 20 patients, and subtotal removal in 7 (35%). The authors used recently defined cavernous sinus approaches in the first 14 cases, including the paraseptal approach in 6, middle turbinectomy in 7, and contralateral middle turbinectomy in 1 case. Combined approaches rather than defined standard cavernous sinus approaches were used in 4 cases and an extended approach in 2.

Results. The tumors included nonsecretory adenomas in 5 cases (25%), growth hormone–secreting adenomas in 7 (35%), adrenocorticotropic hormone–secreting adenomas in 4 cases (20%). Normal growth hormone and insulin-like growth factor 1 levels were achieved in 4 patients (57%) with growth hormone adenomas, and remission criteria were obtained in 3 patients with prolactinomas and 3 patients with adrenocorticotropic hormone–secreting adenomas.

Conclusions. Compared with transcranial and microscopic transsphenoidal surgery, endoscopic transsphenoidal surgery offers a wide exposure for cavernous sinus medial wall adenomas that enables removal of the adenoma from the medial cavernous sinus wall. Because of the necessity for multidisciplinary treatment to achieve satisfactory results, Gamma Knife surgery and medical therapy should be supplementary treatment options after endoscopic transsphenoidal surgery.

Key Words: • endoscopic transsphenoidal surgery • pituitary adenoma • cavernous sinus • extended and expanded approaches • paraseptal approach • middle turbinectomy approach

Treatm ent of pituitary adenomas invading the cavernous sinus is one of the great challenges in neurosurgical practice. Different treatment modalities should be considered to achieve remission during the follow-up period in these patients. In the present study, we discuss the role of the endoscopic technique and other treatment modalities.

Endoscopic endonasal transsphenoidal surgery has gained increasing acceptance by neurosurgeons. In many centers throughout the world, this technique is now routinely used for the same indications as the conventional microsurgical technique. In 1963, Guiot and colleagues first proposed the use of an endoscope as part of a transnasorhinoseptal microsurgical approach. Some authors have reported using an endoscope-assisted technique to complement the microscope in the early or late stages of the traditional procedure. Pure endoscopic endonasal transsphenoidal surgery was described in detail by Jho and Carrau, and the results with expanded and extended endoscopic approaches have been reported over time by other authors.

The endoscopic transsphenoidal approach allowed us to inspect part of the parasellar and middle cranial fossa areas of the cavernous sinus. Some specific endoscopic surgical corridors have been described during the surgical procedure at the level of the medial and ventral portion of the cavernous sinus.

Methods

We conducted a retrospective analysis of 192 endoscopic transsphenoidal approaches to pituitary adenomas that had been performed in our department between September 1997 and January 2008. We used only the stan-

Abbreviations used in this paper: ACTH = adrenocorticotropic hormone; CN = cranial nerve; GH = growth hormone; GKS = Gamma Knife surgery; ICA = internal carotid artery.
dard endoscopic approach in the first 40 cases because endoscopic transsphenoidal surgery requires a learning curve. After gaining some preliminary experience with the endoscopic technique, in the last 5 years of this period we used the endoscopic cavernous sinus approach in 20 patients with invasive pituitary adenomas with expansion into the cavernous sinus. This group is the subject of this report. All patients underwent treatment in the Department of Neurosurgery at Kocaeli University. Preoperative examination with 1.5-T contrast-enhanced MR imaging was performed in all patients, and the imaging features were evaluated using the grading system proposed by Knosp et al.43

Harris and Rhoton29 divided the cavernous sinus into 4 venous spaces based on each region’s relationship to the ICA: anteroinferior (ventral), posterosuperior (dorsal), medial, and lateral.41 The Knosp classification does not specifically address lesions with descent through the paracervical carotid artery vertical segment into the ventral area. These lesions have been previously defined as ventral and inferolateral type by Kitano and colleagues41 and Cottier et al.10 for the classification of intracavernous tumors according to location. In the present study, lesions in this area are classified as ventral (Fig. 1).

Extent of resection was evaluated on the basis of MR images obtained in the immediate postoperative period and again 3 months afterwards. The extent of resection was determined as radical, subtotal (the clear presence of residual tumor but with resection of >80% of the tumor), or partial (the clear presence of residual tumor but with resection of <80% of the tumor). Tumor pathologi
cal type was confirmed by the Department of Pathology at our institution. Despite long-term medical therapy, a surgical approach was indicated in 4 patients with prolactinomas because of persistent hyperprolactinemia and progressive tumor enlargement (Fig. 2).

Endocrinological and ophthalmological examinations were performed preoperatively in all patients. Endocrinological remission criteria were evaluated by comparing preoperative values with early and late (3 months) postoperative values. Tumor remission for endocrine-active pituitary adenomas was defined at prolactin levels below or within the normal range (3–15 ng/ml for men and 3.9–27.7 ng/ml for women), and as freedom from clinical symp
toms in patients with prolactin-secreting adenomas.44 For GH-secreting adenomas, remission was defined as a suppressed serum GH < 1 ng/ml after oral glucose load, and subsequent normal sex- and age-adjusted insulin-like growth factor 1 levels.29 In ACTH-secreting adenomas, remission was defined at a normal circadian rhythm of plasma cortisol levels, normal 24-hour urinary cortisol levels,44,51 and serum cortisol values of 2 μg/dl after an overnight 2-mg dexamethasone-suppression test.44

Ophthalmological examination was performed using the Humphrey perimeter for visual field function and the Hess chart evaluation for ocular motility. The minimum follow-up time was 15 months and the maximum was 45 months (mean 26 months; Table 1).

We performed electrophysiological detection of oc
tulomotor, trochlear, and abducent nerves using intraop
erative monitoring (Nim-Plus, Xomed). The CNs were

![Image](309x447 to 549x716)

Fig. 1. Case 12. Images obtained in a 25-year-old man with a GH-secreting adenoma. Paraclival approach. Intraoperative photograph (A), and pre- (B) and postoperative (C) Gd-enhanced, T1-weighted MR images of the adenoma, which descends through the paracervical carotid artery vertical segment in ventral area and is defined as ventral type. Note the angled suction cannula, designed for suctioning in different directions in parasellar areas. PC = paracervical carotid; SF = sellar floor.

stimulated with a monopolar stimulator electrode and eye movements evoked by the stimulation were monitored with an auditory signal.

Surgical Approaches

Pituitary adenomas without cavernous sinus invasion can be removed without expanding the surgical area to the cavernous sinus: this is the standard endoscopic transsphenoidal approach. More reliable surgical techniques should be performed for the removal of the cavernous sinus component in pituitary adenomas invading the cavernous sinus.

We performed recently defined cavernous sinus approaches1,5,31,32 in our first 14 cases. These included the paraseptal approach (sphenoidotomy extending more laterally by removing the superior and supreme turbinates and opening the posterior ethmoidal cells to obtain a wider view inside the cavernous sinus)31,32 in 6 patients, middle turbinectomy (rostrum of the sphenoid sinus is exposed after removing the middle turbinate)32 in 7 patients, and contralateral middle turbinectomy (the contralateral nostril was preferred to achieve a wider lateral surgical corridor and better inspection of the parasellar subregion) in 1 patient (Table 1). In contrast to the standard approach, after an anterior sphenoidotomy has been performed expanding more laterally from the tumor side, the sellar floor was opened 1-cm wide and enlarged in the
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Fig. 2. Case 2. Preoperative (A) and postoperative (B) coronal, Gd-enhanced, T1-weighted MR images obtained in a 42-year-old man with a prolactin-secreting adenoma. The paraseptal approach was used to remove the tumor (Knosp Grade 4) localized to cavernous sinus.

TABLE 1: Summary of clinical information in 20 patients with adenomas*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Type of Adenoma</th>
<th>Knosp Parasellar Extension Grade</th>
<th>Surgical Approach</th>
<th>Extent of Resection</th>
<th>Length of Follow-Up (mos)</th>
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<tr>
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<td>GH</td>
<td>4</td>
<td>MT</td>
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<td>2</td>
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<td>cMT</td>
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<td>39</td>
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<td>38</td>
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<td>paraseptal</td>
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<td>35</td>
</tr>
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<td>MT</td>
<td>subtotal</td>
<td>34</td>
</tr>
<tr>
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<td>GH</td>
<td>4</td>
<td>MT</td>
<td>subtotal</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>nonsecretory</td>
<td>3</td>
<td>MT</td>
<td>radical</td>
<td>32</td>
</tr>
<tr>
<td>9</td>
<td>ACTH</td>
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<td>MT</td>
<td>radical</td>
<td>31</td>
</tr>
<tr>
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<td>18</td>
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<td>13</td>
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<td>3</td>
<td>MT</td>
<td>radical</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>GH</td>
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<td>paraseptal</td>
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<td>18</td>
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<td>subtotal</td>
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</tr>
<tr>
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<td>extended</td>
<td>radical</td>
<td>16</td>
</tr>
<tr>
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<td>PRL</td>
<td>4</td>
<td>combined</td>
<td>radical</td>
<td>16</td>
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<tr>
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<tr>
<td>20</td>
<td>PRL</td>
<td>3</td>
<td>combined</td>
<td>radical</td>
<td>15</td>
</tr>
</tbody>
</table>

* cMT = contralateral middle turbinectomy; MT = middle turbinectomy; PRL = prolactinoma.
We performed middle turbinate resection on one side and pushed the middle turbinate of the other side laterally. We removed the posterior part of the nasal septum and the rostral part of the vomer, thus widening the operative area so that 2 or 3 surgical instruments could be used simultaneously (curettes, ultrasonic aspirator, and bipolar cautery). After the extended approaches are used, effective dural closure should be performed to avoid postoperative CSF fistula formation. We used a multilayer technique to close the suprasellar defect after closure of the sellar floor and posterior sphenoid sinus wall using a mucosal flap with its pedicle slipped from the nasal septum.

**Results**

Twenty patients, 11 female (53%) and 9 male (47%), with an age range of 11–65 years were included in this study. Four patients with prolactinomas presented with progressive visual loss. The presenting signs and symptoms were headache in 13 patients (65%), diplopia in 7 (35%), visual field defects in 7 (35%), sexual disorders in 5 (25%), and galactorrhea in 2 patients (10%). Ophthalmoplegia was observed in 2 patients preoperatively, 1 with a CN III and the other with a CN VI palsy. Preoperative visual field defects were improved in 5 (71.4%) of 7 patients, and unchanged in 2 postoperatively. Ophthalmoplegia was improved at 2 months in the patient with CN III palsy, and at 3 months in the patient with CN VI palsy. In 1 patient, abducent nerve palsy was seen postoperatively, but improved by 6 weeks after surgery.

Normal GH (after glucose load) and IGF-I levels were achieved in 4 patients (57%) with GH adenomas, and remission criteria were obtained in 3 patients with prolactinomas (75%) and 3 patients (75%) with ACTH-secreting adenomas postoperatively.

The tumors included nonsecretory adenomas in 5 cases (25%), GH-secreting adenomas in 7 (35%), prolactin-secreting adenomas in 4 (20%), and ACTH-secreting adenomas in 4 (20%). Parasellar extension of the tumor was measured according to the Knosp Scale: 10 of 20 were Grade 4, 9 were Grade 3, and 1 was ventral type. Radical removal was achieved in 13 (65%), and subtotal resection in 7 patients (35%; Table 1).

One patient with an ACTH-secreting adenoma underwent GKS, and of the 3 patients with GH-secreting adenomas, 1 received GKS and 2 received medical therapy postoperatively because of insufficient endocrine results. According to late postoperative endocrine results, the patient with the ACTH-secreting adenoma who underwent GKS is in remission. The suppressed serum GH level after oral glucose load in the patient with GH-secreting adenoma who underwent GKS was 1.25 ng/ml; this patient was therefore not considered to be in remission. The other 2 patients with GH-secreting adenomas are still receiving medical therapy but are not in remission. One of 4 patients with prolactinoma required postoperative medical therapy. This patient is not considered to be in remission because although this patient is free of symptoms, prolactin levels are still above normal (Table 2).

A 2-U blood transfusion was performed in 3, temporary diabetes insipidus was seen in 3, and CSF leakage occurred in 3 patients. One patient required endoscopic repair for delayed CSF leakage.
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Fig. 5. Case 3. Images obtained in an 11-year-old girl with a Knosp Grade 4 ACTH-secreting adenoma. The contralateral middle turbinate approach was used. Intraoperative view (A) showing removal of the tumor localized in cavernous sinus using lateral corridor (LC) and intraoperative images of the horizontal (HS), posterior bend (PB), and vertical segment (VS) of the ICA. Preoperative (B) and postoperative (C) coronal, Gd-enhanced, T1-weighted MR images.

Fig. 6. Case 16. Images obtained in a 54-year-old man with nonsecretery adenoma; the middle turbinate approach was used. The lesion was an intrasuprasellar macroadenoma with parasellar extension into the cavernous sinus. Preoperative (A and B) and postoperative (C and D) coronal and sagittal, Gd-enhanced, T1-weighted MR images.

Discussion

Pituitary adenomas usually compress surrounding structures, commonly resulting in sella enlargement and suprasellar extension. Invasion of the cavernous sinus has been described in 6–10% of all pituitary adenomas in the literature. However, in more recent reports of extended microscopic and endoscopic approaches, authors have reported cavernous sinus invasion in >10% of lesions.

Various approaches, including transfacial, transsphe-

moideal, and transsphenoidoethmoidal exposures have been proposed to remove lesions involving the anterior portion of the cavernous sinus. These approaches are limited by a deep, narrow surgical corridor that does not allow adequate exposure of neurovascular structures. The transcranial approach to lesions of the cavernous sinus is regarded as overly aggressive despite recent advances in cranial base surgery. In the literature, low rates have been reported for complete resection via the transcranial approach to pituitary adenomas involving cavernous sinus. Some authors have described their experience with the microscopic transsphenoidal approach to the cavernous sinus. Couldwell noted that the surgical exposure provided by a microscopic transsphenoidal approach is very limited because of the narrow midline corridor around the sella. Kitano et al. reported on a series of cases in which they used a microscopic extended approach. They reported making the operative field up to 30 mm wider using a modified speculum, and performed a more extended submucosal dissection. In their cases, an extensive surgical corridor was provided via posterior ethmoidectomy, and in some cases by resection of the middle turbinate and posterior maxillary sinus wall.

Cavernous sinus surgery has always been a challenge because of the high functional importance of this region. Peripheral vision achievable with the endoscope has led to the development of surgical approaches that allow adequate exposure of the cavernous sinus with a reduction in surgical morbidity. Over the past decade, the use of endoscopy in transsphenoidal surgery has allowed widening of the surgical field, bringing it within the cavernous sinus. Tumors located within the cavernous sinus have been successfully removed with this approach. In the literature, various anatomical and clinical endoscopic transsphenoidal approaches have also been used in the cavernous sinus region.

Frank and Pasquini performed the middle meatal and ethmoid–pterygophenoidal approaches. They described radical tumor removal via an endoscopic endonasal transsphenoidal approach in 21 of 35 patients with

TABLE 2: Treatment modalities and endocrinological remission results in endocrine-active adenomas*

<table>
<thead>
<tr>
<th>Type of Endocrine-Active Adenoma</th>
<th>No. of Patients</th>
<th>Resection</th>
<th>Resection + + GKS</th>
<th>Resection + Drug Tx</th>
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<tr>
<td>GH-secreting</td>
<td>7</td>
<td>4, R</td>
<td>1, NR</td>
<td>2, NR</td>
</tr>
<tr>
<td>ACTH-secreting</td>
<td>4</td>
<td>3, R</td>
<td>1, R</td>
<td>–</td>
</tr>
<tr>
<td>PRL</td>
<td>4</td>
<td>3, R</td>
<td>–</td>
<td>1, NR</td>
</tr>
</tbody>
</table>

* Excludes nonsecretory adenomas. Abbreviations: NR = no remission; R = remission.
nonfunctioning adenomas, and hormonal remission in 13 of 30 patients with functioning adenomas. However, it is advisable for these techniques to be performed by otolaryngologists in endoscopic sinus surgery or by neurosurgeons together with otolaryngologists in the nasal step of cavernous sinus surgery. In our department, such approaches were performed without the help of otolaryngologists after the first 40 cases. A median approach to wide resection may be preferred over the middle meatal approach in adenomas involving the cavernous sinus.

In the endoscopic cavernous sinus approach, the medial and lateral surgical corridors and superior triangular and quadrangular areas that are seen after removal of the lateral wall of the sphenoid sinus and formed by neurovascular structures have been described.\(^4\,5\) One endoscopic surgical corridor is medial to the intracavernous carotid artery, and another wider corridor is lateral to it. To access this area, it is necessary to push the pituitary gland medially and remove the fibrous trabecular structure that forms the parasellar portion of the medial wall of the cavernous sinus. The lateral corridor to the ICA (triangular area) is demarcated by the intracavernous tract of the ICA posteriorly, by the vidian nerve inferiorly, and by the medial pterygoid process anteriorly. The pituitary gland can overlap the intracavernous carotid artery with a tongue-like projection. Most pituitary adenomas extend into the cavernous sinus through the medial corridor.\(^4\,5\) The cavernous sinus has weak points where the dural wall is thin or absent. Instead of meningeal and endosteal layers forming the lateral and the superior walls of the cavernous sinus, the medial wall is formed only by a continuous thin layer of dura, which is incomplete or absent.\(^5\,16\,17\,28\,38\,39\,57\) Most nonfunctioning pituitary adenomas that extend into the cavernous sinus grow through these fragile points of the cavernous sinus wall (Fig. 8).

The ideal lesions for the endoscopic endonasal approach are soft tumors such as pituitary adenomas, which are unlikely to infiltrate the ICA and show a mediolateral growth pattern resulting in lateral displacement of the ICA. In contrast, hard, solid tumors such as meningiomas that are known to infiltrate the ICA may limit the indications for the endoscopic endonasal approach. The medial corridor approach is adequate for Knosp Grades 2 and 3 lesions; however, the tumor should be removed by opening the lateral corridor in Grade 4 and ventral cases. In these cases, both corridors should be used.

Kitano et al.\(^4\,1\) described an extended transsphenoidal microscopic approach in 36 patients with pituitary adenomas and extension into the cavernous sinus. This technique was accomplished by extending the submucosal dissection of the nasal septum to the lateral wall of the nasal cavity using a modified speculum. However, they reported that endoscopic visualization was difficult because the endoscope itself limited the working space with the speculum in medial approaches. The authors reported that the narrow and deep operating field, which poses the risk of ICA injury during a blind procedure, is a major limitation of the microscopic extended transsphenoidal approach. They also noted that endoscopic procedures to cavernous sinus lesions might not be a standard procedure because of the difficulty in controlling unexpected massive hemorrhages from the venous plexus or ICA.\(^4\,1\)

In our department, hemorrhaging in 3 patients was controlled with clip placement (silver surgiclip) for intracavernous venous bleeding (Fig. 9), and hemostatic agents and continued irrigation were used for cavernous sinus bleeding. When these events occurred, surgery was continued; we do not consider such hemorrhagic events to contraindicate the use of the endoscopic transsphenoidal approach.

All segments of the ICA and its branches in the cavernous sinus can be observed with endoscopy (Fig. 10). Although we did not observe any ICA injuries in our patients, we believe that it may be possible to use endoscopy-guided temporary clip placement for various segments of the ICA, especially the paraclival vertical segment, until endovascular intervention can be performed.

The use of a speculum in the transsphenoidal approach results in a narrow surgical field, but the purely endoscopic approach we used without a speculum provides a wide, panoramic visualization that allows the surgeon room to work freehand in the cavernous sinus. This approach also offers advantages for recurrent cases in which mucosal dissection was not used.\(^4\,7\) We performed endoscopic transsphenoidal surgery in 2 patients because of recurrent cavernous sinus involvement.

Prolactinomas involving the cavernous sinus present a great challenge to drug treatment. Surgery is indicated when there is no or only partial response to medical treatment. The residual tumor within the cavernous sinus can continue to cause endocrinological symptoms, and prolactinomas with cavernous sinus invasion are more likely...
to become drug resistant. Residual cavernous sinus lesions in some patients may remain even after continuous drug therapy.28,46,55,56

Choice of Treatment Strategy

Primary treatment is resection in nonfunctional macroadenomas with visual deterioration, adenomas causing acromegaly, and Cushing disease. Remission has been achieved in ~ 60% of patients with acromegaly who underwent transsphenoidal surgery. If remission is not achieved after surgery, both medical treatment and stereotactic radiosurgery can be recommended. Medical treatment is never curative and requires long-term administration, making it costly.41

Stereotactic radiosurgical success in hormone-secreting pituitary adenomas has been reported in ~ 80% of cases; however, the success rate is lower in pituitary adenomas with cavernous infiltration compared with noninfiltrating lesions, both in terms of volume reduction and biological remission rates.41,48,50,52 The effects of stereotactic radiosurgery are seen in the long term, and normalization of GH and IGF-I levels can take up to 5 years to accomplish.41

Endoscopic techniques allow easy approach to the medial and inferior walls of the cavernous sinus, and total excision can be reached in about 65% of cases. In hormone-secreting adenomas, remission can be reached in ~ 57–75% of cases, in 57% of GH-secreting adenomas, in 75% of prolactinomas, and in 75% of ACTH-secreting adenomas; thus, resection should be the first choice of treatment. However, when total resection is unsuccessful or total remission is not achieved, GKS should be added. In GH-secreting adenomas, combined medical treatment should be used during initiation of radiosurgery. Combined medical and stereotactic radiosurgery treatment should be the first choice in elderly and high-risk patients.

Advantages and Disadvantages of Endoscopic Transsphenoidal Surgery

The main advantage to the endoscopic transsphenoidal approach is that tumor removal can be performed while avoiding a transcranial surgical corridor and CNS dissection. There is no need for skin incision or brain retraction either. These advantages lead to a decrease in complications, a faster recovery for the patient, minimal postoperative discomfort, and a reduction in overall costs.

Cavernous sinus bleeding is one of the most impor-
tant complications of endoscopic cavernous sinus surgery. Initial minor bleeding will increase during tumor resection; however, hemorrhaging can be managed with the compression of Surgicel packing material and continuous irrigation. In cases of venous channel or intercavernous sinus bleeding, homeostasis can be achieved using various clips (Fig. 8). We did not note any intraoperative arterial bleeding in our patients. The other potential complications of endoscopic transsphenoidal cavernous sinus surgery include CN injury, ICA rupture, and CSP leakage.

Conclusions

Cavernous sinus invasion causes resistance to treatment in pituitary adenomas. Endoscopic surgical removal of tumors invading the cavernous sinus should be the first choice before drug therapy and GKS. Our results in a limited number of patients are encouraging. Resection and remission rates will be increased as further experience is gained and in future studies. With experience and technical development, endoscopic transsphenoidal cavernous approaches will not be considered aggressive treatment. Resection should be the first choice in prolactinomas resistant to medical treatment, in Cushing disease, and in GH-secreting adenomas with cavernous invasion. After resection, GKS combined with medical treatment should be added if remission is not achieved. Further clinical studies with a larger patient cohort including subtypes of pituitary adenomas, and supported by statistical analysis should be performed.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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