Review

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Transcranial endoscope-assisted keyhole surgery: anterior fossa

Abstract

Objective: The concept and surgical technique of endoscope-assisted keyhole surgery in treating lesions of the anterior fossa and central skull base is described in this article.

Methods: Between 2007 and 2011, 362 patients underwent endoscope-assisted keyhole surgery utilizing the supraorbital subfrontal (SOR, n=218), mini-pterional frontotemporal (PTE, n=105), and frontal interhemispheric (FIH, n=39) approaches. A retrospective case note review was carried out in 244 consecutive cases performed by the lead author to extract data on surgical outcome, followed up with a patient satisfaction survey in 210 patients.

Results: Six patients died from non-surgical complications in the post-operative period (overall mortality was 2.5%). The 30 day post-operative Glasgow Outcome Scores were as follows: five in 212 patients (86.9%), four in 16 (6.6%), three in six (2.5%), and two in four patients (1.6%). There was no statistically significant difference in post-operative complications comparing the SOR, PTE, and FIH approaches (P>0.05). The overall level of satisfaction was high: postoperative cosmesis was rated as very pleasant or pleasant in 203 out of 210 patients (96.7%), and post-operative wound pain as absent or minimal in 196 out of 210 patients (93.3%).

Conclusion: In our study, endoscope-assisted keyhole techniques were associated with excellent surgical outcomes and high patient satisfaction.

Keywords: Anterior fossa; endoscope-assisted keyhole neurosurgery; interhemispheric approach; pterional approach; supraorbital approach; skull base surgery; surgical results.

Introduction

“Primum non nocere”, the axiom of Hippocratic tradition, was interpreted by the American general and neurological surgeon William Halsted in 1924: “The tendency will always be in the direction of exercising greater care and refinement in operating”. In the third millennium, this fundamental philosophy of minimally invasive therapy should be emphasized, the aim of contemporary cranial neurosurgery is to reduce the risk of harm to patients by selecting tailor made keyhole approaches based on detailed neuroanatomical knowledge and careful consideration of patho-anatomical factors.

The impact of brain manipulation was demonstrated in a number of experimental and clinical studies showing significant traumatization of neural tissue and permanent neurological deficits after extensive brain retraction [8, 9, 19]. In addition, exposure of brain tissue to non-physiological surroundings may itself lead to injury. Various methods have been proposed to reduce such approach-related trauma including the use of anesthetic techniques to lessen cerebral edema, and patient-positioning techniques to encourage brain relaxation [1, 21, 22]. Alongside these techniques, the use of tailored image-guided endoscope-assisted keyhole approaches may further minimize exposure and retraction of unaffected brain tissue [14, 15].

Surgical treatment of lesions of the anterior cranial fossa and central skull base utilizing the supraorbital subfrontal (SOR), mini-pterional frontotemporal (PTE), and the frontal interhemispheric (FIH) keyhole approaches are among the best examples of the concept of minimally invasive neurosurgery. In this paper, we describe surgical techniques of these approaches, and report on the surgical outcome and patient satisfaction in our own case series.
Patients and operative techniques

Between January 2006 and December 2010, 362 patients underwent keyhole surgery by the senior authors (R.R. and R.K.) for lesions within the anterior cranial fossa and central skull base. Operations were carried out in the Neurosurgical Departments of the University Hospital, Mainz, Germany; the University Hospital, Zurich, Switzerland; the Royal London Hospital, London, UK; and the Centre for Minimally Invasive and Endoscopic Neurosurgery, Clinic Hirslanden, Zurich, Switzerland.

Preoperatively, cases were carefully evaluated to determine the least traumatic route to pathology. Three different keyhole approaches were used: the SOR in 218, PTE in 105, and the FIH in 39 cases. Image-guidance was used to define the surgical approach, and guide dissection along a trajectory (Medtronic, Inc. Minneapolis, MN, USA or BrainLab, Feldkirchen, Germany). Endoscope-assisted microsurgical technique was utilized in all cases to enhance visualization; tube-shaft instruments were used to aid manipulation within a narrow surgical corridor (Aesculap AG, Tuttlingen, Germany).

Technique of the supraorbital keyhole

Patients were placed in a supine position, with their head fixed in a three-point Mayfield head holder (Codman, Inc. Raynham, MA, USA). Their heads were elevated and retroflexed to about 15° to allow gravity to cause the frontal lobe to fall away from the anterior cranial fossa. The degree of head rotation varied depending on the location of the pathology.

Anatomical landmarks such as the supraorbital foramen, temporal line, level of the frontal cranial base, impression of the Sylvian fissure, and zygomatic arch were determined. Neuronavigation was used to confirm these key-points, and localize the underlying pathology. These surface markings were then used to define the borders of the planned craniotomy and skin incision (Figure 1).

The skin incision was started lateral to the supraorbital foramen within the eyebrow, and carried in a medial-to-lateral direction following the orbital rim. The skin flap was dissected and retracted in the frontal direction to achieve optimal exposure of the supraorbital region. The frontal muscle was then cut with a monopolar knife in a medial-to-lateral direction (Figure 2A). Once the temporal line was reached, it was followed inferiorly towards the zygomatic process of the frontal bone, avoiding unnecessary mobilization of the temporalis muscle. The frontal and temporal muscles were then retracted with sutures and hooks.

A single fronto-basal burr hole was made lateral to the temporal line, using a high-speed drill (Figure 2B). After enlargement of the hole with a 2–3 mm Kerrison punch and mobilization of the dura, a straight line was cut with a high-speed craniotome parallel to the orbital rim in a lateral-to-medial direction (Figure 2C). Thereafter, a “C” shaped line was cut from the burr hole, completing the craniotomy. In this way, a craniotomy was created with a size of approximately 20×15 mm (Figure 2D). After removal of the bone flap, the inner edge of the craniotomy was drilled above the orbital rim, using a diamond burr (Figure 2E). In case the frontal sinus or neighboring pneumatized cells were opened, the bone was carefully sealed. The juga cerebralia were drilled flat before or after opening of the dura to gain more space intradurally.

The dura was opened in a simple “C” shape and retracted in a basal direction, minimally exposing the brain surface (Figure 2F). The frontal lobe was gently mobilized with cottonoid patties, and the carotid cistern was opened to drain cerebrospinal fluid.

Technique of the pterional keyhole

Patients were positioned in a similar way to the supraorbital approach, but with their heads further rotated to accommodate the more laterally placed craniotomy. Anatomical landmarks and neuronavigation were used to plan the craniotomy and incision (Figure 3).

After minimal shaving behind the hairline, a fronto-temporal curved skin incision was performed. The skin flap was minimally retracted to avoid creation of a
Figure 2  Steps of the supraorbital subfrontal craniotomy (SOR). After eyebrow incision, the skin flap is retracted exposing the frontolateral region. The frontal muscle is then cut with a monopolar knife in a medial-to-lateral direction and inferiorly towards the temporal line (A). The single fronto-basal burr hole is made lateral to the temporal line (B). Thereafter, a straight line is cut with a high-speed craniotome parallel to the orbital rim (C) and a “C” shaped line is created from the burr hole, completing the craniotomy (D). After removal of the bone flap, the inner edge of the craniotomy is drilled above the orbital rim, increasing intracranial manipulation (E). The dura is opened in a simple “C” shape and retracted in a basal direction, minimally exposing the brain surface (F).

Figure 3  Placement of the mini-pterional craniotomy and according skin incision in the frontotemporal region.

subcutaneous wound pouch (Figure 4A). The temporal fascia was not separated from the muscle, preserving the frontal branch of facial nerve. The temporalis muscle was cut with a monopolar along the temporal line, and then in the direction of its filaments, creating an “L” shaped myofascial incision (Figure 4B). In cases of thin skin and temporalis muscle and a hairline positioned rather anteriorly, a constellation appearing typically in elderly women, the skin incision was carried out directly onto bone, and the combined myocutaneous flap retracted anteriorly. When the skin and muscle are thoroughly mobilized, the pterion can usually be reached even if the length of the skin incision is just a few centimeters.

The lateral part of the greater sphenoid wing was removed with a high-speed drill, exposing the fronto-basal and temporopolar dura (Figure 4C). A limited craniotomy was then fashioned around the pterion with a diameter of
Figure 4  Steps of the mini-pterional frontotemporal craniotomy (PTE). After curved skin incision behind the hairline, the skin flap is minimally retracted, thus avoiding creation of a subcutaneous wound pouch (A). The temporalis muscle is cut with a monopolar along the temporal line, and then in the direction of its filaments, creating an “L” shaped myofascial incision (B). The lateral part of the greater sphenoid wing is removed (C) and a limited craniotomy is then fashioned around the pterion with a diameter of approximately 20 x 30 mm (D). If necessary, the sphenoid wing can be drilled further with partial or complete resection of the anterior clinoid process (E). The dura is opened in a “C” shaped flap, exposing the frontotemporal surface (F).

approximately 20×30 mm (Figure 4D). If necessary, the sphenoid wing was drilled further with partial or complete resection of the anterior clinoid process (Figure 4E).

The dura was opened in a “C” shaped flap, exposing the frontotemporal surface. The medial part of the Sylvian fissure was opened and CSF drained, exposing the central subarachnoidal spaces without the use of brain retractors (Figure 4F).

Technique of the frontal interhemispheric keyhole

Patients were positioned in a similar way to the supraorbital approach but with their heads greatly rotated towards the side of the planned craniotomy causing the frontal lobe to fall away from the midline, supporting interhemispheric dissection. Anatomical landmarks and neuronavigation were used to plan the craniotomy and incision (Figure 5).

After minimal shaving, a paramedian skin incision was performed, just behind the hairline. In bald patients, incisions were made within a wrinkle of the skin to achieve a pleasing cosmetic result. The skin and the subcutaneous tissue were retracted exposing the galea aponeurotica. The galea and periosteum were incised together in a semicircular fashion with the base of the flap located frontally (Figure 6A). This tissue could be effectively used as a dural graft, and to close the frontal paranasal sinuses in basal approaches.

Figure 5  Placement of the frontal interhemispheric approach and according skin incision behind the frontal hair-line.
Two burr holes were placed over the midline using a cranial perforator. The burr holes were enlarged with fine Kerrison punches along the lateral borders of the superior sagittal sinus. A craniotome was then used from the posterior burr hole approximately halfway along a semilunar shaped line, and then from the anterior burr hole to complete the cut (Figure 6C). Using a fine sharp-cutting burr and, for the last millimeter, a diamond drill, the two holes were now connected, and special care was taken around the dura overlying the superior sagittal sinus (Figure 6D). The bone flap was carefully mobilized with a blunt elevator, protecting the superior sagittal sinus (Figure 6E).

The dura was opened in a semicircular fashion with the base of the flap towards the midline, exposing the falx cerebri (Figure 6F). As a result of the significant head rotation, the brain falls away from the midline, facilitating interhemispheric dissection without the use of retractors.

**Material and methods**

Case notes and imaging were available in all patients of varying pathology (Table 1). A detailed retrospective case note review was carried out in 244 consecutive cases performed by the lead author (R.R.) to extract data on surgical outcome using the 30 day Glasgow Outcome Scale (GOS), and on complications. The rate of complications among the different approaches was compared using the Fisher’s exact or $\chi^2$-test.

In addition, a late follow-on patient satisfaction survey was carried out in patients operated by the first author: 210 from 244 patients were available for a detailed questionnaire. Patients were asked to rate: cosmesis on a scale from 1 to 5 (1=very pleasant, 5=very unpleasant), post-operative scar pain and headache on a scale from 1 to 5 (1=no pain, 5=severe pain), difficulty chewing, frontalis weakness, frontal hypoesthesia, and hyposmia.
Results

Retrospective case analysis

Overall, 362 cases with various pathologies of the anterior cranial fossa and central skull base were treated successfully using minimally invasive approaches. Of these, a detailed retrospective case note review was carried out in 244 consecutive cases performed by the lead author (Table 1). Six patients died from non-surgical complications during the early perioperative period, one from fulminate pulmonary embolism after an operation on a glioblastoma, and five from severe vasospasm after aneurysmal subarachnoid hemorrhage (overall mortality of 2.5%). The GOS for the remaining very heterogeneous group of patients were as follows: five in 212 patients (86.9%), four in 16 (6.6%), three in six (2.5%), and two in four patients (1.6%).

In the cohort of 100 patients with intracranial aneurysms, a total of 132 aneurysms were treated: 76 patients were operated via SOR, 11 via PTE, and 13 via FIH craniotomy (Table 2). The optimal surgical approach was determined according to each case’s unique patho-anatomical factors, and only if neuro-interventional treatment was not feasible. In all, 56 patients were treated with unruptured aneurysms, and 44 patients following aneurysmal subarachnoid hemorrhage (SAH). Of those with unruptured intracranial aneurysms, 54 patients were neurologically intact at the 30 day follow-up (96.4%), and two patients had neurological deficits resulting in moderate disability (3.6%). None of the patients had severe disability or died after surgery. Of the patients with SAH, 34 patients were good grade (Hunt and Hess score 1–3). There was no surgery-related deterioration, however, five patients died from fulminant vasospasm and multi-organ failure.

In the group of 118 patients with skull base meningiomas, the SOR approach was used in 94 cases (79.7%), PTE approach in 20 cases (16.9%), and FIH approach in four cases (3.4%). The most frequent indication for surgery was visual deficit; of these 48 patients, 41 improved after surgery (85.4%), five stabilized (10.4%) and two worsened (4.2%). In all cases, gross total resection was achieved, with the exception of meningiomas infiltrating the cavernous sinus which were managed with adjuvant radiosurgery.

Postoperative surgical complications were uncommon. Routine postoperative computed tomography (CT) or magnetic resonance imaging (MRI) scan showed hematoma within the resection cavity in seven cases (2.9%), but without space occupying effect. Subdural hygroma occurred afterwards in five cases (2.0%), and burr hole drainage was necessary in one patient (0.4%). Wound-healing problems were noted in four cases (1.6%), and surgical revision was necessary in two patients (0.8%). A subcutaneous CSF pouch was observed in 10 patients (4.1%), which was successfully managed conservatively in all cases. Anticonvulsants were not routinely used and postoperative seizures occurred in only one case (0.4%). There was no statistically significant difference in post-operative complications comparing the SOR, PTE and FIH approaches by the Fisher’s exact or \( \chi^2 \)-test (\( P > 0.05 \)).
Table 3  Postoperative approach related complications.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Temporary</th>
<th>Permanent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty chewing</td>
<td>3 (1.4%)</td>
<td>0</td>
<td>3 (1.4%)</td>
</tr>
<tr>
<td>Palsy of frontalis muscle</td>
<td>9 (4.3%)</td>
<td>4 (1.9%)</td>
<td>13 (6.2%)</td>
</tr>
<tr>
<td>Frontal hypoesthesia</td>
<td>13 (6.2%)</td>
<td>6 (2.9%)</td>
<td>19 (9.0%)</td>
</tr>
<tr>
<td>Hyposmia</td>
<td>1 (0.5%)</td>
<td>5 (2.4%)</td>
<td>6 (2.9%)</td>
</tr>
</tbody>
</table>

The overall level of satisfaction after keyhole approaches was high (Tables 3–5). Cosmetic outcome was rated by patients on a scale from 1 to 5 (1=very pleasant, 5=very unpleasant) as very or quite pleasant (score 1–2) in 203 patients (96.7%). Postoperative wound pain was rated on a scale from 1 to 5 (1=no pain, 5=severe pain) as no or minimal (score 1–2) in 196 patients (93.3%). Postoperative problems with chewing were reported transiently in three patients (1.4%). Transient palsy of the frontalis muscle was reported in nine patients (4.3%), and permanent palsy in four patients (1.9%). Transient frontal hypoesthesia was reported in 13 cases (6.2%), and permanent deficit in six patients (2.9%). Transient hyposmia was described in one patient (0.5%), and permanent dysfunction in five cases

Table 4  Satisfaction with the postoperative cosmetic outcome, reported by 210 patients.

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
<th>Score 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>191 (91.0%)</td>
<td>12 (5.7%)</td>
<td>4 (1.9%)</td>
<td>0</td>
<td>3 (1.4%)</td>
<td>210</td>
</tr>
</tbody>
</table>

1=very pleasant, 5=very unpleasant.

Table 5  Postoperative discomfort.

<table>
<thead>
<tr>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
<th>Score 4</th>
<th>Score 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>175 (83.3%)</td>
<td>21 (10%)</td>
<td>6 (2.9%)</td>
<td>6 (2.9%)</td>
<td>2 (1.0%)</td>
<td>210</td>
</tr>
</tbody>
</table>

1=no pain, 5=severe pain.

Figure 7  An illustrative case of supraorbital subfrontal (SOR) with a 13 mm aneurysm of the right internal carotid artery (A). After primary successful interventional coiling (B), recurrent aneurysm occurred. After re-coiling and recurrent reperfusion (C), surgical treatment was indicated, achieving complete closure (D).
(2.4%). Using the Fisher’s exact or $\chi^2$-test, no statistically significant difference could be detected in postoperative satisfaction and approach-related injury comparing the SOR, PTE, and FIH approaches by the P-value >0.05.

Illustrative cases

Supraorbital keyhole: pre-coiled aneurysm of the internal carotid artery

A 42-year-old female presented with an incidental aneurysm of the right internal carotid artery (ICA). The aneurysm was 13 mm in size, and located in the supraclinoid segment of the ICA, proximal to the anterior choroidal artery. Given the patient’s age and aneurysm characteristics, the lifetime risk of hemorrhage was considered significant, and intervention therefore warranted. The aneurysm possessed a narrow neck, and was treated with endovascular coil embolization in the first instance. The postoperative course was uneventful. However, follow-up with digital subtraction angiography (DSA) at 6 months showed re-perfusion of the neck region. After a second failed endovascular intervention surgical clipping was planned. As the partially coiled aneurysm was directed posterolaterally, the fronto-lateral supraorbital approach offered unhindered visualization of the carotid artery and neck of the aneurysm (Figures 7 and 8).

Pterional keyhole: unruptured aneurysm of the middle cerebral artery

A 51-year-old female presented with a sudden headache following physical exertion. CT and MRI excluded subarachnoid hemorrhage, but identified an unruptured irregular formed 5.8 mm aneurysm of the left middle cerebral artery (MCA). Following interdisciplinary discussion, surgical clipping was planned. As the aneurysm was...
located within the lateral Sylvian fissure, and the patient had a large frontal paranasal sinus, high sphenoid wing, and low-seated MCA, a transsylvian exposure via mini-PTE was selected (Figures 9 and 10).

**Frontal interhemispheric keyhole: pre-operated aneurysm of the pericallosal artery**

A 58-year-old patient, with a significant family history of intracranial aneurysms and subarachnoid hemorrhage, underwent clipping of an incidental pericallosal artery aneurysm in the late 1980s. Recent CT and DSA showed a recurrent aneurysm, with a diameter of 9.6 mm. Complex aneurysm configuration made endovascular interventional impossible, therefore, operative clipping via an interhemispheric approach was planned (Figures 11 and 12).

**Discussion**

The extent of acceptance of minimally invasive keyhole approaches depends on the satisfaction of both neurosurgeons and their patients. Surgeons are satisfied if the operative exposure offers reduced operating times and shorter hospitalization, while at the same time equaling or exceeding the anatomical exposure, safety, and efficacy of conventional approaches. Patients are satisfied if, in addition to the above-mentioned factors, the operation...
is associated with few postoperative complaints and good cosmetic results.

Our case series has demonstrated excellent surgical outcomes, few complications, and a high level of satisfaction in patients undergoing keyhole approaches for anterior cranial fossa and central skull base pathologies. The neurosurgical advantages of small approaches are clear and proven by many previous publications; they offer a more direct access to pathologies via a limited skin incision and soft tissue dissection as well as reduced brain exposure to non-physiological surroundings. Hence the use of endoscopes and minimal brain retraction may reduce associated postoperative complications and shorten the hospital length-of-stay [2, 3, 6, 11, 13, 16].

In order to apply the keyhole concept, a careful case selection is mandatory and not all anterior cranial fossa and central skull base pathologies are feasible for keyhole approaches. In patients with a convexity meningioma for example, in which the removal of the dural origin also defines the craniotomy, the keyhole concept does not apply [7, 11–13].

Thorough pre-operative planning is necessary to select the optimal approach, one in which it is both least traumatic, and provides adequate and safe exposure of the surgical target area. We place great emphasis on the detailed analysis of pre-operative imaging for surgical planning. High resolution MRI reveals the spatial relationships of the cerebral vasculature and cranial nerves, with significant implications to surgical approach planning. For the majority of our cases we used a virtual reality environment comprising of stereoscopic image processing, and a spatial user interface. This enables us to fuse MRI and CT imaging, segment the surgically important structures, and simulate the surgical corridor in detail and in three dimensions. The precise shape and size of the craniotomy can be simulated by virtually drilling the reconstructed CT, and subsequently surgical viewpoints can be simulated [17, 18].

Intra-operatively, we use image-guidance routinely to define the skin incision and the craniotomy, as well as to safely find and dissect the surgical target. We usually link the laser guided focal point of the microscope to the navigation system and occasionally also track the endoscope. Recently, we have utilized the intra-operative imaging data of the PoleStar iMRI (Medtronic Inc.) or BrainSuite iCT (BrainLab; Siemens, Inc. Munich, Germany) to update the navigation system during tumor surgery.

Figure 10  Mini-pterional frontotemporal (PTE) – endoscope-assisted surgery via left PTE. After limited craniotomy and dural opening, the Sylvian fissure is opened in retractor-less manner (A). Endoscopic inspection shows a thin-walled highly irregular aneurysm with a wide neck (B). A tube shaft instrument is used and the aneurysm is closed with two angled clips (C). Final endoscopic investigation shows correct clip position with reconstruction of the MCA trifurcation (D).
We strongly believe that the lead neurosurgeon should carry out, or personally supervise, the pre-operative planning, patient positioning, skin incision, craniotomy, and surgical exposure of the target region, as well as the bone and soft tissue closure. We have learned that, especially in a teaching institution, this “skin-to-skin” execution by the senior surgeon is of paramount importance for successful keyhole surgery.

Keyhole approaches are, however, not without drawbacks. Minimally invasive approaches necessitate a precisely defined surgical corridor that, if misplaced, can render subsequent surgical steps difficult or impossible. Furthermore, small craniotomies limit the field of view of the operating microscope and require almost co-axial manipulation, making delicate tissue dissection challenging. These limitations require a learning curve related to the use of endoscopes and tube-shaft instruments, and the adaptation of surgical techniques [5, 11, 20].

In the depth of the surgical corridor, endoscopes complement the armamentarium necessary for safe and effective dissection. The main advantages of endoscopes are increased light intensity and an extended viewing angle, which allow clear visualization of patho-anatomical details, even in “hidden corners” of the surgical field [4, 10]. In the context of endoscope-assisted neurosurgery it is worth pointing out that the bone edges of keyhole craniotomies provide a convenient and stable place to rest the endoscope, which can then be handled by an assistant while the lead surgeon continues to operate with both hands. We utilized endoscope-assisted microsurgical techniques in all cases in our series.

Slim and tube-shaft designed instruments are only the beginning of an evolution of instruments that will enable
Reisch et al., Endoscope-assisted keyhole surgery of the anterior fossa approaches though even narrower corridors. Advances in emerging fields such as robotics, will certainly increase surgical precision and freedom of manipulation, even within the smallest spaces.

In conclusion, we describe the use of the supraorbital subfrontal, the mini-pterional and the frontal interhemispheric approaches to the anterior cranial fossa and central skull base. In our case series, we report a favorable surgical outcome, low rate of postoperative complications and high patient satisfaction when using such minimally invasive surgical approaches. The following points are emphasized: careful case selection and thorough pre-operative planning, execution or close supervision of the surgery by the lead surgeon, image guidance for precise definition of craniotomy and surgical trajectory, endoscopy for enhanced visualization and illumination, and tube-shaft instruments for manipulation through a narrow surgical corridor.

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References


Figure 12 Frontal interhemispheric (FIH) – endoscope-assisted surgery via right FIH. Note re-opening of the pericallosal aneurysm with markedly displacement of the 30-year-old clips (A). Endoscopic investigation shows both pericallosal arteries and complex wide neck of the aneurysm (B). Though the FIH keyhole, tube-shaft instruments were used (C) with complete closure using three clips (D).


The authors stated that there are no conflicts of interest regarding the publication of this article.