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Surgical Clipping of Very Small Unruptured Intracranial Aneurysms: A Multicenter International Study

BACKGROUND: Treatment of very small unruptured intracranial aneurysms (VSUIAs, defined as ≤ 3 mm) can be indicated in selected circumstances. The feasibility and outcomes of endovascular therapy for VSUIAs have been recently published; however, the efficacy and complication rate of surgical clipping has not been reported in any large series to date.

OBJECTIVE: We conducted a multicenter study to examine surgical outcomes for VSUIAs.

METHODS: All consecutive patients undergoing surgery for a VSUIA in 4 neurosurgical centers between October 2001 and December 2012 were retrospectively analyzed.

RESULTS: In the study, 183 patients (128 women, mean age 51.3 years) were treated with 190 procedures for a total of 228 aneurysms. Most were anterior circulation aneurysms ($n = 215$). The majority were directly clipped ($n = 222$, 97.4%), with coagulation or wrapping in the remainder. After 1 reoperation for incomplete clipping, postoperative imaging of 225 aneurysms confirmed complete occlusion in 221 (98.2%), 1 neck remnant (0.44%), and 3 partial occlusions (1.3%). Mortality was 0%. Early postoperative neurological deficit developed in 12 patients (6.6%); posterior circulation location was a significant risk factor for early neurological deficit ($P < .001$). Middle cerebral artery aneurysms had the lowest rate of postoperative deficits at 1.5% ($P = .023$). After the initial 30-day perioperative period, all deficits related to treatment of posterior circulation aneurysms recovered; overall neurological morbidity decreased to 2.7% with no mortality.

CONCLUSION: VSUIA clipping is highly effective and is associated with a low morbidity rate. For VSUIAs selected for treatment, our data support surgical clipping as the modality of choice.

KEY WORDS: Intracranial aneurysm, Outcome, Surgery, Surgical clipping, Unruptured aneurysm

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Very small unruptured intracranial aneurysms (VSUIAs) are defined as unruptured aneurysms with a diameter smaller or equal to 3 mm.^{1,2} Although the risk of rupture for aneurysms of such size has not been specifically studied, they are typically considered to

have an indolent natural history given that observational studies have consistently linked larger aneurysm size with rupture risk.^{3–9} Nonetheless, several other patient and aneurysm factors can affect hemorrhage risk and influence the decision to treat a VSUIA.^{5,7–11} Such treatment is justifiable when the risk of intervention is low enough to outweigh the natural history of the disease. From the perspective of endovascular treatment, VSUIAs are more challenging due to the technical difficulty of coil placement into a small space.^{1,2,12} Although small aneurysms typically carry lower morbidity than larger lesions when treated surgically, VSUIAs can pose their own unique challenges

ABBREVIATIONS: DSA, digital subtraction angiography; mRS, modified Rankin Scale; VSUIAs, very small unruptured intracranial aneurysm

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related to clip application onto the diminutive aneurysmal tissue. Although the feasibility and risks of endovascular treatment for VSUIAs have recently been reported in the literature,^{1,2,13,14} the risk associated with surgical clipping has not been well characterized. In an effort to better delineate the efficacy and complications rates associated with surgical treatment of VSUIAs, we have conducted a retrospective multicenter international study to assess outcomes related specifically to microsurgical treatment of such lesions.

METHODS

All consecutive patients surgically treated for a saccular VSUIA during a 135-month period spanning from October 2001 to December 2012 in 4 neurosurgical centers (Helsinki, Finland; Chicago, Illinois; Geneva, Switzerland; Brussels, Belgium) were included. Patients were excluded if a larger aneurysm was also treated during the same procedure or in case of a blister aneurysm. Prospective and retrospective databases and charts were retrospectively reviewed in each center after approval of the ethics committees at each institution. The informed consent was waived.

For each patient, demographic data, risk factors, reasons for treatment, clinical presentation, and aneurysm characteristics on preoperative imaging were collected. All patients were operated on by a neurosurgeon experienced in aneurysm treatment. Details of intraoperative management were noted. Radiological results after microsurgical clipping were evaluated according to the standard method in each center (intraoperative digital subtraction angiography [DSA], postoperative DSA, or computed tomography angiography) and the aneurysm was considered either completely occluded, with a neck remnant, incompletely occluded if persistent filling of the aneurysmal sac was noted, or failed occlusion. The neurological condition of the patient preoperatively, immediately after surgery, at time of discharge from the hospital, at 4 to 8 weeks postoperatively, and at time of last follow-up was recorded. Clinical outcomes were determined based on Glasgow Outcome Scale and modified Rankin Scale (mRS) to characterize patient disability at last follow-up.

Early (within 30 days) and delayed (at last follow-up) clinical complications were analyzed. Early complications were subdivided into symptomatic neurological complications, neurosurgical complications without neurological deficit (such as asymptomatic CT scan infarction, asymptomatic hematoma, meningitis, and new epilepsy), and systemic complications. Late complications were subdivided into those with and without permanent neurological sequelae.

Statistical Analysis

The data were analyzed using Statistix 9.0 software (Tallahassee, Florida). Continuous variables were presented as mean \pm standard deviation or as median (interquartile range) after checking for normality of the distributions using the Shapiro-Wilk test. Gaussian variables were compared using a 2 samples Student *t* test and non-Gaussian variables were compared using a Mann-Whitney *U* test. Despite the fact that mRS is a non-Gaussian variable, it was also presented as mean \pm standard deviation besides median (interquartile range) in order to better show differences. The discrete data were presented as numbers with percentage of the total. The discrete data were compared using a χ^2 test with Yates' correction when needed. The repeated measurements were compared with a Friedman test for nonparametric data and pairwise comparisons were made using a Wilcoxon signed-rank test. The odds ratios were

calculated when indicated and presented with 95% confidence interval (95% CI). A *P* < .05 was considered significant.

RESULTS

Demographic Data

The study included 183 patients (128 women, 55 men) with 228 aneurysms, operated on during 190 procedures. Mean age of the cohort was 51.3 years (range, 21.2-78.0 years) (Table 1). A single aneurysm was treated in 152 patients (83%) and 31 patients (17%) were operated on for multiple aneurysms: 2

TABLE 1. Demographic Data^a

Patients	183
Aneurysms	228
Surgeries	190 + 1 ^b
Age	51.3 (21.2-78.0)
Male/female	55/128
Hypertension (%)	85 (46.4)
Smoking (%)	94 (51.4)
Stroke (%)	12 (6.6)
Ischemic heart disease (%)	15 (8.2)
Diabetes mellitus (%)	13 (7.1)
Preop mRS	0.34 (0-3)
Reason for treatment (%)	
Incidental	93 (50.8)
History of previous SAH	60 (32.8)
Multiple aneurysms	102 (55.7)
Familial history aneurysms	91 (49.7)
Aneurysm location (%)	
Anterior circulation	215 (94.3)
Ophthalmic	17 (7.5)
PCom	8 (3.5)
AChor	5 (2.2)
Paraclinoid	1 (4.0)
Carotid bifurcation	4 (1.8)
M1	49 (21.5)
MCA bifurcation	88 (38.6)
A1	6 (2.6)
ACom	22 (9.6)
Pericallosal	15 (6.6)
Posterior circulation	13 (5.7)
Basilar artery	5 (2.2)
SCA	5 (2.2)
PCA	1 (4.0)
PICA	2 (9.0)
Left	110 (48.2)
Right	102 (44.7)
Midline	16 (7.0)
Aneurysm characteristics	
Dome size	2.36 (0.9-3.0)
Neck size	2.21 (0.9-3.0)
Dome/neck ratio	1.09 (0.5-2.0)
Blebs	46 (20.2%)

^aA1, AChor, ACom, PCA, PCom, PICA, Preop mRS, M1, MCA, SAH, SCA.

^bOne patient was reoperated on after failure at first surgery.

aneurysms in 21 patients, 3 in 7 patients, 4 in 2 patients, and 5 in 1 patient. One hundred seventy-eight surgeries were done specifically for the occlusion of anterior circulation aneurysms. Ten procedures were dedicated to the treatment of a single posterior circulation aneurysm. Two procedures were performed for the treatment of both anterior and posterior circulation aneurysms: 1 procedure for treating 2 M1 aneurysms and 1 BA aneurysm and 1 procedure for occluding a carotid-ophthalmic aneurysm, a BA aneurysm, and a SCA aneurysm. For purposes of analysis, these procedures were designated as anterior circulation and posterior circulation, respectively, according to the majority of aneurysms treated.

Given natural history data supporting higher rupture risk in the Finnish population,⁸ the majority of the cohort derived from the Finnish center: 125 patients with 151 aneurysms were treated in Helsinki, Finland; 23 patients with 32 aneurysms in Brussels, Belgium; 24 patients with 28 aneurysms in Chicago, Illinois; and 11 patients with 17 aneurysms in Geneva, Switzerland.

Preoperative comorbidities and risk factors for surgery are outlined in Table 1, with hypertension (46.4%) and smoking (51.4%) being most prevalent. Average preoperative mRS was 0.34 (range, 0-3). Of the 183 operated patients, surgical indications were motivated alone or in combination by the previous rupture of another aneurysm in 51 patients (27.9%), the presence of multiple aneurysms in 79 cases (43.2%), or in the context of a familial history of aneurysms in 81 cases (44.3%).

Aneurysms were primarily located in the anterior circulation (n = 215, 94.3%), vs 13 aneurysms (5.7%) in the posterior circulation. The mean dome size was 2.36 mm (0.9-3.0); the mean neck size was 2.21 mm (0.9-3.0) with a dome to neck ratio of 1.09 (0.5-2.0). Aneurysms distribution is detailed in Table 1.

Surgical Procedure

Two hundred twenty-two aneurysms (97.4%) were clipped, 1 aneurysm was coagulated, 3 aneurysms were wrapped, and 2 aneurysms were coagulated and wrapped. The majority of aneurysms, 83.8% (n = 191), were clipped with 1 clip; 29 aneurysms required 2 clips; and 2 adjacent aneurysms were occluded with a single long clip. Two aneurysms ruptured intraoperatively: a 2.2-mm M1 aneurysm and a 3-mm MCA bifurcation aneurysm. These 2 aneurysms were secured with complete occlusion and without any postoperative deficit. Temporary clipping was performed in 71 cases (31.1%) and adenosine-induced temporary cardiac arrest was used in 2 cases (0.9%); neither intraoperative strategy was associated with postoperative infarct on CT ($P = .76$ and $P = .71$, respectively) or early postoperative deficit ($P = .49$ and $P = .89$, respectively). Intraoperative indocyanine (indocyanine green) videoangiography was used to evaluate the clipping result in 129 aneurysms (56.6%) and intraoperative digital subtraction angiography in 15 cases (6.6%). Surgical data are summarized in Table 2.

TABLE 2. Surgical Data^a

Temporary clipping (%)	71 (31.1)
Adenosine (%)	2 (0.9)
Treatment	
Clipping (%)	222 (97.4)
Number clip applied	1.1 (0-2)
Coagulation	1
Wrapping	3
Wrapping and coagulation	2
Trapping	0
ICG videoangiography (%)	129 (56.6)
Intraoperative DSA (%)	15 (6.6)

^aDSA, digital subtraction angiography; ICG, indocyanine green.

Postoperative Course

Clinical Outcome

The average early Glasgow Outcome Score was 4.85 (range, 3-5) in the full cohort, and 4.86 (range, 3-5) after a mean follow-up of 121.3 months in 176 patients; 1 patient died and 4 deteriorated of unrelated causes several years after treatment, and 2 patients were lost to follow-up. For the patients with follow-up, mRS changed significantly in the early postoperative period (mean, 0.47 ± 0.8 ; median, 0 [0-1]; $P = .0085$) compared to the preoperative mRS (mean, 0.36 ± 0.7 ; median, 0 [0-0]), but not at the last follow-up (mean, 0.42 ± 0.7 ; median, 0 [0-1]; $P = 0.21$). No patient experienced a delayed rupture.

Complications and Risk Factors

In the early postoperative period, 12 patients (6.6%) developed a new neurological deficit: 7 patients developed an oculomotor paresis related to surgical manipulation, 3 patients had hemiparesis with (n = 1) and without (n = 2) dysphasia related to an ischemic event, 1 patient demonstrated a memory deficit, and 1 patient complained of dysgeusia. Five out of 11 (45.5%) procedures confined to the treatment of a single posterior circulation aneurysm resulted in a deficit (all oculomotor paresis), as compared to 7 of 179 procedures confined to aneurysms of the anterior circulation (3.9%), resulting in a significantly higher risk of early postoperative deficit with posterior circulation aneurysms ($P < .0001$). BA and SCA locations were associated with the highest complication rate ($P = .0003$ and $P < .0001$, respectively), although the MCA aneurysms distal to M1 were associated with the lowest complication rate (1 complication out of 75 procedures) compared to any other location ($P = .023$). Odds ratios relative to location are shown in the **Table, Supplemental Digital Content 1** (<http://links.lww.com/NEU/A775>). There was no statistical association between the rate of early postoperative neurological deficit and the center of inclusion ($P = .65$).

Postoperative CT scans revealed 2 small asymptomatic infarctions and a subdural hematoma that did not require surgical

evacuation. Neurosurgical complications not associated with a neurological deficit included 3 new onset seizures, 2 infections, 4 CSF fistulae, and 1 reoperation for a retained retraction hook, resulting in a rate of 7.1% per patient or 6.7% per procedure. Systemic complications (1.1% per patient) consisted of 1 episode of atrial fibrillation and 1 pulmonary embolism.

The perioperative mortality was 0% within 30 days after surgery. The majority of early deficits were transient; after postoperative day 30, the neurological morbidity dropped to 2.7% per patient (5 patients), with oculomotor paresis, hemiparesis, memory deficit, dysgeusia, and seizures remaining in 1 patient each. All patients with aneurysms of the posterior circulation recovered their early postoperative deficit.

The overall delayed complication rate increases to 3.8% when including a patient who presented with a clinical suspicion of CSF infection that resolved after antibiotic therapy despite negative cultures in the CSF and a patient who developed a chronic subdural hematoma conservatively treated. Postoperative events are summarized in Table 3.

Imaging Follow-up

Imaging follow-up consisted of computed tomography angiography in 154 patients and DSA, performed either intraoperatively or postoperatively, in 70 patients. One patient underwent an unknown imaging modality and 3 were not imaged after successful

intraoperative occlusion (see Table, Supplemental Digital Content 2, <http://links.lww.com/NEU/A776>). One aneurysm was not occluded and was reoperated on quickly afterwards, increasing the number of surgeries from 190 to 191. After these 191 procedures, complete aneurysm occlusion was depicted in 221 of 225 aneurysms imaged (98.2%), a neck remnant in 1 patient (0.44%), a partial occlusion in 3 patients (1.3%), and no failure.

DISCUSSION

This multicenter international study is the largest reported to date on a subgroup of patients with VSUIAs treated surgically. With a 98.2% complete occlusion rate, 0% mortality, and a 2.7% persistent neurological complication rate, our study demonstrates that VSUIAs can be effectively treated with very low morbidity. Aneurysms of the MCA distal to M1 were the safest to treat with a 1.3% rate of early neurological deficits per procedure. The overall 6.3% rate per procedure of early postoperative neurological deficits was in large part due to the treatment of posterior circulation aneurysms, especially those located in the region of the basilar tip. Posterior circulation aneurysms are typically considered the most risky to treat, but also pose the greater risk of rupture when followed conservatively.^{4,8,9} As reported in the literature for aneurysms in general,⁹ we found a significant difference in the risk of early neurological deficits between anterior and posterior circulation aneurysms, with a 3.9% and a 45.5% rate of new postoperative deficits, respectively. Notably, however, the complications in the posterior circulation cases were primarily attributable to manipulation of the third nerve resulting from the surgical approach, and, hence, transient. Persistent deficits were seen in only 2.7% of cases on long-term follow-up. The overall delayed complication rate increased to 3.8% when considering all inadvertent events, but all non-neurological events had no long-term impact on patient condition and resolved over time.

The only prior surgical series analyzing the results of the surgical treatment of VSUIAs was published in 1999.¹⁵ It included 12 patients with 20 aneurysms in which the VSUIA was treated concurrently with a larger aneurysm as the primary indication for surgery. All VSUIAs in this series were treated by bipolar electrocoagulation, which was followed by reinforcement of the parent artery with muslin gauze. On immediate angiographic examinations, 19 of these 20 (95%) microaneurysms were no longer visible and 1 was substantially smaller (<1 mm irregularity on the parent vessel). No change was observed on angiography after 1-year follow-up. No patients experienced any adverse event related to treatment of their VSUIA.

It is not surprising that the literature on VSUIA treatment is sparse given that small aneurysms have been typically characterized as low risk for rupture.³⁻⁹ Although the rupture risk of VSUIAs has not been specifically addressed in the literature, it can be extrapolated based on existing data on slightly larger aneurysms.⁴⁻⁹ The ISUIA study reported the 5-year cumulative rupture rate of

TABLE 3. Postoperative Results: Complications^a

	n	Per Patient (n = 183), %	Per Procedure (n = 191), %
Early			
Symptomatic neurological complications	12	6.6	6.3
Neurosurgical complications without neurological deficit	13	7.1	6.7
Asymptomatic infarction	2		
Hematoma	1		
Seizure	3		
Infection	2		
CSF fistula	4		
Reop for retained hook	1		
General complications	2	1.1	1.0
Atrial fibrillation	1		
Pulmonary embolism	1		
Total		14.8	14.0
Late			
Permanent neurological deficit	5	2.7	2.6
Without neurological deficit	2	1.1	1.0
Suspicion of infection treated with antibiotics	1		
Nonsurgical chronic SDH	1		
Mortality	0	0	

^aCSF, Reop, SDH.

2 to 7 mm aneurysms to be 0% and 1.5% for anterior circulation aneurysms without and with a history of a subarachnoid hemorrhage, respectively, and 2.5% and 3.4% for posterior circulation aneurysms (including PCom aneurysms).⁹ In patients with a previous history of SAH or a familial history of aneurysms, Wermer et al³ reported that 8.7% of 1 to 3 mm aneurysms enlarged or ruptured after 1.3 years. In Japanese cohorts of UIAs, the annual rupture rate of aneurysms of less than 5 mm was 0.8% in the Ishibashi et al⁴ study and 0.54% in the SUAVE study⁵: 0.34% per year in the case of a single aneurysm and 0.94% per year in the case of multiple aneurysms. In the UCAS study, an annual rupture risk of 0.36% was established for aneurysms of 3 to 4 mm.⁶ In Finnish patients followed over a median follow-up of 21 years, Juvela et al⁷ reported an annual rupture risk of 0.9% in UIAs of 2 to 7 mm, with a cumulative risk at 10, 20, and 30 years, respectively, of 9%, 18%, and 26%. Recently, the annual rupture rate reported in the PHASES study⁸ was 0.4% for aneurysms of less than 5 mm. It is important to note that our multicenter cohort consisted primarily of selected patients with recognized or potential risk factors for rupture: a large number of patients were Finnish,^{7,8,16} and had a history of previous SAH,⁸ a familial history of aneurysms, multiple aneurysms,⁵ or a daughter sac.^{9,10}

VSUIAs can pose specific surgical challenges due to the very small size of the aneurysm: the clip can be large relative to the aneurysm size, and not enough aneurysm wall may be present to stabilize the clip while preserving the patency of the parent vessel. The smallest dome that was occluded measured 0.9 mm; this aneurysm was concomitantly occluded with a larger VSUIA. Two cases of intraoperative rupture appeared in the cohort; these aneurysms were subsequently occluded completely without any consequences. It may be expected that small aneurysm size would be associated with an increased risk of intraoperative rupture, related to the difficulty of applying and stabilizing the clip, but the 0.9% rate of intraoperative rupture is similar to the 0.7% to 1.2% risk generally reported in the literature in larger studies of unruptured aneurysms.^{17,18}

The low neurological morbidity rate and the absence of mortality compare favorably with the results of large studies and meta-analyses of UIA clipping in general, which report a mortality risk between 0.7% and 2.6%.¹⁹⁻²² Furthermore, it is well documented that surgical morbidity increases significantly with larger aneurysm size.^{4-9,22} The lower morbidity we report associated with the surgical treatment of VSUIAs is in accordance with this principle.

Our results also compare favorably to the results of endovascular treatment, which have been reported in 4 studies comparing VSUIAs either with very small ruptured intracranial aneurysms^{2,13,14} or with UIAs larger than 3 mm.¹ A summary of the relevant endovascular literature is provided in the **Table, Supplemental Digital Content 3** (<http://links.lww.com/NEU/A777>). The 4 relevant series on VSUIAs treated by coiling include a total of 165 aneurysms in 160 patients. A female predominance was observed (male:female ratio between 1:4 and 1:2) and the mean age

at treatment was 46.4 to 55 years. Indications for treatment were a SAH history from another aneurysm in 6.7% to 85.1%, multiple aneurysms in 20% to 62.7%, a familial screening or SAH history in 5.9% to 36.2%, an irregular shape in 4.3% to 26.7%, neurological symptoms or mass effect in 2.1% to 5.9%, an additional larger aneurysm treated at the same time in 13.3%, patient emotional distress in 13.3% or patient's preference in 17% to 20%, and after incidental discovery in 12.8% to 51%. Most aneurysms (80.4%-94.7%) were located in the anterior circulation. The 5.3% rate of posterior circulation aneurysms treated endovascularly was similar in the Hwang et al¹⁴ study to our series, but Brinjikji et al² and Pierot et al¹ encompassed a higher proportion of posterior circulation aneurysms. The reported rate of intraoperative rupture was 0% in 2 studies,^{13,14} 3.9%,¹ and 8.5%.² Thromboembolic events were noted in 2.1% to 5%; parent artery occlusion and coil-related complications were reported in 2% each in a series.^{1,2} Endovascular treatment was successful in all cases in 2 series,^{13,14} but failed in 8.5% to 13.7% of the cases in 2 others.^{1,2} Immediate angiographic results demonstrated complete or near complete occlusion in 63.2% to 91.5%, and incomplete occlusion in 8.5% to 21.6%.^{1,2,13,14} After a mean follow-up of 10.6 months, 12.8% in the Brinjikji et al² series needed to be retreated. In the ATENA subgroup published by Pierot et al,¹ the total postoperative change in neurological examination was 3.9%, the permanent neurological deficit 2%, and the 1-month mortality 2%. The permanent neurological deficit was 2.1% in the van Rooij et al¹³ series. A delayed rupture has not been reported in any of these studies.

The endovascular treatment of these very small intracranial aneurysms poses, in fact, specific technical difficulties as stated by the authors with subsequent higher complication rate^{1,13} due to the inability to obtain a stable microcatheter position, the difficulties in microcatheterization of the aneurysm and deploying coils in a limited space, and the risk of perforation induced by manipulation of the micro guidewire or the microcatheter.²

Limitations

Our study is limited by its retrospective nature, and no direct comparison can be made with endovascular series. Refinement in endovascular devices and techniques could also become associated with better endovascular results over time. Nevertheless, based on our study we observe that VSUIAs can be successfully occluded in a very high percentage of cases, with a low morbidity and no mortality. Based on these results, we propose that surgery plays a significant role when treatment of such aneurysms is undertaken.

CONCLUSION

The clipping of VSUIAs by experienced teams is highly effective and associated with a very low morbidity rate. These results should be integrated in the decision-making process for management of these aneurysms. Taking into account a selective approach focused on patients with additional risk factors for rupture, our data lend support to surgical clipping as the modality of choice.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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