Approximately 10%–33% of patients with aneurysmal SAH harbor MIAs. Today, surgery within 72 hours is strongly believed to reduce the risk of rerupture. Cerebral vasospasm is the major cause of morbidity and death after the patient has survived the initial bleeding event and the operation. The cause of cerebral vasospasm is considered to be multifactorial, with vessel and brain manipulation during surgery considered one of the factors. This is supported by the fact that the poorest surgical results are obtained if the operation is performed during the vasospasm period.

Clipping of more than 1 aneurysm in a single operation usually requires more manipulation of the parent vessels and often a prolonged duration of operation. This might increase the risk for the development of cerebral vasospasm and, as a consequence, increase the risk for morbidity and death. This risk leads to the need to define the incidence of vasospasm in the cases in which MIAs are treated in a 1-stage operation compared with the treatment of SIAs after SAH.

Methods

Study Sample

We analyzed a database including 1016 patients with subarachnoid hemorrhage (SAH), identified retrospectively between 1989 and 1996 and prospectively collected between 1997 and 2004. Exclusion criteria were endovascular treatment, surgery after SAH Day 3, and, in patients with MIAs, undergoing more than 1 operation. Cerebral vasospasm was diagnosed by transcranial Doppler (TCD) ultrasonography and was defined as a maximum mean blood flow velocity > 120 cm/second. The diagnosis of symptomatic vasospasm was made if a new neurological deficit occurred that could not be explained by concomitant complications.

Results. A total of 643 patients who experienced 810 aneurysms were included. Four hundred twenty-four patients were female (65.9%) and 219 were male (34.1%) with an average age of 53.1 years. One hundred twenty-one patients (18.8%) were diagnosed with MIAs. Maximum mean flow velocities measured by TCD were 131 cm/second in patients with MIAs and 129.5 cm/second in patients with single intracranial aneurysms. The incidence of TCD vasospasm (p = 0.561) as well as of symptomatic vasospasm (p = 0.241) was not significantly different in the 2 groups.

Conclusions. Clipping of more than 1 aneurysm in a 1-stage operation within 72 hours after SAH can be performed without increasing the risk of cerebral (TCD) vasospasm and symptomatic vasospasm.

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Key Words • subarachnoid hemorrhage • vasospasm • multiple intracranial aneurysm • early surgery • transcranial Doppler ultrasonography
aneurysmal SAH, identified retrospectively between 1989 and 1996 and prospectively collected from 1997 to 2004. Exclusion criteria were endovascular treatment, surgery after SAH Day 3, and treatment of the aneurysms in 2 steps or more in patients with MIAs. A total of 643 patients, 424 female (65.9%) and 219 male (34.1%) with an average age of 53.1 years (range 11–86 years), were included in the final sample.

Initial clinical presentation was documented according to the Glasgow Coma Scale as well as the Hunt and Hess grading system. The outcome assessment was performed by a neurologist (I.K.A.) who was not involved in the management of the patients and was blinded to the number of the treated aneurysms, unless repeated imaging was performed during follow-up investigation.

Imaging Assessment

Diagnosis of SAH was made using CT. The amount of blood noted on the initial CT scan was classified according to the Fisher grading system. All included patients underwent 4-vessel digital subtraction angiography before surgery. Preoperative MR and/or CT angiography were not routinely performed. All patients underwent early postoperative CT scans (within 4 hours after surgery) and repeated CT scans in every case involving neurological decline. Hypodensities on CT scans were believed to be related to vasospasm if they were not noted on previous CT scans and if the TCD-measured CBF velocity was 120 cm/second or higher.

Surgical Procedure

All patients with aneurysmal SAH, presenting within 72 hours after the initial bleeding event, underwent surgery irrespective of the Hunt and Hess grade. In patients with poor Hunt and Hess grades (IV and V), external ventricular drainage was placed, and in patients with good Hunt and Hess grades (I–III), lumbar drainage was placed for intraoperative brain relaxation. The institution’s policy for MIAs was to attempt clipping of all aneurysms either by 1 or 2 craniotomy procedures.

For every aneurysm of the anterior circulation, with the exception of pericallosal artery aneurysms, CSF drainage via the opened lamina terminalis for additional brain relaxation was performed, which required at least the opening of the most proximal part of the sylvian fissure. For aneurysms of the ICA, further opening was rarely necessary, whereas the sylvian fissure opening was extended slightly in ACA and ACoA aneurysms to facilitate brain retraction, and into the area of the bifurcation in MCA aneurysms for parent artery control and aneurysm exposure. Pericallosal aneurysms (A2) were approached via the anterior interhemispheric approach, basilar artery aneurysms via the subtemporal approach, and vertebral artery aneurysms via the transcondylar approach.

In MIAs the exact localization of the aneurysms guided the extent of preparation of the sylvian fissure and the basal cisterns. In comparison with SIA, the preparation for MIAs was substantially more extensive in bilateral aneurysms, followed by MCA/ACoA aneurysms, and less substantially for ICA/ACoA as well as ICA/unilateral MCA aneurysms. In MIAs located at the same parent artery, the amount of preparation was comparable with that of SIA.

MicroDoppler ultrasonography was used after clipping to assure patency of the parent and draining arteries. The operative field was rinsed with nimodipine during the intradural steps of the operation to reduce the risk of vasospasm due to manipulation of intracranial vessels.

Vasospasm Determination

Using a transtemporal approach, mean blood flow velocities were recorded daily by a common 2-MHz transducer between the 1st and 14th day after the initial bleeding event as described by Aaslid et al. Transcranial Doppler vasospasm was defined as a maximum mean blood flow velocity > 120 cm/second, as has been previously proposed. The diagnosis of symptomatic vasospasm was made if a new focal or global neurological deficit occurred that could not be explained by concomitant complications such as hydrocephalus, rebleeding, infection, and metabolic abnormalities. Angiography for confirmation of the TCD results was not performed.

Antivasospastic Therapy

All patients received standard prophylactic therapy with 5 ml (1 mg)/hour of nimodipine for 2 hours, followed by 10 ml (2 mg)/hour over the next 14 days. Hypervolemia was avoided in every patient, and normovolemia was maintained in patients without TCD vasospasm. In any patient with TCD values > 120 cm/second, catecholamines, mainly noradrenaline, were used to induce arterial hypertension (target systolic blood pressure 160 mm Hg) and colloidal substances were used to achieve mild hypervolemia (central venous pressure 8–12 mm Hg). Patients with TCD vasospasm were confined to bed rest. In patients with symptomatic vasospasm, reversal of the neurological deficit by further increase of the blood pressure was attempted. Treatment with papaverine or balloon angioplasty was not performed because of the unproven effect on outcome in matched-pair studies available during the study period.

Statistical Analysis

Statistica version 8 (Statsoft) and SAS version 9.2 (SAS Institute) statistical software were used for analysis. Patient characteristics were summarized as percentiles, ranges, and medians as appropriate. A probability value < 0.05 was considered statistically significant. Two-by-two contingency tables were constructed to define the correlation between multiple aneurysms and vasospasm, DINDs, and ischemic lesions.

Statistical significance was calculated using the chi-square test for categorical variables, t-test for continuous variables, and Mann-Whitney U-test to define the correlation between multiple aneurysms and grouping variables. To assess the risk of multiple aneurysm-related vasospasm we performed multivariable logistic regression analyses (SAS 9.2) adjusting for different variables. In-
Vasospasm in multiple versus single aneurysms
dependent variables according to subject relevance were,
in order of appearance: the existence of multiple aneu-
rysms (SIA group vs MIA group) and the time interval
between the onset of SAH and the surgical intervention
(Day 1 through Day 5). To evaluate a sex-dependent inci-
dence of vasospasm, the incidence of multiple aneurysms
(SIA group vs MIA group) and sex (female vs male) were
defined as independent variables. Transcranial Doppler-
deﬁned vasospasm (no vasospasm group vs vasospasm
group) was considered as a dependent variable in both
multivariable analyses (binary logistic model).

Results

Patient Population

A total of 643 patients were included in the study
population. Of these 643 patients, 424 (65.9%) were fe-
male and 219 (34.1%) were male, with an average age of
53.1 years (range 11–86 years; Table 1). Of 522 patients
who harbored a single aneurysm, 329 (63%) were female
and 193 (37%) were male, with an average age of 52.9
years. Of the 121 patients (18.8%) with more than 1 aneu-
rysms, 95 (78.5%) were female and 26 (21.5%) were male,
with a mean age of 53.4 years. There were 341 patients
(65.3%) with good Hunt and Hess grades (Grades I–III)
and 151 (29%) with poor grades (Grades IV and V) in
the SIA group (missing data in 30 patients), and 81 (67%)
with good grades and 36 (29.8%) with poor grades in the
MIA group (missing data in 4 patients). In the SIA group,
Fisher Grade 4 was diagnosed in the majority of patients
(220 patients [42.1%]), whereas in the MIA group, Fisher
Grades 3 (47 patients [38.8%]) and 4 (46 patients [38%])
were almost equally distributed. Most single aneurysms
were located at the ACoA (212 patients [40.6%]), followed
by the MCA (120 patients [23%]). The predominant sites
of multiple aneurysms were the MCA (104 of 288 total
aneurysms [36.1%]) and the ACoA (72 of 288 [25%]).

Mean arterial blood pressure by the time of admis-
sion to the hospital was 110.8 ± 24.03 mm Hg in patients
with multiple aneurysms and 108.5 ± 21.18 mm Hg in
patients with single aneurysms. On average, patients with
MIAs underwent an operation on Day 1.6 and patients
with SIAs on Day 1.5 after the bleeding event. Nonpara-
metric analysis showed statistical significance regarding
the incidence of multiple aneurysms and sex, in which
female sex was a risk factor for harboring multiple aneu-
rysms (p = 0.0006). There was no statistical significance
between age (p = 0.648), Fisher grade (p = 0.298), or Hunt
and Hess grade (p = 0.648) and the incidence of multiple
aneurysms (Table 2). No statistical significance was found
between the incidences of multiple aneurysms and mean
arterial blood pressure (p = 0.392). Multivariate logistic
regression analysis did not show statistical significance
between the incidence of multiple aneurysms, vasospasm,
and the interval between the initial bleeding event and the
operation (p = 0.703). A compendium of the clinical find-
ings and aneurysm sites is given in Table 1.

Incidence of Vasospasm, DINDs, and Ischemic Lesions

Two hundred and thirty-one patients (44.3%) with

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* AChA = anterior choroidal artery; AICA = anterior inferior cerebel-
lar artery; BA = basilar artery; CMA = callosomarginal artery; OA =
ophthalmic artery; PCA = posterior cerebral artery; PCoA = posterior
communicating artery; PerA = pericallosal artery; PICA = posterior infe-
rior cerebellar artery; SCA = superior cerebellar artery; VA = vertebral
artery.
† In the SIA group, 3 patients were missed with ACoA aneurysms, 2
patients were missed with PICA aneurysms, 1 patient was missed with
an ICA aneurysm, and 1 patient did not undergo angiography.
SIAs and 57 patients with MIAs (47.1%) developed TCD vasospasm (Fig. 1). The incidence of TCD vasospasm did not show statistical significance between these groups (p = 0.561). Because female sex was shown to be statistically significant for harboring multiple aneurysms, we performed a multivariate analysis regarding the correlation between sex, multiple aneurysms, and the incidence of TCD vasospasm, which again was not significant (p = 0.450). Maximum mean flow velocities measured by TCD were 131 ± 50.49 cm/second in patients with MIAs and 129.5 ± 53.17 cm/second in patients with SIAs. Mean onset of TCD vasospasm was on Day 5.4 in the SIA group and on Day 4.9 in the MIA group (range in both groups Day 1–Day 14).

Symptomatic vasospasm developed in 86 patients (16.5%) with SIAs and in 15 patients (12.4%) with MIAs. Maximum mean flow velocities in these patients were 184 ± 42.9 cm/second in the MIA group and 193 ± 47.1 cm/second in the SIA group. Leading symptoms were loss of consciousness, aphasia, hemiparesis, and confusion in both groups. Vasospasm and CT-proven ischemia were found in 11 patients (9.1%) with MIAs and in 53 patients (10.2%) with SIAs. Corresponding maximum mean flow velocities were 188 ± 42.3 cm/second in the MIA group and 181 ± 61.7 cm/second in the SIA group. Clinical outcome (GOS score) was 2.33 in the MIA group versus 2.29 in the SIA group. The incidence of multiple aneurysms versus DIND (p = 0.241), ischemic lesions (0.897), GOS score (p = 0.764), and age (0.648) was not statistically significant (Table 2).

**Discussion**

**Management of Multiple Aneurysms**

There is no clear consensus on how to address patients suffering from aneurysmal SAH, in which pretreatment angiography reveals more than 1 aneurysm. Many favor a 1-step operation in patients with unilateral aneurysms, which can be approached via a single craniotomy.7,21,22,35 In patients with bilateral aneurysms, some have advocated clipping via a unilateral or bilateral craniotomy.8,10 Others propose to postpone treatment of the unruptured aneurysm (or aneurysms) if more than 1 craniotomy is required to expose them.19 One argument for treatment of all accessible aneurysms is the difficulty in unequivocally identifying the symptomatic aneurysm with the risk of rerupture if the symptomatic aneurysm is left untreated.35 A second argument is the assumed lower risk of rupture of 1 of the nonsymptomatic aneurysms in situations of aggressive HHH therapy for symptomatic vasospasm. The scientific proof for this assumption remains lacking and possibly would never be given in a randomized way because ethical considerations would not allow challenging unruptured aneurysms using either more or less aggressive HHH therapy.48

**Vasospasm and Surgery**

The manipulation of cerebral arteries that are already irritated by subarachnoid blood12,32,34,38,44 might result in vasospasm that is not angiographically detectable, but is nonetheless clinically significant because the negative effect of the surgery-induced vasospasm on CBF facilitates the decrease of CBF by the SAH itself.32,49 In addition, retraction of the swollen brain further contributes to an impairment of the CBF.15,55 Thus, CBF studies have shown that patients treated by surgery had significantly lower CBF on the side of surgery.33,41,51 These findings are supported by SPECT imaging demonstrating postoperative local hypoperfusion in the frontotemporal areas at the craniotomy site. Some authors suggested that early surgery has the potential to reduce the risk of postoperative vasospasm due to clot removal and irrigation of the cisterns. However, the CBF and SPECT data appear to indicate that the positive effect of operative removal of the subarachnoid clot is outweighed by the manipulation of the swollen brain and vessels.17,19,20,28,36,37,46 Regarding those factors, early surgery offers an increased risk of vasospasm with a subsequent higher risk of ischemic lesions and poorer outcome.12,45

**Vasospasm and Multiple Aneurysm Surgery**

In cases of long-duration surgery, the time of brain retraction and manipulation increases constantly. Because the treatment of multiple aneurysms usually demands...
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more time, it might offer an augmented risk for vasospasm. However, in reviewing our large patient cohort we clearly disproved this hypothesis. The study demonstrated that patients undergoing surgery for MIA in a 1-step operation did not have significantly higher incidences of TCD vasospasm, DINDs, or vasospasm-induced ischemic lesions than patients treated for SIA. Furthermore, there was no significant difference in clinical outcome measured by the GOS score in the 2 groups. Therefore, early surgery for multiple aneurysms is no risk factor for the aggravation of cerebral (TCD) and symptomatic vasospasm and does not contribute to a poorer outcome. The design of the study—comparing the incidence of vasospasm and outcome in patients undergoing early surgery for either 1 or more aneurysms—does not allow one to answer the question of whether the outcome of patients with MIAs possibly would have been better if the clipping of the nonruptured aneurysm or aneurysms had been postponed to the nonacute phase. However, given the similar outcomes in the present series for SIA and MIA, it does not appear logical to assume that clipping only the ruptured of the multiple aneurysms would result in a better outcome than clipping a single ruptured aneurysm.

Antivasospastic Therapy

Because vasospasm contributes considerably to poor outcome after aneurysmal SAH, a multitude of treatments focused either on preventing vasospasm or avoiding its deleterious effects have been proposed. Nimodipine has been used since the 1980s to prevent vasospasm. Its efficacy was proven in randomized trials and confirmed in meta-analyses. Particularly in Europe, nimodipine is given intravenously because of the assumed better bioavailability. In the present study, intravenous nimodipine was routinely administered in every patient with aneurysmal SAH. Arterial hypotension is a well-described side effect of intravenous administration, but specific toxic effects of intravenously administered nimodipine have not been described so far and were not observed in our patient population. Similar to nimodipine, HHH therapy was introduced in the 1980s and has been refined since then. Induced hypertension and normovolemia to mild hypervolemia gained a more dominant role than hemodilution and hypervolemia. There is an ongoing debate as to whether previously detected TCD vasospasm, or only the occurrence of symptomatic vasospasm, should trigger the treatment. During the entire study period it was our policy to initiate arterial hypertension and mild hypervolemia in all patients immediately after an increase of the blood flow velocity to 120 cm/second or more.

Transcranial Doppler and Vasospasm

Angiography is the reference standard for the diagnosis of vasospasm but its invasiveness and procedure-related risks preclude its use as a monitoring instrument. The pioneering work of Aaslid et al. has suggested a correlation between TCD and angiographic vasospasm. In 2001, Lysakowski and coworkers performed a systematic review of the literature, excluded 19 studies because of poor data quality, and performed a meta-analysis using 7 studies. In this meta-analysis, a good correlation between angiographic vasospasm and TCD vasospasm was found in the MCA, but not in the ACA. In 3 very recent publications including a total of 246 patients, the high sensitivity of TCD for detection of angiographic vasospasm in the MCA was confirmed, and likewise a high sensitivity in the ACA was proven. These findings were challenged by the results of Carrera et al. in 441 patients with aneurysmal SAH. Given the continued scientific uncertainty it appears to be justified to use TCD as a monitoring tool for early recognition of vasospasm and initiation of antivasospastic therapy before the ischemic process progresses and results in clinical symptoms, particularly because no other noninvasive monitoring tool exists. Furthermore, the role of angiography as a reference standard can also be questioned, because only 25% to 81% of cerebral infarcts correlate with the territory of the angiographic vasospasm.

Limitations and Strengths of the Study

The present study has a few limitations. Its partially retrospective nature, the fact that we did not investigate the influence of clot removal on cerebral vasospasm, and the fact that we were not able to distinctly compare the data by the exact duration of the operation might have influenced the results.

Recently, a modified Fisher grading system has been introduced that allows better prediction of vasospasm. However, data collection in the present study began in 1989, which explains why the original Fisher grading scale was used for description of the severity of SAH on CT scans. Endovascular therapy played a minor role in the management of single and multiple aneurysms during the time period of data acquisition. As a consequence, a potential bias of the results by patient selection for 1 of the 2 treatment modalities is eliminated, enabling us to demonstrate in a true surgical series that the surgical treatment of multiple aneurysms after SAH has no impact on the incidence of TCD vasospasm, DINDs, ischemic lesions, or patient outcome.

Conclusions

Clipping of more than 1 aneurysm in a single-stage operation within 72 hours after SAH can be performed without increasing the risk of cerebral vasospasm.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Wachter, Rohde. Acquisition of data: all authors. Analysis and interpretation of data: Wachter. Drafting the article: Wachter. Critically revising the article: Rohde. Reviewed final version of the manuscript and approved it for submission: all authors. Statistical analysis: Wachter.

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