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# Frequency of Cerebral Vasospasm in Patients Treated with Endovascular Occlusion of Intracranial Aneurysms

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**The purpose of this study was to retrospectively compare a group of 19 patients treated with craniotomy and aneurysmal clipping with a group of 18 patients who were treated via endovascular occlusion with Guglielmi detachable coils in regard to frequency and severity of cerebral vasospasm.**

***METHODS:*** **All patients were treated within 48 hours of ictus. In the endovascular group, nine patients had Hunt and Hess grade I subarachnoid hemorrhage, five patients had grade II aneurysms, and four patients had grade III. According to the Fisher classification, one aneurysm was grade I, nine were grade II, and eight were grade III. Twelve of the aneurysms were on the anterior circulation and seven were on the posterior circulation. In the surgical group, 10 patients had Hunt and Hess grade I hemorrhage, seven had grade II aneurysms, and two had grade III. Nine of these were Fisher grade II and 10 were grade III. Eighteen aneurysms were on the anterior circulation and one was on the posterior circulation. Endovascularly treated patients were medically treated identically to those in the surgical group, with prophylactic volume expansion and hemodilution immediately after endovascular occlusion, except that they also received 48 hours of full heparinization followed by 24 hours of dextran infusion after endovascular occlusion.**

***RESULTS:*** **All four patients in the endovascular group in whom delayed neurologic deficits developed as a result of vasospasm responded to elevation of blood pressure and did not require either mechanical or chemical angioplasty to reverse their symptomatology. In the surgical group, 14 of 19 developed clinical vasospasm, with elevation of their transcranial Doppler velocities, and required maximum triple-H (hypertensive, hypervolemic, hemodilutional) therapy. Three of these patients required mechanical and pharmacologic angioplasty. No surgical complications were incurred as a direct result of the craniotomy. One patient in the endovascular group developed a femoral pseudoaneurysm as a complication of the procedure and postocclusion anticoagulation. No thromboembolic events were noted in this group.**

***CONCLUSION:*** **In patients with similar Hunt and Hess grades and Fisher grades, preliminary data suggest that the frequency and severity of cerebral vasospasm may be reduced in those treated by endovascular occlusion of their aneurysm as compared with those treated by direct surgical clipping.**

In North America, an estimated 36 000 people suffer subarachnoid hemorrhage from ruptured intracranial aneurysms each year (1). Fifteen thousand of these, however, suffer untimely death or disability after their initial hemorrhage. The International Cooperative Study on the Timing of Aneurysm Surgery has demonstrated the benefits of early surgical intervention for patients in good clinical condition, but stressed the disappointing neurologic outcome in a subpopulation of patients (2, 3). Over 75% of patients entered into this study were admitted in good neurologic condition; nevertheless, only 58% experienced a good neurologic outcome. The leading causes of poor outcome were vasospasm and rehemorrhage.

Recent progress both in microsurgical techniques and in the administration of anesthetics has enabled early surgical intervention and significantly diminished the toll of early rehemorrhage. Vasospasm remains the single leading cause of death and permanent neurologic disability subsequent to aneurysmal

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**TABLE 1: Characteristics of Patients in Group Treated by Endovascular Occlusion**

| Patient's Age/Sex | Location of Aneurysm(s) | Hunt and Hess Grade | Fisher Grade | Radiologic (R) or Clinical (C) Evidence/Day Vasospasm Developed | Deficit | Vasospasm Grade |
|---|---|---|---|---|---|---|
| 21 M | R superior hypophyseal | I | III | R/3 | . . . | 1 |
| 60 F | Basilar bifurcation | III | III | C/6 | R pronator drift, perseveration | 2 |
| 36 F | Basilar bifurcation | I | II | . . . | . . . | 0 |
| 65 M | Basilar bifurcation<br>*R MCA AVM* | I | I | . . . | . . . | 0 |
| 66 F | R pcomm<br>*L ACA* | I | III | C/4 | Lethargy | 2 |
| 78 F | L pcomm<br>*R pcomm* | III | II | . . . | . . . | 0 |
| 71 F | R MCA *Acomm* | III | II | . . . | . . . | 0 |
| 49 F | Superior cerebellar | II | III | R/11 | . . . | 1 |
| 37 F | Basilar bifurcation<br>*R cavernous carotid* | I | II | . . . | . . . | 0 |
| 54 F | L PICA | I | II | . . . | . . . | 0 |
| 34 F | R carotid-opthalmic | I | II | . . . | . . . | 0 |
| 51 F | Acomm<br>*R MCA* | II | III | R/4 | . . . | 1 |
| 44 M | Acomm | III | III | C/3 | L leg monoparesis | 2 |
| 72 F | Acomm | II | III | C/3 | Lethargy, confusion | 2 |
| 67 M | Basilar bifurcation | II | II | . . . | . . . | 0 |
| 43 F | L pcomm<br>R pcomm | II | II | . . . | . . . | 0 |
| 54 F | R mca<br>*L MCA*<br>*Acomm* | I | II | . . . | . . . | 0 |
| 39 M | R MCA | I | II | . . . | . . . | 0 |

Note.—Italics indicate additional aneurysms that were not treated and considered not responsible for the patient's subarachnoid hemorrhage. AVM indicates arteriovenous malformation; ACA, anterior cerebral artery; acomm, anterior communicating artery; MCA, middle cerebral artery; PICA, posterior inferior communicating artery; pcomm, posterior communicating artery.

subarachnoid hemorrhage. Twenty-eight percent of those in whom subarachnoid hemorrhage occurs suffer clinical deterioration as a result of the ischemic effects of vasospasm, and 50% of these suffer long-term morbidity and mortality (1, 2).

Recently, clinical investigators have described the technique for and results of deploying endovascular coils to exclude saccular aneurysms from the cerebral circulation (4–8). Several of these investigations have shown the efficacy of endovascular treatment in preventing rehemorrhage both in short- and long-term follow-up studies. Our experience also suggests that the severity of vasospasm is diminished in patients treated by endovascular coil occlusion following subarachnoid hemorrhage. The purpose of this study was to retrospectively analyze the frequency and severity of vasospasm in a population of patients undergoing aneurysmal occlusion by Guglielmi detachable coils (GDC) as compared with a control population in whom standard craniotomy for aneurysmal clipping was performed. We report the results obtained by one surgeon and discuss the possible contributing mechanisms.

## Methods

The records of 37 consecutive patients admitted with subarachnoid hemorrhage and treated for saccular aneurysms from October 1995 to April 1996 were reviewed retrospectively. Nineteen patients were treated with standard craniotomy for aneurysmal clipping and 18 were treated with endovascular GDC placement to exclude the aneurysm from the cerebral circulation. Patients who were treated with a combination of surgery and GDC occlusion were excluded from the study. Patients who were admitted with Hunt and Hess grade IV or V aneurysms were also excluded (9). All patients were admitted and treated within 48 hours of ictus. Subarachnoid hemorrhage was diagnosed by clinical presentation and confirmed by computed tomography (CT) examination. The location and morphology of the aneurysm were delineated by four-vessel cerebral angiography. All patients were offered standard craniotomy for clipping of the aneurysm; however, those patients who were of advanced age, poor surgical candidates, had high-risk aneurysms of the posterior circulation or of predictably difficult surgical anatomy, or who refused craniotomy were offered the alternative of endovascular coil placement. Angiographic evidence of a broad aneurysmal neck was considered a relative contraindication to endovascular obliteration.

The endovascular group consisted of 18 patients, of whom five were men and 13 were women. Nine patients had Hunt and Hess grade I aneurysms, five had grade II aneurysms, and four had grade III aneurysms. According to the Fisher classification, one aneurysm was grade I, nine were grade II, and eight were grade III (10, 11). Twelve aneurysms were located on the anterior circulation, seven were on the posterior circulation. The surgical group consisted of 19 patients, of whom six were men and 13 were women. Ten patients had Hunt and Hess grade I aneurysms, seven had grade II aneurysms, and two had grade III aneurysms. Nine of these were Fisher grade II and 10 were grade III. Eighteen aneurysms were located on the anterior circulation

**TABLE 2: Characteristics of Patients in Group Treated by Surgical Clipping**

| Patient's Age | Location of Aneurysm | Hunt and Hess Grade | Fisher Grade | Radiologic (R) or Clinical (C) Evidence/Day Vasospasm Developed | Deficit | Vasospasm Grade |
|---|---|---|---|---|---|---|
| 49 | Basilar bifurcation | III | III | C/3 | Lethargy | 4 |
| 28 | Acomm | I | III | C/6 | Lethargy, R pronator drift | 2 |
| 38 | Pcomm | II | III | C/4 | L drift | 2 |
| 72 | Pcomm | III | II | . . . | . . . | 0 |
| 62 | R MCA | I | II | C/6 | R hemiparesis, lethargy | 2 |
| 27 | Acomm | II | III | C/10 | Lethargy | 3 |
| 41 | R pcomm | II | III | C/10 | Lethargy | 2 |
| 51 | R PICA | I | III | C/7 | Lethargy, R drift | 2 |
| 37 | L MCA | I | II | C/5 | Lethargy | 2 |
| 57 | L PCA | I | II | . . . | . . . | 0 |
| 64 | R pcomm | II | II | C/4 | Lethargy | 2 |
| 63 | Acomm | II | III | C/6 | Lethargy, R hemiparesis | 2 |
| 29 | L PICA | I | II | . . . | . . . | 0 |
| 34 | Acomm | I | III | C/4 | Lethargy, R leg monoparesis | 2 |
| 47 | R pcomm | I | III | C/10 | Lethargy, R hemiparesis | 2 |
| 56 | L MCA | II | II | . . . | . . . | 0 |
| 66 | Acomm | I | III | C/8 | Lethargy R hemiparesis | 3 |
| 53 | L PCA | II | II | C/9 | Lethargy | 2 |
| 69 | R pcomm | I | II | . . . | . . . | 0 |

Note.—Acomm indicates anterior communicating artery; MCA, middle cerebral artery; PICA, posterior inferior communicating artery; PCA, posterior cerebral artery; pcomm, posterior communicating artery.

and one was on the posterior circulation. Clinical data for patients in both groups are provided in Tables 1 and 2.

All patients had an arterial line and central venous or Swan-Ganz catheter placed preoperatively. Postoperatively, all patients were administered colloid and crystalloid solutions for prophylactic volume expansion and hemodilution to maintain a central venous pressure of 8 to 10 mm Hg or a pulmonary artery wedge pressure of 13 to 15 mm Hg as well as a hematocrit of 30 to 35. External ventricular drainage was instituted for all patients with Fisher grade III aneurysms and for any patient in whom hydrocephalus was seen radiologically. The surgical group was administered a bolus of mannitol (1 g/kg) and lasix (20 mg) at the start of the procedure. Pentobarbital bolus and infusion were administered for burst suppression during temporary parent vessel clipping. Hematomas and thick collections of subarachnoid hemorrhage in the surgical bed were removed during the operation. Intraoperative angiography was used to ensure adequate clip placement and to preclude ligation of local vessels. To prevent thromboembolic phenomena, the endovascular population underwent 48 hours of systemic heparinization to maintain a partial thromboplastin time of approximately two times normal, followed by 24 hours of dextran infusion. Postoperatively, patients received frequent neurologic examinations and daily transcranial Doppler sonographic monitoring.

Evidence of neurologic decline included any features on the neurologic examination consistent with diminished cerebral blood flow, either diffusely or in an arterial territory distribution (10–12). This included any significant change in sensorium or level of consciousness. Deficits of the anterior cerebral artery distribution included weakness of the contralateral lower extremity when the spasm was unilateral and there was akinesia, and whispering or mutism, incontinence, frontal release signs, and lower extremity diplegia when the spasm was bilateral. Middle cerebral artery vasospasm was characterized by hemiparesis or monoparesis, dysphasia when involving the dominant hemisphere, and anosognosia when confined to the nondominant hemisphere. Posterior cerebral artery deficits included significant decline in level of consciousness, hemianopsia, or cranial neuropathy. Headache alone was not considered an indicator of cerebral ischemia (Table 3).

Patients who experienced a neurologic deterioration had CT immediately to exclude hemorrhage or hydrocephalus, followed by chemically induced hypertension to maintain a mean arterial blood pressure greater than 120 mm Hg. Patients in whom the deficit could not be reversed within 1 hour underwent cerebral angiography and angioplasty. Significant proximal vessel vasospasm (of the internal carotid or vertebrobasilar arteries or A1, M1, or P1 vessels) was treated with mechanical angioplasty; more distal involvement was treated with intraarterial papaverine infusion (300 mg over 1 hour) through a coaxial microcatheter (12). This was repeated on a daily basis as needed, depending on a combination of factors, including the patient's neurologic status and transcranial Doppler sonographic monitoring.

Patients in each group were studied retrospectively with regard to occurrence and severity of vasospasm. The severity of vasospasm was graded on a scale of 0 to 4 using both radiologic and clinical criteria. Grade 0 indicated no evidence of radiologic (transcranial Doppler sonographic or angiographic) or clinical vasospasm. Grade 1 was assigned to patients who had radiologic evidence of vasospasm but no evidence of clinical deterioration. Grade 2 was given to patients who exhibited evidence of clinical decline amenable to medical management (hypervolemia and hemodilution combined with chemically induced hypertension) with either significant clinical improvement or resolution of deficits. Grade 3 was assigned to patients in whom medical measures failed to elicit a response but whose vasospasm was reversed by endovascular methods. Grade 4 was reserved for patients in whom vasospasm was not responsive to either medical or endovascular management. This grading system is summarized in Table 4. Further statistical analysis was performed in patients with Fisher grade III aneurysms to limit differences between the two populations. All statistical analysis was performed using the ANOVA factorial test.

## Results

The clinical and radiologic records of the 37 patients entered into this study were reviewed retrospectively. Eighteen patients with a total of 19 aneu-

**TABLE 3: Clinical Criteria for Vasospasm**

| Arterial Distribution | Neurologic Deficit |
|---|---|
| Anterior cerebral artery | Weakness of contralateral lower extremity, akinesia, whispering, mutism, incontinence, frontal release signs, lower extremity diplegia. |
| Middle cerebral artery | Hemiparesis or monoparesis, dysphasia, anosognosia. |
| Posterior cerebral artery | Decline in level of consciousness, cranial neuropathy, hemianopsia. |

**TABLE 4: Vasospasm Grading Scale**

| Grade | Criteria |
|---|---|
| 0 | No radiologic (transcranial Doppler sonographic or angiographic) or clinical evidence of vasospasm. |
| 1 | Radiologic evidence of vasospasm without clinical signs or symptoms. |
| 2 | Clinical vasospasm that is responsive to medical management (triple-H therapy). |
| 3 | Clinical vasospasm that is resistant to medical management but responsive to endovascular angioplasty (mechanical or chemical). |
| 4 | Clinical vasospasm that is not responsive to medical or endovascular management. |

rysms were treated with endovascular coils. Nineteen patients underwent standard craniotomy for aneurysmal clipping. Hunt and Hess and Fisher grades were comparable between the two populations. Statistical analysis was used to compare the frequency of clinical vasospasm in the two populations as well as the average vasospasm grade in each population. Because clinical vasospasm in our study was predominantly limited to the Fisher grade III subarachnoid hemorrhage, as noted by other investigators (10), the frequency and severity of clinical vasospasm were also compared in this subpopulation in order to minimize any differences between the two groups.

A femoral pseudoaneurysm developed in one patient in the endovascular group. This was managed conservatively and did not require a second surgical procedure. No thromboembolic complications were noted in the endovascular group. No surgical complications arose as a direct result of the craniotomy.

In the endovascular group, eight (44%) of the 18 patients had Fisher grade III subarachnoid hemorrhage. Four of these (22%) subsequently showed clinical evidence of vasospasm. All four responded to maximal medical management with significant clinical improvement or resolution of deficits. No mortality resulted in this group as a complication of the procedure, vasospasm, or management protocol.

In the surgical group, 10 (53%) of the 19 patients were noted to have Fisher grade III subarachnoid hemorrhage on initial CT scans. Fourteen (74%) of the 19 (including all 10 of the patients with Fisher grade III hemorrhage) went on to show clinical evidence of vasospasm. Three of these (30%) required endovascular angioplasty (mechanical or pharmacologic) to manage delayed ischemic neurologic deficits as a result of vasospasm that failed to respond to maximal medical management (hypertensive, hypervolemic, hemodilutional [triple-H] treatment). Of these three patients, one died of intractable vasospasm and progressive cerebral infarction, one died of acute respiratory distress syndrome, exacerbated by prolonged intubation and aggressive fluid management, and the third suffered a residual hemiparesis.

The frequency of clinical vasospasm in the surgical group (74%) was greater than that in the endovascular group (22%). ANOVA statistical test revealed this difference to be statistically significant ($P < .05$). When analysis of the frequency of clinical vasospasm was limited to patients with Fisher grade III hemorrhage, the difference was still found to be significant ($P < .05$). Among the patients with grade III hemorrhage in whom clinical vasospasm developed, three (30%) of the 10 in the surgical group had medically intractable vasospasm that required angioplasty, whereas none of the four in the endovascular group developed this severe form.

To compare the severity of cerebral vasospasm between the two populations, we computed and analyzed the average vasospasm grade for each population. In the surgical group, the average grade was 1.68 when all patients were included, 2.4 when only patients with Fisher grade III aneurysms were considered. The average vasospasm grade in the endovascular group was 0.61 when all patients were included, 1.38 when only Fisher grade III aneurysms were considered. Analysis of the average vasospasm grade revealed a statistically significant difference between the two populations ($P < .05$). Similarly, analysis of the average vasospasm grade among patients with Fisher grade III aneurysms revealed a statistically significant difference ($P < .05$). No patient in the endovascular group was assigned a vasospasm grade above 2, whereas two patients in the surgical group were assigned vasospasm grades of 3 (amenable to endovascular angioplasty) and one was assigned a grade of 4 (intractable despite medical and endovascular management).

## Discussion

Vasospasm is the leading cause of death and permanent neurologic disability in patients with subarachnoid hemorrhage arising from saccular aneurysms after the initial hemorrhage. Currently accepted techniques to diminish the toll of vasospasm include administration of the dihydropyridine class of calcium-channel blockers and institution of triple-H therapy. Calcium-channel blockers, of which the most commonly used is nimodipine, decrease the availability of extracellular calcium to participate in the contractility of vascular smooth muscle. Influx of extracellular or extracytosolic calcium is also important in cellular apoptosis and death. Triple-H therapy exploits the Hagen-Poiseuille equation, which states that flow through a system with a constant radius is

directly proportional to the pressure and indirectly proportional to the viscosity

$$Q = \frac{\Delta P \Pi r4}{8Ln}$$

where Q defines blood flow, ΔP is the pressure gradient, r is the vessel radius, L is the length, and *n* is the viscosity.

Volume expansion with colloid and crystalloid solutions combined with the use of vasopressors have been shown to diminish vasospasm after subarachnoid hemorrhage. Innovative new strategies to prevent or treat vasospasm include the use of intracisternal thrombolytic infusion, the use of antioxidants to chelate or prevent the liberation of free radicals, and endovascular techniques to increase the radius of spastic arteries (12–18).

Although craniotomy for aneurysmal clipping is the standard and definitive method of treating saccular aneurysms, endovascular occlusion by deployment of coils provides an effective alternative by excluding the aneurysm from the cerebral circulation. This method has been shown to diminish the frequency of rehemorrhage. It has also been our observation that both the frequency and severity of vasospasm appear markedly diminished in patients treated by coil occlusion. In the endovascular group, all four patients in whom delayed neurologic deficits developed consequent to vasospasm responded to medical management and did not require either mechanical or chemical angioplasty to reverse their deficit. In the surgical group, all 10 patients with Fisher grade III aneurysms developed clinical vasospasm with elevation of the transcranial Doppler velocities, necessitating maximal triple-H therapy. In that group, three patients required mechanical and pharmacologic angioplasty. Although the pathophysiology of cerebral vasospasm is still obscure, possible mechanisms for reducing the frequency of vasospasm in the endovascular population can be inferred from the results of studies searching for its cause. Results of several laboratory and clinical studies have suggested that craniotomy results in exacerbation of vasospasm (2, 3, 12, 19–22), which is compounded during the peak period of vasospasm. It has also been observed that vasospasm, often of a prolonged and severe nature, follows craniotomy performed for unruptured aneurysmal clipping. Contributing mechanisms include the release of blood and blood products into the subarachnoid space, the liberation of lipid peroxides (arachidonic acid) and free radicals, and the spastic response of the cerebral vasculature to trauma and manipulation (12, 23). Nevertheless, more recent prospective clinical trials appear to refute this relationship of vasospasm to surgery (24).

The release of blood and blood products into the subarachnoid space has been shown to be vasospastic in both laboratory and clinical investigations. Osaka (25) has shown that fresh serum and platelet-rich plasma induced vasospasm in a feline model, and although fresh blood was not vasospastic, degraded blood after being incubated for 1 to 7 days led to severe and prolonged vasospasm. Other investigators have confirmed this result (12, 26, 27). Fisher et al (10, 11) initially in a retrospective fashion, and, subsequently, prospectively, showed that the volume of blood in the subarachnoid space on CT scans was predictive of vasospasm. Oxyhemoglobin has been implicated as the primary spasminogen responsible for chronic vasospasm after subarachnoid hemorrhage. The mechanism is most likely multifactorial, and includes the release of vasoactive prostaglandins and endothelin from vascular endothelium, the inhibition of endothelium-derived relaxation factor, and the release of free radicals from blood breakdown (1, 17, 18, 23, 28, 29).

Degradation of oxyhemoglobin to methemoglobin results in the liberation of the free radical superoxide molecule. In the presence of iron-containing compounds from hemoglobin degradation, this anion leads to the generation of additional hydroxyl-free radicals through the Haber-Weiss reaction. Free radicals have been shown to be vasospastic in laboratory investigations and are now the target for a new class of 21-aminosteroid compounds, which are undergoing clinical trials (17, 18, 30). In addition to this release of free radicals, dissection and disruption of cerebral parenchyma results in the release of such lipid peroxides as arachidonic acid (17, 18, 31). Arachidonic acid, a structural component of the cellular membrane, is the parent molecule that leads to the synthesis of both additional prostaglandins and free radicals.

Mechanical stimulation of cerebral vessels has been shown to initiate both short- and long-term cerebral vasospasm (12, 32–39). Florey (40) first demonstrated that mechanical stimulation of cerebral vessels resulted in vasospasm in 1925. Landau and Ransohoff (41) subsequently showed that although vasospasm would result from both cerebral manipulation or exposure to blood products, the combination of blood and vessel trauma resulted in prolonged and severe vasospasm. This has been confirmed by other investigators (12, 30).

## Conclusion

In patients with similar Hunt and Hess grades and Fisher grades, preliminary data suggest that the frequency and severity of cerebral vasospasm may be reduced in those treated by endovascular occlusion of their aneurysm as compared with those treated by direct surgical clipping. This evidence is compelling because of the toll vasospasm takes after the initial subarachnoid hemorrhage. The mechanism, although not entirely clear, is most likely multifactorial and may be compounded by the diuresis and relative hypotension required during surgical clipping of aneurysms. Both the frequency and severity of vasospasm deserve further investigation in a randomized and prospective fashion, ideally with a larger population treated endovascularly through a multicenter effort. As endovascular management becomes more commonplace, such research will undoubtedly follow.

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