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Original Article

Endovascular Treatment of Symptomatic Vasospasm after Aneurysmal Subarachnoid Hemorrhage: A Three-year Experience

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Objective : The cause of severe clinical vasospasm after aneurysmal subarachnoid hemorrhage remains unknown, despite extensive research over the past 30 years. However, the intra-arterial administration of vasodilating agents and balloon angioplasty have been successfully used in severe refractory cerebral vasospasm.

Materials and Methods : We retrospectively analyzed the data of 233 patients admitted to our institute with aneurysmal subarachnoid hemorrhage (SAH) over the past 3 years.

Results : Of these, 27 (10.6%) developed severe symptomatic vasospasm, requiring endovascular therapy. Vasospasm occurred at an average of 5.3 days after SAH. A total of 46 endovascular procedures were performed in 27 patients. Endovascular therapy was performed once in 18 (66.7%) patients, 2 times in 4 (14.8%) patients, 3 or more times in 5 (18.5%) patients. Intra-arterial vasodilating agents were used in 44 procedures (27 with nimodipine infusion, 17 with nicardipine infusion). Balloon angioplasty was performed in only 2 (7.4%) patients. The Average nimodipine infusion volume was 2.47 mg, and nicardipine was 3.78 mg. Most patients recovered after the initial emergency room visit. Two patients (7.4%) worsened, but there were no deaths.

Conclusion : With advances in endovascular techniques, administration of vasodilating agents and balloon angioplasty reduces the morbidity and mortality of vasospasm after aneurysmal SAH.

Keywords Subarachnoid hemorrhage, Vasospasm, Endovascular therapy, Morbidity, Mortality

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INTRODUCTION

Cerebral vasospasm remains a leading cause of morbidity and mortality following aneurysmal subarachnoid hemorrhage (SAH).[21] Cerebral vasospasm is a prolonged but reversible narrowing of cerebral arteries beginning days after SAH. Progression to cerebral ischemia is tied mostly to vasospasm severity, and its pathogenesis lies in artery encasement by blood clots, although the complex interactions between hematoma and surrounding structures are not fully understood. Minimizing ischemia by avoiding inadequate blood volume and pressure, administering the calcium antagonist nimodipine, and intervention

with balloon angioplasty, when necessary, constitutes the current best management.[13] The objective of endovascular treatment of cerebral arterial vasospasm is to restore adequate blood flow and to prevent cerebral ischemia and infarction.[41] Two different techniques are applied: mechanical or pharmacological vessel dilatation. Mechanical vasodilatation is achieved by means of transluminal balloon angioplasty and is directed towards a circumscribed proximal vessel segment. Pharmacological endovascular dilatation is based on continuous intraarterial infusion of drug via a microcatheter positioned within the proximal intracranial vessel territory affected by vasospasm.[41] However, vasospasm remains an important determinant of outcome after aneurysm rupture. The aim of this study was to analyze the incidence and results of endovascular treatment of vasospasm.

MATERIALS AND METHODS

A total of 233 patients with aneurysmal SAH were enrolled in this study between January 2012 and December 2014. Patient information and endovascular treatment methods are summarized in Table 1. All patients underwent aneurysm clipping or coil embolization to prevent rebleeding. Vasospasm was confirmed by performing computed tomography (CT) angiography or digital subtraction angiography in symptomatic patients.

Table 1. Patients demographics and endovascular methods

Age (range)	51.8 (27-73)
M : F	11:16
Onset duration (days)	5.3
Modality	
Nimodipine	27
Nicardipine	17
Balloon	2
No. of times	
1	18
2	4
3 or more	5

RESULTS

In our series of 233 SAH patients, 27 (11.6%) developed severe clinical vasospasm requiring endovascular therapy. Vasospasm occurred at an average of 5.3 days after SAH. A total of 46 endovascular procedures were performed in 27 patients. Intra-arterial injections of nimodipine (average dose, 2.47 mg) or nicardipine (average dose 3.78 mg) was performed 44 times in 27 patients and balloon angioplasty was performed in 2 patients. Endovascular therapy was performed once in 18 (66.7%) patients, 2 times in 4 (14.8%) patients, and 3 or more times in 5 (18.5%) patients (Fig. 1).

Location of aneurysms

The most frequent site of aneurysm was the anterior communicating artery, followed by the posterior communicating artery (26.2%) and middle cerebral artery (18.9%) (Table 2, Fig. 2). The most frequent site of aneurysms in symptomatic vasospasm patients was also anterior communicating artery (37.1%), followed by posterior communicating artery (25.9%) and middle cerebral artery (18.5%) (Table 3, Fig. 3).

Prognosis

The clinical results are shown in Table 4. Improvement was observed in 14 (51.9%) patients. Craniectomy was performed in 4 (14.8%). The mortality rate was 11.1%. The causes of death were pneumonia in 2 patients (7.4%) and acute renal failure in 1 patient (3.7%). After the patients were followed-up for 3-6 months, favorable outcomes were observed (average modified Rankin scale score: 3.3). No procedure-related complications were observed.

DISCUSSION

Angiographic vasospasm is common after rupture of an aneurysm, with an overall incidence of 50-90%.[9] Vasospasm is rare in the first 2 days after SAH, but increases after the fourth day.[27] In 530 cases,[28] the highest incidence was between days 10 and 17, peaking on day 13 at 60%. In another series,[16] vasospasm

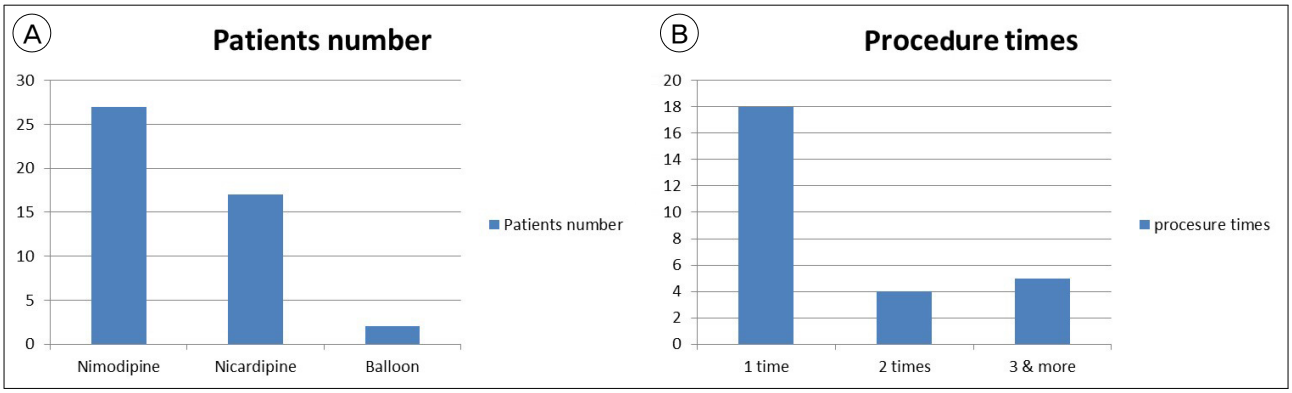

Fig. 1. Number of patients (A) and endovascular procedures (B).

occurred in a third of patients in the first week and in two-thirds in the second week. Accordingly, it is important to remain vigilant for this complication for at least 2 weeks after SAH. The aim of vasospasm management is to optimize cerebral blood flow in order to prevent delayed cerebral ischemia (DCI). Medical treatment is usually the initial step when vasospasm is suspected. However, vasospasm is often refractory to these treatments. Moreover, many patients do not tolerate the combination of induced hypertension, hypervolemia, and hemodilution, which is referred to as 'triple-H' therapy, usually due to cardiac and pulmonary complications including myocardial ischemia, congestive heart failure and pulmonary edema. For these patients, early endovascular treatment appears to be the best alternative.[1)12)29)31)39)44)]

Papaverine was first described as a treatment option for cerebral vasospasm in 1992.[19)20)] Its mechanism is believed to result from inhibition of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate phosphodiesterase in the smooth muscle, as well as from blockage of calcium ion channels in the cell membrane, resulting in vasodilation by inhibition of smooth muscle contraction. Firlik et al.[15)] analyzed the use of papaverine in 15 patients with symptomatic vasospasm after SAH. The vessel caliber improved immediately following treatment on 18/23 occasions. Vasospasm associated clinical symptoms improvement was major on 6 cases, and either minor or nonexistent on 17. The authors concluded that although the papaverine was reduced in the reversal of arterial narrowing in the majority of cases (78%), this angiographic improvement was associated with CBF augmentation in only 46% of the cases and major clinical improvement in only 26%.[15)] Papaverine treatment is effective within the entire vessel territory, often treated and recirculated exerts an effect within

Table 2. Aneurysm location in enrolled patients

Location	N (%)
Acom	68 (29.2)
Pcom	61 (26.2)
MCA	44 (18.9)
Distal ACA	14 (6.0)
Distal ICA	19 (8.1)
Posterior circulation	27 (11.6)
Total	233

Acom = anterior communicating artery; Pcom = posterior communicating artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; ICA = internal carotid artery

Table 3. Aneurysm location in symptomatic vasospasm

Location	N (%)
Acom	10 (37.1)
Pcom	7 (25.9)
MCA	5 (18.5)
Distal ICA	4 (14.8)
Posterior circulation	1 (3.7)
Total	27

Acom = anterior communicating artery; Pcom = posterior communicating artery; MCA = middle cerebral artery; ICA = internal carotid artery

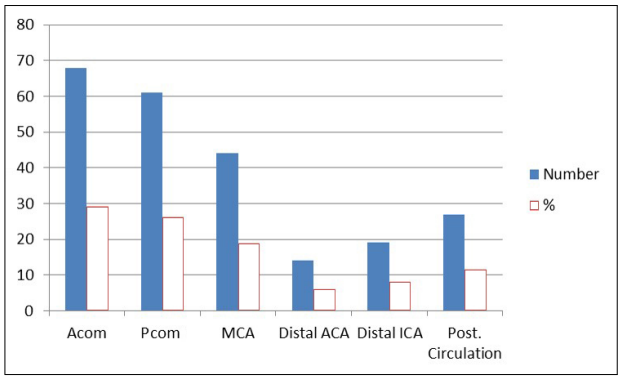

Fig. 2. Aneurysm location in enrolled patients. Acom = anterior communicating artery; Pcom = posterior communicating artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; ICA = internal carotid artery.

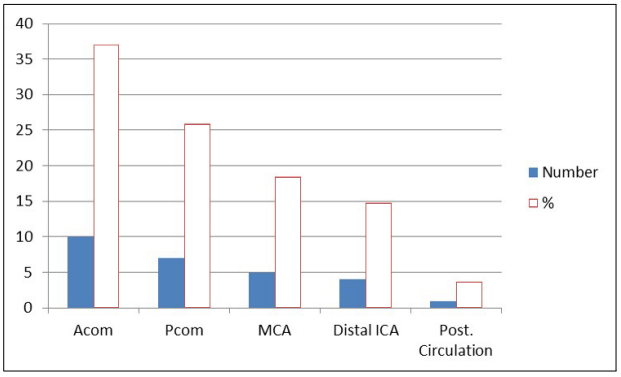

Fig. 3. Aneurysm location in symptomatic vasospasm. Acom = anterior communicating artery; Pcom = posterior communicating artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; ICA = internal carotid artery.

other vascular territories as well. Its action is predominantly directed towards the active component of arterial vasospasm.

Nimodipine was first tested as a treatment for DCI due to its preferential vasodilation of the cerebral circulation and experimental work showing reduced impairment of post ischemic reperfusion.[23] Nimodipine is an L-type dihydropyridine calcium channel antagonist and remains the only intervention shown to consistently reduce the incidence of DCI and improve outcomes after SAH. Calcium plays a critical role in cellular communication and regulation and is important for the maintenance of normal cerebral vascular tone.[36] Nimodipine has a neuroprotective effect in SAH by blocking calcium influx after tissue ischemia at a neuronal level.[32][38] However, as nimodipine does not exert a beneficial effect on other diseases that lead to cerebral ischemia such as ischemic stroke[18] or traumatic brain injury,[28] it seems likely that it acts on a mechanism specific to SAH. Potential complications include hypotension, bradycardia, rash and diarrhea. Rare cases of refractory hypotension leading to death have been reported with the intravenous use of nimodipine.[4] An experimental SAH model suggested that intra-arterial nimodipine might be more effective than intra-arterial papaverine in promoting reversal of vasospasm.[2][14] Biondi et al.[6] studied the efficacy of intra-arterial nimodipine in preventing infarcts in 25 consecutive patients with symptomatic vasospasm.

Nicardipine is a dihydropyridine calcium antagonist, similar to nimodipine, blocks the L-type voltage-gated calcium channels, preventing the influx of extracellular calcium, which would eventfully lead to muscle contraction. Badjatia et al.[3] reported IA nicardipine in the treatment of SAH-induced vasospasm. Forty-four vessels were treated in 18 patients. All vessels treated demonstrated angiographic improvement in the degree of vasospasm. TCD demonstrated significant decreases in peak systolic velocity after treatment. Neurological improvement was seen in about 42% of the patients after treatment. No significant changes in blood pressure or signs of pulmonary edema or renal dysfunction.

Balloon angioplasty is usually limited to the proximal vessels (> 2-3 mm), predominantly the supraclinoid internal carotid artery, the M1 and proximal M2 segments of the middle cerebral artery, the A1

Table 4. Clinical results

Endovascular intervention	27/233 (11.6%)
Craniectomy	4/27 (14.8%)
Improved patients	14/27 (51.9%)
Mortality	3/27 (11.1%)
Average mRS	3.3

mRS = modified Rankin scale

segment of the anterior cerebral artery, the P1 segment of the posterior cerebral artery, and the basilar artery. Distal vessel balloon angioplasty is typically not feasible. Vessel tortuosity, preventing endovascular navigation, is another potential limitation.[8] In a review by Hoh and Ogilvy,[17] balloon angioplasty had an approximately 5% risk of a major complication, including an approximately 1% risk of vessel perforation/rupture, which is usually fatal.[5][10][11][17][31-33][39][47][48] Even though angioplasty is directed to and effective on a proximal vessel segments only, the rational is to improve blood flow, oxygenation and metabolism within the distal arterial territory as well.[15] Balloon angioplasty is superior to chemical angioplasty for the permanent treatment of vasospasm.[22] The durable effects of angioplasty after stretching of the vessel wall are well documented,[7][25] whereas the vasodilatory action of papaverine is short lasting.[26][34]

Numerous pharmacologic agents have been tested in experimental models of SAH and vasospasm, many of which were intended to explore a particular pathogenic theory for vasospasm by targeting a specific pathologic process. For example, ET-1 overproduction by cerebral endothelial cells damaged by SAH is a leading theory in the pathogenesis of cerebral vasospasm. The ETA/B receptor antagonist TAK-044 was found to reduce DCI with an acceptable safety profile in a phase II randomized controlled trial, but with no apparent effect on outcome.[37][42] The ETA receptor antagonist clazosentan, which showed promising results in a multicenter phase IIa study,[46] has now been studied in a randomized, double-blind, placebo-controlled, phase II dose-finding trial (Clazosentan to Overcome Neurological iSChemia and Infarct OccUrring after Subarachnoid hemorrhage [CONSCIOUS-1]).[30] Statins increase nitric oxide biosynthesis and bioavailability, and have great potential for vasospasm prophylaxis in the setting of SAH.[35] A meta-analysis of 6 randomized controlled statin trials found no overall significant reduction in poor neurological outcome, although delayed ischemic deficits were less common in the statin-treated patients.[45] The international, randomized, double-blind Simvastatin in Aneurysmal Subarachnoid Hemorrhage (STASH) trial recruited 803 patients until February 2013. This study failed to detect any short- or long-term benefit in the use of simvastatin 40 mg per day, started within 96 hours of stroke, followed by up to 3 weeks of administration.[24] Magnesium sulfate ($MgSO_4$) has neuroprotective and vasodilatory properties and has therefore been tested for the prevention of vasospasm and ischemia in patients with SAH. One early study found no benefit from intravenous $MgSO_4$ infusions,[47] another showed a variety of beneficial trends toward benefit,[43] and a third suggested efficacy equivalent to nimodipine in preventing ischemic damage.[40]

CONCLUSION

Endovascular intervention may have an important role in selected cases to reduce vasospasm-related morbidity and mortality after aneurysmal SAH. In our experience, endovascular treatment is safe, with a low complication rate, but further studies are required to determine appropriate patient selection and treatment efficacy.

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Disclosure

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

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