Cerebral vasospasm following subarachnoid hemorrhage (SAH): physiopathology, diagnosis and current management. Critical review of literature.

ABSTRACT
Cerebral vasospasm and the delayed cerebral ischemia remain a source of substantial morbidity and mortality following aneurysmal subarachnoid hemorrhage (SAH). Hemodynamic manipulation better known as ‘triple H’ therapy is routinely used in the management of patients with acute vasospasm following SAH. The rationale of inducing hypertension, hypervolemia and hemodilution is to improve blood flow to the injured brain and to prevent secondary ischemia. While the Ca2+ antagonist Nimodipine is still the only drug with proven benefit on neurologic outcome following SAH, several alternatives are under research. Tirilazad is not effective, and studies of hemodynamic maneuvers, magnesium, statin medications, endothelin antagonists, steroid drugs, anticoagulant/antiplatelet agents, and intrathecal fibrinolytic drugs have yielded inconclusive and controversial results. Steroids drugs and anticoagulant/antiplatelet agents have been abandoned so far, because of the lack of efficacy. The purpose of the present paper is to provide a systematic review of the existing literature on the treatment of cerebral vasospasm.

Key words: cerebral vasospasm, subarachnoid hemorrhage, smooth muscle cells, brain aneurysm

RESUMO
O vasoespasmo cerebral e a isquemia cerebral tardia respondem de maneira substancial para a morbidade e mortalidade da hemorrhagia subaracnóide (HSA) de etiologia aneurismática.

A terapia hemodinâmica, mais conhecida como “três-H”, é usada rotineiramente no manejo dos pacientes com vasoespasmo secundário à HSA. A razão de se induzir hipertensão, hipervolemia e hemodiluição nestes doentes é melhorar o fluxo sanguíneo cerebral e evitar a isquemia tardia. Atualmente, apenas o bloqueador de canal de cálcio Nimodipina tem benefício comprovado no tratamento do vasoespasmo na HSA. Várias outras alternativas estão sendo estudadas. O Tirilazad não é efetivo, e vários outros têm resultados controversos, tais como: sulfato de magnésio, estatinas, antagonistas de endotelina, esteróides, antiagregantes plaquetários, e fibrinolíticos intratecais. O objetivo deste trabalho é promover uma revisão sistemática da literatura existente acerca do tratamento do vasoespasmo cerebral.

Palavras-chave: vasoespasmo cerebral, hemorragia subaracnóide, aneurisma cerebral

1- Department of Neurology, Sao Paulo Medical School, São Paulo, Brazil
2- Neurosurgeon from Sírio Libanés Hospital, São Paulo, Brazil
3- Neurologist from Sírio Libanés Hospital, São Paulo, Brazil
4- Neurologist from Sírio Libanés Hospital and Santa Paula Hospital, São Paulo, Brazil
5- Department of Neurological Surgery of Tulane University, New Orleans Louisiana, United States
6- Department of Neurosurgery, St Marien Hospital Amberg, University of Erlangen-Nuremberg, Germany

Received in May 2009, accepted in June 2009.
INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is reported with a mortality of about 50%. In addition to the hazards of a second hemorrhage, vasospasm contributes substantially to secondary brain damage and postoperative stroke. Vasospasm refers to a contraction of smooth muscle cells in the wall of cerebral arteries. However, its pathophysiology is not well understood.

This article reviews the existing literature on this important topic in vascular neurosurgery and highlights some of the most recent findings and treatment options.

DEFINITION

The term “cerebral vasospasm” is commonly used to refer to the combination of a delayed onset of ischemic neurological deficits following aneurysmal SAH (“symptomatic vasospasm”) and the narrowing of cerebral vessels documented by angiography or other vessels documented by angiography or other studies (“angiographic or arterial vasospasm”) (Fig. 1). Arterial vasospasm typically appears 3 to 4 days after rupture of an aneurysm and reaches a peak incidence and severity at 7 to 10 days.

Fig. 1: Angiographic vasospasm in aneurysm of middle cerebral artery (lateral angiographic view).

EPIDEMIOLOGY

The incidence and time course of symptomatic vasospasm parallels that of arterial vasospasm. However, while in 40% to 70% of patients arterial narrowing is evident – as documented by angiography or transcranial doppler sonography, only 20% to 30% develop the clinical symptoms. The most important factors determining the clinical effect of arterial vasospasm are the severity and extent of vessel narrowing. Symptomatic vasospasm typically begins 4 to 5 days after SAH, and is characterized by the insidious onset of confusion and a decreasing level of consciousness. When the arterial narrowing is pronounced, these symptoms may progress to focal neurological deficits, infarction, coma and death. In less severe cases, neurological recovery can be expected as soon as the arterial narrowing resolves.

Cerebral vasospasm will develop in more than half of SAH patients, and symptomatic vasospasm will occur in approximately one-third, which is associated with neurologic symptoms of ischemia.

According to a demographic study at the University of Mississippi, 1993 to 1999, patients with symptomatic vasospasm have a high prevalence of pre-existing chronic morbidity. 75% of patients have a known medical history of either hypertension or diabetes, or both. While mortality in African American and Caucasian males did not differ significantly, it was statistically higher in the combined female groups.

A systemic review of untreated unruptured cerebral aneurysms (UCA) in Japan showed that the risk of rupture is significantly higher than that reported by a large-scale North American and European cohort studies. This difference in the rupture risk may result from differences in the racial or genetic background, although a study bias may be evident. Morita et al conclude that untreated UCAs in Japan may have a significantly higher rate of rupture. These findings can partially explain an excessive number of SAH and vasospasm in Japan.

Female gender is a significant risk factor determining the onset of vasospasm following SAH, and may be as high as 1:9 according to the casuistic study of Quinn et al. However it has to be considered that there exists a female predominance among patients with aneurysmal SAH. The approximated male to female ratio has been reported as 1:2, with a similar mortality ratio. Hormonal changes due to menopause have been suggested as an explanation for gender differences. Recent research has advocated that hormone replacement therapy may have a protective role against SAH. The decline of estrogen levels during and after menopause may result in a decrease of collagen content within arterial vessel walls, and hence predispose to aneurysm formation.
Based on a recent study in West Yorkshire, with 100 cases of aneurysmal SAH cases per year among a population of 2.5 million, the mean age of patients with SAH was 51 years, both in male and female, while within the vasospasm group, the mean age was 49 years.

With respect to the total vasospasm group, half progress to cerebral infarction and half recover without deficit. However, it is important to recognize that angiographic findings may not correlate with the patient’s clinical presentation. Several factors are associated with the risk of ischemia: large volume of initial SAH, dehydration, use of antifibrinolytic agents, arterial hypertension, increased intracranial pressure, and reduced oxygen delivery. Furthermore, in the past decades studies demonstrated risk factors for the development of vasospasm: thickness of blood clot on the initial cranial computed tomography (CT), early increase in transcranial Doppler flow velocities, Glasgow coma score < 15, presence of a carotid or anterior cerebral artery aneurysm, age < 50 years, good neurological grade – World Federation of Neurological Surgeons (WFNS) grade 1 and 2 – and hyperglycemia.

Applying the WFNS grading scale in a study of 1635 SAH patients in Europe, Australia, New Zealand, South Africa and North America 1991 to 1997, an unfavorable outcome due to vasospasm occurred in 13% WFNS 1, 20% WFNS 2, 42% WFNS 3, 51% WFNS 4 and 68% WFNS 5.

An unfortunate case is shown to emphasize the poor outcome that vasospasm secondary to subarachnoid hemorrhage may develop (Fig. 2).

**Figure 2**: A 54-year-old female patient with SAH. Angiography (A) shows an anterior communicating artery aneurysm, and CT scan (B) shows a Fisher grade IV SAH. After clipping, the patient developed a severe vasospasm confirmed clinically and by Transcranial Doppler, and was submitted to a decompressive craniectomy (C).

**Physiopathology**

**General Aspects**

Arterial vasospasm most likely involves alterations in the structure of the vessel wall resulting from prolonged smooth muscle contraction. Hypertrophy, fibrosis, and degeneration as well as inflammatory changes in the vessel wall are secondary delayed effects. Extensive research demonstrated the event initiating the cascade resulting in vasospasm is the release of the blood breakdown product oxyhemoglobin.

However, the exact mechanism by which oxyhemoglobin induces vasoconstriction is unknown. The multifactorial process involves the generation of free radicals, lipid peroxidation, and activation of protein kinase C as well as phospholipase C and A2 with subsequent accumulation of diaclyglycerol and the release of endothelin-1. These events create a positive feedback loop that, in turn, produces a tonic state of smooth muscle contraction and inhibition of endothelium-dependent relaxation.

**Calcium**

Sasahara et al, 2008, used a genome-wide canine oligonucleotide microarray analysis to investigate alterations in gene expression on day 7 in a double SAH model. A decrease in vessel caliber of basilar arteries was accompanied by an up- and down-regulation of diverse genes. Network analyses demonstrated a significant association with molecules belonging to Ca2+ cell signaling and the p38 MAPK stress response pathway. Although the approach chosen may have documented late-stage changes of the disease process rather than early, diseas-causing pathomechanisms, the results support an important role for intracellular Ca2+ homeostasis.

Constriction of small (100-200 µm diameters) cerebral arteries in response to increased intravascular pressure plays an important role in the regulation of cerebral blood flow. In cerebral arteries from healthy animals, these pressure-induced constrictions arise from depolarization of vascular smooth muscle leading to enhanced activity of L-type voltage-dependent calcium channels. Enhanced pressure-induced constrictions and the resulting decrease in cerebral blood flow may contribute to the development of neurological deficits in SAH patients following cerebral aneurysm rupture. Thus, small diameter arteries may represent important targets for current treatment modalities (e.g. Hypertensive, Hypervolemic, Hemodilution \ “triple H” therapy) used in SAH patients.
POTASSIUM (K+) CHANNELS

Smooth muscle contraction, and thus arterial diameter, is influenced by the membrane potential, which is determined by the K+ conductance. Voltage-gated (Kv) and large-conductance, Ca2+-activated K+ channels dominate in arterial smooth muscle K+ conductance. Vasospastic smooth muscle cells are depolarized relative to normal cells, and it has been hypothesized that K+ channels may be involved in this imbalance. However, Jahromi et al, 2008 demonstrated, following SAH in dogs, that there were no significant differences in Ca2+-activated K+ current density, kinetics, Ca2+ and voltage sensitivity, single-channel conductance or apparent Ca2+ affinity between normal and vasospastic basilar-artery myocytes. Hence, other ionic conductances may underlie the membrane depolarization and vasoconstriction observed during vasospasm after SAH.

NITRIC OXIDE

Nitric oxide (NO) is produced by the endothelial NO synthase (eNOS) in the intima and by the neuronal NO synthase (nNOS) in the adventitia of cerebral vessels. By activating soluble guanylyl cyclase, NO increases the production of 3-5cGMP, which relaxes smooth muscle cells and dilates the arteries in response to shear stress, metabolic demands and changes of pCO (chemoregulation). 3-5cGMP is then metabolized by phosphodiesterases (PDEs). Following aneurysmal SAH, this regulation of cerebral blood flow (CBF) is disturbed. It has been speculated that oxyhemoglobin, gradually released from erythrocytes in the subarachnoid space surrounding the conductive arteries, destroys nNOS-containing neurons and thereby deprives the arteries of NO. A transient eNOS dysfunction evoked by increased levels of the endogenous NOS inhibitor, asymmetric dimethylarginine (ADMA) in cerebrospinal fluid (CSF) in response to the presence of bilirubin-oxidized fragments, prevents reactive vasodilatation. This eNOS dysfunction sustains vasospasm until ADMA CSF levels decrease and NO release from endothelial cells increases. Thus, exogenous delivery of NO has been speculated to provide a therapeutic modality to prevent and treat vasospasm.

ENDOTHELIN

Increased levels of endothelin-1 (ET-1), one of the most potent endogenous vasoconstrictors, have been suggested to play a role in cerebral vasospasm. The synthesis of ET-1 by endothelial cells is activated by physicochemical factors such as shear stress, hypoxia, and elevated oxidized low-density lipoproteins. These stimuli may trigger ET-1–mediated vasospasm, although the exact intracellular signaling mechanisms are not yet fully understood. Effects of the selective endothelin A receptor antagonist Clazosentan on cerebral perfusion and cerebral oxygenation following severe SAH has been investigated in phase II trial. At the moment, a randomized, double-blind, placebo-controlled, dose-finding study assesses the efficacy and safety of intravenous Clazosentan following SAH.

PROTEIN KINASE

About 30 years ago, protein kinase C (PKC) has been discovered and its pathophysiological functions remain a subject of great interest. Beside its role as ubiquitary second messenger in receptor signaling, PKC plays a role in the regulation of the myogenic tone. PKC may directly amplify vascular reactivity to different agonists, but may also interact with other signaling pathways as myosin light chain kinase, NO, intracellular Ca2+, protein tyrosine kinase (PTK) and its substrates such as mitogen-activated protein kinase (MAPK). The role of PTK and MAPK in cerebral vasospasm has been investigated with some vigor.

PTK regulates Ca2+ signaling, especially Ca2+ entry, and PTK antagonists Ca2+ release from internal stores and Ca2+ entry, and probably through this action its relaxant effect on cerebral arteries is mediated.

MAPK is activated following experimental SAH, and as a dual substrate to serine/threonine kinase and PTK it may serve as a “common pathway” to relay signals. Accordingly, MAPK inhibitors reduced cerebral vasospasm following experimental SAH.

INFLAMMATION

Some studies indicate that inflammation plays a putative role in cerebral vasospasm after SAH. C-Jun N-terminal kinase (JNK), a member of the mitogen-activated protein kinase group, has been shown to be involved in the response to a variety of extracellular stresses and has been implicated in numerous physiological processes including inflammation. SP600125, an inhibitor of the JNK signaling pathway reduced angiographic and morphological vasospasm in the basilar artery of dogs following SAH.

DIAGNOSIS

In the diagnosis of cerebral vasospasm, it is recommended to follow the patient closely for clinical signs of vasospasm, correlating them with daily transcranial doppler (TCD) sonography. Associated with vasospasm, hyponatremia may occur and has to be ruled out by checking repeatedly serum electrolytes.
Several factors may increase the risk of vasospasm-related ischemia; these include large volume of initial SAH, dehydration, use of antifibrinolytic agents, arterial hypotension, increased intracranial pressure, and reduced oxygen delivery.

**TRANSCRANIAL DOPPLER SONOGRAPHY**

A daily TCD examination performed by an experienced person should be used routinely to provide early identification of patients at high risk for vasospasm (Fig. 3, 4 and 5). A clinical study, comparing angiography, clinical findings and TCD in diagnosis of cerebral vasospasm, calculated by the receiver operating characteristics analysis TCD threshold of 100 cm/s to detect angiographic vasospasm, and of 160 cm/s to detect clinical vasospasm (Fig. 6).

Cerebrovascular responses to variations in blood pressure and CO2 are attenuated during vasospasm after SAH. However, cerebral blood flow velocities (CBF-V) as measured by TCD, may not necessarily reflect cerebral blood flow (CBF). While in controls, pCO2 levels were correlated with both CBF-V (r = 0.94, p < 0.001) and CBF (r = 0.87, p = 0.005), in vasospasm CBF-V was correlated with pCO2 (r = 0.54, p = 0.04) but CBF was not (r = -0.09, p = 0.83). Thus, in the presence of vasospasm, but blood flow velocities as measured by TCD do not necessarily reflect CBF.

In a series of 18 patients with vasospasm after SAH (Hunt Hess III-IV), TCD indices were used to estimate the optimal arterial blood pressure in hypervolemia/hypertension/hemodilution therapy. An increase in the CBF index was associated with better performance on neurologic examination. However, comparing the cerebral perfusion pressure (CPP) estimated from TCD analysis with CPP derived from direct measurement of intracranial pressure, there was no correlation (r = 0.15, p = 0.26).

In 15 patients with clinical vasospasm, the critical closing pressure (CCP) was measured by two different TCD methods (Aaslid and Michel). Soehle et al showed that CCP decreased significantly (p<0.05) during vasospasm (CCP\text{Aaslid}=6.3\pm22.9 \text{ mm Hg}, CCP\text{Michel}=14.9\pm16.5 \text{ mm Hg, mean\pmSD}) as compared with baseline (CCP\text{Aaslid}=24.4\pm20.3 \text{ mm Hg}, CCP\text{Michel}=27.8\pm19.4 \text{ mm Hg}). In addition, CCP was significantly decreased during vasospasm.
lower on the side of vasospasm (CCPA_{Astd}=11.9±24.2 mm Hg, CCP_{Michel}=18.4±19.6 mm Hg) as compared with the contralateral nonvasospastic side (CCPA_{Astd}=24.7±22.3 mm Hg, CCP_{Michel}=28.2±18.0 mm Hg) \textsuperscript{15}. Interestingly, assuming vasospasm to increase vasomotor tone, opposite to these findings an increase in CCP would have been expected. Alternatively, CCP might have decreased during vasospasm because of a vasodilatation distal to the spastic vessel. Thus, interpretation of CCP in vasospasm is difficult and may be overshadowed by nonlinear hemodynamic effects.

Comparing younger (<68 years-old n=47) and older (\geq 68 years-old n=34) patients following SAH, Torbey et al. found middle cerebral artery (MCA) and internal carotid artery (ICA) mean flow velocity to be respectively lower in older patients (median 76 versus 114 cm/s and 76 versus 126 cm/s (p<0.003). Older patients have a lower incidence of symptomatic vasospasm (44\% versus 66\%; p=0.05), and such vasospasm develops at lower CBF-V than in younger patients (MCA median 57 versus 103 cm/s; p=0.04 and ICA median 54 versus 81 cm/s, P=0.02). A quadratic relationship was found between age and CBF-V (p<0.0001) \textsuperscript{72}.

**TREATMENT**

**GENERAL CONSIDERATIONS ABOUT THE CURRENT TREATMENT**

The main goal of current treatment is to prevent or limit the severity of symptomatic vasospasm. At the moment, two therapies are generally accepted to be of substantial value in reducing the ischemic complications related to vasospasm: treatment with cerebroselective calcium channel blocker nimodipine (Nimotop®) to reverse vasospasm and hypervolemic, hypertensive hemodilution to elevate the CPP and thus provide blood to regions of the brain with marginal perfusion because of arterial spasm.

**CLINICAL TREATMENT**

**“TRIPLE-H” TREATMENT**

The efficacy of the “triple-H” therapy (hypertension, hypervolemia, and hemodilution) for cerebral vasospasm has not been demonstrated in controlled clinical trials \textsuperscript{46-58,75}. Nevertheless, several uncontrolled studies indicate that this treatment may aid in the resolution of deficits caused by vasospasm. Triple-H therapy is associated with significant risk, which includes heart failure, electrolyte imbalance, cerebral edema, and potential aneurysmal rupture, and therefore patients usually receive intensive care monitoring. Triple-H therapy is recommended for preventing and treating ischemic complications from vasospasm, with the aneurysm to be clipped surgically when possible. While transcranial cerebral oximetry seems to be of limited value for the detection of vasospasm, it may be useful in estimating the clinical impact of triple-H therapy in such patients \textsuperscript{13}.

A considerable variation exists regarding fluid management and the use of vasopressors and inotropes. Blood pressure augmentation, volume expansion and cardiac contractility enhancement may improve CBF in ischemic areas, ameliorate vasospasm and improve clinical condition \textsuperscript{15}. High doses of catecholamines may cause adverse adrenergic effects. Alternatively, Arginine vasopressin (AVP), which has been shown to stabilize advanced shock states while facilitating reduction of catecholamine doses, may be considered as an alternative supplementary vasopressor in SAH \textsuperscript{44}. The limited available data suggest that low-dose AVP does not cause brain edema \textsuperscript{44}. Besides volume replacement to induce moderate hypervolemia and hypertension, and considering previous pulmonary condition, is mandatory to avoid fluid restriction. Hemodilution may result in coagulation problems and can be discussed depending on ICP and cerebral oximetry, and is therefore not an integral part of therapy in most centers.

Triple-H therapy may cause additional shear stress on unsecured aneurysms, and is therefore associated with the risk of bleeding. Risk factors for dissecting aneurysms secondary to triple-H therapy are unclear, but patients are often smokers and have low apolipoprotein E levels \textsuperscript{2}. If these patients suffer SAH, management is complicated. A prophylactic obliteration during the early acute stage of SAH may lead to better outcomes. An obvious aneurysmal dilatation or pearl-and-string sign is safely treatable with endovascular trapping \textsuperscript{2}.

**CALCIUM ANTAGONISTS**

**NIMODIPINE**

In the treatment of vasospasm, the only reported drug to considerably improve outcome is Nimodipine, with a 40 to 86\% reduction of vasospasm \textsuperscript{39,49}. Guidelines from the AHA Stroke Council indicate that “oral nimodipine is strongly recommen-
ded to reduce poor outcome related to vasospasm.” These guidelines indicate that the value of other calcium antagonists, whether administered orally or intravenously, remains uncertain. Decreased blood pressure is the most common side effect, occurring in 4.4% of patients.

Therefore, blood pressure should be monitored continuously. Other side effects occurring at a low frequency of ≤1.0% include headache, nausea, and bradycardia. No clinically significant effects on hematologic factors, renal or hepatic function, or carbohydrate metabolism have been causally associated with oral nimodipine, and Nimotop® does not appear to affect anesthetic management.

A detailed review of 41 studies by Weyer et al in 2006 resulted in the conclusion that the only proven therapy for vasospasm is nimodipine.

A previous meta-analysis of all published randomized trials on prophylactic nimodipine included 1202 patients. Nimodipine was associated with an improvement in the odds ratio (OR) of good and of good plus fair outcomes by 1.9:1 and 1.7:1, respectively (p<0.005 for both measures). OR of either deficit or mortality attributed to vasospasm and of cerebral infarction on cranial computed tomography were reduced by 0.5:1 to 0.6:1 in the nimodipine group (p<0.008 for all measures).

NICARDIPINE

Local intra-arterial infusions of verapamil and nicardipine have also been used to treat cerebral vasospasm. Only a few reports of early clinical experience and limited data are available regarding their cerebral physiological activity. Lavine et al assessed the efficacy of intracarotid administration of verapamil and nicardipine on augmenting cerebral blood flow in New Zealand white rabbits. They compared the capability to reverse topical endothelin (ET)-1-triggered vasospasm, and concluded that intra-arterially administered nicardipine is a more potent cerebral vasodilator and is superior to verapamil.

Recently selective intra-arterial injection of nicardipine during angiography has also been suggested as a therapeutic modality for the management of distal vasospasm not amenable to balloon angioplasty. Systolic but not diastolic or mean arterial pressure decreases significantly after the injection, can cause significant hemodynamic instability and requires supportive management by an anesthesiologist.

FASUDIL

Fasudil (Eril; Asahi Kasei Pharma Corp, Tokyo, Japan) is a potent Rho-kinase inhibitor, and Fasudil hydrochloride (hexahydro-1-(5-isooquinolinesulfonyl)-1H-1,4-diazepine hydrochloride, FH, AT877) has been developed to treat vasospasm.

In order to find an ideal dose for administration of Fasudil in SAH, a daily dose of 20, 40, 60, 90 and 120-180 mg were compared. AT877 was given by intravenous infusion over 30 min two or three times a day for 14 days after surgery. Although AT877 did not completely abolish angiographic vasospasm, severe vasospasm was less frequent following higher doses. Only mild hypotension was seen. Part of its effect may be attributable to protection of the brain from ischaemic insults due to chronic cerebral vasospasm.

A prospective randomized placebo-controlled double-blind trial of Fasudil or AT877 was performed with the cooperation of 60 neurosurgical centers in Japan. 267 patients, who underwent surgery within 3 days after SAH, received either 30 mg AT877 or a placebo (saline) by intravenous injection over 30 minutes, three times a day for 14 days. AT877 reduced angiographically demonstrable vasospasm by 38% (from 61% in the placebo group to 38%, p = 0.0023), low-density regions on computerized tomography associated with vasospasm by 58% (from 38% to 16%, p = 0.0013), and symptomatic vasospasm by 30% (from 50% to 35%, p = 0.0247). Furthermore, AT877 reduced the number of patients with a poor clinical outcome by 54% (from 26% to 12%, p = 0.0152).

Zhao et al, 2006 investigated the efficacy and safety of FH in a randomized open trial with nimodipine as control including 72 patients who underwent surgery following aneurysmal SAH (Hunt& Hess I to IV). During 14 days following surgery, patients got either 30 mg of FH iv over 30 minutes three times a day or nimodipine 1 mg/hr iv. Neither the incidence of symptomatic vasospasm, CT findings or recovery evaluated by the Glasgow Outcome Scale (GOS) was different between the FH vs. the nimodipine group. However, applying a score for aphasia, upper and lower extremities, authors found FH to improve neurological deficits significantly more than nimodipine.

OZAGREL

Ozagrel is a thromboxane A₂ synthase inhibitor, and has been found to ameliorate vascular contraction and platelet aggregation. Suzuki et al 2008 analyzed the surveillance data of 3690 patients comparing the safety and efficacy of fasudil plus ozagrel to fasudil alone. The occurrence of low density areas on CT and symptomatic vasospasm were significantly lower in the fasudil alone group. There was no difference with regard to adverse effects. Hence, the combination of fasudil plus ozagrel was well tolerated, but did not result in better efficacy than fasudil alone.

The experimental use of controlled-release biocompatible compounds that deliver a desired drug locally into the subarachnoid space is under investigation. This technology makes it possible to achieve high local concentrations of therapeutic
agents while minimizing systemic toxicity and circumventing the need to cross the blood-brain barrier. Animal studies have shown promising results, and the few human studies that have been published using controlled-release systems with papaverine or nicardipine report similarly encouraging outcomes.45

**MAGNESIUM SULFATE**

Wong et al, 2006, compared in 60 patients with aneurysmal SAH the effect of magnesium sulfate (MgSO4) 80 mmol/day plus nimodipine with nimodipine alone. There was a strong trend to decrease the incidence of symptomatic vasospasm from 43% to 23% by MgSO4 infusion. Duration of elevated mean flow velocity > 120 cm/s was significantly decreased by MgSO4 (p<0.01). However, there was no significant effect on functional recovery or GOS. The incidence of adverse events such as brain swelling, hydrocephalus, and nosocomial infection was comparable.78 A study recruiting approximately 800 patients would be required to test for possible neuroprotective effects of MgSO4 after SAH.

**STATINS**

Independently of their cholesterol-lowering effect, statins have multiple biological properties, including downregulating inflammation and upregulating endothelial NO synthase. Thus, a positive effect on vasospasm may be hypothesized. In a single center pilot study, Lynch JR et al randomized 39 patients with angiographically documented aneurysmal SAH to receive either simvastatin (80 mg daily) or placebo for 14 days. Highest mean MCA TCD velocities were significantly lower in the simvastatin-treated than in the placebo group (p<0.01). These findings were confirmed by Kerz T et al 2008, enrolling 100 patients into a case control study.33

**CORTISONE**

Hyponatremia following SAH is a result of excess renal sodium excretion (natriuresis), and may occur in 10 to 34% of those patients.41 Sodium replacement may induce further sodium excretion. The mineralocorticoid properties of either fluocortisone or hydrocortisone (1200 mg/day) promote renal sodium retention and attenuate hyponatremia and hypovolemia in patients with SAH.43

**TIRILAZAD**

Oxygen radical-induced, iron-catalyzed lipid peroxidation within the vascular wall may play a key role in the occurrence of vasospasm. The 21-aminosteroid tirilazad mesylate was developed (Pharmacia & Upjohn) as a potent inhibitor of lipid peroxidation and may work by a combination of radical scavenging and membrane stabilizing properties. Indeed, in experimental models of SAH and focal cerebral ischemia tirilazad has been shown to ameliorate vasospasm and improve cerebral blood flow as well as to reduce the size of cerebral infarction.19,64 Recently, a meta-analysis of 5 randomized clinical trials of tirilazad including 3,797 patients with SAH was published.23 Tirilazad did not significantly decrease unfavorable clinical outcome on the GOS (odds ratio [OR] 1.04, 95% confidence interval [CI] 0.89-1.20) or cerebral infarction (OR 1.04, 95% CI 0.89-1.22). However, there was a significant reduction in symptomatic vasospasm in patients treated with tirilazad (OR 0.80, 95% CI 0.69-0.93).23

**EBSELEN**

Ebselen is a seleno-organic compound with antioxidant activity that may act through a glutathione peroxidase–like action. In a multicenter, placebo-controlled, double–blind clinical trial enrolling 286 patients with SAH oral ebselen treatment (150 mg, twice a day) was compared with placebo. The incidence of clinically diagnosed delayed ischemic neurological deficits was unaltered. There was a significantly better outcome after Ebselen treatment (p=0.005, chi2 test), and a decrease in the incidence and extent of low-density CT-areas (p=0.032, Wilcoxon rank sum test).54

**PANAX NOTOGINSENG SAPONINS**

Panax notoginseng (Burk) F.H. CHEN is a herb whose roots are used in Chinese medicine and its extracts and major compounds, such as ginsenosides and the notginsenoside, exert various pharmacologic activities. Triterpenoid saponins are the major bioactive constituents, and its underlying mechanism of action is anti-inflammatory and may contribute to neuroprotective effects in brain ischemia.82

**SURGICAL TREATMENT**

**VENTRICULAR CSF DRAINAGE**

From a mechanical point of view, removal of cerebrospinal fluid (CSF) containing clot following SAH would reduce the amount of hemoglobin breakdown products and would prevent or reverse cerebral vasospasm (Fig. 7). In a series of Sonobe et al, 185 patients operated on for aneurysmal SAH, the incidence of vasospasm was 11% in 150 patients with CSF drainage and 29% in 35 patients without drainage.67 In a series
of Ito et al, 25 SAH patients underwent clipping and cisternal CSF drainage. The effect of the drainage was graded as fair (>150 mL/day), moderate (50-150 mL/day), or poor (<50 mL/day). Symptomatic vasospasm occurred in 32, 60, and 78% of patients with fair, moderate, and poor drainage, respectively.

On the contrary, in a series of Kasuya et al, in 92 patients operated on for aneurysmal SAH, the incidence of cerebral infarction at 48 hours was higher in patients with higher CSF drainage volumes.

**Figure 7**: Surgical view of a ventricular CSF drainage.

**LUMBAR CSF DRAINAGE**

Alternatively to a ventricular drainage, lumbar drainage may clear blood from the basal cisterns. Lumbar drainage may be safer and more easily performed than a ventricular drainage. In a retrospective study, Schmidt and Klimo observed less cerebral vasospasm following lumbar drainage than without lumbar drain (p<0.001), with a better recovery in the group treated with lumbar drainage.

**THROMBOLYTIC THERAPY**

Intracisternal thrombolytic therapies may aid in clearing blood from the CSF. Recombinant TPA has been used in several clinical trials with moderate success. Findlay et al reported to decrease the rate of vasospasm by a single dose of rTPA instilled at the time of surgery. In a cohort study, Kodama et al treated 217 patients with a combination of ventricular drainage and continuous intrathecal irrigation with urokinase and ascorbic acid.

**FENESTRATION OF THE LAMINA TERMINALIS**

In more than 60% of SAH patients, a coexistence of vasospasm and hydrocephalus is observed. Anecdotal reports suggest that fenestration of the lamina terminalis during surgery could improve the outcome and might decrease the rate of ventriculoperitoneal shunting for hydrocephalus.

Fenestration of the lamina terminalis (Fig. 8) can be performed with or without additional fenestration of the membrane of Lillequist. In a series of 100 patients, Fisher grade 3, Andaluz and Zucarello reported a reduction of vasospasm from 53% in patients without lamina terminalis fenestration to 33% in those with fenestration (p<0.001).

**Figure 8**: Surgical view after anterior communicating artery aneurysm clipping, the fenestration of lamina terminalis between the two optic nerves is performed by us as routine.
Endovascular treatment options include transluminal balloon angioplasty and intraarterial papaverine infusion \(^{57}\) and may be applied for treatment of vasospasm in those patients who have failed conventional therapy \(^{39}\). Several uncontrolled studies indicate that transluminal angioplasty may provide neurologic improvement. Hemodynamic effects resulting from angioplasty of vasospastic arteries can be quantified using combined perfusion- and diffusion-weighted (PW/DW) magnetic resonance (MR) imaging. In cases of a severe PW/DW mismatch, successful angioplasty of proximal vasospasm improved tissue perfusion and prevented cerebral infarction \(^{9}\).

**GENE THERAPY**

Transfer of genes that encode vasoactive products via the CSF may prevent vasospasm after SAH. Alternatively, neuroprotective genes, or genes targeting proinflammatory mediators may reduce ischemic stroke. Several fundamental advances, as improvement of vectors, are required before gene therapy can be adopted in clinical routine \(^{73}\).

**REFERENCES**


44. MUEHLSCHELEGEL S, DUNSER MW, GABRIELLI A, WENZEL V, LAYON AJ. Arterine vasospresin as a supplementary vasopressor in refractory hypertensive, hypervolemic, hemodilutional therapy in subarachnoid hemorrhage. Neurocrit Care. 2007; 6:3-10.


---

**CORRESPONDING AUTHOR**

Antônio Santos de Araújo Júnior  
**Work Address:** Rua Peixoto Gomide, 515, cj 96, Cerqueira César; São Paulo, SP, Brazil.  
**CEP:** 01409-001  
**Phone:** 05511-35647404 **Fax:** 05511-32890411  
**Cell:** 05511-84567404  
**E-mail:** dr.anthonioaraujojr@gmail.com