Efficacy of Nimodipine Administration on Vasospasm after Subarachnoid Hemorrhage

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Introduction

Subarachnoid hemorrhage (SAH) is a common and frequently devastating condition, accounting for 5% of all strokes, and affecting as many as 30,000 Americans each year (Bederson, 2009). The incidence of angiographic vasospasm after aneurysmal subarachnoid hemorrhage has been estimated to occur in 50% to 70% of patients with aneurysmal SAH, with approximately 50% of those exhibiting symptoms of clinical vasospasm (Marshall, 2010).

Aneurysmal subarachnoid hemorrhage (aSAH) is a hemorrhagic stroke whereby blood from the vasculature enters filling the subarachnoid space. Aneurysms typically form in the bifurcations of the large vessels that make up the circle of Willis (American Association of Neuroscience Nurses, 2009). When one of these vascular lesions ruptures, blood leaks into the subarachnoid space and is known as an aSAH. Morbidity and mortality of patients with aneurysmal subarachnoid hemorrhage (aSAH) is significantly related to the development of chronic cerebral vasospasm. Aneurysmal subarachnoid hemorrhage (aSAH) remains a leading cause of morbidity and mortality in patients who survive the initial ictus, primarily as a result of the development of delayed or chronic vasospasm (Pradilla, 2010).

Nimodipine (Nimotop), a calcium channel blocker, is the only drug currently approved by the FDA for the prevention and treatment of vasospasm following aSAH. Nimodipine crosses the blood–brain barrier and inhibits calcium ions from entering into cells, subsequently reducing the contractile state of the vascular smooth muscle cells during depolarization, which results in the inhibition of vasoconstriction (Micromedex).
Background and Significance

A cerebral (brain or intracranial) aneurysm is an area where a blood vessel in the brain weakens, resulting in a bulging or ballooning out of part of the vessel wall. Usually, aneurysms develop at the point where a blood vessel branches, because the “fork” is structurally more vulnerable. The disorder may result from congenital defects or from other conditions such as high blood pressure, atherosclerosis (the build-up of fatty deposits in the arteries), and less commonly, head trauma or infection (American Association of Neurological Surgeons, 2009).

Aneurysms are usually found at the base of the brain just inside the skull, in an area called the subarachnoid space. In fact, 90 percent of subarachnoid hemorrhages (SAHs) are attributed to ruptured cerebral aneurysms and the two terms are often used synonymously. (American Association of Neurological Surgeons, 2009)

Aneurysms range in size, from quite small – about 1/8 inch – to nearly one inch. Aneurysms larger than one inch are called giant aneurysms, pose a particularly high risk, and are difficult to treat.

Prevalence and Incidence (American Association of Neurological Surgeons, 2009)

- Every year, an estimated 30,000 people in the United States experience a ruptured cerebral aneurysm, and up to 6 percent of the population may be living with an unruptured aneurysm.
- Worldwide statistics vary greatly depending on the country and demographics, ranging from as low as 5.1 cases per 100,000 persons to as high as 19.6 cases per 100,000 persons, based on age-adjusted incidence studies.
- About 40 to 50 percent of patients with ruptured aneurysms survive; 20 percent of these patients will have no permanent physical deficits.
- Re-hemorrhage occurs in about 20 percent of cases within the first 14 days after the initial rupture.
- Aneurysms occur in all age groups, but the incidence increases steadily for individuals ages 25 and older.
- Aneurysms are most prevalent in people ages 50 to 60.
- Aneurysms are about three times more prevalent in women.
- The presence of multiple aneurysms or a family history of aneurysms increases risk.

**Risk Factors** (American Association of Neurological Surgeons, 2009)

- Hypertension (high blood pressure)
- Cigarette smoking/nicotine use
- Diabetes
- Excessive alcohol consumption
- Congenital (genetic) predisposition
- Injury or trauma to blood vessels
- Complication from some types of blood infections

**Warning Signs/Symptoms** (American Association of Neurological Surgeons, 2009)

People who suffer a ruptured brain aneurysm may have warning signs, including:

- Localized migraine-like headache
- Nausea and vomiting
- Stiff neck
- Blurred or double vision
- Sensitivity to light (photophobia)
- Loss of sensation
Many people with unruptured brain aneurysms have no symptoms. However, others might experience some or all of the following symptoms, which indicate possible signs of an aneurysm:

- Cranial nerve palsy
- Dilated pupils
- Double vision
- Pain above and behind eye
- Localized headache
- Progressive weakness or numbness

**Evidence Based Practice Statement of Purpose**

Evidence based practice guiding nimodipine administration efficacy on improving clinical outcomes of patients with vasospasm following aneurysmal subarachnoid hemorrhage aSAH.

**Literature Review**

**Article 1: Angiographic Features and Clinical Outcomes of Intra-Arterial Nimodipine Injection in Patients with Subarachnoid Hemorrhage-Induced Vasospasm**

**Purpose** – The aim of this study was to determine the role of intra-arterial (IA) nimodipine injections for cerebral vasospasm secondary to ruptured subarachnoid hemorrhage (SAH) and to investigate the factors that influence vasodilation and clinical outcomes (Sang-Shin, 2012).

**Type of research design** – This study was designed around a Prospective Correlational Quasi-Experimental approach. The degree of vasodilation shown in angiography was measured, and the
correlation between the degree of vasodilation and both the interval from SAH to cerebral
vasospasm and the interval from clipping to cerebral vasospasm was determined (Sang-Shin,
2012).

**Sample selection** – Between 2009 and 2011, 29 patients underwent aneurysm clipping for
ruptured cerebral aneurysms. Out of the 29 enrolled patients included in the study, 14 were men
and 15 were women with an average age of 50.8 years, and ranging from 32 to 64 (Sang-Shin,
2012).

**Methodology** – The change in blood flow rate after IA injection was assessed by transcranial
doppler ultrasound. Multiple clinical parameters were completed before and after IA nimodipine
injection to evaluate any improvements in clinical symptoms (Sang-Shin, 2012).

**Major findings** – Patients who received IA nimodipine injection for cerebral vasospasm after
ruptured SAH demonstrated improvements in blood vessel diameter and clinical symptoms in
angiography. Additionally, a significant positive correlation between the degree of blood vessel
expansion and the improvement in clinical symptoms was observed. The time interval between
SAH and vasospasm was significantly positively correlated with the degree of vasodilation after
IA nimodipine injection. Likewise, the time interval between surgery and vasospasm was
significantly positively correlated with the degree of vasodilation after injection. This study
suggests that IA nimodipine injection for vasospasm after SAH is a safe and effective method to
improve clinical outcomes (Sang-Shin, 2012).

**Article 2: Continuous intra-arterial infusion of nimodipine at the onset of resistant
vasospasm in aneurysmal subarachnoidal haemorrhage.**
**Purpose** – Usual treatment to resolve cerebral vasospasm is performed through intra-arterial infusion of nimodipine, and given the fact that its effect lasts for several hours, but then decreases many patients require more than one interventions. To improve the number of treatments required to control for vasospasms, the researchers administered continuous nimodipine through catheters in both ICAs directly into the spastic arteries (Doukas, 2011).

**Type of research design** – This study utilized a Descriptive Clinical Case Series approach, with one illustrative case provided (Doukas, 2011).

**Sample selection** – This clinical case series included four patients with severe aneurysmal subarachnoid hemorrhage and refractory vasospasm. The patients were chosen according to the following parameters: evidence of increased flow velocities via Doppler sonography (abnormal Gosling, Pourcelot indexes) with impairment of the brain tissue perfusion in the perfusion CAT scan led to immediate angiography (Doukas, 2011). Therefore, the researchers selected patients with unresolved vasospasm, according to the designated indexes, and those who clinically deteriorated. The researchers did not use Hunt and Hess score or Fisher grades to select participants.

**Methodology** – The vasospasms were documented via transcranial Doppler (TCD) and perfusion CAT scans were used to confirm. Two four-French diameter catheters were proximally implanted via the femoral arteries in both extracranial internal carotid arteries. 5 mg nimodipine was slowly administered via infusion pump with 5 ml/h for each side. The following day the angiography was repeated, and if the vasospasms had not resolved the infusion was continued. The maximal duration of the infusion has been 72 hours. Daily angiographic images, TCD work
ups and Perfusion CAT scans were performed to determine the efficacy of the therapy (Doukas, 2011).

**Major findings** – In the cases where conservative treatment cannot achieve resolution of the vasospasms, and the eventually following ischemic deficits, and where the intra-arterial nimodipine administration shows good vessel widening, a continuous nimodipine infusion via catheters in the ICA could be the last treatment chance (Doukas, 2011).

**Article 3: Continuous Local Intra-arterial Nimodipine Administration in Severe Symptomatic Vasospasm after Subarachnoid Hemorrhage**

**Purpose** – The purpose of this study explored whether continuous local intra-arterial nimodipine administration (CLINA) can reverse vasospasm and prevent delayed ischemic neurological deficit (Musahl, 2011).

**Type of research design** – The researchers performed a Retrospective Observational Series of Consecutive Cases, with one observational case provided (Musahl, 2011).

**Sample selection** – Between September 2007 and February 2009, 6 patients (5 women) were treated with CLINA after aneurysmal SAH. The patients’ ages ranged from 39 to 58 years with a mean age of 47.2 years (Musahl, 2011).

**Methodology** – Six consecutive subarachnoid hemorrhage patients (5 women; mean age, 47.2 years) with severe CV despite maximum medical therapy underwent CLINA within 2 hours after the onset of clinical symptoms. After anticoagulation, micro-catheters were inserted distally in the concerning supra-aortic vessels. Glyceryl trinitrate injection (2 mg) was followed by CLINA (nimodipine 0.4 mg/h for 70-147 hours). Duration of CLINA was determined by neurological
status, transcranial Doppler sonography, and partial tissue oxygen pressure values. Four of the six enrolled patients were awake and developed focal neurological symptoms, whereas two of the patients were sedated and ventilated and showed a massive decrease in partial tissue oxygen pressure (ptiO2). All 6 patients underwent digital subtraction angiography (DSA) within the first 2 hours after onset of clinical symptoms and decrease in ptiO2, respectively (Doukas, 2011).

**Major findings** – Preliminary data show that CLINA is a straightforward, effective, and safe option for patients with severe CV refractory to medical therapy. Dilation of spastic arteries starts within a few hours and is lasting. Indication for CLINA is peripheral and diffuse CV at any location. It has a fast and extended relaxing effect on spastic vessels. Particular indications are peripheral, diffuse, and multilocular vasospasm that can be uni- or bilateral (Doukas, 2011).

**Personal Opinion**

The outcome for patients with SAH remains poor, with population-based mortality rates as high as 45% and significant morbidity among survivors (Bederson, 2009). Given the evidence for the neuroprotective effect of calcium antagonists like nimodipine described in the articles above against poor outcomes like secondary ischemia and vasospasm in aSAH, it is a vital part of providing care for this patient population. In addition, the particularly poor outcomes (death or dependence on help for activities of daily living ADL’s) associated with aSAH and the low risk level of adverse effects with CLINA further increases its necessity during treatment. Overall, calcium antagonists reduced the risk of poor outcome: the relative risk (RR) was 0.82 (95% confidence interval (CI), 0.72 to 0.93); the number of patients needed to treat (NNT) to prevent a single poor outcome event was 20 (95% CI, 12 to 59). For oral nimodipine alone the RR was 0.70 (0.58 to 0.84); the NNT was 8 patients (95% CI, 5 to 15) (Dorhout Mees, 2005). This
treatment is especially effective in treating the smaller intra-arterial brain vessels that present with recurrent or persistent symptoms. However, going forward further research is needed to determine for instance the optimal dose, the optimal time window for administration, and whether or not other calcium channel blockers or other treatments can offer superior protection in these cases. Furthermore, the risk for dissection, thromboembolic events increases given the risk of maintaining a catheter in the intracranial vasculature over an extended period of time. Therefore, it is always important to provide anticoagulation therapy to prevent this complication, especially in aggressive hypertensive therapy. Patients need constant neurological and hemodynamic assessment as well as continuous monitoring to prevent or limit infection. In addition, these patients should also receive standard triple-H (hypervolemia, hypertension, and hemodilution) therapy as well. As severe cerebral vasospasm constitutes the dominant factor of secondary morbidity and mortality after aneurysmal subarachnoid hemorrhage, systemic administration of the calcium channel blocker nimodipine will continue to play a vital role in providing the best clinical outcomes possible (Hänggia, 2008). These evidence based studies offer support that nimodipine can improve clinical outcomes in patients with vasospasm following aSAH. However, the small number of participants included in the three studies presented limits the generalizability of nimodipine’s efficacy. Therefore, given the devastatingly high degree of mortality and morbidity rates, and the positive impact of nimodipine, a larger evidence based outcome study is needed to gain a better overall picture on clinical outcomes.
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References


http://www.aans.org/Patient%20Information/Conditions%20and%20Treatments/Cerebral%20Aneurysm.aspx


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