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EFFECT OF INTRA-ARTERIAL NIMODIPINE ON SUBARACHNOID HEMORRHAGE INJURED BRAIN

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Abstract

Subarachnoid hemorrhage is a pathological condition of the brain, caused by rupture of intracerebral aneurism or arteriovenous malformation, with high morbidity and mortality rate. SAH may conceive permanent brain damage with persistent disability.

Vasospasm is the most characteristic pathological state of the vasculature, whose development coincides with onset of bleeding with asymptomatic presentation. The critical extend as a risk factor presents with symptom presentation and indication of brain damage development. Early vasospasm treatment is a priority in prevention of brain ischemia and disability. Existing methods of vasospasm treatment are conservative, endovascular and combined, with simultaneous intraarterial vasodilator application.

The aim of this study was to determine whether intraarterial application of Calcium- blocker Nimodipine will generate immediate vasodilation, facilitating endovascular aneurism treatment, resulting in longterm resolution of the condition.

Fifteen patients with SAH received endovascular treatment in the first 48 hours of hemorrhage onset, with consequent intraarterial Nimodipine application if vasospasm was detected. All patients had ruptured aneurism of anterior circulation. Vessel diameter was measured before and after Nimodipine application. The occurrence and degree of vasodilation, as a difference between both diameters, were considered a confirmation of drug effectiveness.

Complete spasm relief occurred in 10 patients, residual vasospasm persisted in 4 patients, no VS relief occurred in 1 patient.

Intraarterial Nimodipine application during endovascular brain aneurism treatment effectively relieves vasospasm. Early coiling reduces complication risks and development of postischemic brain damage.

Key words: vasospasm, SAH, Nimodipine, intraarterial, endovascular treatment.

Introduction

Spontaneous subarachnoid hemorrhage (sSAH), as a pathological state of the brain that occurs as a result of a rupture of intracranial aneurism or arterio-venous malformation is followed by high morbidity and mortality incidence [1, 2, 3].

Persistent invalidity evolves with the development with delayed cerebral ischemic damage (DCI) in many patients with SAH.

Vasospasm (VS) is the most characteristic pathological disorder of the blood vessels associated with the development of a SAH [4, 5]. It occurs immediately after rupture and may develop as asymptomatic VS, also refers to angiographic VS, because at this point it can be detected only with imaging methods. But it represents significant risk factor with simultaneous development of symptoms, known as symptomatic VS, when it indicates a higher risk of persistent brain tissue damage [6].

VS evolves from the organized blood clot from extravasated blood that surrounds the ruptured blood vessel, enters the brain and compresses and damages the surrounding tissue. It develops during the first 7 days of the initial ictus, but the general state of the patients must be evaluated continuously.at least 14 days after the rupture, a period when neurological state of the patient may

progress, as a sign of occurrence and progression of symptomatic VS and consequent DCI, as a reversible brain damage, only if immediate treatment is taken over [1, 4, 5, 6].

Primary, there are changes in the level of consciousness, reduced attention, difficulties in verbal expression or newly developed changes in coordination of the upper extremities, intense headaches described as "the worst experienced", to the level of agitation and somnolence [7].

The rest of the symptoms depend on the bleeding vessel vascular pool, whether the anterior or posterior circulation is affected, with the most often worsening symptom being monoparesis or hemiparesis with aphasia, if the bleeding vessel is in the dominant hemisphere with medial cerebral artery (MCA) rupture, or changes in lower extremities, onesided or bilateral, somnolence, changes in verbal expression and abulia with rupture of anterior communicating artery (AComA) [8].

All these symptoms may be followed and detected in patients with good neurologic state during the hospital stay, but not in patients whose neurologic state requires intensive care treatment or even mechanical ventilation. With these symptoms as newly occurred, there is an indication for radiology control of the brain because it points out on amplified symptomatic VS and possible rebleeding. These changes can also be a marker of DCI with necessity of changing the patients' treatment, conservative or even endovascular for bleeding vessel aneurism repair and VS recovery [9]. This treatment will reduce the possibility of DCI development, withall the consequences that brings to the patient.

There are many methods for VS treatment, conservative, endovascular (EVT) or combination of both [2, 3, 9, 10].

In most cases, immediately after the ictus, "3H" therapy is implemented (hypertension, hypervolemia, hemodilution) with application of oral medications with vasodilatoryeffect on the cerebral vessels, but this treatment is only acceptable if the patients` condition allows it [4, 6, 7].

According to the latest studies, hypervolemia is excluded as a step in this treatmentand is replaced with euvolemia, with the main purpose to avoid the side effects of volume overload, but to provide adequate brain tissue perfusion. If the patients` condition is serious and oral therapy cannot be implemented, then intravenous iv vasodilator therapy is indicated. Our study covers the early treatment of intracerebral aneurisms and immediate treatment of VS with EVT and simultaneous intra-arterial vasodilator application for existing VS.

The aim of this study was to confirm whether intraarterial application of Ca-channel blocker Nimodipine during the early endovascular repair of ruptured cerebral aneurisms in spontaneous SAH will cause vasodilatation that will enable the endovascular approach and reduce the risk of development of DCI and permanent invalidity.

Materials and methods

This study enrolled 15 patients from the UC for Neurosurgery with aSAH, who underwent EVT for aneurism repair. Six patients had ruptured aneurism on PcomA, 7 with ruptured AComA aneurism and ACA, and 2 patients with aneurism on MCA. All patients were with GCS 12-15 and H and H grade 1-2 on admission. Immediate brain CT was made as a primary investigation followed by brain CTA for precise detection of the ruptured vessel. All patients were treated endovascularly with ia Nimodipine application 1-3mg bolus dose, in the first 24-48h after admission, if angiographic VS was detected.

Anesthesia approach was with iv analgo-sedation with Midazolam and Fentanyl, 2% Lidocaine and 1,5% MgSO4, and additional therapy for blood pressure and heart rate stabilization. If signs of VS were present prior to EVT, continuous iv Nimodipine infusion was administered in dose of 5-10ml/h. Also, continuous monitoring of vital signs (blood pressure, heart rate, saturation) was applied. In one patient, as a result of rapid worsening of the neurologic state, general anesthesia was administered and instead of CTA, Seldinger angiography was conducted and EVT treatment was simultaneously done.

Inclusion criteria for the study were both sexes, age 32-77y, with or without previous hypertension treatment, ruptured aneurism of the anterior circulation with SAH, but no other form of cerebral bleeding, admitted in the course of the first hours after the ictus. Excluding criteria were GCS<8, traumatic SAH, existence of ICH and patients admitted more than 48h after the initial bleed

and those patients with rapid worsening of the neurologic state as a result of rebleeding and developed DCI.

Table 1. Criteria for early endovascular treatment with intraarterial Nimodipine application. GCS-Glasgow Coma Scale, H&H-Hunt and Hess, AVS-angiographic vasospasm, SVS- symptomatic vasospasm, PDB - proximal diameter before Nimodipine, DDB - distal diameter before, DA-Diameter after Nimdipine

Patient	Age	Aneurism	GCS	H&H	HTA	AVS	SVA	PDB	DDB	DA
1	47	Pcom	13	2	NO	YES	YES	4sm	2sm	4sm
2	62	Acom	15	1	YES	YES	NO	2sm	1sm	2sm
3	41	Pcom	12	3	YES	YES	YES	5sm	3sm	4sm
4	33	Acom	15	1	NO	YES	YES	2,5sm	1,3sm	2,5sm
5	66	Pcom	14	1	YES	YES	NO	3sm	0,5sm	2,5sm
6	78	Acom	12	2	YES	YES	YES	2,5sm	1sm	2sm
7	63	Pcom	14	1	YES	YES	NO	2sm	1,5sm	2sm
8	57	MCA	13	2	YES	YES	YES	3sm	1,5sm	3,5sm
9	72	Pcom	15	1	YES	YES	NO	4sm	3sm	4sm
10	73	Acom	12	1	YES	YES	NO	2sm	0,5sm	2sm
11	49	Acom	14	1	YES	YES	YES	2,3sm	1,5sm	2,5sm
12	64	MCA	13	2	YES	YES	NO	3,5sm	1,5sm	3,5sm
13	44	Acom	15	1	NO	YES	YES	2,5sm	1sm	1sm
14	57	Pcom	12	2	YES	YES	YES	3,5sm	2,5sm	4sm
15	61	Pcom	13	2	YES	YES	YES	3sm	1,5sm	2,3sm

Results

In total number of 15 treated patients, in10 patients there was a complete relief of VS after ia Nimodipine, in 4 patients only partial VS appeared and in 1 patient there was no visible VS relief. Additionally, 1 patient was with GCS 12 and H and H grade 2-3on admission, which implicates worsening of the neurologic condition and possibility of fast development of a secondary brain injury, but because of his age (41) it was decided that EVT would be performed. In 14 of the patients EVT was performed in the first 24-48h from initial bleed, while 1 patient had immediate EVT as a result of rapid deterioration. Among all 15 patients, 3 patients never had hypertension, 2 had untreated hypertension and other 10 had regular antihypertensive therapy. On admission, all patients had angiographic VS, but only 9 patients had Symptomatic VS.

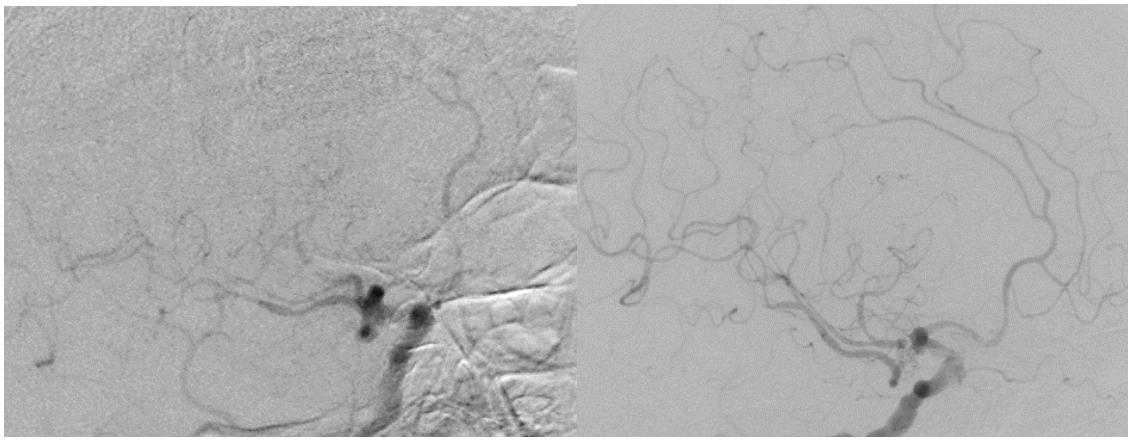
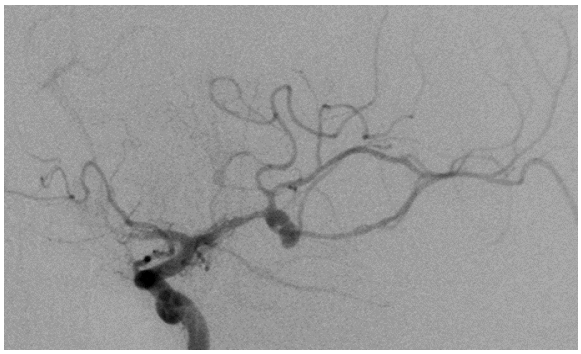


Figure 1. Ruptured PCom artery aneurism with proximal and distal angiospasm of MCA, resolved with iv Nimodipine.



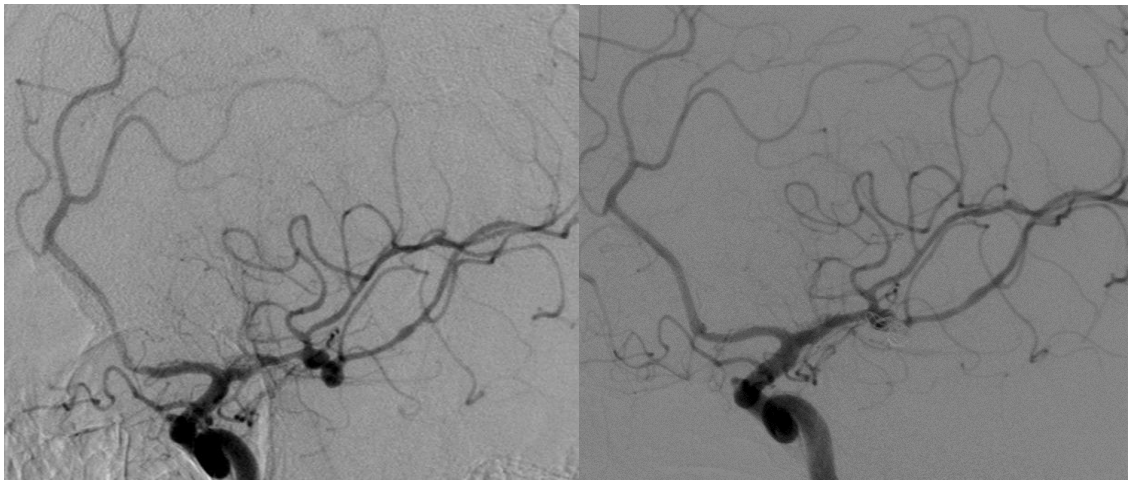


Figure 2. Ruptured MCA aneurism with proximal and distal vasospasm, resolved with iv Nimodipine.

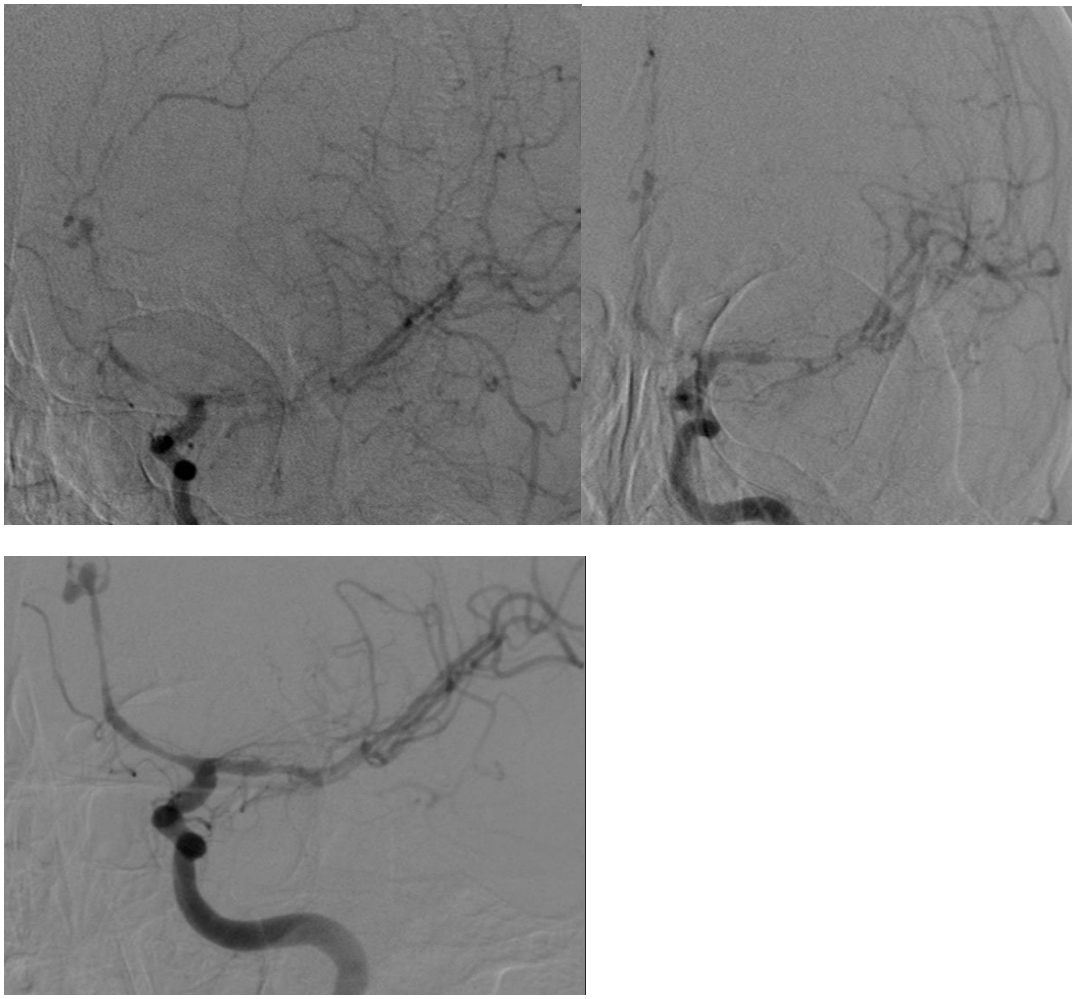


Figure 3. Ruptured A2 aneurism with diffuse vasospasm, resolved with iv Nimodipine.

Discussion

Cerebral VS represents prolonged but reversible narrowing of the cerebral arteries. It develops in the first days from the initiation of the sSAH, as a result of a ruptured intra-cerebral aneurism [11]. It is present in 5-8 patients in 100000 people a year and is characterized with high morbidity and mortality rate. People in their fifth decade are most commonly affected [6].

VS develops in intradural arteries and arteries and arterioles of the brain surface. According to distribution, it can be focal or diffuse and according to the degree it can be mild (<25%), moderate (25-50%) or severe (>50%) in comparison with the vessel lumen before VS appearance.

Angiographic VS can be exclusively detected with imaging technics, occurs immediately after aneurism rupture and develops to its highest degree on the 7thday of the initial bleed, with incidence between 50-90% [7].

After detection of angiographic VS, in 50% of the patients symptomatic VS occurs as a result DCI development and possibility of brain infarction. One analysis of 2741 patients in a SAH study from 1990s reported existence of cerebral infarction in 26% of ruptured aneurism patients in the first 6 months, which strongly correlates with a worse outcome. Primary brain injury as a result of apeak in ICP and global cerebral edema at the moment of aneurism rupture triggers a cascade of pathological processes as inflammation, cortical depression, capillary microthrombosis, BBB dysfunction, cerebral edema and neuronal apoptosis [4, 5, 11].

Cerebral ischemia progression is related primarily with the degree of VS and pathogenically related with the blood clot which surrounds the outer wall of the ruptured artery, although many

chemical processes of complex interaction between hematoma and the surrounding brain tissue are affected. Persistent blood clot with a large volume for a longer period of time is the most significant risk factor for VS. The second significant risk factor is delayed reabsorption of the existing clot. Other risk factors are thickness of the subarachnoid coagulum, IVH development with hydrocephalus progression, poor neurological condition on admission, loss of consciousness associated with the bleeding or rebleeding, preexisting hypertension, diabetes etc. [4,11].

There are various methods to set the diagnosis of VS such as transcranial Doppler, measuring of cerebral blood flow and perfusion with SPECT, CT perfusion, NIRS (simple noninvasive monitoring of cerebral ischemia after SAH) [6,11], cerebral tissue oxygenation (direct cerebral oximetrywith commercially available intraparenchymal probe- Licox Brain Tissue Oxygen probe, Integra Neurosciences) (6), vascular imaging methods (DSA, MRI, CTAwith sensitivity and specificity of 80-93%) [6, 11].

The primary treatment of SAH patients fromruptured aneurism is conservative with the aim to prevent the occurrence and development of symptoms after presentation of angiographic VS [7]. However, the latest views are directed to decision making on early definite treatment in securing the aneurism. This will raise the probability of preventing the ischemic stroke and infarction progression like DCI with irreversible brain damage and patients` immobility. Invasive treatment refers to open surgery, but the less invasive one is EVT with coil or stent placementor balloon dilation of the bleeding vessel [4].

Conclusion

In our study EVT with coil placement was performed during the initial 48-72 hours of the rupture, simultaneous intraarterial Nimodipine application with aim to reverse the VS and secure the aneurism with coil placement to prevent rupture and rebleeding. Nimodipine as a Ca-channel blocker prevents intracellular Ca-ion accumulation by blocking the dyhidropiridine Ca-channels.

By measuring the Post infusion Improvement ratio (measuring the diameter of the spastic artery) before and 10 minutes after Nimodipine application, we determined the effectiveness of Nimodipine vasodilatory activity, which, according to our study, showed effectiveness in relieving the cerebral arterial VS. Although our results showed a positive effect of Nimodipine in cerebral VS treatment, more studies are required to confirm whether this effect is only neuroprotective or with its mechanism of action has a direct effect on cerebral VS.

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