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## **Intra-arterial nimodipine for the treatment of vasospasm due to aneurysmal subarachnoid hemorrhage**

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**Abstract:** The cerebral vasospasm is still considered the most devastating complication for the patients with aneurysmal subarachnoid haemorrhage. The aim of this study was to evaluate the efficiency of intra-arterial nimodipine administration in cerebral vasospasm diminutions and outcome of the patients.

**Key words:** cerebral vasospasm, aneurysmal SAH, intra-arterial nimodipine

### **Introduction**

Cerebral ischemia due to severe vasospasm is the major factor of secondary morbidity and mortality for the patient with aneurysmal subarachnoid hemorrhage. The medical management of this clinical situation has been improved over the last decades and the current strategies for preventing vasospasm comprise both medical and interventional measures. Thus, the use of intraoperative intracisternal thrombolysis or intracisternal application of nicardipine-prolonged implants followed by oral nimodipine administration and hemodynamic therapy demonstrates effectiveness in preventing cerebral vasospasm. Even with these therapeutic methods, the level of permanent disabilities due to cerebral vasospasm is still significant (10% - 20%) [1, 3, 4]. This situation led to

development of alternative endovascular strategies such as balloon angioplasty and intra-arterial spasmolysis with nimodipine or papaverine.

The objective of our study was to investigate the effect of intra-arterial nimodipine administration to the patient with aneurysmal subarachnoid hemorrhage treated in our clinic.

### **Material and methods**

51 patients with aneurysmal subarachnoid hemorrhage were endovascular treated for 54 aneurysm at our institution between September 2015 and September 2016. From this group of patients 10 cases underwent intra-arterial injection of nimodipine for the treatment of subarachnoid hemorrhage induced vasospasm. 7 patients received intra-

arterial nimodipine injection immediately before and after the procedure of aneurysm occlusion with coils. These were due to the delayed addressing to our clinic (day 5 to day 9 after rupture) in which the cerebral vasospasm was imaging and clinical manifested. The other 3 patients benefit of intra-arterial nimodipine injection a few days after the procedure of aneurysm coils occlusion for cerebral vasospasm highlighted on echo Doppler monitoring and clinically manifested.

The following protocol is discussed to be used at our institution for the management of sever cerebral vasospasm after aneurysmal subarachnoid hemorrhage. After the procedure of aneurysm occlusion, continuous monitoring of intracranial flow velocities detected by transcarnial Doppler (TCD) is started daily in at least two arterial segments on both parts. For asymptomatic patients with TCD flow acceleration above 120 cm/s, a moderate hypertensive and hypervolemic therapy is applied along with continuing to use the oral administration of 60 mg of nimodipine doses every 4 hours. When vasospasm is suspected clinically (conscious patient with transient neurological deficits or confused patient), a brain computer tomography is performed to confirm the presence or absence of ischemia. The patient is then transferred to the Intensive Care Unit and a maximal triple H therapy is administrated. If the patient's clinical status continues to worsen

and the intracranial flow velocities as detected by TCD exceeds 150 cm/s, a endovascular intra-arterial nimodipine injection is taken in to discussion to be initiated. A catheter it will be placed within internal carotid artery (segment C3-C2) and a bolus of 1mg (5ml nimodipine and 15ml saline) will be administrated in a time of 5 minutes. The follow-up angiography will be performed after 10 minutes. If only minor angiographic effects are visualized a second bolus injection is performed. For the next 7 days a treatment with 1 mg of nimodipine, i.e. 5 ml Nimotop solution, (about 15 µg/kg bw/h), should be infused each hour via a central catheter. Patients of body weight less than 70 kg or with unstable blood pressure should be started on a dose of 0.5 mg nimodipine per hour (2.5 ml of Nimotop solution), or less if necessary. If the neurological status it will stabilize in this period of time a change to Nimotop tablets could be initiated and the total duration of treatment should not exceed 21 days.

We retrospectively reviewed clinical dates and imaging reports (angiography and CT) of these 10 patients who received intra-arterial nimodipine administration. The endovascular angiography and procedure were performed using a 5F or 4F diagnostic catheter placed in the internal carotid artery. Nimodipine was administrated in a solution of NaCl 9% (5ml nimodipine and 15ml NaC 9%). The dose varied from 1mg to 3 mg per vessel. Blood pressure and heart rate were continuously

monitored as parameters for systemic side-effect. Repeat angiography control exposures were performed at 10 minutes after each session of nimodipine administration. The frontal angiography projections on arterial phase were compared with focalization on A1 and M1 segments. The post endovascular procedure clinical examinations were determined as improved, stable or worse. Cerebral CT scan acquisitions before and after treatment were confronted to identify same particular signs as edema, infarction, hydrocephalus or a new hemorrhage.

## Results

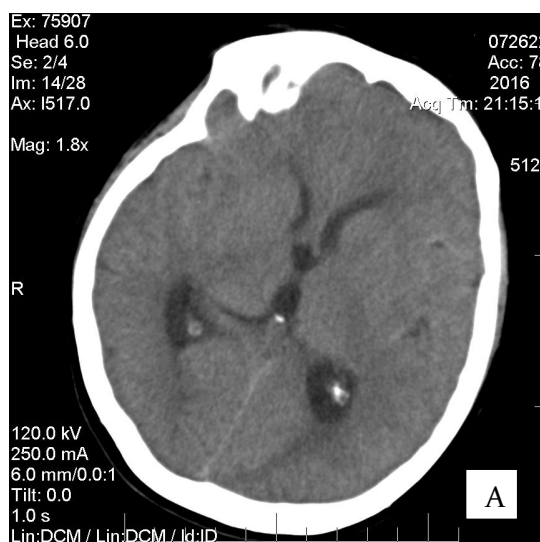
Of the 51 patients with ruptured aneurysm treated by endovascular coil occlusion 10 patient received intra-arterial nimodipine administration. The mean age of patients was 53.4 (interval range, 36 to 74 years). The sex (male and female) ratio was equal. 5 patients had Hunt&Hess grade III, 2 had grade II, one had grade IV and 2 had grade I. The average dose of nimodipine per patient was 2 + 0.5mg. Only two patients received two separate treatments. Nine injection procedures were performed under general anesthesia and three only with local one. Notable angiographic vascular dilatation was identified in 9 of the 12 procedures and in 8 patients. The comparative analysis of brain CT scans pre and post-procedural showed ischemic changes in 2 patients. Administration of intra-arterial nimodipine had insignificant systemic effects.

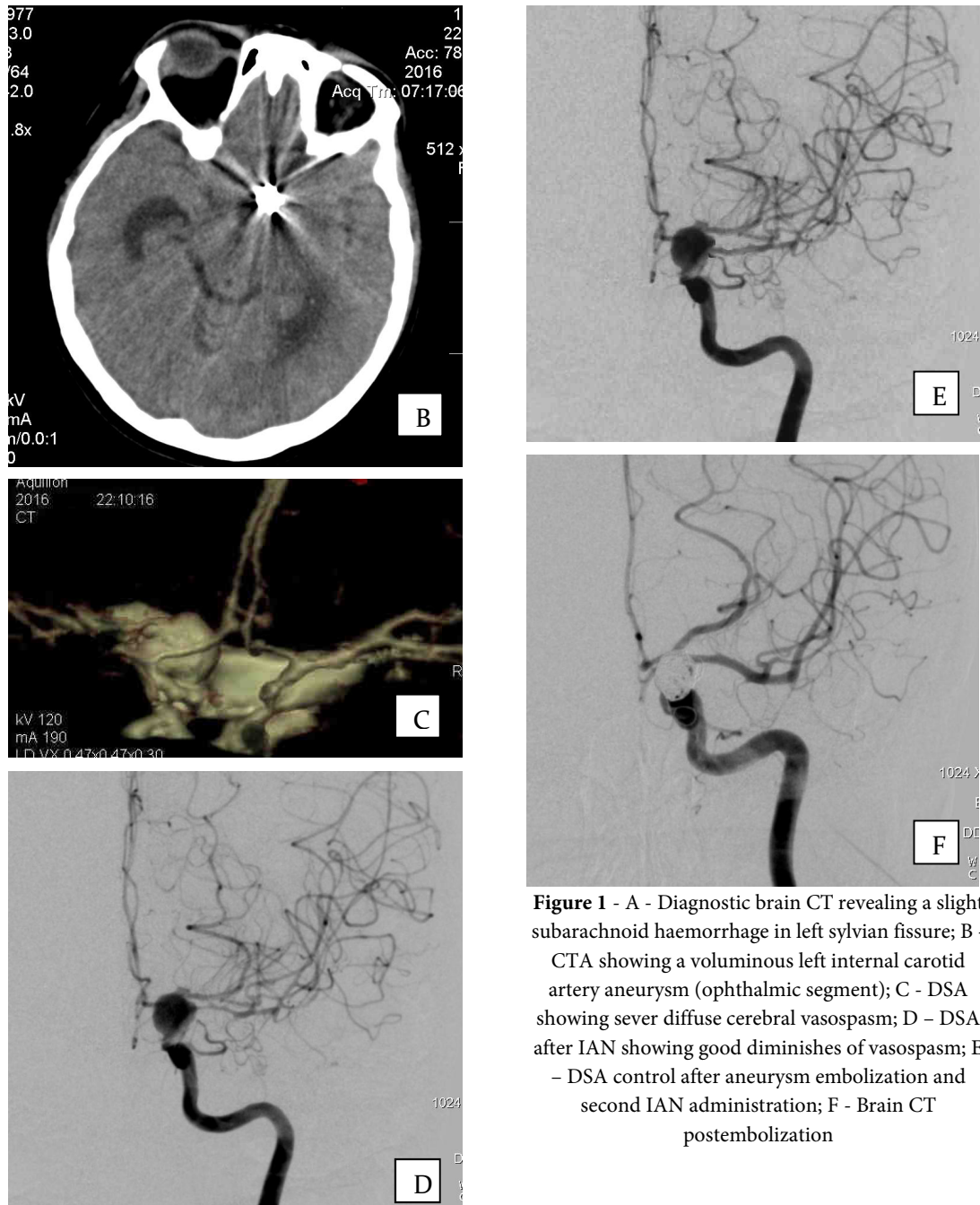
In two patients the systolic blood pressure dropped with 30 mmHg. There was no severe bradycardia or significant elevation of intracranial pressure (Table 1).

Clinical evolution after the endovascular chemical treatment was improved in 6 patients (GOS 5), stable in two (GOS 3) and worse in one (GOS 4). One patient died at 3 days after second session of intra-arterial nimodipine administration (GOS 1) due to an uncontrollably severe vasospasm that caused extensive hemispheric ischemia.

## Illustrative cases

A 48 year-old female presented to our clinic with confusion and severe headache syndrome. The family declared the onset of symptoms after seven days. Brain CT at admission revealed a slight subarachnoid haemorrhage in left sylvian fissure.





**Figure 1** - A - Diagnostic brain CT revealing a slight subarachnoid haemorrhage in left sylvian fissure; B - CTA showing a voluminous left internal carotid artery aneurysm (ophthalmic segment); C - DSA showing severe diffuse cerebral vasospasm; D - DSA after IAN showing good diminishes of vasospasm; E - DSA control after aneurysm embolization and second IAN administration; F - Brain CT postembolization

Table I

Patients' characteristics

Patient No	Age / Sex	H&H Grade	Fisher Grade	Aneurysm Location	Day of Surgery	Day of IAN administration	Dose of IAN/ Session	GOS
1	54/F	II	2	AcoA	0	9	1	5
2	42/M	III	3	AcoA	8	8	2	3
3	62/F	IV	4	MCA	6	6, 8	4	1
4	48/F	III	2	ACI oft	7	7	1,5	5
5	53/M	III	4	AcoA	3	5	1,5	5
6	49/F	I	1	MCA	5	5	1	5
7	74/M	III	3	PcoA	1	12, 13	4	4
8	55/M	I	2	AcoA	2	10	2	5
9	36/M	II	2	MCA	4	8	2	5
10	61/F	III	4	PcoA	9	9	1	3

## Discussion

The clinical effects of the endovascular methods used to treat symptomatic vasospasm after aneurysmal subarachnoid haemorrhage were investigated by many studies. Intra-arterial nimodipine injection and balloon angioplasty are widely accepted as rescue therapies in most of neurosurgical Units when maximized medical therapy fails. The balloon angioplasty is well known as the most effective endovascular procedure due to nearly permanent reversal of vasospasm. This procedure is limited to proximal vessel segments and may be accompanied by a series of complications. The most serious complications are vessel occlusion or rupture and coils or clip displacement. Because this procedure can be accompanied by several technical difficulties it should be performed in centers with experienced endovascular surgeons [1, 2, 4].

Intra-arterial administration of vasodilators has been demonstrated a good alternative to mechanical angioplasty with

optimal results in reversing angiographic vasospasm and in reducing flow velocities detected by TCD. The literature studies have reported using nimodipine, nicardipine or verapamil as calcium channel blockers for intra-arterial treatment of cerebral vasospasm. Biondi et al reported a 76% of clinical improvement, 63% notable angiographic vessel dilation after intra-arterial nimodipine administration and 72% of patients with favourable outcome. Hanggi and all reported also 63% patients with significant vascular dilatation with a 93% clinical improvement after the procedure [2, 5, 6].

The clear efficiency of IAN is still questionable. Most of the investigations showed that nimodipine is effective in diminishing vasospasm in case where intensive medical therapy fails, the therapy could be done in the same session with aneurysm coil occlusion, the procedure is temporary and may need repeated sessions, and the administration is more efficient in dilating small branches than large one [4, 7, 8].

## Conclusion

Our study is by some factors like number of cases and additional monitoring investigations (perfusion parameters: MTT – mean transit time, Tmax – selective time to peak of the brain parenchyma, rCBV – regional cerebral blood volume, rCBF – regional cerebral blood flow) [3]. The results of our retrospective analysis suggest that IAN is effective and safe in selected cases of vasospasm following aneurysmal SAH. We consider that a prospective and large randomized study is needed to confirm these results.

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