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CONTINUOUS INTRAVENOUS NIMODIPINE APPLICATION FOR PREVENTION OF VASOSPASM BEFORE ENDOVASCULAR TREATMENT OF RUPTURED CEREBRAL ANEURISMS

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Abstract

Early recognition of vasospasm (VS) in patients with aneurismal subarachnoid hemorrhage (aSAH) is an imperative for timely treatment and prevention of delayed cerebral ischemia (DCI). VS, the pathologic response of the vascular damage in aSAH, is the main risk factor for irreversible brain damage. The first step in successful solving of aneurismal bleeding is prevention and treatment of VS. The aim of this study was to determine whether medical treatment with continuous infusion of intravenous Calcium blocker Nimodipine, without radiology verified VS will impact the degree of arterial vasoconstriction during the endovascular aneurismal treatment (EVT).

A total of 20 patients with aSAH, confirmed by CT-angiography and hospitalized in UC for Neurosurgery were included in the study. In 10 patients, a continuous iv Nimodipine infusion was initiated on admission, the other half remained on their own antihypertensive therapy. If signs of VS or neurologic deterioration had developed, iv vasodilator therapy would have been initiated.

Control angiography and immediate EVT were performed on the 4th day of admission at Radiology Institute. Using angiography, the vascular diameter was measured and compared with the same vessel diameter on CTA, to determine whether iv Nimodipine is effective in the pretreatment period.

In 8 of 10 treated patients with iv Nimodipine, VS resolved in pre EVT period. Among the patients from the non-treated group, 1 had developed DCI, 1 had no VS, 6 had persistent and in 2 patients VS resolved spontaneously. The conclusion is that continuous iv Nimodipine in pre EVT period has vasodilatory potency on the vascular pool.

Keywords: aneurismal subarachnoid hemorrhage, vasospasm, intravenous Nimodipine, endovascular treatment.

Introduction

Cerebral vasospasm (VS), one of the most significant entities of spontaneous aneurismal subarachnoid hemorrhage (aSAH), still remains the main factor for high morbidity and negative outcome in patients with cerebral bleeding from ruptured aneurism. Although reversible, this condition is the leading cause of delayed cerebral ischemia (DCI) and irreversible neurologic deficit [1, 2, 3, 4].

DCI is expressed with 50% mortality rate in patients who survive this initial period after aneurismal rupture and early treatment [1, 2, 5].

Therefore, immediately after hospitalization of aSAH patients, it is essential to establish high susceptibility for VS occurrence and prompt monitoring of the signs and symptoms, with immediate examination and treatment, as to avoid the progression of the cerebral ischemia and neurologic deficit from infarct demarcation [1, 6].

VS is defined as reversible narrowing of the subarachnoid arteries, that develops between the 3rd and the 15thday of the initial hemorrhage, with the peak reached on the 10thday [2, 3, 5, 6].

Angiographic VS is radiologically confirmed narrowing of the arteries in comparison to their initial anatomic width before rupture [6].

The blood vessels of the skull base are primarily affected, but it can also spread to the blood vessels with smaller caliber or it can spread as a diffuse spasm, affecting the entire cerebral vasculature [5]. Except angiographic, symptomatic VS can also be present, confirmed by patients` symptomatology, but its evolution represents bad prognostic sign for DCI development [1]. In literature, symptomatic VS is described as early DCI, condition that is still reversible, but only with immediate and adequate treatment [1, 3, 6].

Small caliber cerebral arteries have significant auto regulatory function in cerebral blood flow, adjusting the blood delivery to neuronal activity [3, 5, 6].

These arteries with smaller caliber than 1mm, which cannot be angiographically visualized, with VS development can lead to DCI occurrence. Strongly expressed VS can compromise distal flow and if persistent for a certain time interval and spread in longer vessel segment, it increases the risk for infarction [1, 6].

According to digital subtraction angiography (DCA), an imaging method that is a golden standard for VS detection, 25% reduction in vessel lumen is defined as mild, 25-50% reduction as moderate and >50% reduction represents severe VS [1, 7].

The risk of infarction is also associated with collateral circulation, minute volume, blood pressure and intracranial pressure (ICP) [6].

Primary presentation of DCI developed immediately after the first bleed is a focal neurological dysfunction, dependent on the cerebral area affected by the bleeding [1, 3, 7].

DCI is a multifactorial process with gradual development. The initial 24-48 hoursfrom the rupture are defined as early brain damage phase manifested with severe headache, signs of elevated ICP and transitory global brain ischemia [1, 7].

Pathological alterations of this phase are brain edema, blood-brain barrier (BBB) damage, activation of the sympathetic system, autoregulation inhibition, microthrombosis, cortical spread of depolarization and inflammation [2, 3, 7]. With the development of the newly occurred pathological state of the brain, blood extravasation activates the destructive brain pathways and determines the development of DCI on 4-10th day after rupture [1].

Etiology and pathogenesis of VS

Vascular dysfunction may represent probable mechanism for cerebral hypoperfusion and has a mechanical origin [5].

Elevated ICP and developing brain edema lead to reduced brain perfusion which still has transitory characteristics, but becomes a trigger factor for catecholamine release stimulation as a result of ischemic hypothalamic injury and sympathetic nervous system activation. The raise in plasma catecholamine levels is persistent during the first days after rupture, but their constant elevated levels imply a bad prognosis. The transitory brain ischemia leads to endothelial cell damage and BBB break, thereby activating the coagulation cascade with exposure of subendothelial collagen and vasogenic edema development. At the same time Endothelin-1 process is activated by hypoxia which amplifies the vasoconstriction [2, 3, 5, 6].

The exact etiology and pathogenesis of cerebral VS is still obscure, but one complex theory that is still not confirmedimplies that there is an inflammatory cascade with dynamic intracellular exchange of calcium ions and Nitric Oxide (NO) flux, as a basic factor for VS occurrence [1]. The initiating factors are degradation blood products which accumulate in the subarachnoid space and act as trigger factors for endothelial dysfunction and intramural inflammatory response. This is confirmed by the fact that prolonged persistence of the perivascular coagulum induces prolonged VS [2, 3, 6, 7].

In the process of erythrocyte lysis, hemoglobin is released from the perivascular coagulum in the subarachnoid space and converted to oxyhemoglobin with an array of chemical reactions. It is established that this oxyhemoglobin has a strong vasoconstrictive ability on cerebral blood vessels. Through many reactions, although none has been confirmed as exact, oxyhemoglobin changes the synthesis of eicosanoids in the blood vessel wall, reduces the prostaglandin I-2 production and triggers prostaglandin E-2 release. It oxidizes spontaneously in methemoglobinwith superoxide release which triggers the lipid peroxidation with resultant vasoconstriction. In addition, they inhibit endothelium-dependent relaxation. Despite all these processes, it is considered that they are not able

to cause the level of VS present in SAH patients and additional factors interact in this process [3, 6, 7].

Another important factor for VS is inflammation [1, 6, 7]. With BBB damage, lymphocytes are transferred to the cerebrospinal fluid (CSF) and infiltrate the arterial walls. Activated monocytes in the CSF release ET-1 as a potent vasoconstrictor [5].

Inflammatory reaction in SAH triggers abundant proinflammatory factors secretion such as Interleukin-1, Interleuki-6, interleukin-6 and Tumor necrosis factor –alpha directly in the injured brain tissue. These changes in the cytochrome concentration act on the velocity of blood flow [3, 6, 7].

Another key factor of endothelialorigin is NO, which in normal circumstances has a vasodilatory activity [5, 6, 8].

Its mechanism of action is by elevating the cGMP levels in smooth muscle cellscausing vasodilation and it potentiates the blood flow. In SAH, there is a drop in NO levels with biphasic distribution, 30 minutes and 7 days after the initial ictus. It is considered that this phasic activity is primary a result of its binding to oxyhemoglobin and action on the inflammatory cytokines. On the 7-th day of the initial bleedthere is a reduction of NO-synthase levels or its inhibition by Protein-kinase C from the inflammatory reaction [3, 6, 7, 9].

ET-1 also originates from endothelial cells, but has a strong vasoconstrictive activity [5, 6]. This activity is expressed with binding to ETA receptors on the smooth muscle cells of the vessels, whose stimulation leads to intracellular Ca elevation. Elevated levels of ET-1 in SAH patients are also a result of an inflammatory process and are stimulated by oxyhemoglobin. These elevated levels are in circulation with developing symptoms as a sign of DCI (symptomaticVS) [3, 6, 7].

Intracellular Calcium levels have the most important role in contractile activity of the smooth muscles. In cerebral VS, Ca-dependent and Ca-independent vasoconstriction occurs. Blood degradation products in SAH stimulate the protein receptors like G-protein receptor and Tyrosine-kinase receptor. In Ca-dependent vasoconstriction, elevation of intracellular Ca is induced by Tyrosine-kinase on the smooth muscle cells. Consequently, due to this intracellular Ca concentration elevation, pathologic vasoconstriction develops [6].

Treatment

Methods for VS treatment are diverse, including conservative treatment with pharmacologic maintenance of hemodynamic stability, EVT and combination of both mentioned [1, 5, 10]. Maintenance and control of blood pressure levels before, during and after EVT is very important step in prevention of VS and the risk of rebleeding. Before EVT, lower BP values are allowed, but high enough to support adequate perfusion pressure. After the treatment BP should be maintained in higher levels 150-175mmHg with monitoring of the signs of adequate perfusion [5, 10].

Simultaneous volume load and hydration should be maintained. According to many treatment protocols, 3H therapy (hypertension, hypervolemia, hemodilution) should be applied immediately after the admission with oral drug application with vasodilatory effect of the vessels only if the patients` condition is adequate. Lately, hypervolemia has been replaced with euvolemia to avoid the side effects of volume overload, but cerebral perfusion should always be achieved [3, 5, 10]. If the patient is unable to cooperate, then intravenous therapy is introduced.

In recent studies, Ca-channel blockers are medications that achieved their use in the treatment of spontaneous aSAH and show effectiveness in VS treatment [6].

Oral drug administration in the initial period is widely used, but intravenous and intraarteriolar routes are as effective as oral Nimodipine [3, 5, 7, 8, 11].

Nimodipine is a second generation dihydropyridine Ca-channel blocker and acts by blocking the L-type Ca-channels on the surface of the smooth muscle cells in the vessel wall, and by blocking the intracellular Ca-ion flux in higher concentration in SAH patients, it inhibits vasoconstriction. Its action is significant on cerebral vasculature because of itslipophilic characteristics and facilitated BBB transport [3, 5, 10, 11, 12].

The aim of this study was to confirm whether intravenous administration of Nimodipine in SAH patients, without radiologic verification of VS is effective as a treatment tool and the degree of its vasodilatory ability during EVT.

Materials and Methods

The study included 20 patients hospitalized in the UC for Neurosurgery with aSAH aged over 31. They were divided into 2 groups. The first group consisted of patients with intravenous Nimodipine infusion immediately after admission and the second group received only their own prescribed oral antihypertensive therapy. All patients were with GCS>8, and H and H grade 1-3. Ruptured aneurism was verified with CT angiography (CTA)in all patients on admission. Detailed anamnesis was taken with information about previous hypertension with or without treatment and information about other comorbidities and therapy, with the aim of continuing the active treatmentof these conditions and avoiding worsening of the newly developed condition or false image of neurological deterioration. In both groups 6 patients were female and 4 were male. In the Nimodipine group, 5 patients had untreated hypertension, 4 had treated and 1 did not have hypertension. In the untreated group, all 10 patients had their own antihypertensive therapy.

After hospitalization, all patients continued with their own therapy and in half of them intravenous nimodipine and Magnesium Sulfate (MgSO4) were applied.In those patients with signs of symptomatic VS, immediate Nimodipine was applied in dose of 1ml/h for the first 2h and if the parameters allowed the dose was elevated and titrated for 1 extra ml/h every second hour until adequate cardiocirculatory and neurologic parameters were achieved.

If no hypertension was present before bleeding, Nimodipine was started with 0,5ml/h with gradual elevation of the dose until adequate effect was achieved. In neurologicallystable patients, the treatment was controlled by the ordinal surgeon. Exclusion criteria from this study were age <18, presence of additional hemorrhage except SAH, poor neurologic state and need for Mechanical ventilation.

On the 3-6th day (4th), of admission, EVT was performed at Radiology Institute with the aim of securing the ruptured artery. The diameter of the artery was measured before the treatmentand was compared to the diameter of the same vessel on CTA. The difference in the diameters indicated the effectiveness of Ca-channel blocking agent and its justified use as a systemic dilating agentin asymptomatic patients.

Results

This study included a total of 20 patientswith ruptured aneurism on EVT, 10 patients with continuous iv. Nimodipine infusion pre intervention for VS treatment, the other 10 patients received only their usual antihypertensive therapy. Comparing the results of the imaging techniques on admission and at the beginning of the EVT it was seen that VS in treated group with Ca-channel blocker and Mg sulfate improved, in 8 patients there was a complete VS relief and in 2 patients there was a persistent VS respectively. In the untreated group, 1 patient had already developed infarction, 1 patient did not develop VS at all, 6 patients had remarkable VS and in 2 patients there was a spontaneous VS relief. EVT as conducted on 3-6th day of the initial ictus in all patients.

Table 1. Patients treated with continuous IV Nimodipine infusion. There is relaxation of vasospasm in 8 of 10 patients.

No	Gender	Age	Comorbidities	HTA Th	Artery	Vasospasm	Dimension Before/mm	Dimensions After/mm
1.	F	63	HTA, CAD,CMPchr	+	ACI	+	A2-0,4 M1-1,4	A2-1 M1-2
2.	F	61	HTA,ADSY	+	Acom	+	A2-0,5	A2-2
3.	M	39	HTA,DM	+	Pcom	+	ICA-2	ICA-4
4.	F	48	HTA	-	MCA	+	M2-0,8	M2-1,3
5.	F	51	HTA	-	Acom	+	**A2-0,9**	**A2-0,9**
6.	M	65	HTA	-	Pcom	+	A1-0,5 A2-0,7	A1-2 A2-2,2
7.	M	48	HTA	+	Acom	+	**A1-0,9**	**A1-0,9**
8.	F	69	HTA	+	Pcom	+	M1-1,2	M1-2,5

9.	F	60	HTA	-	Pcom	+	ICA-2	ICA-4
10.	M	55	///	/	Acom	+	A1-0,4 A2-2	A1-2 A2-2,2

Table 2. Patients not treated with IV infusion, but their own antihypertensive therapy. There is spontaneous relaxation in 2 patients, there is no spasm in 2 patients, there is infarction in 1 patient and there is persistent vasospasm in the rest of the patients.

No	**Gender**	**Age**	**Comorbidities**	**HTA**	**Artery**	**Vasospasm**	**Dimensions Before/мм**	**Dimensions After/мм**
1.	M	55	HTA,CVI	+	Acom	+	Infarct	
2.	F	42	HTA	-	Pcom	+	ICA-2	ICA-2
3.	F	59	HTA	-	Pcom	+	ICA-1,7 A2-0,5	ICA-1,7 A2-0,5
4.	F	60	HTA,DVT	+	Acom	-	No spasm	
5.	F	49	HTA	+	Pericalosa	+	A2-0,5	A2-0,5
6.	F	44	HTA	+	Acom	-	**A2-0,5**	**A2-1**
7.	F	63	HTA,RA,EPI Hiperthyreosis	+	MCA	-	**M1-1**	**M1-3,2**
8.	M	50	HTA	+	ACI	+	M1-1	M1-1
9.	M	31	HTA	+	Acom	-	No spasm	
10.	M	64	HTA	+	Pcom	-	ICA-2,4	Partial spasm

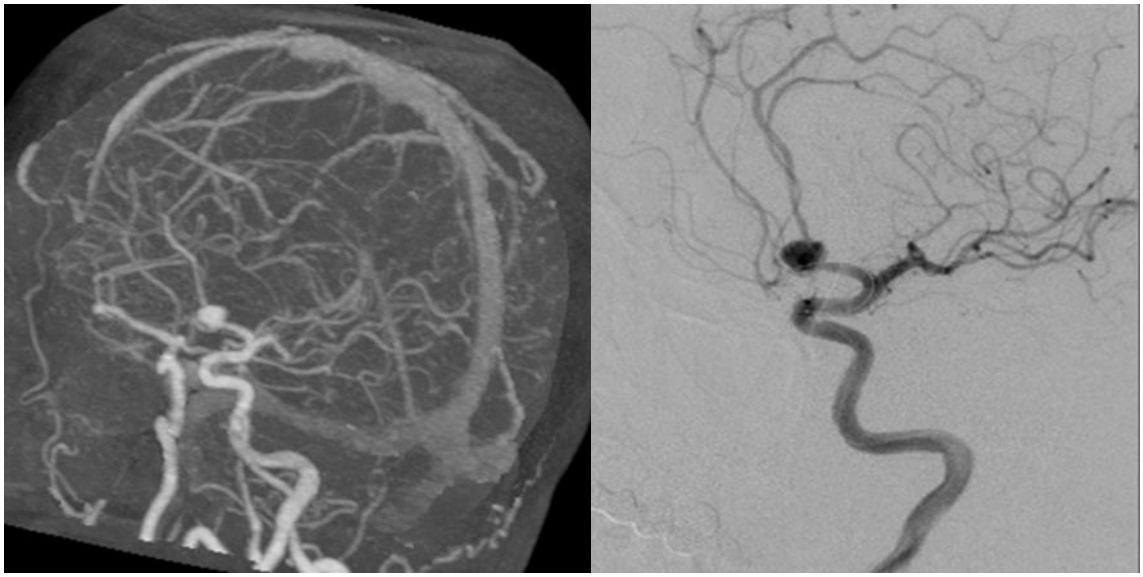

Figure 1. Initial CTA and DSA of right A2 before EVT, 51-year old patient with ruptured aneurism of right anterior communicant artery, treated with IV Nimodipine from admission, there is no relaxation of vasospasm

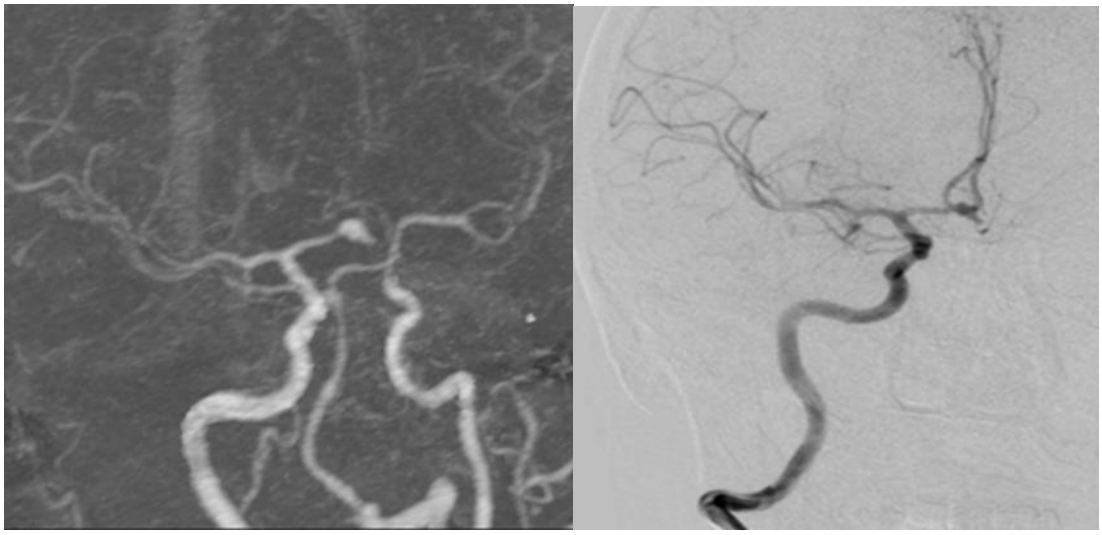

Figure 2. Initial CTA of bilateral A2 and DSA of left A2 before EVT, 61-year old patient with ruptured aneurism of anterior communicant artery, bilateral angiospasm, treated with IV Nimodipine on admission, there is relaxation of VS

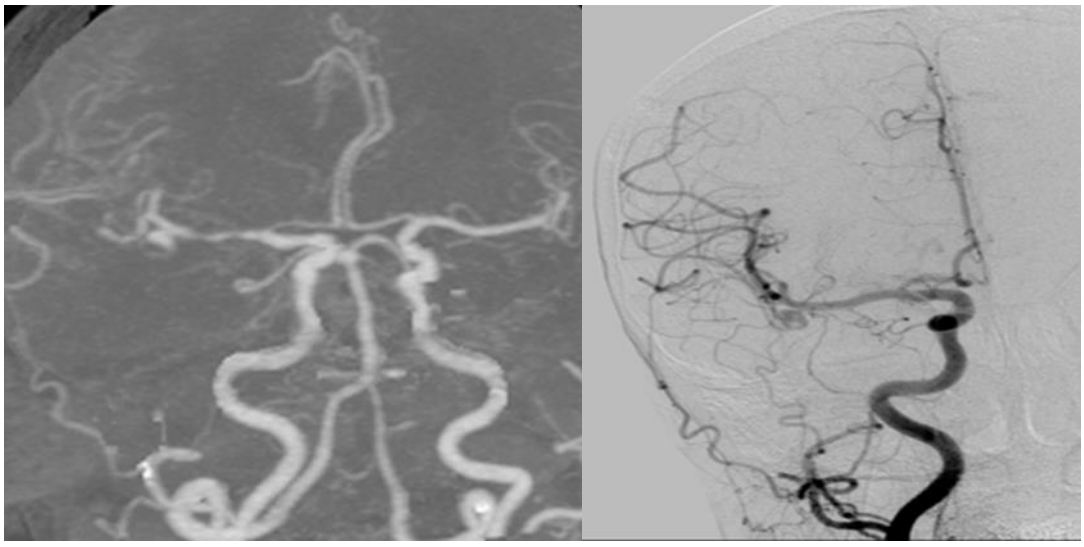

Figure 3. Initial CTA and /DSA of M! and distal M2 before EVT, 63-year old patient with ruptured aneurism of medial cerebral artery, VS on M1 and M2 segments, not treated with IV Nimodipine, there is spontaneous VS relaxation

Discussion

Cerebral VS is one of the leading causes of neurological deterioration in patients with aneurismal SAH [6].

Consequently, VS determines high morbidity and mortality rate in these patients. Although symptomatic VS implies to worse outcome, it may have a protective role as an indicator for early therapy for prompt VS treatment. If angiographic VS is present, but not detected in a timely manner, it can also be a bad prognostic sign. The incidence of aSAH in general population is 9 in 100000 people, predominantly in female gender in their fifth decade of life.

This timeframehas somehow changed in the last years, with SAH becoming a common state in younger people in their third and fourth decade. According to many studies, SAH still has a high morbidity rate, with almost 80% of all SAH patients having negative outcome. For that reason, early detection and treatment of VS is emphasized as the main approach in patients with aneurism rupture.

Elevated ICP and consequent global cerebral ischemia which develop after aneurism rupture, initiate a cascade of pathological processes such as inflammation, cortical depression, capillary thrombosis, BBB dysfunction, cerebral edema and neuronal apoptosis with resultant primary brain injury [1, 2, 3, 6, 7].

The degree and duration of VS are responsible for the progression of the ischemic brain injury and they depend on complex interaction between a periarterial hematoma and the surrounding brain tissue. Other factors that contribute to VS persistence are the degree of SAH expression, additional brain injury such as epidural, subdural, intracerebral or intraventricular hematoma and hydrocephalus, rebleeding, persistent hypertension, diabetes, cigarette smoking etc [1, 7, 10].

As intracellular Ca-ions are responsible for the contractile activity of the smooth muscle cells and consequently lead to persistent VS, blocking of their entry in these cells may be the adequate pathway for brain protection from additional injury [1, 11].

Ca-channel blocker have the major role in the treatment of cerebral VS. These medications have the potential to prevent Ca-dependent VS development through reduced release of ca-ions and therefore inhibit contraction of the smooth muscle cells in the vessel wall. The most valuable among all Ca-channel blockers is Nimodipine with its oral, intravenous and intra-arterial application [7, 11, 12, 13].

The proof of its effect with oral application is based on four randomized placebo-control trials in 853 patients who presented with functional improvement. However, these trials cannot confirm whetherthe improvement is a result of spasm relief or just neuroprotective effect of Nimodipine [5, 8]. Until today, Nimodipine is the only medication with Class 1 data for its action in reduction of the DCI incidence to 40% without changes in VS [3, 7, 10, 11, 12].

A very rare side effect of Nimodipine is hypotension. It is considered that oral and intravenous Nimodipine application in regulating the blood pressure has identical effect, although hypotension is commonly seen with its iv application [5, 8, 11, 12, 14, 15].

Mg-ions also act as a blockers of voltage - gated Ca-channels, as competitive antagonists of Ca-ions for binding site on the Ca-receptor [6, 7].

According to some studies, hypomagnesaemia was detected in 38% of SAH patients and is a predictor of DCI [5].

According to MASH (Magnesium aneurism subarachnoid hemorrhage) randomized, double-blind, placebo-control trialof 283 patients, Mg use lowered the incidence of DCI and bettered patients' outcomein a three-month period, but with no statistical difference from the placebo group [5].

Although, neither of these studies confirm vasodilatory effect of Mg-ions, its neuroprotective ability is obvious, especially in combination with other drugs [3, 10, 14, 15].

The results from this study of iv Nimodipine application immediately after the initial bleed, in the period of developing factors which result in VS, showed that this method of medication application has positive effect on cerebral VS, which confirms the difference in measurements of the vessel diameter before and after its application. By monitoring the patients' outcome, it is noticeable that in treated group there is no neurological deterioration and cerebral infarction. Because of the simultaneous use of Nimodipine and MgSO4 in protective doses, there is a possibility that the additive effect of both medications is responsible for the better outcome in thetreated group.

Conclusion

One of the main factors that lead to successful treatment of cerebral VSis understanding the degree of early brain injury that evolves immediately after SAH occurrence. Many studies relate VS development with consecutive neurological dysfunction. Inflammatory process that leads to CVS was the most probable mechanism whose progression leads to DCI. Therefore, inflammatory process treatment may prevent CVS development. Although CVS is one of the most important factors that lead to DCI, it is not a single factor for neurological deterioration.

The results of this study showed that continuous iv Nimodipine infusion in combination with MgSO4 in pretreatment period is an effective tool in treating CVS and DCI prevention. Although it is still not confirmed whether this effect is a result of their combined activity, their vasodilatory or

neuroprotective activity, their positive effect is proved. Additional studies are required to confirm this fact.

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