Intra-Arterial Nimodipine Infusion for Cerebral Vasospasm in Patients with Aneurysmal Subarachnoid Hemorrhage

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Summary

This study evaluated the efficacy of intra-arterial nimodipine infusion for symptomatic vasospasm in patients with aneurysmal subarachnoid hemorrhage (aSAH). Clinical data collected from 42 consecutive patients with symptomatic vasospasm after aSAH were retrospectively reviewed. Forty-two patients underwent 101 sessions of intra-arterial nimodipine infusion. Angiographic response, immediate clinical response, and clinical outcome were evaluated at discharge and six months later.

Angiographic improvement was achieved in 82.2% of patients. The immediate clinical improvement rate was 68.3%, while the deterioration rate was 5.0%. A favorable clinical outcome was achieved in 76.2% at discharge and 84.6% six months. Vasospasm-related infarction occurred in 21.4%. There was no drug-related complication. The nimodipine group showed satisfactory outcomes. Nimodipine can be recommended as an effective and safe intra-arterial agent for the treatment of symptomatic vasospasm after aSAH.

Introduction

Symptomatic vasospasm is a major cause of disability and death after aneurysmal subarachnoid hemorrhage (aSAH). It occurs in about 30% of patients between the fourth and fourteenth day after initial bleeding and may last up to the fourth week [1]. Preventive therapies include oral medication of nimodipine [2], lumbar drainage of bloody cerebrospinal fluid [3], cisternal toilet [4] and intra-venous infusion of magnesium sulfate [5], while therapeutic measures against symptomatic vasospasm comprise 'triple-H therapy' (hypertension, hypervolemia, and hemodilution) as well as endovascular treatments such as balloon angioplasty and intra-arterial drug infusion [6-26]. Moreover, new drugs are under investigation [27-29].

Balloon angioplasty was introduced in the early 1980s. It is effective in vasospasm of the proximal and large vessels, and its effect is known to be more sustainable than that of intra-arterial drug infusion. However, it has a limitation to reach the small and distal vessels, and it requires expert neurointerventionists due to the high risk of arterial dissection, rupture and occlusion [9,30,31]. Papaverine has been widely used as an intra-arterial drug for vasospasm therapy since 1992 [15,16]. It is effective in relieving vasospasm of the small and distal vessels as well as large and proximal ones, and the procedure is easier than that of balloon angioplasty. In addition, clinical results have been favorable [8-10,12,19,22,24,26]. However, the effect is frequently transient and some problems have been identified, including the discrepancy between angiographic response and clinical outcome. Neurological complications after papaverine infusion have also been reported, such as an increase in intracranial pressure (ICP), monocular blindness and brainstem depression

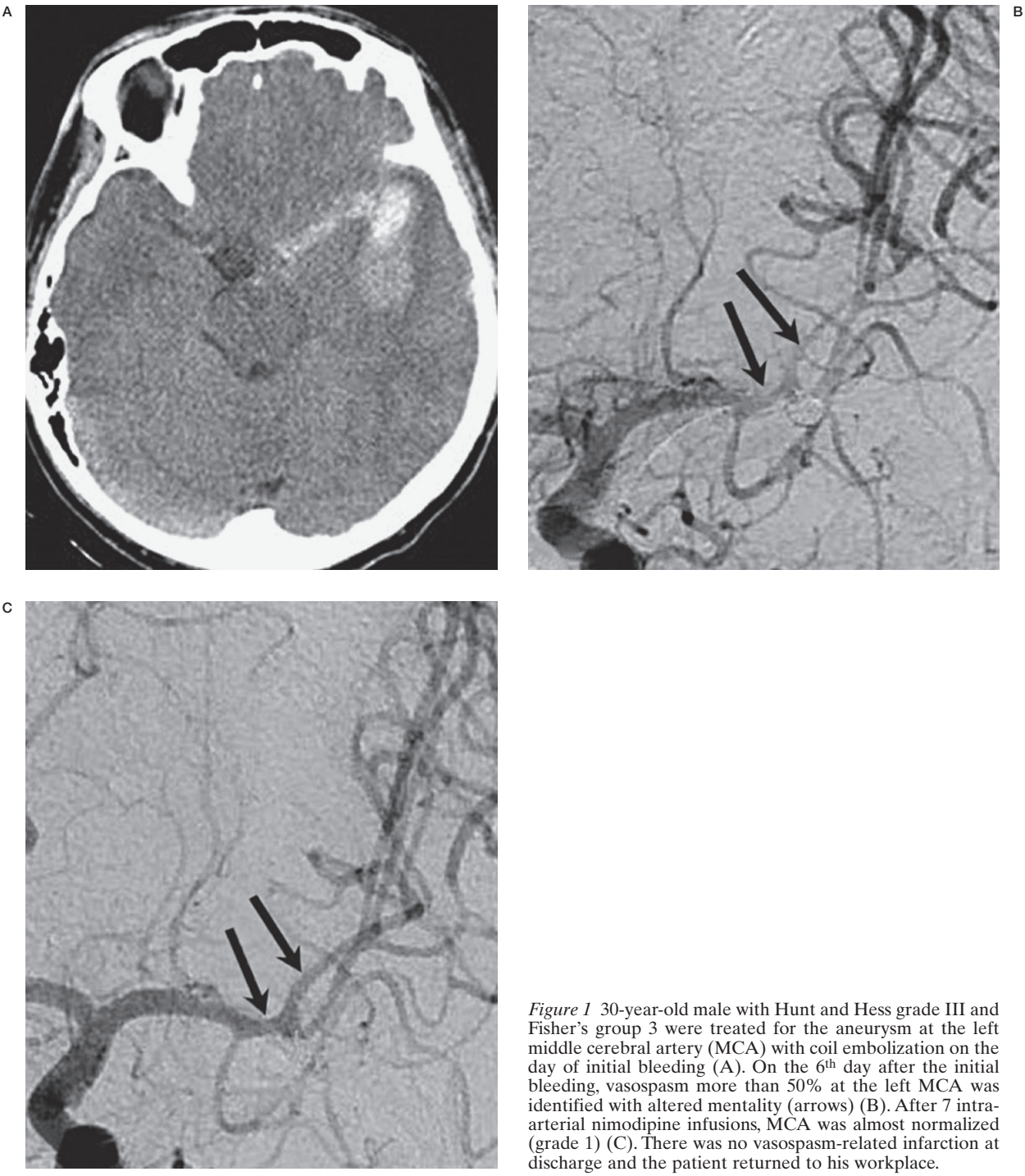

Figure 1 30-year-old male with Hunt and Hess grade III and Fisher's group 3 were treated for the aneurysm at the left middle cerebral artery (MCA) with coil embolization on the day of initial bleeding (A). On the 6th day after the initial bleeding, vasospasm more than 50% at the left MCA was identified with altered mentality (arrows) (B). After 7 intra-arterial nimodipine infusions, MCA was almost normalized (grade 1) (C). There was no vasospasm-related infarction at discharge and the patient returned to his workplace.

[8,12,16,19,22,24,30,31]. On the contrary, results of the recent preliminary studies with calcium channel blockers such as nimodipine, nicardipine and verapamil have been favorable, and the complication rates were low [7,12-14,17, 18].

At our institute, papaverine had been used until 2005. After experiencing some complications related to papaverine infusion, we substituted nimodipine for papaverine as an agent for intra-arterial delivery.

The purpose of this study was to evaluate the efficacy of intra-arterial nimodipine for the treatment of symptomatic vasospasm after aSAH.

Materials and Methods

Patient Population

A total of 451 patients were treated for ruptured intracranial aneurysms at our institute during the past three years between January 2006 and December 2008. Under the approval by the Institutional Review Board, we retrospectively reviewed medical records and imaging data of 42 patients (9.3%), who received intra-arterial nimodipine infusion for symptomatic cerebral vasospasm.

Management of Patients with Ruptured Intracranial Aneurysms

When a ruptured aneurysm was identified in a patient, immediate surgical or endovascular treatment was performed within hours after admission. Open surgery was performed in 14 patients (12 clipping and two clipping plus bypass), and endovascular treatment was performed in 28 patients (26 coil embolization and two trapping of parent vessels). Ventricular drainage was performed as necessary in 20 patients with poor clinical grades for the control of ICP and removal of intraventricular blood. Lumbar drainage was initiated in eight patients with acute symptomatic and unobstructed hydrocephalus. Cisternal lavage of hematoma was not routinely done during surgery. All the patients received intravenous infusion of nimodipine (2 mg/h) followed by the oral medication (60 mg every 4 h) for 21 days, with maintenance of normovolemic status.

Medication for seizure prevention was indicated in patients with cerebral parenchymal injury. Medical conditions (serum electrolyte, glucose, renal function, and cardiopulmonary function) as well as nutritional status were regularly checked and corrected if abnormal findings were noted.

Management of Symptomatic Vasospasm

We performed daily checks on flow velocity using transcranial Doppler (TCD). When the flow velocity tended to increase, we started 'triple-H therapy'. Cerebral angiography was performed in patients with symptomatic vasospasm accompanied by a significant increase in flow velocity on TCD as well as clinical symptoms/signs refractory to medical treatment without other causes (rebleeding, hydrocephalus, seizure, brain swelling, electrolyte imbalance, and other medical problems).

Vasospasm was suspected when TCD values were mean flow velocity of ≥120 cm/s and peak flow velocity of ≥190 cm/s, or the flow velocities increased more than 50 cm/s above the initial value [32].

Once symptomatic vasospasm was identified, intra-arterial drug infusion was performed immediately. Sometimes the procedures were repeated in cases of recurrent symptomatic vasospasm until clinical symptoms and signs did not deteriorate.

Nimodipine was diluted with normal saline (1: 3 dilution). After a microcatheter was placed proximal to the affected vessel, nimodipine was infused from 3 to 6 mg at a rate of 6 mg/h per vessel. When transient hypotension occurred during procedure, infusion was stopped temporarily until blood pressure became normalized.

Imaging Analysis

To evaluate the angiographic response to intra-arterial nimodipine infusion, diameters of the narrowest segment of affected vessels were measured on the pre and post-treatment angiogram. The degree of vasospasm at each period was rated as *mild* when narrowing was 0% to 24%, *moderate* when 25% to 49% and severe when 50% or more, with the diameter on initial angiography as a reference.

The reference diameter was obtained from the follow-up angiography when a patient showed angiographic vasospasm on the ictus day. Angiographic response was determined as *poor* when the degree was unchanged and *good* when improved, comparing the pre- and post-treatment angiograms (Figure 1).

In cases with multiple affected vessels, the result was considered *good* when there was at least one good response and *poor* when there were all poor responses. All these assessments were made blindly.

Vasospasm-related cerebral infarction was evaluated with the follow-up computed tomographic scan and/or magnetic resonance imaging (MRI) at least two weeks after completion of vasospasm therapy. Pre-existing infarction before aSAH, and infarction related to clipping or embolization were excluded. If the infarction gave rise to significant neurological deficits, it was considered *major* infarction. If it had trivial or non checkable deficit, it was considered *minor* infarction.

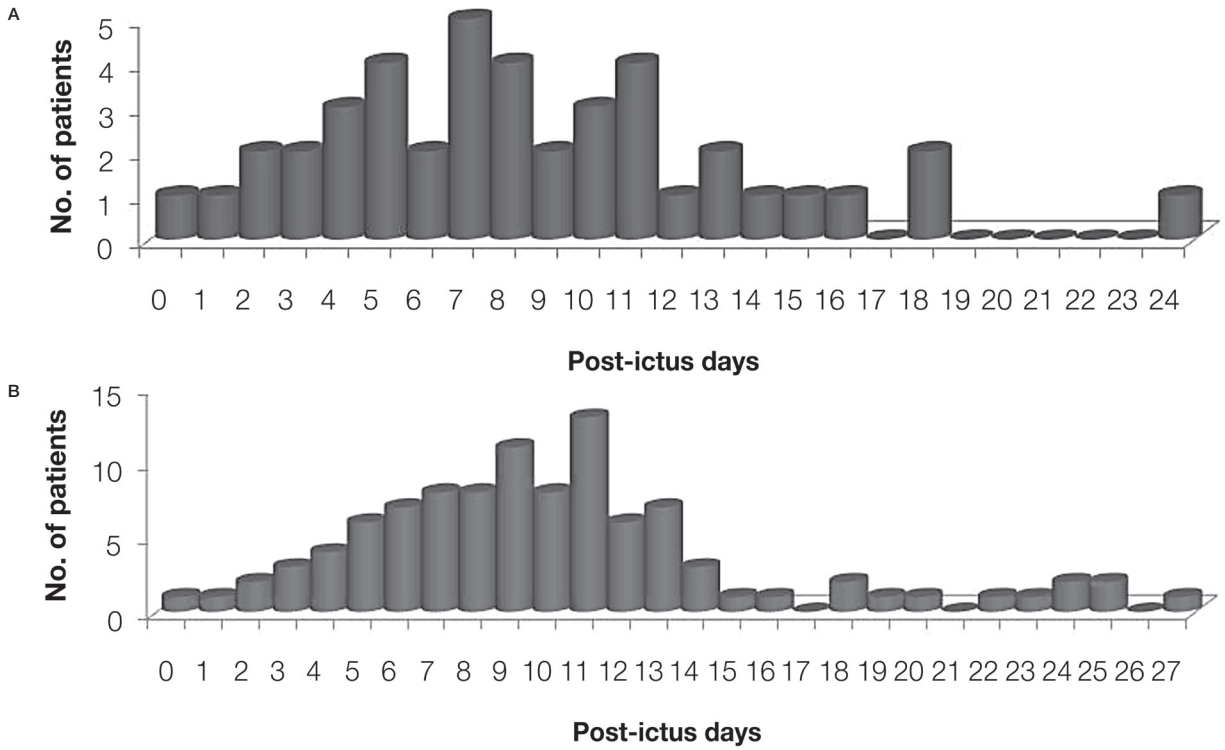

Figure 2 Distribution of the interval between bleeding and intra-arterial nimodipine infusion for the symptomatic vasospasm in patients with aneurysmal subarachnoid hemorrhage. Mean interval between initial bleeding and initial treatment for the symptomatic vasospasm was 8.5±5.0 days (range, 0-24 d) (A). Mean interval between initial bleeding and total vasospasm therapy (including repeated procedures) was 10.1±5.4 days (range, 0-27 d) (B).

Table 1 **Clinical information of the patients with aneurysmal subarachnoid hemorrhage.**

No. of patients	42
Sex (M : F)	20:22
Age, mean ± SD (years)	45.9 ± 13.2
HH grade, no. (%)	
I	3 (7.2)
II	24 (57.1)
III	10 (23.8)
IV	4 (9.5)
V	1 (2.4)
F group, no. (%)	
1	0 (0)
2	7 (16.7)
3	32 (76.2)
4	3 (7.1)
Location of aneurysm, no. (%)	
Internal carotid artery	12 (28.6)
Anterior cerebral artery	12 (28.6)
Middle cerebral artery	16 (38.1)
Posterior circulation	2 (4.7)
Treatment for aneurysm, no. (%)	
Clipping	14 (33.3)
Coil embolization	28 (66.7)

F group: Fisher's group [35], HH grade: Hunt and Hess grade [34], SD: standard deviation.

Clinical Evaluation

Short-term clinical response was defined as a change in clinical symptoms within 24 hours after intra-arterial drug infusion, and it was graded as *improved, unchanged* or *deteriorated*. Clinical outcome was assessed at discharge and six months later, using the modified Glasgow Outcome Scale (GOS) score (GOS score of 5, good recovery; 4, moderate disability; 3, severe disability; 2, vegetative state; 1, death) [33]. The clinical outcome was categorized into a favorable (GOS scores of 4) and 5) and unfavorable outcome (GOS scores of 1 to 3). Procedure and drug-related complications were evaluated. When abrupt changes in neurological signs and symptoms occurred during drug infusion or they recovered after stopping the drug, this was designated drug-related complications. Transient change in blood pressure was not included. Mortality was defined as a patient having passed away within one month after the initial bleeding.

Results

Baseline Characteristics

Clinical information of the patients with aSAH is presented in Table 1. The male to female ratio was nearly 1:1 (20:22), and the mean age was 45.9±13.2 years old (range, 14-72).

Table 2 **Treatment outcome of symptomatic vasospasm.**

Interval between bleeding and initial IA drug infusion, mean days ± SD (range)	8.5 ± 5.0 (0-24)
Location of vasospasm, no. of sessions (%)	
Bilateral	28 (28.0)
ACA alone	8 (7.9)
MCA alone	23 (22.8)
ACA + MCA	53 (52.5)
ICA + ACA + MCA	14 (13.9)
Others*	2 (2.0)
Vasospasm-related symptoms, no. of sessions (%)	
Altered mentality	33 (32.7)
Neurological deficits	31 (30.7)
Both	37 (36.6)
Sessions per patient (mean ± SD)	101/42 (2.4 ± 1.9)
Angiographic response, no. of sessions (%)	
Good	83 (82.2)
Poor	18 (17.8)
Short-term clinical response, no. of sessions (%)	
Improved	69 (68.3)
Unchanged	27 (26.7)
Deteriorated	5 (5.0)
Favorable GOS (4 and 5), no. of patients (%)	
At discharge	32 (76.2)
At 6 months after discharge	33 (84.6)
Mortality, no. of patients (%)	1 (2.4)
Vasospasm-related infarction, no. of patients (%)	9 (21.4)
Major infarction	4 (9.5)
Minor infarction	5 (11.9)
Complications, no. of sessions (%)	3 (3.0)
Procedure-related	3 (3.0)
Drug-related	0 (0)

ACA: anterior cerebral artery, GOS: Glasgow outcome scale score [33], IA: intra-arterial, ICA: internal carotid artery, MCA: middle cerebral artery, ns: not significant, SD: standard deviation.

* One was at the ICA and the other was at ICA + MCA.

Table 3 **Literature review.**

Study [ref. no.]	Drug	No. of patients	Dose (mg)	Radiological improvement (%)	Short-term clinical improvement (%)	Final favorable clinical outcome (%)	Complications (%)	Infarction (%)	Mortality (%)
Clouston et al. (1995) [8]	PPV	14	150-600	95	50	50	21.4	na	7.1
Elliott et al. (1998) [9]	PPV	13	300	100	69	62	0	na	0
Fandino et al. (1998) [10]	PPV	10	300-360	100	100	70	Na	na	na
Firlik et al. (1999) [12]	PPV	15	300-600	78	26	Na	20	na	na
Kaku et al. (1992) [15]	PPV	10	6-20	92	80	80	0	na	0
Kassell et al. (1992) [16]	PPV	12	60-300	66.7	33.3	Na	16.7	na	0
Liu et al. (2004) [19]	PPV	17	60-165	36	71	59	23.5	11.8	17.6
McAuliffe et al. (1995) [22]	PPV	21	300-500	76	52	Na	14.3	na	9.5
Sawada et al. (1997) [24]	PPV	14	na	47	21	Na	64.3	na	na
Vajkoczy et al. (2001) [26]	PPV	8	300	51	0	0	Na	80	50
Biondi et al. (2004) [7]	NMP	25	1-5	43	76	72	0	na	8
Hänggi et al. (2008) [13]	NMP	26	0.8-3.2	69.2	18.2	61.1	23.1	61.1	5.6
Hui and Lau (2005) [14]	NMP	9	mean 3.3	66.6	89	77.8	11.1	na	0
Kim et al. (2009) [18]	NMP	19	3-5	79.3	68.4	79.0	Na	na	0
Badjatia et al. (2004) [6]	NCP	18	2.5-5	100	42.1	Na	33.3	na	na
Tejada et al. (2007) [25]	NCP	11	10-40	100	91	90	36.4	30	9.1
Nogueira et al. (2009) [23]	NCP	6	2-10	41±43	na	Na	Na	na	na
Feng et al. (2002) [11]	VPM	29	3.1±0.3	44±9	29.4	Na	0	na	na
Keuskamp et al. (2008) [17]	VPM	10	41±29	83.3	66.7	Na	0	na	na
Mazumdar et al. (2006) [21]	VPM	15	2.5-10	0	na	Na	Na	na	na
Current study	NMP	42	3.3 ± 1.0	82.2	68.3	84.6	3.0	21.4	2.4

Na: not available, NCP: nicardipine, NMP: nimodipine, PPV: papaverine, VPM: verapamil.

Hunt and Hess (HH) grades [34] II and III were the most common (81.0%), and Fisher's (F) group [35] 3 was the most common (76.2%). Most (92.9%) ruptured intracranial aneurysms were distributed in the anterior circulation system. Coil embolization was performed twice more than surgical clipping (28 versus 14).

Basal information of intra-arterial nimodipine infusion for the symptomatic vasospasm is shown in Table 2.

The mean interval between initial bleeding and intra-arterial nimodipine infusion for the symptomatic vasospasm was 8.5±5.0 days (range, 0-24) (Figure 2A). Four patients showed symptomatic vasospasm within 3 days. Vasospasm therapy was frequently repeated (Figure 2B).

Overall, 101 sessions of vasospasm therapy were performed in 42 patients, and the mean session per patient was 2.4±1.9. In detail, the numbers of sessions were one in 21 patients (50%), two in six, three in six and four or more in nine.

Treatment Results

Short-term therapeutic response is summarized in Table 2. Angiographic response after intra-arterial nimodipine infusion was satisfactory in 82.2% of the sessions. With regard to the short-term clinical response, the improvement rate was 68.3% of the sessions.

Overall, 39 out of 42 patients (one patient died and two were lost) were followed up at six months. Favorable clinical outcome was achieved in 76.2% of 42 patients at discharge, and 84.6% of 39 patients at six months after discharge (Table 2).

The mortality rate was 2.4% (n=1), and the cause of death was brain swelling after the vasospasm-related infarction. Vasospasm-related infarction occurred in 21.4% of the patients and the rate of major infarction was 9.5% (Table 2).

The procedure-related complication rate was 3.0%. Complications included two asymptomatic thromboses in the middle cerebral artery (MCA) branches, one of which was resolved using intra-arterial tirofiban injection, and one transient catheter-related MCA spasm. On the other hand, there was no drug-related complication (Table 2).

Transient decrease in blood pressure below 90/60 mmHg during the drug infusion occurred during 14 sessions in nine patients (14%).

Discussion

Short-Term Radiological and Clinical Responses

Papaverine was a prototype drug for intra-arterial infusion in cerebral vasospasm. In the literature, radiological and clinical responses after papaverine infusion ranged from 43% to 100% and 0% to 100%, respectively (Table 3) [8-10,12,19,22,24,26]. However, the effect of intra-arterial papaverine infusion was measured with different methods in each study, and clinical response was generally worse than radiological one. In a review article, cerebral blood flow was improved in 60% of patients after papaverine infusion, while clinical improvement was achieved in only 43% [30]. Recently, the results in preliminary studies with nimodipine have been reported (Table 3) [7,13,14,18]. In the current study, short-term angiographic and clinical responses were satisfactory (82.2% and 68.3%, respectively), and clinical deterioration rate was low (5%). There was no discrepancy between clinical and angiographic responses. Clinical improvement was compatible with or sometimes better than angiographic one. Therefore, we consider the intra-arterial nimodipine therapy as an effective treatment modality for cerebral vasospasm.

Clinical Outcome

Clinical outcome in the current study was satisfactory in about 80% of the patients. Studies with papaverine have reported that favorable clinical outcome was variably achieved in 0% to 80%, and those with nimodipine showed favorable outcome in 61% to 79% (Table 3). Papaverine studies reported mortality rates ranging from 0% to 17.6%, and nimodipine studies from 0% to 5.6%. In the current study, mortality was 2.4%, the cause of which was related to vasospasm. In our opinion, nimodipine seemed to show comparable clinical outcome and lower mortality rate. Clinical outcome has seldom been the focus of previous studies on vasospasm therapy because vasospasm is one of the factors influencing clinical outcome and it is difficult to identify and compare each factor. A series of factors may influence clinical outcome, such as patient factors (severity of initial hemorrhage, age, sex, medical conditions), aneurysm factors (size, location, morphology), and institutional factors (availability of endovascular treatment, patient volume,

type of facility) [36]. Therefore, it would be appropriate to understand that the clinical outcome is related to intra-arterial drug infusion to a degree.

Vasospasm-Related Infarction

The incidence of infarction in patients with aSAH is not widely known in spite of its clinical impact (Table 3). According to Heros et al. [37], one fourth of patients with aSAH demonstrated symptomatic vasospasm, and half of those patients later died of infarction. In a papaverine study, eight out of ten vascular territories in eight patients succumbed to infarction [26]. In another study [19], 12% (2/17) of patients died of cerebral infarction after receiving papaverine infusion. In the current study, vasospasm-related infarction was identified in 21.4% (major infarction in 9.5% and minor infarction in 11.9%). In a nicardipine study, 30% of patients experienced infarction [25]. On the basis of the previous reports and the current study, nimodipine seemed to be at least as effective as papaverine in the prevention of vasospasm-related infarction.

Complications Related to Intra-Arterial Drug Infusion

The estimated complication rate of intra-arterial papaverine infusion has been reported to be about 10% [30,31]. Complications included increase in ICP, mydriasis, monocular blindness, brainstem depression, seizure, thrombocytopenia, precipitation of crystal and paradoxical vasospasm (Table 3). At our institute, the papaverine-related complication rate was 19.3% of the patients and most of them resulted from the increase in ICP (unpublished data). In contrast, we observed no nimodipine-related complications except transient hypotension. Transient decrease in blood pressure normally recovered within a few minutes.

No neurological complications have been reported from the use of nimodipine in the literature [7,13,14]. In other studies with verapamil and nicardipine, complication rates ranged from 0% to 36.4%, and most of them were procedure-related complications and transient hypotension [6,11,17,21,23,25]. A nicardipine study reported transiently increased ICP [6]. Thus, calcium channel blocker including nimodipine seemed to be superior in terms of complications.

Differences in the Drug Pathomechanisms

As shown in Table 3, the papaverine studies show a discrepancy between the angiographic and clinical response, and a higher complication rate than nimodipine and other kinds of calcium channel blockers. One of the causes might be the direct neurotoxic effect of papaverine.

One study demonstrated high signal intensity on diffusion-weighted and fluid-attenuated inversion recovery MRI at the gray matter within the vascular territories treated with papaverine, and concordant neuronal injury upon pathological examination [38]. In animal studies, opening of the blood brain barrier and endothelial cell injury after papaverine infusion were reported [39,40].

On the contrary, nimodipine is known to have neuroprotective properties as well as a vasodilating effect, including inhibition of free radical, reduction of cellular damage induced by calcium influx at reperfusion and an increase in cerebral oxygen metabolism [41-43].

An alternative explanation could be that they exert a differential effect on regional microcirculation.

One study with papaverine demonstrated that it reduced cerebral blood flow in ischemic regions [44], while a study with nimodipine revealed that the magnitude and duration of vasodilatation of the penetrating arterioles were greater and longer than those of superficial pial arterioles after nimodipine infusion in rat brain [45].

The other explanations include the paradoxical vasospasm occurring after papaverine infusion [12,46], embolism caused by precipitation of papaverine [28], and anaphylactoid reaction by papaverine itself or preservatives.

Duration of the Effect of Intra-Arterial Drug Infusion

Recurrent vasospasm after intra-arterial drug infusion has long been a problem. Many drugs directly act on smooth muscle cells of the cerebral vasculature [46,47], and prompt vasodilatation after drug infusion is commonly observed. However, the effect sometimes does not last long enough to maintain normal cerebral perfusion and the exact duration is unknown. There are only some animal studies on the duration of action after papaverine [48-50] and nimodipine infusion [47,51], respectively.

In the current study, nimodipine tended to show short duration of action.

Twenty-one (50%) out of 42 patients underwent intra-arterial drug infusion more than once, with a mean session number of 2.4±1.9. Regarding the session numbers of drug infusion in the clinical studies, it was hard to find a difference.

Elliott et al. [9] and Liu et al. [19] demonstrated that repeated infusions of papaverine were performed in 54% and 68% within 24 hours, respectively.

Mean sessions per person in the papaverine study were 1.5 to 1.7 [9,12,30]. On the other hand, about 11% to 90% of patients received repeated infusion within various time interval (range, 1-8 days), and 1.1 to 2.8 sessions per person were performed in the nimodipine studies [7,13,14,18]. To overcome the short duration, there has been an attempt to infuse a nimodipine continuously via a catheter placed in the internal carotid artery or vertebral artery for several days [20]. However, the risk of thromboembolism can be a problem with this procedure. Therefore, further studies on the pharmacological characteristics of existing drugs and development of a new drug with high efficacy, long duration, and low complication are needed.

Study Limitations

This study collected data retrospectively and the number of patients was small. It was difficult to rule out the cumulative or exponential effect of oral/ intravenous and intra-arterial administration of nimodipine.

Conclusions

In the current study, nimodipine demonstrated favorable results in angiographic response and clinical outcome, and low complication rate. Intra-arterial nimodipine infusion is an effective and safe treatment for symptomatic vasospasm. In the future, development of new drugs for the prevention and treatment of cerebral vasospasm with greater efficacy and longer duration is anticipated.

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