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Clinical Article

Intraarterial Nimodipine Infusion to Treat Symptomatic Cerebral Vasospasm after Aneurysmal Subarachnoid Hemorrhage

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Objective : Cerebral vasospasm leading to cerebral ischemic infarction is a major cause of morbidity and mortality in the patients who suffer with aneurysmal subarachnoid hemorrhage. Despite adequate treatment, some patients deteriorate and they develop symptomatic vasospasm. The objective of the present study was to investigate the efficacy and clinical outcome of intraarterial nimodipine infusion on symptomatic vasospasm that is refractory to hemodynamic therapy.

Methods : We retrospectively reviewed the procedure reports, the clinical charts and the transcranial doppler, computed tomography and digital subtraction angiography results for the patients who underwent endovascular treatment for symptomatic cerebral vasospasm due to aneurysmal SAH. During the 36 months between Jan. 2005 and Dec. 2007, 19 patients were identified who had undergone a total of 53 procedures. We assessed the difference in the arterial vessel diameter, the blood flow velocity and the clinical outcome before and after these procedures.

Results : Vascular dilatation was observed in 42 of 53 procedures. The velocities of the affected vessels before and after procedures were available in 33 of 53 procedures. Twenty-nine procedures exhibited a mean decrease of 84.1 cm/s. We observed clinical improvement and an improved level of consciousness with an improved GCS score after 23 procedures.

Conclusion : Based on our results, the use of intraarterial nimodipine is effective and safe in selected cases of vasospasm following aneurysmal SAH. Prospective, randomized studies are needed to confirm these results.

KEY WORDS : Subarachnoid hemorrhage · Vasospasm · Intraarterial nimodipine infusion.

INTRODUCTION

Cerebral vasospasm is the most common cause of acute focal cerebral ischemia after an aneurysmal subarachnoid hemorrhage. Vasospasm is defined as the delayed, reversible narrowing of the cerebral vessels. This condition most commonly involves the proximal arteries that make up the circle of Willis, and it typically occurs 4 to 14 days after subarachnoid hemorrhage (SAH).

The incidence of nontraumatic SAH ranges from 7.8/100,000 to 21.4/100,000, while symptomatic vasospasm occurs in about one third of the patients who have SAH. Approximately one third of these SAH patients die from the vasospasm, and another one third are left disabled, and so vasospasm is a dreaded complication following SAH[13,14].

The clinical evidence suggests that calcium channel blockers inhibit the constriction of the vascular smooth muscle cells, and so this can reduce the incidence of delayed ischemic deficits. Therefore, the intravenous or oral application of nimodipine is currently recommended as the first-line medication to prevent vasospasm[15,21]. However, despite adequate treatment, some patients deteriorate and develop symptomatic vasospasm. In these cases, hypertension, hypervolemia and hemodilution (triple-H) therapy is generally used.

For symptomatic vasospasm that is refractory to hemodynamic therapy, endovascular strategies such as balloon angioplasty and intraarterial spasmolysis with papaverine or nimodipine have been recommended.

More recently, major clinical centers have been utilizing intraarterial nimodipine in patients with symptomatic vasospasm to successfully treat cerebral vasospasm[2,10]. The

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objective of the present study was to investigate the efficacy and the clinical outcome of intraarterial nimodipine infusion by assessing the patients' clinical conditions with performing transcranial doppler (TCD), digital subtraction angiography (DSA).

MATERIALS AND METHODS

Patient population

At our department, all patients admitted for SAH, as confirmed by computed tomography (CT) or lumbar puncture, are examined by means of four-vessel angiography or in rare cases, CT angiography. During the 36 months between Jan. 2005 and Dec. 2007, 270 patients presented with SAH due to a ruptured intracranial aneurysm. In 237 of 270 patients, the aneurysm was treated by a neurosurgical procedure, 33 patients underwent an endovascular procedure. Among the 270 patients, 19 (7.0%) had findings compatible with symptomatic vasospasm that was refractory to hemodynamic therapy. Therefore, these patients underwent cerebral angiography for intraarterial nimodipine infusion.

We retrospectively reviewed patients' clinical charts and the procedural reports. Six women and thirteen men (mean age : 51.3 ± 12.5 years) received treatment. In 17 of 19 patients (89.5%), the aneurysm was treated by a neurosurgical procedure, whereas only 2 patients (10.5%) underwent an endovascular procedure.

A total of 53 endovascular nimodipine infusions were performed in 19 patients. The patients experienced symptomatic vasospasm from day 5 through day 19 after SAH (mean days after SAH : 9.6 ± 3.1 days).

At admission, the patients' clinical condition was assessed using the Hunt-Hess grading scale. The CT scan images were evaluated according to Fisher's classification. The patients' characteristics are summarized in Table 1.

All patients received nimodipine (as an intravenous or oral drug) upon the diagnosis of aneurysmal SAH. This treatment was continued until 21st day for the patients who developed vasospasm. The drug was temporarily suspended only if refractory hypotension or hypoxemia developed.

Indications for treatment

Patients were considered for undergoing angiography and chemical angioplasty if they showed at least one of the following conditions : 1) altered consciousness or clinical worsening based on the Glasgow coma scale (GCS) scores, 2) neurological deficits that were referable to the vascular territory of the angiographic vasospasm, 3) a mean flow velocity > 200 cm/s with a ratio of the middle cerebral artery (MCA) to the internal carotid artery (ICA) mean flow velocities greater than 3 (the Lindegaard ratio) or 4) an increase of the blood velocity above 50 cm/s/day.

Table 1. Summary of the patients

Case	Sex	Age	H-H grade	Fisher score	Site of aneurysm	Aneurysm treatment	Days after SAH	Site of vasospasm	Number of procedure	GOS score
1	M	53	4	3	L MCA	Surgery	9	MCA	2	4
2	M	38	4	4	L MCA	Surgery	8	Diffuse*	4	4
3	M	53	2	4	L MCA	Surgery	10	Diffuse*	2	4
4	F	53	4	4	L MCA	Surgery	5	MCA	3	3
5	M	42	2	3	Acom	Surgery	7	Diffuse*	2	5
6	M	49	4	4	Acom	Endovascular	13	Diffuse*	2	4
7	M	40	2	4	Acom	Surgery	7	Diffuse*	4	5
8	M	42	4	4	Acom	Surgery	11	Diffuse*	2	4
9	F	77	3	3	R Pcom	Endovascular	10	Diffuse*	2	5
10	M	34	2	3	Acom	Surgery	7	Diffuse*	8	5
11	M	61	2	2	Acom	Surgery	19	Diffuse*	1	2
12	F	68	3	3	L ICA bif	Surgery	6	Diffuse*	4	5
13	M	40	2	3	Acom	Surgery	11	Diffuse*	4	5
14	F	52	3	2	Acom	Surgery	10	Diffuse*	2	4
15	M	53	2	3	Acom	Surgery	12	ACA	2	5
16	F	69	3	3	Acom	Surgery	9	Diffuse*	3	3
17	M	66	5	4	Acom	Surgery	10	Diffuse*	1	4
18	M	71	3	3	Acom	Surgery	9	Diffuse*	2	3
19	F	48	2	3	L ICA bif	Surgery	9	Diffuse*	3	4

*Diffuse : combined ICA, ACA, MCA involvement. ACA : anterior cerebral artery, Acom : anterior communicating artery, bif : bifurcation, F : female, GOS : Glasgow outcome scale, H-H grade : Hunt-Hess grade, ICA : internal carotid artery, L : left, M : male, MCA : middle cerebral artery, Pcom : posterior communicating artery, R : right, SAH : subarachnoid hemorrhage

When vasospasm was suspected, cerebral CT scanning was first performed to exclude other causes of clinical deficits such as hydrocephalus or rebleeding. The patients who had cerebral infarction related to cerebral vasospasm, as indicated by CT scans, were excluded. Afterward, the patients underwent diagnostic angiography to confirm the vasospasm. Intraarterial nimodipine was administered only in the patients with angiographic evidence of a spasm in a territory compatible with the neurologic deficit or in those territories with a substantially elevated mean flow velocity, as determined by a TCD study.

Patients were considered for repetitive intraarterial nimodipine treatment if they showed at least one of the following conditions at the day after procedure : 1) altered consciousness or clinical worsening based on the GCS scores, 2) sustained continued neurologic deficit, and 3) sustained continued blood velocity.

Nineteen patients were treated with intraarterial nimodipine infusion for vasospasm. In most patients, this was performed at least twice, therefore, a total of 53 endovascular procedures were performed (mean : 2.8 ± 1.6 procedures/patients).

Angiographic evaluation

Diagnostic angiography and subsequent chemical angioplasty were performed within 12 hours of the onset of symptomatic vasospasm that is refractory to hemodynamic therapy in all the cases. The same as in the previous studies[19,20,22], a spasm observed on the pretreatment angiogram was assessed semiquantitatively and subjectively by neuroradiologists.

A diagnostic catheter was inserted into the cervical internal carotid artery on the side of the vasospasm. The infusion catheter didn't have to select the ophthalmic artery and to advance to the more distal ICA, which was involved in the vasospasm. A dose of 10 mg nimodipine (50 mL of Nimotop) was prepared after dilution with 50 mL of physiologic saline (to obtain a 10% dilution). Slow continuous infusion of the solution at a rate of 1 mL/min (0.5 mL/min Nimotop, 0.1 mg/min nimodipine) was achieved by using an electric pump. The dose of nimodipine infused intraarterially was 1-3 mg per treated vessel and the total dose of nimodipine infused intraarterially for a given patient was maintained within 5 mg. In unilateral procedures of vasospasm, depending on the severity of vasospasm and patients' conditions, an intraarterial infusion of nimodipine 1-3 mg was performed. In bilateral procedures of vasospasm, nimodipine 3 mg was infused to the more severe side and nimodipine 2 mg was infused to the less severe side.

The spasms were graded as mild when the arterial narrowing was < 50% and as severe when the narrowing was > 50%. The initial admission angiogram, which was without any obvious vasospasm, was used as a reference and this was compared with the pre- and post-treatment angiograms.

The degree of vasospasm was severe in 7 procedures and mild in 46 procedures. The internal carotid artery on the side of the vasospastic cerebral vessels was the only vessel infused in 25 of 53 procedures (47.2%). Nimodipine was infused into both internal carotid arteries in 28 procedures. These procedures were performed by neuroradiologists.

The angiographic response was graded as poor if there was no improvement in vessel caliber, good if most of the treated vessels improved, and excellent if vessels normalized in vessel caliber.

TCD evaluation

Assessment of the flow velocity in the major intracerebral vessels by means of TCD monitoring was performed, yet complete results were available for review for only 33 procedures.

Clinical evaluation

Clinical assessment was obtained from the clinical chart and using the GCS scores immediately after intraarterial nimodipine infusion.

The outcomes for the patients at discharge were assessed using the Glasgow outcome scale (GOS) score. A favorable outcome consisted of a GOS score indicating good recovery (grade 5) or moderate disability (grade 4). Unfavorable outcomes were severe disability (grade 3), a vegetative state (grade 2) and death (grade 1).

RESULTS

Angiographic results

In 16 patients, vasospasm of the total ICA, MCA and anterior cerebral artery (ACA) was found with the total ICA and MCA being involved in two patients and the total ICA and ACA being involved in one patient.

Notable vascular dilatation was observed in 42 of 53 procedures. The angiographic response, as previously assessed, was excellent in 11 and good in 31 endovascular procedures. Vasospasm never worsened after the intraarterial nimodipine infusion (Table2).

TCD results

The velocities of the affected vessels before and after endovascular treatment were available for 33 of 53 procedures. In 4 procedures, the velocity before and after endo-

Table 2. Data from the patients who have underwent intraarterial nimodipine infusion

Case number	Number of treatment	Nimodipine dose(mg)	Spasm severity*	Angiographic improvement†	GCS pre : post procedure	TCD pre : post procedure
1	1	3	Severe	Poor	10 : 10	180 : 130
	2	3	Severe	Good	10 : 11	180 :
2	1	5	Mild	Good	14 : 15	230 : 130
	2	5	Mild	Good	15 : 15	180 :
	3	5	Mild	Good	15 : 15	180 :
	4	5	Mild	Good	15 : 15	200 :
3	1	3	Mild	Good	15 : 15	150 :
	2	3	Mild	Good	15 : 15	160 : 60
4	1	3	Mild	Good	10 : 11	230 :
	2	3	Mild	Good	10 : 11	220 : 130
	3	3	Mild	Excellent	10 : 11	160 : 100
5	1	5	Mild	Excellent	14 : 15	220 : 110
	2	5	Mild	Excellent	14 : 15	230 : 90
6	1	5	Mild	Excellent	11 : 11	220 : 110
	2	5	Mild	Excellent	11 : 12	180 : 100
7	1	5	Mild	Poor	15 : 15	200 : 90
	2	5	Mild	Poor	15 : 15	190 : 110
	3	5	Mild	Poor	15 : 15	210 : 100
	4	5	Mild	Poor	15 : 15	230 : 80
8	1	5	Mild	Good	12 : 13	220 : 140
	2	5	Mild	Good	12 : 13	180 :
9	1	3	Mild	Poor	15 : 15	180 :
	2	5	Mild	Poor	15 : 15	
10	1	3	Mild	Good	14 : 15	180 : 120
	2	3	Mild	Excellent	14 : 15	
	3	3	Mild	Good	14 : 15	190 : 160
	4	3	Mild	Excellent	14 : 15	190 : 190
	5	3	Mild	Good	15 : 15	170 : 170
	6	3	Mild	Good	15 : 15	170 : 170
	7	3	Mild	Good	15 : 15	160 :
	8	3	Mild	Good	15 : 15	140 :
11	1	3	Mild	Good	8 : 8	120 : 120
12	1	5	Severe	Poor	14 : 15	180 : 140
	2	3	Severe	Good	14 : 15	
	3	5	Severe	Poor	15 : 15	210 : 160
	4	3	Severe	Poor	15 : 15	
13	1	5	Mild	Good	15 : 15	210 :
	2	5	Mild	Good	15 : 15	180 : 140
	3	5	Mild	Good	15 : 15	180 : 80
	4	5	Mild	Good	15 : 15	180 :
14	1	5	Mild	Good	14 : 15	120 :
	2	3	Severe	Poor	14 : 15	
15	1	3	Mild	Good	15 : 15	160 : 80
	2	3	Mild	Excellent	15 : 15	
16	1	5	Mild	Excellent	10 : 10	160 :
	2	3	Mild	Excellent	10 : 10	120 : 70
	3	3	Mild	Excellent	10 : 11	210 : 70
17	1	5	Mild	Good	14 : 15	190 : 70
18	1	5	Mild	Good	11 : 12	200 : 140
	2	3	Mild	Good	12 : 12	200 : 120
19	1	3	Mild	Good	14 : 15	220 : 130
	2	3	Mild	Good	14 : 15	210 : 150
	3	3	Mild	Good	15 : 15	170 : 100

*Spasm was graded as mild when the arterial narrowing was < 50% and severe when the narrowing was >50%, †Angiographic response was graded as poor if there was no improvement in the vessel caliber, good if most of the treated vessels improved, and excellent if the vessels normalized. GCS : Glasgow coma scale, TCD : transcranial doppler

vascular treatment were unchang-ed and 29 procedures exhibited a decrease of velocity (mean change of velocity after endovascular nimodipine treatment : 84.1 ± 31.8 cm/s). The velocities before and after endovascular treatment were never increased (Table 2).

Clinical Results

In 23 procedures, clinical improvement and an improved level of consciousness with an improved GCS score were observed.

The outcomes for patients at discharge were observed (Table 2).

DISCUSSION

Cerebral vasospasm following a aneurysmal SAH continues to be a leading cause of morbidity and mortality, and cerebral vasospasm is a significant independent risk factor for a poor outcome after a SAH[1,9,12].

Because vasospasm is first and the foremost a hemodynamic problem, the current treatment measures are geared toward optimizing cerebral perfusion and minimizing the secondary brain injury. Hypervolemia and hypertension, in addition to oral nimodipine, are the conceptual mainstays to achieve this goal.

For those patients whose condition are refractory to maximal medical therapy, endovascular treatment remains an important therapeutic intervention to mechanically and chemically address the cerebral vasospasm.

Mechanical angioplasty has been used most effectively in reversing a vasospasm in the large, proximal segments of the cerebral vessels and these are composed of thick muscular walls. However, angioplasty of distal vessels is not possible. Many patients have tortuous vessels, and this makes access difficult. Mechanical angioplasty of the intracranial vessels is associated

with a risk of vessel rupture, vessel perforation, thromboembolic events, intracranial hemorrhage, arterial dissection, reperfusion injury and hemorrhage from unsecured aneurysms. Major complication rates of 4% to 6% are typically reported[18]. Further, systemic anticoagulation therapy is also necessary.

Intraarterial papaverine infusion has been the mainstay of endovascular vasospasm treatment. Intraarterially administered papaverine has been shown to increase the diameter of vasospastic vessels as well as to improve the cerebral circulation times[16]. Papaverine is thought to have a direct inhibitory effect on smooth-muscle contraction. In recent reports, intraarterial papaverine administration has been associated with a risk of cortical necrosis, elevated intracranial pressure (ICP), permanent toxic effects to the human brain (including monocular blindness, brain stem dysfunction and seizure), other transient focal neurological deficits and formation of crystal emboli[2].

The limitations of papaverine infusion have led to experimentation with using other pharmacological agents. In several studies, investigators have demonstrated that calcium antagonists (e.g., nicardipine, nifedipine, verapamil, nimodipine etc.) reduce the proportion of patients with a poor outcome and ischemic neurological deficits after aneurysmal SAH[17].

Other treatments, such as the intrathecal delivery of nitric-oxide donors, the systemic administration of endothelin receptors antagonists or various inhibitors of phosphodiesterase enzymes, are also under intensive investigation, but their clinical efficacy has not yet been demonstrated[4].

Nimodipine is a specific blocker of the L-type voltage-gated calcium channels[7]. The contractile processes of cerebral arterial smooth muscle cells rely on the entry of calcium ions into the cells. Nimodipine crosses the blood-brain barrier and it blocks the influx of extracellular calcium, which is necessary for the contraction of large cerebral arteries and thus, nimodipine selectively increases cerebral blood flow and reverses the cerebral vasospasm without altering the cerebral oxidative metabolism[5]. It is thought to also have a neuroprotective effect by preventing calcium overload in ischemic neurons. Oral and intravenous nimodipine has been widely used for treating cerebral vasospasm to achieve these effects. When it is administered intravenously, it may be associated with a few minor complications such as hypotension or arrhythmia[23,24].

Infusing intraarterial nimodipine in patients with symptomatic vasospasm has been reported on by several authors. Two early clinical studies have presented conflicting results[3,8]. Boker et al.[3] reported on the use of selective intraarterial nimodipine infusion for treating three patients with vasospasm following aneurysmal SAH, and they concluded that intraarterial nimodipine was angiographically effective. Grotenhuis et al.[8] treated six patients with intraarterial nimodipine (0.068-1 mg); however, the treatment was ineffective when administered after the onset of vasospasm. Another experimental study demonstrated the efficacy of selective intraarterial nimodipine administration in a SAH rabbit model at a dose of 0.05 mg/kg[6].

Two other groups have recently reported their clinical findings regarding the use of intraarterial nimodipine to treat the cerebral vasospasm caused by aneurysmal SAH. In both studies, intraarterial nimodipine led to a significant improvement in the vessels' diameters and the clinical status of the patients with cerebral vasospasm and who had not responded to previous medical therapy[2,10].

Intraarterial papaverine infusion produce crystal embolization. A super-selection of the area where a vasospasm was present and thereby the administration site was minimized. In particular, a special attention should be paid to the ophthalmic artery whose blood flow rate is relatively slow. Intraarterial papaverine can therefore be infused into the ACA and MCA simultaneously by placing the microcatheter tip into the supraclinoid segment of the ICA just above the ophthalmic artery branch point[11]. Unlike intraarterial papaverine infusion, intraarterial nimodipine infusion does not produce a crystal embolization. Thus, in this procedure, selection of the ophthalmic artery is not necessary. A super-selection of the distal ICA where a vasospasm is present is also unnecessary.

According to our results, an intraarterial nimodipine infusion significantly improved the vessel diameter in patients with severe cerebral vasospasm who were refractory to the medical treatments. Besides, relatively good clinical outcomes were also obtained. There were no persistent, fatal complications associated with the procedure. Although one patient was in a vegetative state at discharge, this patient already had a mental deterioration prior to the procedure.

CONCLUSION

From our data, the use of intraarterial nimodipine was effective and safe in selected cases of vasospasm that followed aneurysmal SAH. Prospective, randomized studies are needed for evaluating the cerebral blood flow to confirm our results. Additional investigation is also needed into novel techniques and procedures to improve the cerebral blood flow and the clinical outcomes of the patients who display vasospasm after suffering an aneurismal SAH.

References

1. Baldwin ME, Macdonald RL, Huo D, Novakovic RL, Goldenberg FD, Frank JI, et al. : Early vasospasm on admission angiography in patients with aneurysmal subarachnoid hemorrhage is a predictor for in-hospital complications and poor outcome. **Stroke 35** : 2506-2511, 2004
2. Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, et al. : Intra-arterial Nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid haemorrhage : preliminary results. **AJNR Am J Neuroradiol 25** : 1067-1076, 2004
3. Böker DK, Solymosi L, Wassmann H : Immediate postangiographic intraarterial treatment of cerebral vasospasm after subarachnoid haemorrhage with nimodipine. Report on 3 cases. **Neurochirurgia (Stuttg) 28 Suppl 1** : 118-120, 1985
4. Chow M, Dumont AS, Kassell NF : Endothelin receptor antagonists and cerebral vasospasm: an update. **Neurosurgery 51** : 1333-1341; discussion 1342, 2002
5. Findlay JM, Macdonald RL, Weir BK : Current concepts of pathophysiology and management of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. **Cerebrovasc Brain Metab Rev 3** : 336-361, 1991
6. Firat MM, Gelebek V, Orer HS, Belen D, Firat AK, Balkanci F : Selective intraarterial Nimodipine treatment in an experimental subarachnoid haemorrhage model. **AJNR Am J Neuroradiol 26** : 1357-1362, 2005
7. Fujii Y, Takahashi A, Ezura M, Mizoi K : Balloon angioplasty immediately after surgical clipping for symptomatic vasospasm on admission. Report of four cases. **Neurosurg Rev 18** : 79-84, 1995
8. Grotenhuis JA, Bettag W, Fiebach BJ, Fiebach BJ, Dabir K : Intracarotid slow bolus injection of nimodipine during angiography for treatment of cerebral vasospasm after SAH. A preliminary report. **J Neurosurg 61** : 231-240, 1984
9. Harrod CG, Bendok BR, Batjer HH : Prediction of cerebral vasospasm in patients presenting with aneurysmal subarachnoid hemorrhage : a review. **Neurosurgery 56** : 633-654; discussion 633-654, 2005
10. Hui C, Lau KP : Efficacy of intra-arterial Nimodipine in the treatment of cerebral vasospasm complicating subarachnoid haemorrhage. **Clin Radiol 60** : 1030-1036, 2005
11. Kaku Y, Yonekawa Y, Tsukahara T, Kazekawa K : Superselective intra-arterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. **J Neurosurg 77** : 842-847, 1992
12. Kassell NF, Torner JC, Haley EC Jr, Jane JA, Adams HP, Kongable GL : The International Cooperative Study on the Timing of Aneurysm Surgery. Part 1 : overall management results. **J Neurosurg 73** : 18-36, 1990
13. Linn FH, Rinkel GJ, Algra A, van Gijn J : Incidence of subarachnoid hemorrhage : role of region, year, and rate of computed tomography : a meta-analysis. **Stroke 27** : 625-629, 1996
14. Macdonald LR, Weir B : **Epidemiology in cerebral vasospasm.** San Diego (CA) : Academic Press, 2001, pp17-43
15. Meyer FB : Calcium antagonists and vasospasm. **Neurosurg Clin N Am 1** : 367-376, 1990
16. Milburn JM, Moran CJ, Cross DT 3rd, Diringer MN, Pilgram TK, Dacey RG Jr : Increase in diameters of vasospastic intracranial vessels by intraarterial papaverine administration. **J Neurosurg 88** : 38-42, 1998
17. Mindea SA, Yang BP, Bendok BR, Miller JW, Batjer HH : Endovascular treatment strategies for cerebral vasospasm. **Neurosurg Focus 21** : E13, 2006
18. Muizelaar JP, Zwienenberg M, Rudisill NA, Hecht ST : The prophylactic use of transluminal balloon angioplasty in patients with Fisher Grade 3 subarachnoid hemorrhage : a pilot study. **J Neurosurg 91** : 51-58, 1999
19. Numaguchi Y, Zoarski GH, Clouston JE, Zagardo MT, Simard JM, Aldrich EF, et al. : Repeat intra-arterial papaverine for recurrent cerebral vasospasm after subarachnoid haemorrhage. **Neuroradiology 39** : 751-759, 1997
20. Polin RS, Hansen CA, German P, Chadduck JB, Kassell NF : Intra-arterially administered papaverine for the treatment of symptomatic cerebral vasospasm. **Neurosurgery 42** : 1256-1264 ; discussion 1264-1267, 1998
21. Rinkel GJ, Feigin VL, Algra A, van den Bergh WM, Vermeulen M, van Gijn J : Calcium antagonists for aneurysmal subarachnoid haemorrhage. **Cochrane Database Syst Rev 25** : CD000277, 2005
22. Schuknecht B, Fandino J, Yüksel C, Yonekawa Y, Valavanis A : Endovascular treatment of cerebral vasospasm : assessment of treatment effect by cerebral angiography and transcranial colour Doppler sonography. **Neuroradiology 41** : 453-462, 1999
23. Treggiari-Venzi MM, Suter PM, Romand JA : Review of medical prevention of vasospasm after aneurysmal subarachnoid haemorrhage : a problem of neurointensive care. **Neurosurgery 48** : 249-261; discussion 261-262, 2001
24. Yasudah SU, Tietze KJ : Nimodipine in the treatment of subarachnoid hemorrhage. **DICP 23** : 451-455, 1989