Kobe J. Med. Sci. 47, 169/179, August 2001

Intraarterial Infusion of Papaverine and Change of Cerebral Hemodynamics in Symptomatic Cerebral Vasospasm

HIROAKI MINAMI[1], KEIICHI KUWAMURA[1], and NORIHIKO TAMAKI[2]
Department of Neurosurgery, Hyogo Prefectural Awaji Hospital, Sumoto 656-0013, Japan[1]*;*
Department of Neurosurgery, Kobe University Graduate School of Medicine[2]

Received 17 July 2001/ Accepted 10 September 2001

Key words: vasospasm; papaverine; subarachnoid hemorrhage; cerebral circulation time

In 43 cases with symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage treated by intraarterial infusion of papaverine (IAP), we studied cerebral hemodynamics by measuring cerebral circulation time (CCT) using digital subtraction angiogram. CCT on the middle cerebral artery site was defined as CCT-LAV and on the anterior cerebral artery side as CCT-MAV. In the CCT-LAV, two phases were further defined; the arterial phase (CCT-A) and the capillary phase (CCT-CAP). Mean CCT-LAV before and after IAP was 6.35 ± 1.69 sec, 4.91 ± 1.56 sec, and mean CCT-MAV was 6.15 ± 1.68 sec, 4.80 ± 1.58 sec, each showing a significant shortening. Mean CCT-A before and after IAP was 0.274 ± 0.105 sec, 0.226 ± 0.066 sec and mean CCT-CAP was 6.00 ± 1.62 sec and 4.60 ± 1.55 sec. The shortening rate of CCT-A and CCT-CAP were 11.2 ± 25.7% and 22.7 ± 14.6% respectively.

Our study confirmed that IAP shortened CCT and improved cerebral hemodynamics. Compared with CCT-A, CCT-CAP was shortened significantly, suggesting that IAP is working not only in the proximal vessels but also in the distal vessels, that is, effective for resolution of vasospasm in the view of cerebral microcirculation. Clinical outcome was not improved statistically, however, it is the fact that there are not a few cases improved neurologically and IAP is still useful for vasospasm as a means to directly dilate intracranial peripheral arteries.

Angiographic vasospasm has been reported to occur in about 30 to 70% of patients with subarachnoid hemorrhage (SAH) (2,20,22,24) and symptomatic vasospasm may developed in about 20 to 40% of patients (2,6,11,22,24). For the prevention of symptomatic vasospasm, various approaches have been applied clinically; hypertensive hypervolemic hemodilution therapy (20), removal of subarachnoid clots by early surgery (16), intrathecal administration of thrombolytic drugs such as urokinase and tissue plasminogen activator, irrigation of the clot in cerebral cistern (17,23) and systemic administration of calcium channel blocker (2,6) have been reported. However, once vasospasm becomes symptomatic, it cannot easily be remitted. As one of the endovascular approach for this is intraarterial infusion of papaverine (IAP) (9,10,13). In our institute, we administered a continuous intravenous injection of nicardipine, a calcium antagonist, immediately after the onset of aneurysmal SAH as a prophylactic therapy (2,6). IAP was indicated in addition to those medications when vasospasm became clinically symptomatic (3). In this study, we evaluated the cerebral hemodynamics before and after treatment of IAP by calculating the cerebral circulation time (CCT) obtained with digital subtraction angiogram (DSA) as a quantitative measurement.

Phone:81-799-22-1200 Fax: 81-799-24-5704. E-mail: minami@awaji-hosp.sumoto.hyogo.jp

CLINICAL MATERIALS AND METHODS

1. Patient Selection

Between July, 1994 and May, 2001, 161 cases with SAH due to ruptured cerebral aneurysms were surgically treated at the Hyogo Prefectural Awaji Hospital. Of these, 43 cases were analyzed in this study, which were surgically clipped within 48 hours of the onset and IAP was performed for the treatment of symptomatic cerebral vasospasm. All the patients were successfully clipped with external decompression and either with extraventricular or cerebrospinal fluid drainage placed postoperatively. The patients were medically treated with standardized protocol; hypertensive hypervolemic hemodilution therapy and intravenous administration of nicardipine ranging from 0.01 to 0.2 mg/kg/hr.

Eighteen cases were male and 25 were female, ranging in age from 37 to 77 years (mean 61.1 ± 10.1 years). The World Federation of Neurological Societies (WFNS) grading scale on admission were grade I in 12 cases, grade II in 12 cases, grade III in 4 cases, grade IV in 9 cases and grade V in 6 cases. The severity of SAH on computerized tomography (CT) was classified as Fisher group 2 in 6 cases, group 3 in 22 cases and group 4 in 15 cases. The location of aneurysm was at the internal carotid artery (ICA) in 12 cases, anterior cerebral artery (ACA) in 19 cases, middle cerebral artery (MCA) in 9 cases and basilar artery in 3 cases. All the patients' characteristics are summarized in Table Ⅰ.

TABLE Ⅰ. *Clinical characteristics of 43 patients with vasospasm after aneurysmal subarachnoid hemorrhage.*

Chartacteristic	No. of Cases
Age (yrs)	
< 50	6
50 – 59	11
60 – 69	15
≥ 70	11
Sex (M/F)	18 / 25
WFNS scale	
I	12
II	12
III	4
IV	9
V	6
Fisher's group	
2	6
3	22
4	15
Location of Aneurysm	
ICA	12
ACA	4
AcoA	15
MCA	9
BA	3

Abbreviations: WFNS = World Federation of Neurological Surgery; ICA = internal carotid artery; ACA = anterior cerebral artery; ACoA = anterior communicating artery; MCA = middle cerebral artery; BA = basilar artery

Twenty cases , which were composed of 12 men and 8 women , ranging in age from 37 to 84 years (mean 61.4 ± 14.2 years) showing no cerebrovascular disease and no focal lesions were studied and used as the control.

2. Diagnosis and Evaluation of Vasospasm

Postoperative cerebral angiography was performed at the onset neurological deterioration for confirming diagnosis of symptomatic vasospasm. Neurological deterioration was considered significant when a decrease of more than 2 points in Glasgow Coma Scale score (8) was observed, and/or appearance and aggravation of focal neurological signs were observed. After the confirmation of the area of vasospasm that was responsible for neurological signs, IAP was indicated. Neurological status was evaluated immediately after and 24 hours after IAP. An increase of more than 2 points in Glasgow Coma Scale or of more than 1 point in manual muscle test as to paresis were taken as significantly improved.

The degree of narrowing of spastic vessels was judged from DSA before and after IAP. According to the modified grading of the Kassell's scale (10), angiographic vasospasm was classified as severe with more than 50% narrowing of that on the initial angiography, as moderate with 25 to 50% narrowing and as mild with less than 25% narrowing. Additionally, vasospasm was classified as the diffuse type when it occurred widely in the vascular area of either the ACA or the MCA and as the focal type when it occurred only locally at the main trunk.

3. Intraarterial Infusion of Papaverine

Papaverine hydrochloride (0.4%) ranging from 20 to 120 mg (mean 57.7 mg) was infused at a rate of 4 mg / minute via a 5-Fr catheter retained in the C5 portion of the ICA. Ten minutes after completion of infusion, cerebral angiography was repeated. In 6 cases, superselective injections of papaverine ranging from 10 to 100 mg (mean 38.8 mg) were performed at M1, A1 and C1 portion.

4. Evaluation of CCT

The CCT was calculated at the initial angiography and before and after IAP. In measuring CCT, the time between the filling of the ophthalmic artery (Fig.1A) and the filling of the parietal lateral ascending vein on the lateral image (Fig.1B) was defined as CCT-LAV and between the ophthalmic artery and the parietal medial ascending vein as CCT-MAV. Vein of Rolandi or veins near it were selected as the parietal ascending vein for measurement. For the evaluation of differences of CCT-LAV depending on circulation phase, the time between the ophthalmic artery and the Sylvian point (Fig.1A) was defined as arterial phase (CCT-A) and from the Sylvian point to the parietal lateral ascending vein as capillary phase (CCT-CAP). The shortening rate of CCT was calculated by the equation: [(value before IAP - value after IAP) ÷ value before IAP]. The DSA was performed with REX super-G system (Toshiba, Tokyo, Japan).

Statistical analysis was calculated by using Mann-Whitney's U test, Wilcoxon signed-ranks test, Student's t-test and Kruskal-Wallis test.

RESULTS

1. Clinical Course

In 43 cases, blood vessels in 220 areas were studied and IAP was performed in a total of 76 times with 110 procedures. In 3 cases with recurrent vasospasm and in 14 cases with insufficient clinical improvement, the IAP administration was repeated twice in 5 cases, 3 times in 8 cases and 4 times in 4 cases. After IAP, neurologic improvement was found to be transient in 7 cases and permanent in 13 cases. In the cases with transient improvement, an increased level of consciousness was observed in 6 cases and improvement in motor function

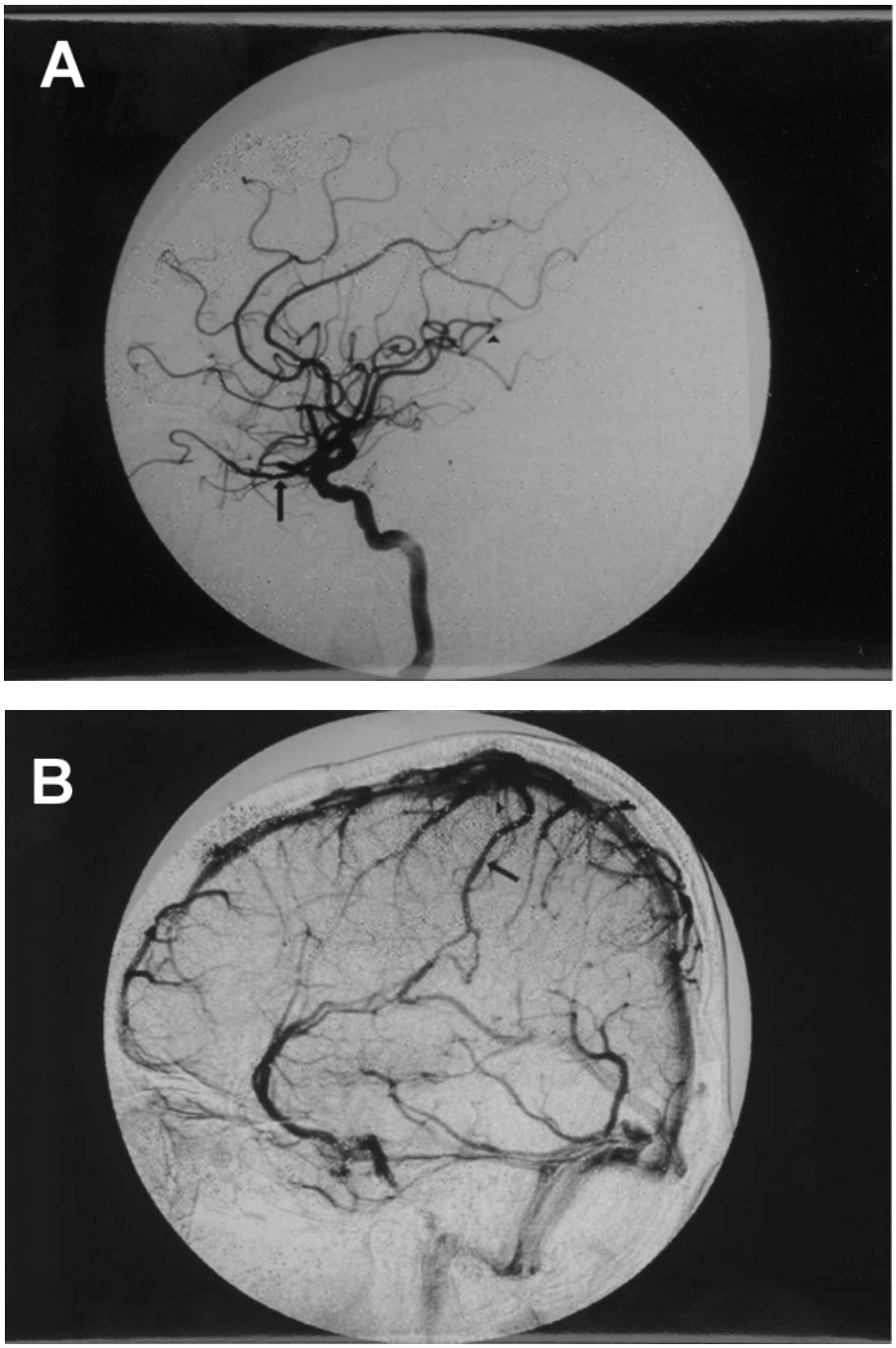

Fig. 1. In measuring CCT, the time between the filling of the ophthalmic artery (A; arrow) and the filling of the parietal lateral ascending vein (B; arrow) was defined as CCT-LAV and between the ophthalmic artery and the parietal medial ascending vein (B; arrow head) as CCT-MAV, and the time between the ophthalmic artery and the Sylvian point (A; arrow head) was defined as CCT-A and from the Sylvian point to the parietal lateral ascending vein as CCT-CAP.

in 1 case, while in the cases with permanent improvement, an increased level of consciousness in 10 cases, improvement in motor function in 1 case and remission of aphasia in 2 cases. Of 110 procedures, 106 could be obtained with the DSA images. Angiographic improvement in the vascular diameter was found in 102 (96.2%) out of 106 procedures; complete resolution in 9 procedures, partial resolution in 93 procedures and no change in 4 procedures.

2. Preoperative CCT with SAH

All the data of CCT in each phase and the shortening rate of CCT before and after IAP were summarized in Table Ⅱ. In the control group, the mean CCT-LAV, CCT-MAV, CCT-A, and CCT-CAP were 4.88 ± 0.74 sec, 4.50 ± 0.80 sec, 0.27 ± 0.12 sec, and 4.61 ± 0.68 sec respectively. In the SAH group, the mean CCT-LAV, CCT-MAV, CCT-A, and CCT-CAP at the first angiography were 6.39 sec ± 1.38 sec, 5.92 sec ± 1.50 sec, 0.39 ± 0.14 sec and 6.05 ± 1.34 sec respectively, each being significantly prolonged compared with the control group ($p<0.0001$ by Mann-Whitney's U test).

TABLE Ⅱ. Change of the mean CCT in each phase before and after IAP.

	CCT-LAV (sec)	CCT-MAV (sec)	CCT-A (sec)	CCT-CAP (sec)
Control group	4.88 ± 0.74	4.50 ± 0.80	0.266 ± 0.117	4.61 ± 0.68
SAH group				
Preoperative	6.39 ± 1.38*	5.92 ± 1.50*	0.391 ± 0.143*	6.05 ± 1.34*
Before IAP	6.35 ± 1.69	6.15 ± 1.68	0.274 ± 0.105	6.00 ± 1.62
After IAP	4.91 ± 1.56**	4.80 ± 1.58**	0.226 ± 0.066**	4.60 ± 1.55**

Datas are presented as means ± standard deviation of the means: CCT = cerebral circulation time; IAP = intraarterial infusion of papaverine; LAV = lateral ascending vein ; MAV = medial ascending vein; A= artery; CAP = capillary

* $p < 0.0001$; significant between Control group and Preoperative group by Mann-Whitney's U test,

** $p < 0.0001$; significant between Before IAP group and After IAP group by Wilcoxon signed-ranks test.

3. Preoperative CCT and WFNS Grading

In relation between the WFNS scale of SAH at admission and CCT at the first angiography, CCT tended to be prolonged in proportion to the severity except in WFNS grade III, in which the number of cases was too small. The mean CCT-LAV and CCT-MAV of low grade group of patients with WFNS grade I to III were 5.93 ± 1.06 sec, 5.36 ± 1.09 sec, respectively, and those of high grade group including patients with WFNS grade IV and V were 7.22 ± 1.50 sec, 6.95 ± 1.62 sec, respectively. There were statistical significant differences between the low grade group and the high grade group in both CCT-LAV and CCT-MAV (Fig.2 ; $p<0.001$ by Student's t-test).

4. Diffuse Type vs. Focal Type

Regarding the differences between diffuse type and focal type, the CCT values before IAP were correlated with the degree of angiographic vasospasm in the diffuse type ($p<0.01$ by Kruskal-Wallis test) whereas no significant correlation was found in the focal type (Fig.3A and B).

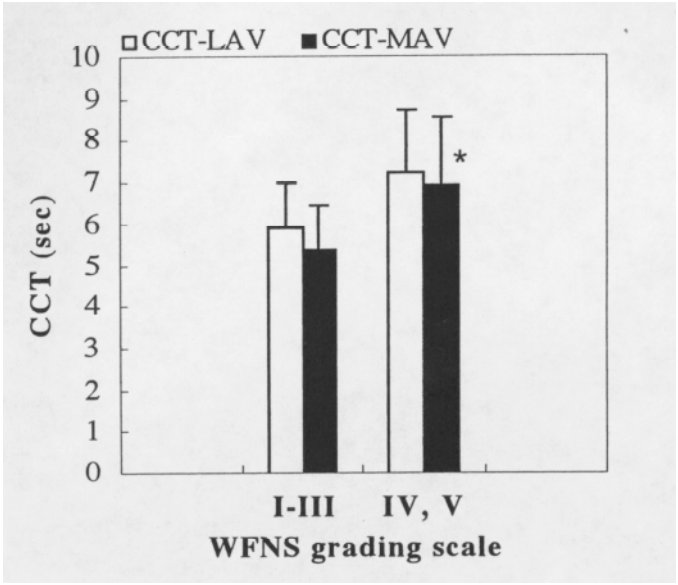

Fig. 2. Bar graph showing the comparison of CCT in patients divided into the low grade group (WFNS grade I-III) and the high grade group (WFNS grade IV, V). The mean CCT of the high grade group prolonged significantly compared with that of the low grade group in both CCT-LAV and CCT-MAV (* $p<0.001$ by Student's t-test).

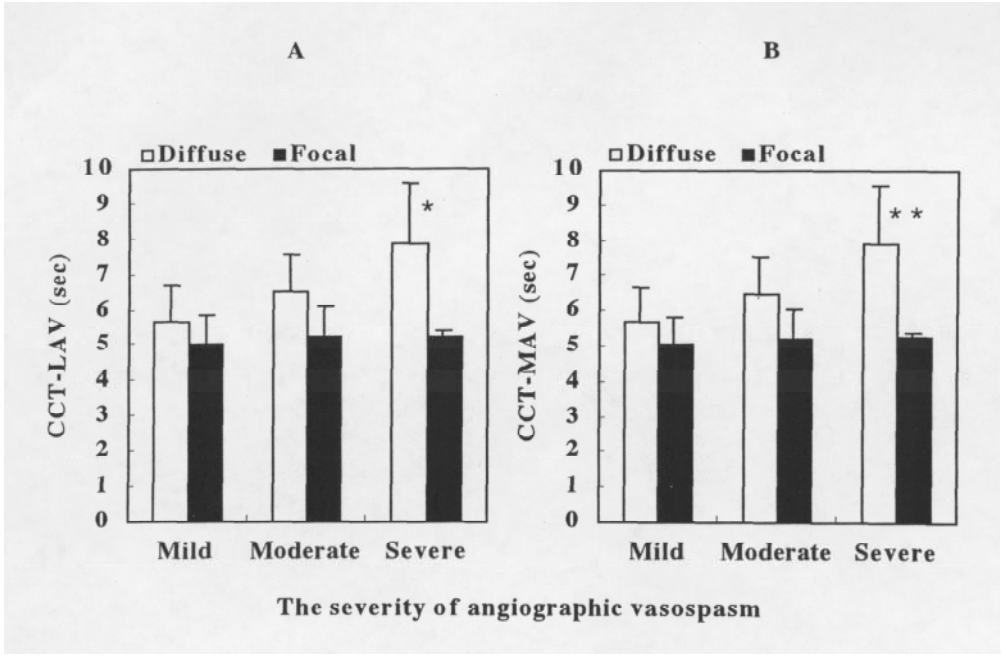

Fig. 3. Graph displaying the relationship between the severity of angiographic vasospasm and CCT. The severity of angiographic vasospasm correlated with CCT-LAV **(A)** and CCT-MAV **(B)**. In particular, analysis shows a significant correlation in diffuse type (Multivaliant analysis ; * $p<0.01$ by Kruskal -Wallis test, ** $p<0.01$ by Kruskal -Wallis test)

5. CCT-MAV vs. CCT-LAV

The mean CCT-LAV and CCT-MAV before IAP were 6.35 ± 1.69 sec and 6.15 ± 1.68 sec respectively, each being prolonged significantly compared with the control ($p<0.0001$ by Mann-Whitney's U test). The mean CCT-LAV and CCT-MAV after IAP were 4.89 ± 1.56 sec and 4.81 ± 1.51 sec respectively. The shortening rate was 21.3 ± 15.4% and 20.6 ± 14.1%, respectively. Significant shortening in both CCT-LAV and CCT-MAV after IAP were found (Table Ⅱ; $p<0.0001$ by Wilcoxon signed-ranks test).

6. CCT-A vs. CCT-CAP

The mean CCT-A before and after IAP were 0.274 ± 0.105 sec, 0.226 ± 0.066 sec, while the mean CCT-CAP were 6.00 ± 1.62 sec, 4.60 ± 1.55 sec. The mean CCT-A before IAP had no significant difference with the control, while the mean CCT-CAP before IAP was prolonged significantly compared with the control ($p<0.0001$ by Mann-Whitney's U test). The mean shortening rate of CCT-A and CCT-CAP before and after IAP were 11.2 ± 25.7% and 22.7 ± 14.6% respectively. The mean CCT-A and CCT-CAP were shortened significantly after IAP ($p<0.0001$ by Wilcoxon signed-ranks test). The shortening rate was significantly higher in CCT-CAP than in CCT-A (Table Ⅲ; $p<0.01$ by Wilcoxon signed-ranks test).

TABLE Ⅲ. The shortening rate of CCT before and after IAP.

	Before IAP (A) (sec)	After IAP (B) (sec)	Shortening rate before and after IAP[(A) - (B)] / (A) × 100 (%)
CCT-A	0.274 ± 0.105	0.226 ± 0.066	11.2 ± 25.7
CCT-CAP	6.00 ± 1.62	4.60 ± 1.55	22.7 ± 14.6*

Datas are presented as means ± standard deviation of the means: CCT = cerebral circulation time; IAP = intraarterial infusion of papaverine; A= artery; CAP = capillary

* $p < 0.01$; significant between the shortening rate of CCT-A and that of CCT-CAP by Wilcoxon signed-ranks test

TABLE Ⅳ. Clinical Outcome and CCT change.

GOS	Preoperative CCT-LAV* (sec)	Preoperative CCT-MAV* (sec)	Shortening rate of CCT-LAV** (%)	Shortening rate of CCT-MAV** (%)
GR	5.98 ± 1.62	5.46 ± 1.47	20.7 ± 14.4	21.2 ± 12.5
MD	6.78 ± 1.48	6.45 ± 1.47	11.6 ± 18.7	14.9 ± 19.4
SD	6.93 ± 1.79	6.48 ± 1.90	23.9 ± 15.4	22.3 ± 16.1
VS	7.19 ± 1.51	6.44 ± 1.87	23.2 ± 16.9	21.3 ± 14.6
D	6.80 ± 0.95	6.19 ± 0.16	24.0 ± 13.3	19.2 ± 7.7

Datas are presented as means ± standard deviation of the means: CCT = cerebral circulation time; IAP = intraarterial infusion of papaverine; A= artery; CAP = capillary; GOS = Glasgow Outcome Scale; GR = good recovery; MD = moderately disabled; SD = severely disabled; VS= persistent vegetative state; D = death

* no significant relation between GOS and preoperative CCT by Kruskal-Wallis test

** no significant relation between GOS and the shortening rate of CCT by Kruskal-Wallis test

7. Clinical Outcome and CCT Change

Using the Glasgow Outcome Scale (7) one month after SAH, 23 cases showed good recovery, 7 were moderately disabled, 5 were severely disabled, 4 were persistent vegetative

state and 4 were death, but it was not correlated with angiographical improvement, CCT value and CCT shortening rate by Kruskal-Wallis test (Table Ⅳ). And there was no significant relationship between CCT value and CCT shortening rate among the cases with neurological improvement and those of the cases without neurological improvement by Mann-Whitney's U test.

Prolongation of CCT after IAP was seen in 10 cases of 12 procedures. Of them, 3 procedures were included with the case in which IAP was administered from A1 portion of the ACA. The steal phenomenon of the side of a dilated vessel was considered accountable for it. There was no case in which symptoms were aggravated by this steal phenomenon. Complications due to IAP were found in 3 cases; hypotension in 2 cases and hypertension in 1 case. Finally, 14 cases showed focal infarction on CT.

DISCUSSION

Papaverine is benzyl isoquinoline opium alkaloid that can dilate contracted vessels independent of endothelium-delivered factors (EDF), and its potential vasodilating effect is well documented. In 1992, the first attempt of IAP administration was reported the efficacy for vasodilatation (9,10). Clinical efficacy of IAP still remains controversial (9,10,12,13,21). In the previous reports since 1992, the improvement by IAP has been reported to be 95-100% on angiographical dilatation of vessels however only 25-80% on clinical symptom (9,10,12,13), indicating a discrepancy between these two parameters. In agreement with the previous studies, this study demonstrated that angiographical improvement was seen to occur 96.2% whereas clinical improvement was seen to occur 16.3% in transient cases and 30.2% in permanent cases.

The changes in hemodynamics in cerebral blood circulation is not a simple mechanism defined only by the diameter of vessels but should be evaluated from various viewpoints, such as changes in small arteries and microcapillaries. In this study, therefore, we studied the efficacy of IAP in detail on the basis of CCT.

We have evaluated previously the change in cerebral hemodynamics with IAP by mean transit time (MTT)(3). It takes an enormous time to calculate MTT and since Gado, et al. have suggested that CCT is proportional to MTT (4), we therefore analyzed hemodynamics in this study by CCT, which can be calculated more simply. Greitz defines CCT as the time interval between maximal filling of the carotid siphon and maximal filling of the parietal vein (5). Normal values of CCT were reported 4.13 ± 0.78 sec, 5.9 sec ± 0.8 and 10.7 ± 3 sec (1,5,16), depending on the choice of veins or arteries and the location and the range of region of interest. CCT-LAV in this study is supposed to represent hemodynamics in the MCA area and CCT-MAV in the ACA area.

At the initial angiography, CCT was well correlated with the clinical severity of SAH. At the second angiography with spasms before the IAP, the comparison between CCT and vascular diameter demonstrated good correlation with the degree of narrowing of vessels in the diffuse type, but not in the focal type. Similarly a previous study using transcranial doppler has been reported that CCT is prolonged significantly in peripheral type in severe vasospasm group (19). Our study is in agreement with this previous study but further suggested that CCT is useful for evaluating cerebral vasospasm in the diffuse type regardless the severity of angiographical vasospasm.

CCT was significantly shortened by the IAP administration (15), showing the improvement of blood circulation. Furthermore, the CCT was significantly shortened in the capillary phase. This result clearly demonstrated that IAP is working on the peripheral vessels as well as on the main trunk. Milburn, et al. have previously studied in detail the vascular diameter before and after IAP administration and confirmed that blood vessels are

dilated by IAP in the proximal, intermediate, and distal artery (14). In other study using CCT and cerebral blood flow (CBF) in aneurysmal SAH, it has been pointed out that changes in microcirculation mainly affect on cerebral ischemia during cerebral vasospasm (18). Therefore, our present study is partially in agreement with these studies. DSA usually demonstrates the vasodilatation occurring immediately to the distal lumen of IAP injected site and there may be the possibility of additional effect for shortening CCT-CAP due to raised perfusion pressure following the vasodilatation on the proximal site of the trunk artery.

In 10 cases, the prolongation of CCT after IAP was observed unexpectedly. It was thought to be concerned with a steal phenomenon (12). This paradoxical result suggests that injected papaverine flows into mild or no spastic vessels, rather than into the severe spastic vessels which should be dilated. The superselective IAP in spastic vessels may be more effective and safe.

In IAP, there are problems to be resolved such as optimal dose, continuity of the effect, timing of the treatment and resistance of the contracted vessels to papaverine. However, it is the fact that there are not a few cases showed remarkable clinical improvement and IAP is still useful as a means to directly dilate intracranial peripheral arteries for vasospasm. We expect new drugs which have more continuous effect and less side effects than papaverine for the management against cerebral vasospasm.

CONCLUSION

In our present study of the cerebral circulation time, it was confirmed that CCT is useful as a quantitative measurement for cerebral circulation and IAP produces the improvement of cerebral circulation not only in the proximal vessels but also in the distal vessels in patients with vasospasm. These results suggest that IAP is effective for resolution of cerebral vasospasm in the view of improvement of cerebral microcirculation.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Tatsuya Nagashima and Dr. Kazumasa Ehara (Department of Neurosugery, Kobe University Graduate School of Medicine) for their editorial assistance and Dr. Atsushi Fujita, Dr. Kohei Ohta, Dr. Yosuke Ishihara, Dr. Katsu Mizukawa and Dr. Shoji Morishita (Hyogo Prefectural Awaji Hospital) for their clinical assistance.

REFERENCES

1. **Celesis P., Chan M., Marc-Vergnes J. P., Leydet P., Viallard G., Charlet J. P., and Danet B.** 1985. Measurement of cerebral circulation time in man. Eur. J. Nucl. Med. **10**:426-431
2. **Flamm E. S., Adams H. P. Jr., Beck D. W., Pinto R. S., Marler J. R., Walker M. D., Godersky J. C., Loftus C. M., Biller J., Boarini D. J., O'Dell C., Banwart K., and Kongable G.** 1988. Dose-escalation study of intra-venous nicardipine in patients with aneurysmal subarachnoid hemorrhage. J. Neurosurg. **68**:393-400
3. **Fujita A., Kuwamura K., Ohta K., Goto R., Nagashima T., and Tamaki N.** 1998. Cerebral circulation before and after intraarterial infusion of papaverine for cerebral vasospasm due to subarachnoid hemorrhage studied by dynamic DSA. Jpn. J. Neurosurg (Tokyo) **7**:477-483
4. **Gado M., Eichling J., Grubb R., Phelps M., Raichle M., and Ter-Pogossian M. M.** 1975. Appraisal of the angiographic circulation time as an index of cerebral blood flow.

Radiology **115**:107-112
5. **Greitz T.** 1956. A radiologic study of the brain circulation by rapid serial angiography of the carotid artery. Acta. Radiol.(Suppl)**140**:1-123
6. **Haley E. C. Jr., Kassell N. F., and Torner J. C.** 1993. A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. J. Neurosurg. **78**:537-547
7. **Jennett B. and Bond M.** 1975. Assessment of outcome after severe brain damage. A practical scale. Lanset **1**: 480-484
8. **Jennett B., Teasdale G., Braakman R., Minderhoud J., Heiden J., and Kurze T.** 1979. Prognosis of patients with severe head injury. Neurosurgery **4**:283-289
9. **Kaku Y., Yonekawa Y., Tsukahara T., and Kazekawa K.** 1992. Superselective intraarterial infusion of papaverine for the treatment of cerebral vasospasm after subarachnoid hemorrhage. J. Neurosurg. **77**:842-847
10. **Kassell N. F., Helm G., Simmons N., Phillips C. D., and Cail W. S.** 1992. Treatment of cerebral vasospasm with intraarterial papaverine. J. Neurosurg. **77**:848-852
11. **Kassell N. F., Torner J. C., Haley E. C. Jr., Jane J. A., Adams H. P., and Kongable G. L.** 1990. The international cooperative study on timing aneurysm surgery, 1: overall management results. J. Neurosurg. **73**:18-36
12. **Katoh H., Shima K., Shimizu A., Takiguchi H., Miyazawa T., Umezawa H., Nawashiro H., Ishihara S., Kaji T., Makita K., and Tsuchiya K.** 1999. Clinical evaluation of the effect of percutaneous transluminal angioplasty and intraarterial papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. Neurol. Res. **21**:195-203
13. **Kinoshita Y., Terada T., Nakamura Y., Nakai E., Nakai K., Itakura T., Naka Y., Naka D., Takehara R., Imai H., Tsuji N., Kido T., Kakishita K., Hyotani G., and Kuriyama T.** 1995. Endovascular treatment of cerebral vasospasm with intraarterial papaverine infusion. Neurol. Surg. **23**:881-887
14. **Milburn J. M., Moran C. J., Cross III D. T., Diringer M. N., Pilgram T. K., and Dacay R.G. Jr.** 1988. Increase in diameters of vasospastic intracranial arteries by intra-arterial papaverine administration. J. Neurosurg. **88**:38-42,
15. **Milburn J. M., Moran C. J., Cross III D. T., Diringer M .N., Pilgram T. K., and Dacay R. G. Jr.** 1997. Effect of intraarterial papaverine on cerebral circulation time. Am. J. Neuroradiol.**18**:1081-1085
16. **Mizukami M., Kawase T., Usami T., and Tazawa T.** 1982. Prevention of vasospasm by early operation with removal of subarachnoid blood. J. Neurosurg. **10**:301-307
17. **Mizoi K., Yoshimoto T., Takahashi A., Fujiwara S., Koshu K., and Sugawara T.** 1993. Prospective study on the prevention of cerebral vasospasm by intrathecal fibrinolytic therapy with tissue-type plasminogen activator. J. Neurosurg. **78**:430-437
18. **Ohkuma H., Manabe H., Tanaka M., and Suzuki S.** 2000. Impact of cerebral micro-circulatory changes on cerebral blood flow during cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke **31**:1621-1627
19. **Okada Y., Shima K., Nishida M., Yamane K., Hatayama T., Yamanaka C., and Yoshida A.** 1999. Comparison of transcranial doppler investigation of aneurysmal vasospasm with digital subtraction angiographic and clinical findings. Neurosurgery **45**: 443-450
20. **Origitano T. C., Wascher T. M., Reichman O. H., and Anderson D. E.** 1990. Sustained increased cerebral blood flow with prophylactic hypertensive hypervolemic hemodilution ("triple-H" therapy) after subarachnoid hemorrhage. Neurosurgery

27:729-740

21. **Polin R.S., Hansen C.A., and Kassel N.F.** 1998. Intraarterially administration papaverine for the treatment of symptomatic cerebral vasospasm. Neurosurgery **42**:1256-1267
22. **Sundt T. M. Jr. and Whisnant J. P.** 1978. Subarachnoid hemorrhage from intracranial aneurysms. Surgical management and natural history of disease. N. Engl. J. Med. **299**:116-122
23. **Yoshida Y., Ueki S., and Takahashi A.** 1985. Intrathecal irrigation with urokinase in ruptured cerebral aneurysm cases. Basic study and clinical application. Neurol. Med. Chir.(Tokyo) **25**:989-997
24. **Weir B., Grace M., Hansen J., and Rothberg C.** 1978. Time course of vasospasm in man. J. Neurosurg. **48**:173-178