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Early Operation of Aneurysmal Subarachnoid Hemorrhage— Use of Nicardipine, a Calcium Channel Blocker

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In the preceding 2.5 years, we tried to operate on the patient with ruptured cerebral aneurysm as early as possible, so far as the patient reaches us before day 5 after the most recent attack of rupture. In addition, an administration of a calcium channel blocking agent, Nicardipine, was started immediately after admission and continued for 2 to 3 weeks.

The purpose of this paper is to summarize the result of our series of early operation under the coverage with a calcium channel blocking agent.

Clinical Material and Methods

In 32 months covering from May 1981 through December 1983, 98 patients were operated upon for ruptured intracranial aneurysm in our clinic. Of these 98 cases, 38 patients with aneurysms of the anterior circulation admitted and operated upon on day 0 through day 5 (counting the day of rupture as day 0) constitute the material of this retrospective survey.

All these 38 patients were studied by computed tomography (CT) scan and angiography as soon after admission as possible. Four-vessel angiography was carried out in most cases. In a small number of patients in whom angiography of the carotid arteries alone was done prior to operation, the vertebrobasilar system was studied postoperatively. Postoperative angiography was performed in the second week after rupture in most patients except for 2 patients, who expired before the planned angiography. When deemed necessary, CT scans were repeated after operation.

Angiographic finding was classified as follows: *Group 1*: No narrowing, *Group 2*: Minimal vessel changes, *Group 3*: The proximal segment of the anterior cerebral artery (AC) or the middle cerebral artery (MC) is narrowed, but the lumen is distinct with a diameter not less than 1 mm, *Group 4*: The lumen of the AC or the MC is narrowed to about 0.5 mm. The outline of shadow is

Key words: Calcium blocker, Cerebral aneurysm, Nicardipine, Operation, Subarachnoid hemorrhage, Vasospasm.
索引語：カルシウム拮抗剤，脳動脈瘤，ニカルジピン，手術，クモ膜下出血，脳動脈攣縮.
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distinct, delayed forward flow and often border zone collateral anastomoses are evident. If the supraclinoid segment of the internal carotid artery (IC) is involved, the lumen is approximately 1.5 mm, *Group 5*: The lumen of the proximal AC or MC is less than 0.5 mm, forward flow is almost halted. The diameter of the supraclinoid IC is less than 1.5 mm.

Hemorrhage on CT scans was classified into the following 4 groups: *Group 1*: No subarachnoid blood visualized, *Group 2*: Diffuse or thin sheet of blood in the subarachnoid space, *Group 3*: Clot or thick layer of blood in the subarachnoid space, *Group 4*: Diffuse or no subarachnoid hemorrhage with intracerebral or intraventricular clots[6]. In 19 patients in whom CT scan with contrast medium enhancement was available on admission, presence or absence of abnormal gyral enhancement was also examined.

Tranexamic acid in a dosage of 6000 mg/day was given intravenously during the preoperative period. A continuous intravenous infusion of Nicardipine was started immediately after admission with a standard dosage of 6 mg/day. Later in the postoperative stage, this was followed by an oral dose in 25 cases. The intravenous administration in 38 patients varied in dosage from 1.5 to 9.0 mg/day with an average of 6.1 mg/day, and in duration from 4 to 26 days with an average of 8.1 days, whereas the oral administration in 25 patients varied in dosage from 60 to 180 mg/day with an average of 124 mg/day, and in duration from 5 to 30 days with an average of 15.4 days. Corticosteroids, osmotic diuretics and low molecular weight dextran were given when necessary throughout the pre-, intra-, and post-operative periods.

The operation was performed via a pterional approach under an operating microscope. An induced hypothermia or an artificial hypotension below 100 mmHg systolic was not used in any case. A temporary clipping of the proximal vessel was used in a few patients.

A clinical outcome was graded at the time of discharge and at the latest follow-up visit 3 to 30 months later. Those patients with an excellent result were able to return to their previous occupations with no neurological handicap. A good result was one in which the patient suffered a permanent neurological deficit but was able to live and work independently. A poor result was one in which the patient suffered a severe disabling neurological deficit either before or after treatment.

Results

Thirty-eight patients were distributed in age from 32 to 70, with an average age of 49. Nineteen patients were male and 19 were female (Table 1). Thirty-two patients harbored a single aneurysm, and 6 patients had multiple aneurysms (2 in each patient), a total number of aneurysms being 44. Sites of aneurysms were summarized in Table 2.

CT findings of hemorrhage on admission were classified as group 1 in 5 patients, group 2 in 15, group 3 in 11, and group 4 in 7. Abnormal gyral enhancement was seen in 14 patients, and it was absent in 5. The remaining 19 patients received no contrast medium at CT scan on admission. Presence or absence of gyral enhancement was correlated with the types of hemorrhage on CT in Table 3.

Four patients were operated upon on day 0, 18 patients on day 1, and 8 patients on day 2.

Table 1. Age and gender of 38 patients with ruptured anterior circulation aneurysms.

Decade	4th	5th	6th	7th	8th	Total
Male	5	6	5	3	0	19
Female	2	6	8	2	1	19
Total	7	12	13	5	1	38

Table 2. Sites of aneurysms (44 aneurysms in 38 patients).

Sites of aneurysms	Ruptured	Unruptured	Total
Anterior communicating complex	21	1	22
Middle cerebral artery	8	2	10
Internal carotid artery	7	2	9
Pericallosal artery or proximal anterior cerebral artery	2	1	3
Total	38	6	44

Thirty patients out of 38 underwent an operation on day 2 or earlier. All 38 ruptured aneurysms were successfully excluded from circulation by means of a neck clipping. Of 6 incidentally found aneurysms in patients with multiple aneurysms, two were clipped and two were dealt with either by a wrapping or by a trapping procedure. Two unruptured aneurysms in the remaining two patients with multiple aneurysms were not operated upon, as one patient expired before a planned second stage operation for it, and in the other patient the unruptured aneurysm involved the cavernous portion of the internal carotid artery. At the time of operation for the ruptured aneurysm, the clinical condition of the patients was in grade 1 (Hunt and Kosnik) in 1 patient, grade 2 in 20, grade 3 in 15 and grade 4 in 2. None was in grade 5.

All 5 patients who showed no gyral enhancement were in grade 2 at the time of operation, whereas 7 of 14 patients with gyral enhancement were in grade 3 or 4 (Table 4).

Postoperative angiography was performed in 36 patients. Angiograms were essentially normal in 16 patients (group 1), whereas they demonstrated a minimal narrowing of the vessels in 9 (group 2). Eight patients were classified in group 3, and 2 patients in group 4. In 1 patient,

Table 3. Gyral enhancement correlated with types of hemorrhage on admission computed tomotraphy scan.

Gyral enhancement	Admission CT scan				Total
	Group 1	Group 2	Group 3	Group 4	
Present	—	8	3	3	14
Absent	3	1	—	1	5
Not performed	2	6	8	3	19
Total	5	15	11	7	38

Table 4. Gyral enhancement versus clinical condition at operation.

Gyral enhancement	Grades at operation					Total
	1	2	3	4	5	
Present	1	6	5	2	—	14
Absent	—	5	—	—	—	5
Not performed	—	9	10	—	—	19
Total	1	20	15	2	—	38

angiographic non-filling of the intracranial vessels was observed shortly before death (group 5) (Tables 5 and 6).

Symptomatic vasospasm developed in 6 patients. Three of them showed angiographic vasospasm as well (group 2 change in 1 patient and group 3 change in 2 patients). They recovered, however, and a final clinical outcome was excellent in all. The remaining 3 patients expired. One of them showed group 3 angiographic vasospasm. The second patient who deteriorated fulminantly showed angiographic non-filling. No postoperative angiograms were available in the third patient. Angiographic findings were correlated with findings of admission CT scans in Table 5, with clinical outcome in Table 6 and with symptomatic vasospasm in Table 7.

Table 5. Admission computed tomography correlated with postoperative angiography.

Postoperative angiography	Admission CT scan				Total
	Group 1	Group 2	Group 3	Group 4	
Group 1	4	8	2	2	16
2	—	5	3	1	9
3	1	1	4	2	8
4	—	1	1	—	2
5	—	—	—	1	1
Not done	—	—	1	1	2
Total	5	15	11	7	38

Table 6. Findings of postoperative angiography versus clinical outcome.

Postoperative angiography	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
Group 1	15	1	—	—	16
2	8	1	—	—	9
3	7	—	—	1	8
4	2	—	—	—	2
5	—	—	—	1	1
Not done	—	—	—	2	2
Total	32	2	0	4	38

Table 7. Findings of postoperative angiography correlated with symptomatic spasm.

Postoperative angiography	Symptomatic vasospasm		Total
	Present	Absent	
Group 1	—	16	16
2	1	8	9
3	3	5	8
4	—	2	2
5	1	—	1
Not done	1	1	2
Total	6	32	38

Table 8. Findings of postoperative angiography correlated with gyral enhancement.

Postoperative angiography	Gyral enhancement			Total
	Present	Absent	Not performed	
Group 1	6	4	6	16
2	3	—	6	9
3	1	1	6	8
4	2	—	—	2
5	1	—	—	1
Not done	1	—	1	2
Total	14	5	19	38

One of 5 patients with no gyral enhancement developed postoperative angiographic vasospasm (Group 4), and the remaining 4 patients showed no significant arterial narrowing postoperatively. On the other hand, 4 of 14 patients with gyral enhancement showed angiographic vasospasm of either group 3, 4, or 5 (Table 8). Symptomatic vasospasm developed in 3 of 14 patients with gyral enhancement, whereas none of 5 patients without gyral enhancement showed symptoms and signs of cerebral ischemia after operation (Table 9).

A clinical outcome was classified as excellent in 32 patients, and good in 2. In none was it poor (Table 10). Two patients with aneurysm of the anterior communicating artery showed

Table 9. Development of symptomatic vasospasm correlated with gyral enhancement.

Gyral enhancement	Symptomatic vasospasm		Total
	Present	Absent	
Present	3	11	14
Absent	—	5	5
Not performed	3	16	19
Total	6	32	38

Table 10. Clinical outcome of patients versus sites of ruptured aneurysms.

Sites of aneurysms	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
Anterior communicating complex	18	2	—	1	21
Middle cerebral artery	8	—	—	—	8
Internal carotid artery	5	—	—	2	7
Pericallosal artery and proximal anterior cerebral artery	1	—	—	1	2
Total	32	2	—	4	38

Table 11. Clinical outcome of patients versus timing of operation.

Operation	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
day 0	3	—	—	1	4
1	15	2	—	1	18
2	6	—	—	2	8
3	3	—	—	—	3
4	3	—	—	—	3
5	2	—	—	—	2
Total	32	2	0	4	38

paresis of the leg on awakening from anesthesia. CT showed a small low density lesion in the deep frontal region. When discharged, both patients were self-dependent but a minimal weakness of leg still persisted and the results were classified as good. Both patients were operated upon on day 1, and the vasospasm does not seem to be responsible for their minor deficits. We assume rather that the perforating branch might have been damaged at operation in these two patients.

Four patients expired (Table 11). Vasospasm was thought to be a cause of death in three of them. The fourth patient who was operated upon on day 1 in grade 4 did not regain consciousness and expired on day 5. Although neither a postoperative angiography nor an autopsy was performed, we assume that the vasospasm is an unlikely cause of death of this patient. Hydrocephalus developed in this series in only 3 patients.

Table 12. Outcome versus clinical grades at operation.

Grade	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
1	1	—	—	—	1
2	20	—	—	—	20
3	11	2	—	2	15
4	—	—	—	2	2
5	—	—	—	—	0
Total	32	2	0	4	38

Table 13. Clinical outcome versus computed tomographic findings of hemorrhage.

Hemorrhage	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
Group 1	5	—	—	—	5
2	14	1	—	—	15
3	8	1	—	2	11
4	5	—	—	2	7
Total	32	2	0	4	38

Table 14. Clinical outcome versus computed tomographic evidence of gyral enhancement.

Gyral enhancement	Clinical outcome				Total
	Excellent	Good	Poor	Dead	
Present	12	—	—	2	14
Absent	5	—	—	—	5
Not performed	15	2	—	2	19
Total	32	2	0	4	38

Table 15. Findings of admision computed tomography vs. symptomatic vasospasm.

Symptomatic vasospasm	Addmission CT				Total
	Group 1	Group 2	Group 3	Group 4	
Present	0	1	3	2	6
Absent	5	14	8	5	32
Total	5	15	11	7	38

An outcome was tabulated in relation with the location of the aneurysm (Table 10), with the timing of operation (Table 11), with grade at operation (Table 12), with CT findings of hemorrhage (Table 13), and with presence or absence of gyral enhancement (Table 14). Symptomatic vasospasm was correlated with the findings of admission CT scanning in Table 15.

Discussion

Recent advances in anesthetic techniques and refinements of microsurgical instruments including various spring clips have made the intracranial operation of ruptured aneurysms a reasonably safe and radical procedure. There are now very few aneurysms which could not be handled successfully by a direct attack. Delayed vasospasm, however, still remains to be a single most important factor adversely affecting the morbidity and mortality of the patients. Also controversial is the timing of operation. The reasonings behind the early operation are firstly to avoid

rebleeding, and secondly to wash out the clot from the subarachnoid space as soon as possible. The opponents to the early operation believe that the operation in the acute stage not only is technically difficult, but also tends to aggravate the vasospasm and eventually the ischemic damage of the brain.

Although the number of patients is not large, our results of the earliest possible operation for patients admitted not later than day 5 and in clinical grades 1 to 3 seem to be promising. With the use of mechanical hyperventilation, steroids, hypertonic solution of glycerol and occasionally a cerebrospinal fluid drainage from the ventricle, clipping of the aneurysmal neck was possible without undue retraction of the brain. Premature rupture of the aneurysm did not happen, and an application of a temporary clip was seldom necessary in this series.

KASSELL et al. reported the overall results of early management and delayed operation (operation performed no sooner than 12 days after the rupture) in 249 patients admitted on days 0 through 3 after aneurysmal subarachnoid hemorrhage[10]. Three months after the initial subarachnoid hemorrhage, a favorable outcome was obtained in only 43 per cent of the patients. The management morbidity was 23 per cent and the management mortality was 34 per cent. The results were better when the 190 patients admitted in good neurological conditions (grades 1 through 3) were selected, but a favorable outcome was still limited to 51 per cent, and 27 per cent died with delayed operation[2].

In the series of LJUNGGREN et al., 31 patients were admitted under the conditions nearly equal to those of a series of KASSELL et al. and underwent early operation[11]. A favorable outcome was obtained in 87 per cent. Two patients (6 per cent) died and two had a poor outcome. In the present series, the mortality was 11 per cent, and 89 per cent had a favorable outcome (excellent in 84 per cent and good in 5 per cent). In none was the outcome poor. When the patients operated on in good neurological conditions (grades 1 to 3) were analyzed, 94 per cent had a favorable outcome and 6 per cent died. Our results thus seem to confirm those obtained in the previous reports indicating that the early operation in patients in good conditions yields a better results than the delayed operation[12,15].

In the period covering this study, we noted that the incidence of delayed ischemic symptoms was much less when compared to our experiences in the preceding 2 years when we had adopted a policy of delayed operation. In the present series, an angiographic vasospasm of moderate to severe degrees (groups 3 to 5) developed in 11 of 36 patients studied with postoperative angiography (31 per cent). A symptomatic vasospasm, however, developed only in 6 of 38 patients (16 per cent). In 3 of them, severe postoperative vasospasm was the direct cause of death of the patients, but the remaining 3 patients made a good recovery from ischemic symptoms and a clinical outcome was finally excellent in all of them. Accordingly, the delayed ischemia due to vasospasm adversely affected the final outcome in our series in only 3 of 38 patients (8 per cent), a figure much less than reported in most previous reports.

Correlating the development of vasospasm to subarachnoid hemorrhage visualized by CT scanning, FISHER et al. found severe vasospasm in 25 of their 47 patients (53 per cent)[6]. Twenty-two of these 25 patients with severe angiographic spasm developed ischemic clinical symptoms,

and in 10 the deficits persisted at least 6 weeks after the ictus and 3 expired. Of particular interest is the fact that in their 24 patients showing a clot or thick layer of subarachnoid hemorrhage on CT scans (group 3), 23 developed angiographic spasm (96 per cent) and 22 of them became symptomatic. In 10, ischemic symptoms persisted at 6 weeks after the ictus and 3 expired. In comparison, 11 patients showed similar CT appearances on admission in our present series, but a moderate to severe angiographic vasospasm was noted in 5 and symptomatic vasospasm in only 3 of them (27 per cent) (Tables 1 and 15).

We suppose that the good results in our series may be due at least partly to the pharmacological effects of Nicardipine in protecting the brain from ischemia. Nicardipine, a 1,4-dihydropyridine derivative, is a calcium channel blocking agent with a potent vasodilator effect on the cerebral blood vessels of both man and experimental animals[7,8,14,17]. Nicardipine has been known to effectively protect or ameliorate the vasospasm in experimental animals.

Using this same agent, a multicenter open study reported the results of 84 patients with a proven subarachnoid hemorrhage operated on in the acute stage[13]. A moderate to severe vasospasm developed in 39 of 63 patients studied by postoperative angiography (62 per cent), whereas a symptomatic vasospasm developed in 23 of 81 patients (28 per cent). Excluding 3 patients died of unrelated causes, the final clinical outcome in 81 patients was as follows: good recovery in 57 (70 per cent), moderately disabled in 11 (14 per cent), severely disabled in 6 (7 per cent), vegetative survival in 2 (2 per cent), and death in 5 (6 per cent). Although the routes of administration and dosages are not well controlled in this trial, the results indicate that Nicardipine is effective in protecting the brain from developement of cerebral ischemia due to late vasospasm in patients with aneurysmal subarachnoid hemorrhage, not older than 70 in age, in clinical grades 1 through 3, not associated with a massive intracerebral or intraventricular hematoma, and operated upon in an early stage after the ictus.

Beneficial effects of other calcium channel antagonists on the cerebral vasospasm have been also reported both in experimental animals and in human patients[2,3,5,20]. In recently completed double blind trial using Nimodipine[1], 121 patients with aneurysmal subarachnoid hemorrhage ranging in age from 15 to 80 years were studied. All patients showed no neurological deficits on admission within 96 hours after the ictus, and a calcium channel blocking agent, Nimodipine, was given orally for 21 days. In 56 treated patients, only one died of severe vasospasm (2 per cent), whereas in 60 patients treated with a placebo, 8 patients developed severe vasospasm (13 per cent), and 3 of them died (5 per cent). This result is statistically significant ($p=0.03$).

All these results seem to support the usefulness of calcium channel blocking agent in the management of patients with aneurysmal subarachnoid hemorrhage. Calcium channel blocking agents have been known to have a variety of physiologic effects which should be theoretically beneficial in treatment of aneurysm patients. These include the ability to inhibit contraction of cerebral vessels to various stimuli[18,19], to dilate pial vessels[4] and to increase the cerebral blood flow[9]. Initially we and apparently other investigators used calcium blocking agents in an attempt at ameliorating, or preventing the development of, cerebral arterial spasm. The ischemic symptoms developed less often and a final outcome of patients was much better with the use of calcium

channel blockers in most reports. Angiographic vasospasm, however, does occur and is often severe even with the use of this agent. We are presently more inclined to consider that the beneficial effect of calcium channel blocking agent in the treatment of aneurysm patients might be due to its effects protecting the ischemic brain[16], rather than the effect primarily against the development of vascular spasm.

Summary

In 32 months 98 patients were operated upon for ruptured cerebral aneurysms. Of these 98, 38 patients with aneurysm of the anterior circulation admitted and operated upon on day 0 through 5 constitute the material of this retrospective study. Thirty-eight patients harbored a total of 44 aneurysms. All aneurysms except for 2 unruptured ones were successfully dealt with by a direct attack. In all patients, an administration of a calcium blocking agent, Nicardipine, was started immediately after admission. Dosage and duration were on the average 6 mg/day for the initial 8 days intravenously, followed by 120 mg/day for another 15 days orally.

Angiographic and/or symptomatic vasospasm and final outcome of the patients were assessed and correlated with the clinical grade at operation, timing of operation, grade of subarachnoid hemorrhage as seen on the computed tomography scan, and other factors. A moderate to severe angiographic vasospasm developed in 11 patients, whereas symptomatic vasospasm was seen in 6 patients. Four patients expired, and vasospasm was considered to be the cause of death in 3 of them. Outcome was interpreted good in two patients. Both of them showed a mild weakness of the leg, but it was due to an operative damage to the perforating vessel and not to the vasospasm.

Although this study is a retrospective one with no double-blind basis, the results seem to suggest that the early operation of the ruptured aneurysm of the anterior circulation yields a reasonably good results, and that the use of calcium blocking agent in such patients may well protect the brain from ischemia due to vasospasm.

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和文抄録

破裂脳動脈急性期の手術—Ca 拮抗剤ニカルジピンの使用

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過去32カ月に経験した脳動脈瘤98例中，内頸動脈系動脈瘤で発作当日を第0病日として第5病日までに入院した38例に，第5病日までに直達手術を行なった．多発性例は6例で動脈瘤総数は44個，うち責任(破裂)動脈瘤は全て clipping を行なった．未破裂動脈瘤6個の中2個は clipping，2個は wrapping または trapping を行なった．残りのうち1例は予定した第2回手術前に死亡，1例は海綿洞部動脈瘤で，手術を行なわなかった．

全例入院直後よりニカルジピン平均 6 mg/day 8日間静注，ついで 120 mg/day 15日間経口投与を行なった．CT 所見，術後脳血管撮影，臨床的な脳虚血症状の発現，3カ月後の成績を検討した．血管撮影上中等度以上の動脈攣縮は，36例中11例にみられたが，脳虚血症状は6例でみられたにすぎず，成績は死亡2例，軽微な症状を残したもの2例，excellent 32例であった．これらの成績を文献例と比較し Ca 拮抗剤の意義についてふれた．