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The Delayed Ischemic Deficit Secondary to Spontaneous Subarachnoid Hemorrhage with Reference to the Effect of Medication

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= Abstract = 137 cases of spontaneous subarachnoid hemorrhage were analyzed retrospectively to evaluate the effect of medication on the delayed ischemic deficit. CT-visualized subarachnoid blood amount was most important in the occurrence of the deficit. Diuretics increased the incidence of the deficit, and nifedipine decreased. Other variables as age, sex, and use of kanamycin and reserpine were not statistically significant. We suggest that nifedipine may be beneficial to ischemia by various mechanisms, and that diuretics should be best avoided in patients with subarachnoid hemorrhage.

Key Words: ***Subarachnoid hemorrhage, Vasospasm, Delayed ischemic deficit, Calcium channel blockers, Diuretics***

INTRODUCTION

The delayed ischemic deficit (DID) that develops after spontaneous subarachnoid hemorrhage (SAH) due to ruptured saccular aneurysm is a major cause of morbidity and mortality, and an apparently clear relationship between the presence of severe vasospasm and the DID was found by Fisher *et al.* (1977), although other etiolgies as acute proliferative vasculopathy have been proposed (Kapp *et al.* 1982; Smith *et al.* 1985). Numerous substances have been suggested for this vasospasm, and each has its conflicting *in vivo* and *in vitro* experimental results (Wilkins 1980). As serotonin, released from platelets in the subarachnoid space blood, is considered one of the most potent spasmogenic substances, serotonin antagonists as kanamycin and reserpine,now known to have negligible antispasmogenic activity, are still advocated by some authors (Adams and Victor 1985).

Although the exact causes of vasospasm are still unknown, since calcium ion is the "final common pathway" of contraction in vascular smooth muscle, calcium channel blockers (CCBs), which inhibit the influx of calcium through the smooth muscle cell membrane, were extensively studied in the hope that cerebral vasospasm might be prevented or treated. CCBs have another advantage that they are selective in smooth muscle systems. So some can accomplish selective dilatation of cerebral arteries without inducing systemic hypotension, thus enabling increased cerebral perfusion. Among them the most promising drugs are the dihydropyridine derivatives, nimodipine and nifedipine.

In this study we used combination of kanamycin and reserpine sine 1980, and nifedipine since 1983 independently as antispasmodic drugs, and analyzed the result retrospectively. As volume expansion has been reported to be effective in treating the DID, we also analyzed the effect of diuretics, a volume depleter.

MATERIALS AND METHODS

Among the 273 cases of spontaneous SAH probably due to aneurysmal rupture who were admitted to our hospital between March 1980 and May 1985, 137 cases were selected according to the following criteria (Table 1). Brain CT scans were done in every case. All the patients followed the proposed management stated below. The criteria of

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Table 1. Criteria for patient selection

1. spontaneous onset of symptoms, without head trauma
2. bloody or xanthochromic cerebrospinal fluid (CSF), not caused by a traumatic puncture
3. brain CT scan without evidence of an unsuspected parenchymal source
4. no evidence of an arteriovenous malformation on four vessel angiography when it is done
5. exclude patients with bleeding diathesis
6. treatment started within 72 hours after the ictus
7. exclude patients who were thought to have a DID when therapy was started
8. observation period* of longer than 7 days

* defined as the shortest interval between the ictus and rebleeding, discharge, death or surgical manipulation

a DID was gradual development of focal neurologic deficit with or without infarction on a brain CT scan without rebleeding. Many neurologic deficits which might be attributable to other causes (Fisher *et al.* 1977) were carefully excluded. The initial coma status was classified according to Botterell's (1956). Brain CT scans were done as early as possible, but there was a delay as long as 7 days in 3 cases. As the blood amount in subarachnoid space is known to have a direct relationship with development of the DID, we classified CT-visualized subarachnoid blood into four groups (Fisher *et al.* 1980): I. no blood visualized; II. a diffuse deposition or thin layer with all vertical layers of blood (interhemispheric fissure, insular cistern, ambient cistern) less than 1mm thick; III. localized clots and/or vertical layers of blood 1mm or greater in thickness; and IV. associated with intracerebral or intraventricular clots.

Our guidelines for management are as follows. All patients undergo an initial brain CT scan. If blood is not demonstrated, or if a brain CT scan is delayed from various reasons, lumbar puncture is done to confirm bloody or xanthochromic CSF. Then they are placed on a routine medical regimen: narcotics for headache control; stool softners; mannitol (225 gm per day) and dexamethasone (16 mg per day) with tapering over one and two weeks; and tranexamic acid (6 gm per day). Anticonvulsants, mainly phenytoin, are used if indicated. To keep systolic blood pressure between 120 and 140 mm Hg, antihypertensive agents, hydralazine, propranolol, or diuretics as furosemide are used according to the charged physician's preference. As antispasmodic drugs, combination of kanamycin (1 gm p.o. qid) with reserpine (0.2 mg s.c. qid) was used since 1980; and nifedipine (10 mg p.o. tid) since 1983. They were used independently, *i.e.* there is a group which used no antispasmodic drug, other group which used one of them, and other group which used both. Operation is usually delayed until 21 days after the ictus.

Although there could be many variables that would affect the outcome, the DID, we restricted the variables to age, sex, coma scale, CT-visualized subarachnoid blood amout (AMT), and use of nifedipine, combination of kanamycin and reserpine (KR), or diuretics. All data were coded, and entered into a computer. Statistical analyses used were cross-tabulation and discriminant analysis in the Statistical Package for the Social Sciences (Klecka 1975).

RESULTS

The characteristics of the group with cross-tabulation are listed in Table 2. Of the 137 cases, 60 cases developed the DID (43.8%). Deeper coma ($p < .01$), higher-grade of CT-visualized subarachnoid blood amount ($p < .001$), and use of diuretics ($p < .001$) had an increased occurrence of the DID. Use of nifedipine ($p < .01$) was associated with decreased occurrence of the DID. Age, sex, and use of kanamycin and reserpine were not statistically

Table 2. Characteristics of the group with cross-tabulation

		DID#			
		−	+	Total	p-value*
Age					p= .7281
	20—	3	1	4	
	30—	14	7	21	
	40—	21	21	42	
	50—	24	18	42	
	60—	14	11	25	
	70—	1	2	3	
Sex					p = .6865
	male	32	27	59	
	female	45	33	78	
Coma scale					p = .0046
	I	49	20	69	
	II	14	21	35	
	III	9	9	18	
	IV	3	9	12	
	V	2	1	3	

AMT#					p = .0002
	I		30	7	37
	II		22	13	35
	III		11	23	34
	IV		14	17	31
KR#					p = .1510
	−		54	35	89
	+		23	25	48
Nifedipine					p = .0090
	−		41	45	86
	+		36	15	51
Diuretics					p = .0001
	−		60	27	87
		+	17	33	50
Total			77	60	137

* p-value is calculated by Student's t-test

see text for abbreviations

significant ($p<.05$).

Although age, sex, coma scale, and CT-visualized subarachnoid blood amout were not significantly different among the groups of various medication, as the variables could be confounded, we used discriminant analysis in the Statistical Package for the Social Sciences. Both direct and stepwise methods were used. In the direct method, all the variables are entered into the analysis concurrently, and the discriminant functions are created from the entire set of variables, regardless of the discriminating power of each variable. In the stepwise method, the "next best" discriminator is sequentially selected at each step until all variables are selected or no additional variables provide a minimum level of improvement. The statistics used was Wilks method. Although discriminant analysis requires that the variables be independent, coma scale and CT-visualized subarachnoid blood amount might not be independent. But we were able to interpret the results by comparing the results of the direct and stepwise methods with inclusion or exclusion of CT-visualized subarachnoid blood amount.

Table 3 shows the results of the analysis. The standardized coefficient is the score from each function with a mean of zero and a standard deviation of one, which represents the relative contribution. The sign merely denotes whether the variable is making a positive or negative contribution. The interpretation is analogous to that of beta weights in multiple regression. The unstandardized coefficients are such that when these are multiplied by the raw values of the associated variables, they arrive at a discriminant score after adding a constant, but they do not report the relative importance of the variables.

CT-visualized subarachnoid blood amount, diuretics, and nifedipine in this order contributed to the development of the DID. Other variables were not statistically significant. Coma scale turned out to be not significant, which was interpreted as it did not discriminate further in addition to CT-visualized subarachnoid blood amount. (When CT-visualized subarachnoid blood amount was excluded in the analysis, coma scale turned out to be significant.)

Table 3. Results of the discriminant analysis

	Stepwise method		Direct method	
	standardized coefficient	unstandardized coefficient	standardized coefficient	unstandardized coefficient
AMT#	.69488	.64485	.62160	.58527
Diuretics	.63279	1.33706	.62120	1.35069
Nifedipine	—.45285	—.95401	—.43241	—.91095
Age			.01006	.00093
Sex*			.06450	.12938
Coma scale			.03071	.07653
KR#			.12304	.25796
Constant		—1.71849		—1.91166

see text for abbreviations

* male = 1: female = 0

Table 4. Characteristics of the revised group with cross-tabulation

		DID#			
		−	+	Total	p-value*
Age					p = .8182
	20—	2	.0	2	
	30—	12	6	18	
	40—	17	14	31	
	50—	21	14	35	
	60—	10	8	18	
	70—	1	1	2	
Sex					p = .9878
	male	25	17	42	
	female	38	26	64	
Coma scale					p = .0101
	I	46	20	66	
	II	11	14	25	
	III	6	5	11	
	IV	0	4	4	
AMT#					p = .0001
	I	30	7	37	
	II	22	13	35	
	III	11	23	34	
KR#					p = .1560
	−	45	25	70	
	+	18	18	36	
Nifedipine					p = .0126
	−	35	34	69	
	+	28	9	37	
Diuretics					p = .0001
	−	50	18	68	
	+	13	25	38	
Total		63	43	10	

* p-value is calculated by Student's t-test
\# see text for abbreviations

In the stepwise method, the sensitivity of the discriminant function with variables of CT-visualized subarachnoid blood amount, diuretics, and nifedipine was 70.0% (42 out of 60), and specificity was 72.7% (56 out of 77). Overall, 98 cases were correctly classified with a classification rate of 71.5% (98 out of 137). In the direct method, the sensitivity of the discriminant function with the entire set of variables was 71.7% (43 out of 60), and specificity was 72.7% (56 out of 137). Overall, 99 cases were correctly classified with a classification rate of 72.3% (99 out of 137), which is not significantly greater than that of the stepwise method.

The observation period, delay in performing a brain CT scan, and delay in starting treatment among each group were not significantly different ($p<.05$).

DISCUSSION

Hypertension and diabetes mellitus could have been meaningful variables, but evaluation was difficult because of acutely-disturbed condition of the patients, and were excluded. Mannitol may improve cerebral circulation by elevating blood pressure, decreasing intracranial pressure, or decreasing the sludging of erythrocytes, but we do not think it was a significant variable, as it was routinely used in every case, though with some dosage variation. High dose steroids were advocated by some authors (Chaytte *et al.* 1983), but the dose used in this study was relatively small, and it was also routinely used. And we do not think hydralazine and propranolol significant, because they have preferential action on peripheral vessels. Although there was a report that subarachnoid enhancement was valuable for predicting cerebral infarction due to vasospasm (Hirata *et al.* 1982), the timing of a CT scan would determine the enhancement, and we do not do a contrast-enhanced CT scan routinely in clinically suspected SAH, if not indicated otherwise.

CCBs are a recently developed class of vasodilators that prevent the influx of calcium into vascular smooth muscle cells. This unique pharmacologic effect of these agents provides a theoretical basis for their use in the prevention of vasospasm, as they would inhibit the actions of all vasoactive substances on intracerebral smooth muscle cells via a blockade of the "final common pathway" of cellular contraction, instead of blocking specific and individual receptors. Some of these agents have preferential action on intracerebral versus peripheral arteries. The most potent and selective drugs are nimodipine and nifedipine, and there was a well controlled clinical study using nimodipine (Allen *et al.* 1983). Although most researchers believe that the DID is caused by a pathologic narrowing of the cross-sectional area of intracerebral arteries which again is the result of vasospasm due to increased vascular smooth muscle tension, it still can be argued that it is actually due to other causes as compression of the arteries by increased intracra-

Table 5. Results of the discriminant analysis of the revised group

	Stepwise method		Direct method	
	standardized coefficient	unstandardized coefficient	standardized coefficient	unstandaridized coefficient
AMT#	.65753	.87066	.63663	.84258
Diuretics	.58974	1.31925	.58815	1.31570
Nifedipine	—.39056	—.83649	—.38711	—.82910
Age			—.01625	—.00155
Sex*			.08897	.18017
Coma sclae			.24673	.30864
KR#			.24673	.30864
Constant		—2.20415		—2.43237

see text for abbreviations

* male = 1; female = 0

nial pressure, edema of the vessel wall, or pathologic thickening of the arterial wall. Whatever the pathogenesis may be, we think that CCBs may be beneficial to ischemia by various mechanisms other than antispasmodic action. It is well-known that CCBs play a beneficial role in patients with acute myocardial infarction by limiting the amount of necrosis that results from a given ischemic insult and therefore preserving myocardial integrity and function. The mechanisms involved are: maximizing myocardial oxygen supply by preventing coronary vasospasm; increasing collateral blood flow to the ischemic zones; minimizing myocardial oxygen demands by decreasing some or all of the major determinants of oxygen demands; and providing protection to the subcellular myocardial component, perhaps by limiting the amount of calcium reaccumulation that enters the cell during ischemia (Stone and Braunwald 1985). By analogy, the same may be applied to cerebral ischemia. In addition to preventing vasospasm, CCBs may increase collateral circulation to the ischemic area, minimize oxygen demands, and provide a protection to the damaged brain cells. Nosko *et al.* (1985) reported an experimental result that nimodipine was not effective in the prevention of cerebral vasospasm and delayed ischemic deficit after SAH in monkeys. But in this report, mean arterial blood pressure (MABP) and cerebral blood flow (CBF) was decreased in a high dose group (12 mg per Kg q8h), and neurologic deficits appeared in this group. On the contrary, MABP and CBF was increased in a low dose group (3 mg per Kg q8h), and no neurologic deficit appeared. We suppose that even though nimodipine is quite selective, high doses may be detrimental by inducing systemic hypotension.

Serotonin *per se* is quite vasoactive, but its contribution to vasospasm is questioned: it is less vasoactive than blood; its concentration in CSF has poor correlation with vasospasm; and its level in CSF falls off rapidly after 24 hours while vasospasm occurs after 3 days.

There was a preliminary report on the detrimental effect of diuretics on the DID (Rosenwasser *et al.* 1983), and as volume expansion has been one of the most promising treatment of ischemic deficits in SAH (Kassel *et al.* 1982), we think that the volume status of patients with SAH should be adequate, and diuretics should be avoided.

Although there was almost a linear increase in the development of the DID from grade I to III of CT-visualized subarachnoid blood amount, grade IV was not associated with higher occurrence of the DID than that of grade III as was noted by Fisher (1980) and Allen (1983). Fisher (1980) thought he found the reason: the amount of blood in subarachnoid space in grade IV is not necessarily larger than that in grade III. We agree with his point, and as the question that vasospasm *per se* can induce ischemia is still controversial, *i.e.* increased intracranial pressure by hematoma or hydrocephalus may play a role to induce ischemia in grade IV in addition to vasospasm, it would be better to exclude grade IV in future studies (see Appendix).

Fisher's suggestion (1980) that older patients may be at greater risk of severe vasospasm because their capacious subarachnoid space allows larger blood accumulation was not observed in this study. It is well-known that associated migraine

which is thought to be due to severe vasospasm occurs in younger patients when their vessels are pliable. And there are reports that younger patients with migraine tend to respond better to CCBs than older patients (Louis 1981; Amery 1983). So we suggest that sclerotic vessles of older patients that are less pliable negate the effect of larger clots and narrowed arteries. Another reason we think is the possible diluting effect of widened subarachnoid space with same blood amount.

There was a case, not included in this study, that the patient's condition deteriorated with no focal symptom on the fifth day after the last rebleeding. Ophthalmoscopy showed bilateral retinal arterial narrowing. Light reflex was sluggish bilaterally. Angiography, done on the day for an emergency operation, revealed generalized severe arterial narrowing. There was a case report on retinal arterial narrowing with transient blindness in SAH (Thygesen and Rosenørn 1982), and we suggest that retinal arterial narrowing can be the first sign of vasospasm in some cases, and this should be carefully evaluated in SAH as well as preretinal hemorrhage and ocular motor palsies.

Appendix

Grade IV of CT-visualized subarachnoid blood amount was excluded in the revised group, and cross-tabulation and discriminant analysis were done (Table 4 & 5).

In the stepwise method, the sensitivity was 60.5% (26 out of 43),specificity 79.4% (50 out of 63), and classification rate 71.7% (76 out of 106). In the direct method, the sensitivity was 62.8% (27 out of 43), specificity 79.4% (50 out of 63), and classification rate 72.6% (77 out of 106).

The results are quite similar to those of the original group,and statistical significance is not significantly different when the sample size is smaller (106 compared with 137).

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= 국문초록 =

자발성 지주막하출혈에서의 지연형 허혈성 결손

—약제들의 효과를 중심으로—

서울대학교 의과대학 신경과학교실

노재규 · 전범석

지주막하출혈에서 지연형 허혈성 결손은 지주막하출혈의 예후를 나쁘게 하는 가장 중요한 요인의 하나이나, 그 발생기전은 아직 확실히 정립되어 있지 않고, 따라서 예방 및 치료에서도 여러가지 방법이 시도되고 있는 정도이다.

저자들은 1980년 3월부터 1985년 5월까지 서울대학교병원에 입원한 동맥류파열로 인한 것으로 생각된 자발성 지주막하출혈 환자 273례중 137례를 선택하여, 환자들의 상태 및 각 치료방법에 따른 지연성 허혈성 결손의 발생빈도를 판별함수를 써서 후향성으로 분석하였다. CT 상 보인 지주막하출혈량이 지연형 허혈성 결손의 발생과 가장 밀접한 연관을 가지고 있었고, 환자의 나이 및 성별은 유의한 연관을 갖지 않았다. 혈액용적의 고갈제인 이뇨제를 사용한 환자에서는 이 결손의 발생이 증가되어 있었고, Ca^{++} 길항제인 nifedipine을 사용한 환자에서는 적었다.

Serotonin 길항제인 kanamycin, reserpine은 이 결손의 발생과 유의한 연관을 갖지 않았다.