

Ameliorated Outcome of Subarachnoid Hemorrhage Patients Treated with Reduced Form Glutathione

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This study was designed to investigate the effects of glutathione (GSH) on delayed vasospasm and the outcome of subarachnoid hemorrhage (SAH) patients. Seventy-seven SAH patients who were admitted to 4 hospitals and operated on within 72 h after SAH, were injected intravenously with GSH (2.4 g/day) every 6 h for 14 days. Seventy SAH patients who were not treated with GSH in the same period were selected as the control group. Patient background, the outcome at 3 months after SAH according to the Glasgow Outcome Scale and the occurrence of symptomatic vasospasm were investigated. There were no statistically significant differences in patient backgrounds between the 2 groups. Regarding patient outcome, 57 patients (74%) showed good recovery, 8 (10%) were moderately disabled, 9 (12%) were severely disabled, 2 (3%) were in vegetative survival and 1 (1%) died in the GSH group, versus 39 (56%), 9 (13%), 15 (21%), 3 (4%) and 4 (6%) in the control group, respectively. These overall outcomes in the GSH group were significantly better than those in the control group ($P < 0.05$). In the GSH group, 31 patients (40%) showed symptomatic vasospasm, significantly lower than 46 (66%) in the control group ($P < 0.01$). Administration of GSH could be a good treatment for SAH patients.

Key words: glutathione; lipid peroxide; patient outcome; subarachnoid hemorrhage; vasospasm

Although outcomes of patients who suffer from subarachnoid hemorrhage (SAH) have been improving over the last decade because of upgrading in microsurgical techniques and patient management, along with the development of various anti-spasmogenic drugs, these outcomes are not yet satisfactory to most neurosurgeons especially in elderly patients and patients graded into the worse group according to their conditions on admission. Disney and colleagues (1988) reported that 6 of 79 SAH patients (7.6%) aged more than 60 years and 30 of 184 patients (16.3%) classified as Grade III, IV or V on the Hunt and Hess scale showed good recovery on the Glasgow Outcome Scale at 3 months after the onset. Lipid peroxidations based on free radical reactions were reported to increase in the cerebrospinal fluid, vascular vessels and

serum after SAH and were thought to play a pertinent role in the pathogenesis of delayed cerebral vasospasm (Asano et al., 1981; Sasaki et al., 1981a, 1981b; Romero et al., 1984; Shimizu et al., 1988; Watanabe et al., 1988a, 1988b, 1992). Recently in Japan, anti-lipid peroxidative drugs or radical scavengers such as nifedipine fumarate (Ohta et al., 1986), ozagrel sodium (Suzuki et al., 1989), AVS [1,2-bis(nicotinamide)-propane, (Asano et al., 1984, 1996)], ebselen (Watanabe et al., 1990, 1997; Saito et al., 1998) and MCI-186 [3-methyl-1-phenyl-pyrazolin-5-one (Nakagome et al., 1990; Watanabe et al., 1994)] have been applied to SAH patients to prevent the occurrence of vasospasm and have had some considerable effects on patient outcomes. These agents are however all artificial and foreign to the human body. Activation of

Abbreviations: CT, computerized tomography; GOS, Glasgow Outcome Scale; GSH, glutathione; SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurological Surgeons

natural anti-lipid peroxidative systems such as the glutathione (GSH) cycle which are inherent in living organisms was considered to lower the lipid peroxide content and to have beneficial effects on delayed vasospasm (Watanabe et al., 1988b). Reduced form GSH is converted to its oxidized form by GSH peroxidase, reducing lipid peroxides in the process and the oxidized form GSH is converted back to GSH by GSH reductase. Administration of GSH was expected to reduce lipid peroxide levels, since it was very difficult to increase these 2 enzyme activities. We observed that GSH injected intravenously decreased lipid peroxide contents in the serum and 5-lipoxygenase activity in the basilar artery compared with the untreated group and simultaneously ameliorated angiographical delayed vasospasm of the basilar artery in a canine two-hemorrhage model (unpublished data). The present study was designed to investigate the effects of GSH on delayed cerebral vasospasm and the outcome of SAH patients. We administered GSH to SAH patients randomly and compared the findings with data from patients who were not treated with GSH.

Subjects and Methods

Patient Group

The SAH patients admitted to Tottori University Hospital, Nojima Hospital, Tokyo Police Hospital and National Yokohama Hospital between January 1986 and January 1993 and underwent clipping surgery within 72 h after SAH were nominated for this study. No patients were ruled out in terms of sex, age, site of ruptured aneurysm or clinical state before operation, the only exception being a patient under 20 years old. The number of total SAH patients in the 4 hospitals in the above period was 478, of whom 291 were operated on within 72 h after SAH, 75 were operated on after 72 h, and 112 received no operation.

Of the 291 candidates, 77 patients were selected at random before surgery and treated with 2.4 g/day of GSH after informed consent

was obtained. Every 6 h, 0.6 g of GSH which was dissolved with 100 mL of saline, was administered to the patient intravenously for 1 h. This treatment was started just after operation and was continued for 14 days. In this GSH group, no other drugs which were generally accepted as therapeutic against delayed vasospasm were administered. Temporary administration of calcium antagonists and steroids for the purpose of decreasing arterial blood pressure and reducing brain swelling after the surgery were permitted.

As a control group, 70 patients were selected randomly from the remaining 214 candidates, retrospectively. These patients were treated with at least one of several therapeutics such as nifedipine fumarate, ozagrel sodium, AVS, Ebselen and MCI-186.

In both groups, no other aggressive treatments such as cisternal perfusion therapy or hypervolemic hypertensive therapy were performed.

Clinical Assessment

After admission, each patient's neurological condition was assessed using the Japan Coma Scale and/or the Glasgow Coma Scale, and the presence or absence of paresis was assessed every day and at any time when required. The patient's state before the operation was graded from I to V according to the World Federation of Neurological Surgeons (WFNS) SAH scale (Drake, 1988).

A computerized tomography (CT) scan was taken on admission and classified according to Fisher's grouping (Fisher et al., 1980). When the patient's state deteriorated due to rerupture of the aneurysm before surgery, a further CT scan was performed and was employed as a pre-operative test. Serial CT scans were done to diagnose cerebral infarctions due to the vasospasm. The CT scan taken immediately after the operation could reveal brain damage due to surgery.

The site of the ruptured aneurysm was determined from the results of the first cerebral angiography, the CT scan and the operation. In most cases, the second angiography was performed between Day 21 and Day 60, not to veri-

Table 1. Characteristics of patients in the 2 treatment groups

Factor	GSH group		Control group		P value
Number of patients	77		70		
Sex					0.20
Male	40	(51.9)	29	(41.4)	
Female	37	(48.1)	41	(58.6)	
Age (year)	55.0 ± 11.6		54.7 ± 11.6		0.89
WFNS grade					0.13
I	29	(37.7)	35	(50.0)	
II	19	(24.7)	15	(21.4)	
III	4	(5.2)	4	(5.7)	
IV	20	(26.0)	12	(17.1)	
V	5	(6.5)	4	(5.7)	
Location of ruptured aneurysm					0.70
Anterior communicating artery	26	(33.8)	21	(30.0)	
Middle cerebral artery	25	(32.5)	22	(31.4)	
Internal carotid artery	19	(24.7)	21	(30.0)	
Anterior cerebral artery	3	(3.9)	5	(7.1)	
Vertebral artery	3	(3.9)	1	(1.4)	
Basilar artery	1	(1.3)	0	(0.0)	
Fisher CT group					0.59
1	1	(1.3)	0	(0.0)	
2	7	(9.1)	14	(20.0)	
3	49	(63.6)	36	(51.4)	
4	20	(26.0)	20	(28.6)	

Shown are number and (%), except age expressed as mean ± SD.

There were no statistically significant differences in patients' backgrounds between the 2 groups.

CT, computerized tomography; GSH, glutathione; WFNS, World Federation of Neurological Surgeons.

Results

fy the angiographical vasospasm but to confirm the proper clipping of the aneurysmal neck.

Deterioration in the neurological conditions of patients which occurred between Day 4 and Day 16 was judged to be due to symptomatic vasospasm when other possible causes such as brain damage due to surgery, hydrocephalus, serum electrolytes disorder, meningitis and epilepsy were excluded.

Patient outcome was assessed 3 months after SAH and was graded as good recovery, moderately disabled, severely disabled, vegetative survival and dead by the Glasgow Outcome Scale (GOS).

Statistical Analysis

The data based on the clinical variables from the 2 groups were examined by Student's *t*-test, or the chi-squared test, or the Mann-Whitney *U* test with the level of significance set at 0.05.

Comparability of treatment groups

Distribution of sex, age in years, site of ruptured aneurysm, preoperative WFNS grade and Fisher's preoperative grouping by CT scan in both the GSH and the control groups are indicated in Table 1. As far as these factors were concerned, there were no statistically significant differences between the 2 groups ($P > 0.1$). *P* values were obtained by the use of the chi-squared test for sex and site of ruptured aneurysm, Student's *t*-test for age, and the Mann-Whitney *U* test for the WFNS grade and Fisher grouping by CT, respectively (Table 1).

Symptomatic vasospasm and infarction due to vasospasm

Table 2 shows the incidence of symptomatic vasospasm and infarction due to vasospasm in

Table 2. Incidence of symptomatic vasospasm and infarction due to vasospasm in the 2 treatment groups

Factor	Group	
	GSH	Control
Symptomatic vasospasm	31* (40.3)	46* (65.7)
Infarction due to vasospasm	22 (28.6)	25 (35.7)

Shown are number and (%).

* $P < 0.01$ by chi-squared test.

both groups. The incidence of symptomatic vasospasm in the GSH group was 31/77 (40%), which was significantly lower than the value of 46/70 (66%) in the control group ($P < 0.01$, chi-squared test). Infarction due to vasospasm was revealed on the CT scan in 22 cases (29%) in the GSH group and 25 cases (36%) in the control group. The difference between these figures was not statistically significant, although the incidence of infarction due to vasospasm in the GSH group was lower than that in the control group.

Patient outcome

Table 3 shows the patient outcome of both groups in each preoperative WFNS grade. In all grades, 57 of the 77 patients (74%) in the GSH group demonstrated good recovery at 3

months in the GOS versus 39 of 70 patients (56%) in the control group. Regarding the other outcomes, moderately disabled, severely disabled, vegetative survival and dead in the GSH group consisted of 8 patients (10%), 9 (12%), 2 (3%) and 1 (1%), respectively, while these outcomes were observed in 9 patients (13%), 15 (21%), 3 (4%) and 4 (6%) in the control group. The outcomes in WFNS grades II and IV and also in all patients of the GSH group, were significantly better than those of the control group as shown in Table 3 ($P < 0.05$, Mann-Whitney U test). Figure 1 which shows patient outcomes according to the GOS at 3 months is divided into 2 classes, namely good recovery and others (moderately disabled, severely disabled, vegetative survival and dead) in each preoperative WFNS grade. The number of patients whose preoperative WFNS grade was I and represented a good recovery outcome was 26 of 29 (90%) in the GSH group and 30 of 35 (86%) in the control group; and in the cases of WFNS grades II, III, IV and V, 18 of 19 (95%), 2 of 4 (50%), 10 of 20 (50%) and 1 of 5 (20%) showed good recovery at 3 months in the GSH group versus 6 of 15 (40%), 2 of 4 (50%), 1 of 12 (8%) and 0 of 4 (0%) in the control group, respectively.

Table 3. Outcome of all patients in the 2 treatment groups by WFNS grade

WFNS grade	Group	Good recovery	Moderately disabled	Severely disabled	Vegetative survival	Dead
I	GSH	26 (89.7)	2 (6.9)	1 (3.4)	0 (0.0)	0 (0.0)
	Control	30 (85.7)	2 (5.7)	2 (5.7)	1 (2.9)	0 (0.0)
II	GSH*	18 (94.7)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
	Control*	6 (40.0)	2 (13.3)	7 (46.7)	0 (0.0)	0 (0.0)
III	GSH	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)
	Control	2 (50.0)	1 (25.0)	1 (25.0)	0 (0.0)	0 (0.0)
IV	GSH*	10 (50.0)	5 (25.0)	4 (20.0)	0 (0.0)	1 (5.0)
	Control*	1 (8.3)	4 (33.3)	4 (33.3)	0 (0.0)	3 (25.0)
V	GSH	1 (20.0)	0 (0.0)	2 (40.0)	2 (40.0)	0 (0.0)
	Control	0 (0.0)	0 (0.0)	1 (25.0)	2 (50.0)	1 (25.0)
Total	GSH*	57 (74.0)	8 (10.4)	9 (11.7)	2 (2.6)	1 (1.3)
	Control*	39 (55.7)	9 (12.9)	15 (21.4)	3 (4.3)	4 (5.7)

Shown are number and (%).

GSH, glutathione; WFNS, World Federation of Neurological Surgeons.

Outcome was evaluated according to the Glasgow Outcome Scale.

* $P < 0.05$ by Mann-Whitney U test.

Vasospasm and outcome in elderly patients

In elderly patients 60 years or older, the incidence of symptomatic vasospasm in the GSH group was 12/29 (41%) which was significantly lower than 25/27 (93%) in the control group ($P < 0.001$, chi-squared test). Infarctions due to delayed vasospasms as shown on the CT scan occurred in 9 cases (31%) in the GSH group and 14 cases (52%) in the control group. This difference was not statistically significant. Table 4 shows the outcome of elderly patients in each preoperative WFNS grade. Concerning all patients, 17 of 29 cases (59%) in the GSH group and 7 of 27 cases (26%) in the control group demonstrated good recovery at 3 months. Regarding the other classes of outcomes, moderately disabled, severely disabled, vegetative survival and dead in the GSH group were observed in 3 (10%), 6 (21%), 2 (7%) and 1 case(s) (3%), respectively, while these were observed in 4 (15%), 11 (41%), 3 (11%) and 2 cases (7%) in the control group. These outcomes in the GSH group were

significantly better than those in the control group ($P < 0.05$, Mann-Whitney U test). In

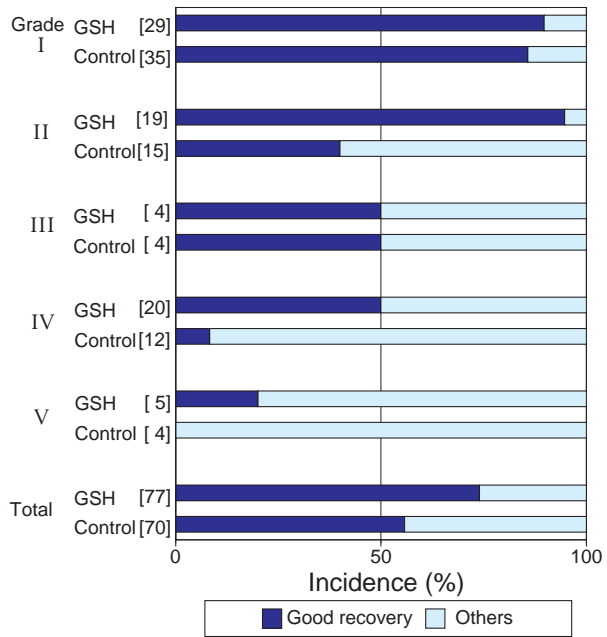


Fig. 1. Bar graph showing outcomes of all patients in the reduced form glutathione (GSH) and the control groups in each preoperative World Federation of Neurological Surgeons (WFNS) grade. Dark bars and light bars indicate good recovery and the other outcomes based on the Glasgow Outcome Scale, respectively. The number of patients is indicated in brackets.

Table 4. Outcome of elderly patients in the 2 treatment groups by WFNS grade

WFNS grade	Group	Good recovery	Moderately disabled	Severely disabled	Vegetative survival	Dead
I	GSH	8 (80.0)	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)
	Control	4 (50.0)	1 (12.5)	2 (25.0)	1 (12.5)	0 (0.0)
II	GSH	5 (83.3)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
	Control	3 (30.0)	2 (20.0)	5 (50.0)	0 (0.0)	0 (0.0)
III	GSH	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Control	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)
IV	GSH	2 (33.3)	1 (16.7)	2 (33.3)	0 (0.0)	1 (16.7)
	Control	0 (0.0)	0 (0.0)	3 (60.0)	0 (0.0)	2 (40.0)
V	GSH	1 (20.0)	0 (0.0)	2 (40.0)	2 (40.0)	0 (0.0)
	Control	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
Total	GSH*	17 (58.6)	3 (10.3)	6 (20.7)	2 (6.9)	1 (3.4)
	Control*	7 (25.9)	4 (14.8)	11 (40.7)	3 (11.1)	2 (7.4)

Shown are number and (%).

GSH, glutathione; WFNS, World Federation of Neurological Surgeons.

Outcome was evaluated according to the Glasgow Outcome Scale. "Elderly patients" is defined as patients aged 60 years or older.

* $P < 0.05$ by Mann-Whitney U test.

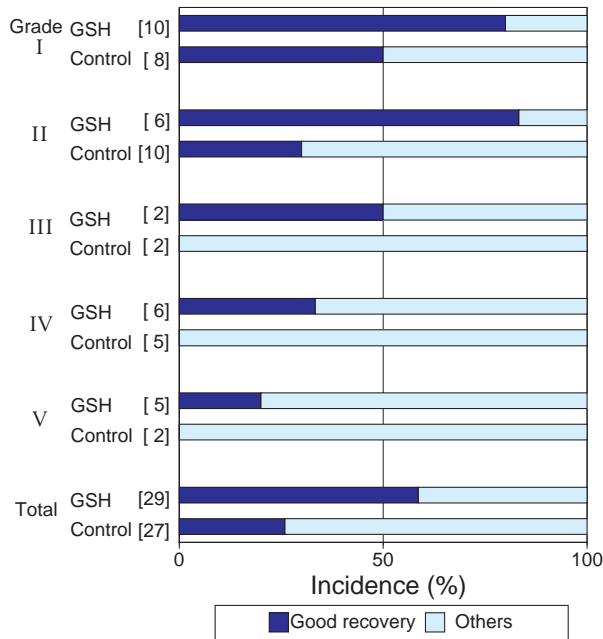


Fig. 2. Bar graph showing outcomes of elderly patients aged over 60 in the reduced form glutathione (GSH) and the control groups in each preoperative World Federation of Neurological Surgeons (WFNS) grade. Dark bars and light bars indicate good recovery and the other outcomes based on the Glasgow Outcome Scale, respectively. The number of patients is indicated in brackets.

each preoperative WFNS grade, the outcome in the GSH group showed a tendency to be better than that in the control group, although the differences were not statistically significant. As shown in Fig. 2, the ratio of the patients whose outcomes were good recovery to the patients of the GSH group in each preoperative WFNS grade seemed to be higher than that in the control group.

Discussion

Although this was a retrospective study, the assumption was that it was worthwhile to compare the clinical outcomes of these 2 groups, since there were no statistically significant differences in the backgrounds among patients, such as sex, age, preoperative WFNS grade, site of ruptured aneurysm or Fisher's grouping by CT scan. Of these factors, the patient's pre-

operative condition, amount and location of subarachnoid clot, and patient's age were suggested to be crucial for eventual outcome (Fisher et al., 1980; Disney et al., 1988). The mean age in both groups was about 55 and almost equal to each other. The ratio of the number of patients classified into WFNS grades IV and V to all patients in the GSH group was 33%, which was higher than the 23% value in the control group, although the *P* value in comparing the 2 groups by the Mann-Whitney *U* test was 0.13, which was rather low. The incidence of Fisher's groups 3 and 4 in the GSH group was 90% which was higher than the 80% value in the control group. Thus, if the patient outcomes in the GSH group would be better than those in the control group, as indeed they were, these results would be reliable, since the GSH group was at a disadvantage compared to the control group in terms of the latter 2 factors. Moreover, only GSH was administered as an agent against delayed vasospasm in the GSH group, while one or more kinds of drugs were used in the control group as mentioned above.

GSH has been applied to other kinds of diseases such as hepatitis, toxicosis, toxemia of pregnancy, exanthema, dermatitis, cataracts, etc., but the cost for the administration of GSH to SAH patients is not covered by health insurance in Japan. Therefore, it was impossible for us to use GSH for all SAH patients. This fortunately enabled us to compare the outcome of the GSH group with that of the control group. GSH is a drug which we can safely use for patients, because it shows almost no side-effects such as allergy, hypotension of arterial blood pressure or platelet dysfunction. Administration of GSH for 14 days also costs far less than any other treatment against vasospasm currently in use in Japan. This is and will be a very important matter regardless of whether the health insurance system covers its use or not.

As shown in Tables 2 and 3, the administration of GSH for 2 weeks not only reduced the

incidence of symptomatic vasospasm but also ameliorated the outcome in SAH patients, although it did not significantly reduce the incidence of infarction caused by delayed vasospasm. Regarding each preoperative WFNS grade, patient outcomes in the GSH group in grades II and IV were significantly better than those in the control group as clearly shown in Fig. 1, while there were no statistically significant differences between the outcomes of the 2 groups in grades I, III and V. The numbers of patients of both groups in grades III and V were 8 and 9, respectively, which were too small to compare statistically. In grade I, 90% of patients in the GSH group and 86% in the control group recovered to the level of good recovery according to the GOS at 3 months. This suggests that patients who suffered from mild SAH would recover well irrespective of which drug is administered.

Also, in the elderly patients 60 years or older, the administration of GSH significantly reduced the incidence of symptomatic vasospasm and ameliorated the clinical outcome, but did not significantly reduce the incidence of infarction due to vasospasm. As shown in Fig. 2, GSH treatment tended to improve patient outcome in each preoperative WFNS grade, although there were no statistically significant differences probably because of the small number of cases.

In the younger patients under 60 and classified into preoperative WFNS grades I to III, 32 of 34 patients (94%) in the GSH group and 31 of 34 patients (91%) in the control group showed an outcome at 3 months of good recovery. In the case of younger patients who were in good condition after SAH, clinical outcomes were already too good to be improved. It may be almost impossible for an agent against delayed vasospasm to significantly ameliorate an outcome of just 9% of patients, since these patients would suffer from surgical brain damage and various kinds of complications at a certain rate. In WFNS grade IV, 8 of 14 younger patients (57%) in the GSH group and 1 of 7 patients (14%) in the control group showed good recovery in the GOS. In the younger and severe SAH patients, GSH treatment tended to show beneficial effects in patient outcome.

Good effects from GSH in outcomes were observed in patients who were older than 60 or suffered from severe SAH. This has to be stressed when we investigate effects of anti-spasmodic drugs on SAH patient outcomes. Actually, Petruk and colleagues (1988) reported that nimodipine treatment increased the rate of good outcomes in poor-grade SAH patients in a double-blind study, although Öhman and colleagues (1991) and Mercier and colleagues (1994) reported that nimodipine treatment had no effect on overall outcome in either good-grade patients or all patients. The mean ages in years of SAH patients in recent studies were from 44 to 55 (Öhman et al., 1991; Haley et al., 1992, 1993, 1994; Shibuya et al., 1992), which were equal to or lower than those in our study. If the mean age in our study would have been 45, there might have been no statistically significant difference in overall outcomes between the GSH group and the control group. The age of SAH patients is becoming higher with the increasing span of life; actually, the mean age of SAH patients in Tottori University Hospital was 64 in the past year. We should thus make a great effort to treat these elderly SAH patients and should learn how to manage them effectively.

Above all, the administration of GSH had beneficial effects on not only the occurrence of symptomatic vasospasm but also on the outcome of the SAH patient, although the incidence of infarction due to delayed vasospasm was not significantly reduced by GSH treatment. In recent reports dealing with anti-spasmodic agents, nimodipine (Petruk et al., 1988; Öhman et al., 1991; Mercier et al., 1994), nicardipine (Haley et al., 1993), AT877 (Shibuya et al., 1992), AVS (Asano et al., 1996) and ebselen (Saito et al., 1998) could not alter the overall outcome of SAH patients, although these drugs had beneficial effects on some parameters such as symptomatic vasospasm, infarction shown on CT scan, etc. These findings revealed that these drugs could not only have beneficial effects on delayed vasospasm but also detrimental effects on patients, even if the occurrence of delayed vasospasm could affect only a small part of the outcome of SAH pa-

tients. Öhman and colleagues (1991) reported results contrary to ours, namely that the administration of nimodipine reduced the incidence of infarction due to delayed vasospasm but did not ameliorate patient outcome. These conflicting results suggest that the occurrence of infarction shown on CT scan could have a rather less effect on patient outcome according to the GOS.

Regarding the amount of GSH for SAH patients, we began with 2.4 g/patient/day, that is 1/5 of the dose (per body weight) with which the experimental SAH dogs were treated, and continued to use this dose for all patients. Therefore we have no information concerning the effects of other doses. Lesser doses of GSH may exert the same effects on vasospasm as observed in this study, or higher doses may have more effects than that in the case of 2.4 g/day.

In conclusion, intravenous administration of 2.4 g/day of GSH for 14 days ameliorated the overall outcome of SAH patients, concomitantly decreasing the incidence of symptomatic vasospasm. GSH can be used rather easily because of its rare detrimental effects and its low cost, and GSH administration does not inhibit any other treatments for SAH patients. Therefore, GSH treatment should be a good choice for management of SAH patients, or at least this should be added to treatments which have been already available for such patients.

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