Urokinase Cisternal Irrigation Therapy for Prevention of Symptomatic Vasospasm After Aneurysmal Subarachnoid Hemorrhage

A Study of Urokinase Concentration and the Fibrinolytic System

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Background and Purpose—Cisternal irrigation therapy with urokinase (UK) was performed in multiple institutions to prevent symptomatic vasospasm. The efficacy and safety of this therapy were evaluated, and the optimal concentration of UK was estimated.

Methods—This therapy was performed in 28 patients who underwent surgery within 72 hours of the onset of severe subarachnoid hemorrhage (Fisher’s group 3, CT number [Hounsfield units] >60). After the aneurysm was clipped, irrigation tubes were placed in the Sylvian fissure (inlet) unilaterally and in the prepontine or chiasmatic cistern (outlet). Lactated Ringer’s solution with UK (30, 60, or 120 IU/mL) was infused at a rate of 30 mL/h. The presence of symptomatic vasospasm was evaluated by changes in the clinical symptoms and the presence of a new low-density area on CT scan. Drained irrigation fluid and peripheral blood were examined chronologically to evaluate the fibrinolytic system.

Results—Symptomatic vasospasm was observed transiently in 3 cases (10.7%) without any low-density area on CT scan. In the 120-IU/mL group, no symptomatic vasospasm occurred. Analysis of drainage fluid suggested that UK 120 IU/mL is effective. The mean values of total drained blood volume for the respective groups were as follows: 58 mL in 30 IU/mL, 106 mL in 60 IU/mL, and 143 mL in 120 IU/mL. No abnormal changes were observed in the coagulative and fibrinolytic systems after UK irrigation.

Conclusions—These results suggest that cisternal irrigation therapy with UK is safe and effective for the prevention of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage. (Stroke. 2000;31:1256-1262.)

Key Words: fibrinolysis ■ irrigation ■ subarachnoid hemorrhage ■ urokinase ■ vasospasm

Symptomatic vasospasm is one of the most hazardous problems affecting morbidity and mortality after aneurysmal subarachnoid hemorrhage (SAH).1 It is now generally considered that cerebral vasospasm is induced by some spasmogenic substances produced from a clot around the cerebral arteries. Cisternal irrigation therapy with urokinase (UK) has been performed to prevent symptomatic vasospasm by dissolving and removing SAH, and excellent results have been obtained.2 Recently, some studies have shown that the use of tissue plasminogen activator (tPA) is effective in preventing symptomatic vasospasm.3–12 However, these studies showed many hemorrhagic complications and did not evaluate the fibrinolytic system in detail.

Cisternal irrigation therapy has been performed in multiple institutions with UK alone. We evaluated the efficacy and safety of this therapy for preventing symptomatic vasospasm after aneurysmal SAH. The optimal concentration of UK was estimated by studying the fibrinolytic system in drained irrigation fluid and peripheral blood.

Subjects and Methods

Patient Population

Patients included in this study were selected from all patients with SAH admitted to 4 neurological institutions in Japan (Fukushima Medical School, National Sendai Hospital, Southern Tohoku Hospital, and Sendai City Hospital). The trial protocol was reviewed and
Procedure of Cisternal Irrigation

Cisternal irrigation was performed only from the unilateral Sylvian fissure regardless of whether a hematoma existed in the bilateral Sylvian fissures. After the aneurysm was clipped, irrigation tubes were placed in the Sylvian fissure (inlet) unilaterally and also in the prepontine or chiasmatic cistern (outlet). Lactated Ringer’s solution without UK was infused for 12 hours to prevent postoperative hemorrhage. Then, UK irrigation was performed at a rate of 30 mL/h. UK 30 IU/mL was used in 10 cases, and 60 and 120 IU/mL were given in 9 cases each. The allotment of each concentration was random; however, a double-blind procedure was not used in this study. A CT slice from each patient is shown in Figure 1. The solution for irrigation was adjusted to the same pH (7.2 to 7.6) and osmotic pressure (280 to 300 mOsm/kg) as those of the normal cerebrospinal fluid (CSF). A microdrop system was used to control the flow rate, and a millipore filter was also connected to the infusion tube to prevent infection. As a rule, the therapy was terminated when red blood cells and fibrin degradation products (FDP) in drained irrigation fluid decreased to <10,000/mm³ and 5 μg/mL, respectively.

Occurrence of Symptomatic Vasospasm

The primary efficacy was assessed by the occurrence of symptomatic vasospasm. The presence of symptomatic vasospasm was evaluated by the presence of neurological worsening. This can be called delayed ischemic deficit (DID) due to vasospasm. The diagnosis of symptomatic vasospasm was clinically based, and the following criteria were used: (1) classic symptoms of vasospasm (onset occurring from day 4 to 14 after SAH; insidious onset of confusion, disorientation, and/or drowsiness; and focal deficits, which often fluctuated); (2) negative CT findings, to rule out causes of neurological deterioration such as rebleeding or hydrocephalus; (3) no other identifiable causes of neurological deterioration, such as electrolyte disturbance, hypoxia, or seizure. To be counted, the change had to last for a minimum of 8 hours. With regard to reference finding of the occurrence of symptomatic vasospasm, the presence of a new low-density area on CT scan was also evaluated. The first CT scan was performed within 24 hours after surgery. Then, postoperative CT scans were performed at least twice a week or when the patient’s neurological condition worsened. The period of observation was 1 month after surgery, and at that time, the outcome of each patient was evaluated with the Glasgow Outcome Scale.

Drainage Irrigation Fluid Parameters

Secondary efficacy was examined by drainage fluid parameters. Drained irrigation fluid was collected on consecutive days until the termination of irrigation, and the following items were examined after the fluid had accumulated for 24 hours and had been stirred: red blood cells, supernatant hemoglobin, estimated total drained blood volume, UK activity, UK antigen, FDP, D-dimer, thrombin-antithrombin III complex (TAT), α2-plasmin inhibitor (PI), total and free plasminogen activator inhibitor (PAI)-1, white blood cells (WBC), glucose, and protein. The red blood cells, supernatant hemoglobin, FDP, WBC, glucose, and protein were analyzed by each institution. The laboratory technicians who analyzed activity and antigen of UK, FDP (again), D-dimer, thrombin-antithrombin III complex (TAT), α2-plasmin inhibitor (PI), total and free plasminogen activator inhibitor (PAI)-1, white blood cells (WBC), glucose, and protein were analyzed by each institution. A repeated-measures ANOVA (significant difference, P<0.05) was used to assess the differences in time course, and the Bonferroni method of multiple comparison test (significant difference, P<0.0167) was used to assess differences among the groups. Total drained blood volume was calculated from red blood cells and supernatant hemoglobin. One-factor ANOVA (significant difference, P<0.05) was used to assess the difference in total drained blood volume among the 3 groups.

Peripheral Blood Parameters

The safety of this therapy was investigated by examination of peripheral blood parameters. Blood was collected 4 times: before the start of UK administration, at 24 and 48 hours after the start of UK, and at the end of irrigation. Fibrinogen, FDP, D-dimer, α2-PI, plasminogen, UK activity, UK antigen, prothrombin time (PT), and activated partial thromboplastin time (APTT) in the blood were measured. The laboratory technicians who analyzed fibrinogen, FDP, D-dimer, α2-PI, plasminogen, UK activity, UK antigen, prothrombin time (PT), and activated partial thromboplastin time (APTT) in the blood were analyzed by the Bonferroni method of multiple comparison test (significant difference, P<0.0167).

Occurrence of Complications

We investigated the safety of cisternal irrigation therapy by the occurrence of complications, such as hemorrhagic complication or infection. We counted not only symptomatic complications but also approved by the local independent ethics committee of each institution. Entry criteria included the following: (1) the degree of SAH of the patients was classified as Fisher CT group 3-4; (2) the highest CT number (Hounsfield number) exceeded 60 in SAH; (3) patients underwent surgery within 72 hours of the onset of SAH; (4) patients were between 18 and 80 years of age; (5) preoperative Hunt and Kosnik grades of patients were I to IV. Informed consent was obtained from each patient (or from a legally authorized representative) before enrollment in this study. Patients were excluded if they had fusiform, traumatic, or mycotic aneurysms; severe concomitant medical, neurological, or psychiatric illness; or serious cardiovascular complication. Other exclusion criteria included patients during pregnancy or puerperium. Basically any other preventive therapy for cerebral vasospasm, such as induced hypertensive, hypervolemic, and hemodilution therapy or calcium antagonists, was prohibited. When the patients received such therapy, the investigator declared the therapy used. After occurrence of symptomatic vasospasm, no restrictions were applied, and the therapy method was determined by the investigator.

Figure 1. Representative CT slice from each patient.
subclinical ones, including CT evidence of subclinical intracranial hemorrhage.

Results
Twenty-eight patients comprising 11 men and 17 women (40 to 76 years old; mean age, 60.5 years) with severe SAH took part in this study. The number of patients in each institution was as follows: 14 in Fukushima Medical School, 6 in National Sendai Hospital, 4 in Southern Tohoku Hospital, and 4 in Sendai City Hospital. All patients underwent surgery within 72 hours of the onset of SAH. The surgeons were 4 of the authors (N.K., Y.S., K.W., and T.O.). The distribution of preoperative Hunt and Kosnik grades and location of the aneurysms are given in Table 1. These patients were selected from consecutive series, excluding those patients who did not provide informed consent. There was no exclusion criterion based on operative procedures. Other preventive therapies, such as induced hypertensive, hypervolemic, or hemodilution therapy, were not used in any cases. None of the patients received calcium antagonists (eg, nimodipine).

Occurrence of Symptomatic Vasospasm
The average irrigation period was 9.6 days (range 6 to 14 days, SD 2.5 days). Symptomatic vasospasm occurred in 1 of 10 cases in the 30-IU/mL group and 2 of 9 cases in the 60-IU/mL group. These 3 patients developed mild hemiparesis and deterioration of consciousness due to the cerebral vasospasm. All 3 of these patients underwent induced hypertensive and hypervolemic therapy just after the onset of symptoms, and they recovered completely. The development of symptomatic vasospasm was not observed in the 120-IU/mL group. In all groups, there were no cases in which

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Fisher group 3+4 indicates intracerebral and/or intraventricular blood with thick subarachnoid blood; Grade (H & K), preoperative neurological grade according to Hunt and Kosnik; Acom, anterior communicating artery aneurysm; IC, internal cerebral artery aneurysm; MC, middle cerebral artery aneurysm; AC, anterior cerebral artery aneurysm; BA, basilar artery aneurysm; GOS, Glasgow Outcome Scale; GR, good recovery; MD, moderately disabled; and SD, severely disabled.
symptoms due to vasospasm remained and no cases in which a new low-density area appeared. The outcome assessed at 1 month after surgery with the Glasgow Outcome Scale 15 was “good recovery” in 20 cases, “moderately disabled” in 4 cases, and “severely disabled” in 4 cases.

Drainage Irrigation Fluid Parameters

The chronological changes in drained blood volume from red blood cells are shown in Figure 2 (top left). Drained blood volume in the 120-IU/mL group was significantly higher than that in the 30-IU/mL group ($P < 0.0167$, Bonferroni). The chronological changes in drained blood volume calculated from supernatant hemoglobin are shown in Figure 2 (top right). There was no statistical difference. The mean values and standard errors (SE) of total drained blood volume for the respective groups were as follows: 58±5 mL in the 30-IU/mL group, 106±23 mL in the 60-IU/mL group, and 143±27 mL in the 120-IU/mL group ($P < 0.05$, 1-factor ANOVA, between the 30- and 120-IU/mL groups). In the 3 cases with symptomatic vasospasm, the drained blood volume was 49, 70, and 98 mL, respectively. The level of FDP in drainage fluid (Figure 2, middle left) was highest in the 120-IU/mL group followed by the 60- and 30-IU/mL groups. However, these values were not significantly different. On the other hand, levels of D-dimer (Figure 2, middle right) in each group were not significantly different. UK activity (Figure 2, bottom left) and UK antigen levels (Figure 2, bottom right) in drainage fluid were found to be significantly higher in the 120-IU/mL group than those in the 60- or 30-IU/mL groups ($P < 0.0167$, Bonferroni). Over the irrigation period, the mean values of daily WBC (per mm$^3$) ranged as follows: 30-IU/mL group, 111 to 2659; 60-IU/mL group, 269 to 1803; and 120-IU/mL group, 268 to 1244. The mean WBC values decreased gradually from day 4. Over the irrigation period, the ranges of mean values for the 3 groups were as follows: glucose 40.1 to 64.6 mg/dL; protein 38.2 to 277.6 mg/dL; TAT 0.3 to 2.5 µg/mL; α2-PI 158.0 to 243.3 µg/mL; PAI-1 (total) 12.8 to 45.8 µg/mL; and PAI-1 (free) 7.4 to 36.3 ng/mL. Although no significant differences were observed among the 3 groups, the levels of protein, TAT, and total and free PAI-1 were...
slightly higher in the 120-IU/mL group than in the other 2 groups.

**Peripheral Blood Parameters**

Preirrigation and end-of-irrigation values (mean±SD) for fibrinogen, FDP, D-dimer, α2-PI, plasminogen, UK activity, UK antigen, PT, and APTT in the blood are shown in Table 2. Levels of FDP and D-dimer at preirrigation were higher than normal. However, other parameters, including fibrinogen, α2-PI, PT, and APTT, were normal in each group both before and after irrigation. Levels of plasminogen at the end of irrigation were significantly higher than those at preirrigation (P<0.05, repeated-measures ANOVA). Activity and antigen of UK did not significantly increase after irrigation. There were no significant differences among the 3 groups.

**Occurrence of Complications**

One patient (3.6%) developed purulent meningitis. Bacterial culture of the CSF showed that the organism was *Staphylococcus epidermidis*. He improved after irrigation of cefazolin sodium in the lateral ventricles and systemic administration of γ-globulin and cefazolin sodium. He was discharged without neurological deficit. Intracranial bleeding did not occur in any of the patients.

**Discussion**

Symptomatic vasospasm after SAH has been the most serious problem in treating ruptured aneurysms. In 1980, Fisher et al reported that vasospasm was found in almost all cases with a thick and widespread subarachnoid clot on CT scan (group 3 according to their grading scale). Their study clarified that the volume of the clot correlated with the occurrence of symptomatic vasospasm and/or neurological deterioration due to vasospasm. On the basis of these results, we hypothesized that the best means to prevent symptomatic vasospasm might be to remove as much of the clot as possible, as early as possible.

Irrigation therapy with UK was first reported by Yoshida et al in 1983. However, their results did not demonstrate significant benefit. In their study, relatively low UK concentrations (<48 IU/mL) and different irrigation systems were used than in our present study. We had previously performed cisternal irrigation therapy with UK and ascorbic acid. Of the 217 patients in that study, symptomatic vasospasm was observed in 6 cases (2.8%), and 2 of these 6 cases demonstrated sequela. Recently, many studies have shown that the use of tPA is effective in preventing symptomatic vasospasm. However, an established method has not been developed yet owing to differences in dosage of tPA, application methods, and rates of occurrence of hemorrhagic complications. Hemorrhagic complications have been reported in tPA studies, with an incidence between 0% and 70%. To evaluate the efficacy and safety of UK in cisternal irrigation therapy for prevention of symptomatic vasospasm, we performed unilateral cisternal irrigation therapy using UK alone in multiple institutions. In addition, the optimal concentration of UK and the fibrinolytic system in drained fluid and blood were also studied in detail.

According to a literature review of >30,000 cases by Dorsch and King, symptomatic vasospasm or DID occurred in 32.5% of SAH cases. Thirty percent of those with symptomatic vasospasm died, and permanent neurological deficit occurred in 34% of cases. In the present study, 3 patients transiently developed mild hemiparesis and deterioration of consciousness due to vasospasm. Although the overall incidence of symptomatic vasospasm was 10.7%, there were no cases in which symptoms due to vasospasm remained or cases in which a new infarction appeared. The results could be considered satisfactory thus far, although the number of patients studied in the current investigation is much too small to draw definitive conclusions. However, the incidence of symptomatic vasospasm in the present study was higher than that in our previous study in which we performed cisternal irrigation therapy using UK with ascorbic acid (2.8%). This higher incidence may be related to the use of...
unilateral irrigation, nonuse of ascorbic acid, and use of a low concentration (30 IU/mL) of UK in 10 cases in the present study. Recently, prophylactic use of transluminal balloon angioplasty in SAH patients has been reported.17 The results of that pilot study revealed that none of the 13 patients developed DID due to vasospasm. However, 1 patient died of a vessel rupture during the procedure, and 2 elderly patients died of medical complications associated with poor clinical conditions on admission. This method can also be used in patients undergoing coil embolization. Their results suggest that prophylactic transluminal angioplasty might become an established method for prevention of symptomatic vasospasm. At present, however, we are not able to draw definitive conclusions. A large randomized study is required to determine whether prophylactic transluminal angioplasty is efficacious enough to prevent symptomatic vasospasm.

Data from the studies of drained fluid revealed the efficacy of 120 IU/mL UK. The drained blood volume in each case was highest in the 120-IU/mL group (P<0.05, ANOVA compared with the 30- and 120-IU/mL groups). In addition, UK activity and antigen levels were significantly higher in the 120-IU/mL group than in the other 2 groups. From the results of the experimental dissolution of a clot, the highest dissolution rate was obtained with UK concentrations of 60 and 120 IU/mL.18 UK activity and antigen levels in drainage fluid in the 120-IU/mL group were <20 and 60 IU/mL, respectively. This was thought to be caused by adhesion to the tube walls and intrathecal tissues and consumption and inactivation of UK. These results suggested the efficacy of 120 IU/mL, because activity and antigen levels of UK in the 120-IU/mL group were significantly higher than those in the other 2 groups. TAT, which does not exist in plasma, showed a high level (0.3 to 2.5 μg/mL) in drainage fluid. The TAT level was the highest in the 120-IU/mL group, and it gradually decreased during the irrigation period. Suzuki et al19 reported that thrombin in CSF is involved in the pathophysiology of vasospasm, but no symptomatic vasospasm occurred in the 120-IU/mL group. It is possible that TAT or thrombin within the clot was released into the drainage fluid because of clot lysis. The α2-PI level in the drainage fluid was 4 times higher than that in plasma, although the reason for this is not known. A remarkable sequential change was not observed. PAI-1 was also the highest in the 120-IU/mL group, and it gradually decreased during the irrigation period. Ikeda et al20 reported that patients whose PAI-1 levels in CSF were >20 ng/mL had a high incidence of vasospasm and a poor outcome. However, the fact that TAT and PAI-1 were highest in the 120-IU/mL group in the present study suggested that these results were due to clot lysis or clot volume. Therefore, we cannot exclude the possibility that patients in the 120-IU/mL group may have had a much larger subarachnoid hematoma at the onset.

Complication with meningitis was observed in 1 case (3.6%). The diagnosis of purulent meningitis was sometimes difficult because WBC level in drainage fluid was high. In most cases, the level of WBC decreased gradually from day 4. Therefore, when the WBC level does not decrease after day 4, infection should be suspected. This therapy requires an open system, and the risk of infection should be kept in mind.

No hemorrhagic complications were observed in the present study. Many hemorrhagic complications are reported in tPA studies, although those studies have demonstrated the efficacy of tPA in preventing vasospasm.3–12 We believe that single or multiple administration of a high dose of tPA caused these complications. We therefore used a relatively low concentration of UK (30 to 120 IU/mL) and continuous irrigation. Safety is most important, considering the purpose of this therapy.

From data of blood, levels of FDP and D-dimer at preirrigation were higher than the normal values. These data showed activated coagulation and fibrinolytic systems in SAH patients. We do not know the precise mechanism of the plasminogen increase; however, levels remained near normal values. There were no negative effects in systemic blood, such as plasminogen consumption. Activity and antigen of UK did not increase significantly after UK irrigation was completed. All of these data support the safety of this therapy.

These results suggest that cisternal irrigation therapy with UK is safe and effective for the prevention of symptomatic vasospasm after aneurysmal SAH. Unilateral cisternal irrigation therapy with UK 120 IU/mL was more effective in dissolving SAH than that with UK 60 or 30 IU/mL. To the best of our knowledge, this is the first report detailing the evaluation of the fibrinolytic system in cisternal clot lysis therapy.

References


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