Microcatheter Intrathecal Urokinase Infusion Into Cisterna Magna for Prevention of Cerebral Vasospasm
Preliminary Report

Jun-ichiro Hamada, MD; Takamasa Mizuno, MD; Yutaka Kai, MD; Motohiro Morioka, MD; Yukitaka Ushio, MD

Background and Purpose—The feasibility of preventing vasospasm by intrathecal anterograde infusion of urokinase (UK) into the cisterna magna was studied in patients with recently ruptured aneurysms who had just undergone the placement of a Guglielmi detachable coil (GDC).

Methods—Immediately after complete embolization with the use of GDC-10 coils, 15 patients with Hunt and Hess neurological grades III and IV received 60,000 IU of UK in normal saline through a microcatheter advanced into the cisterna magna. UK infusion was repeated once or twice over a period of 2 to 3 days according to a decision based on CT evidence of a subarachnoid clot remaining in the cisterns. Before administering the last UK infusion, we obtained CT confirmation of almost complete clearance of clots in the basal cisterns.

Results—In all 15 patients, the microcatheter was advanced easily into the cisterna magna by use of the over-the-wire microcatheter technique. In 8 patients who received thrombolytic therapy within 24 hours of the ictus, there was almost complete clearance of the clot in the basal cisterns within 2 days of suffering the insult. When UK was injected at 24 to 48 hours after the insult, 7 patients manifested CT evidence of clearance at the latest 4 days after suffering the insult. In all 15 patients, CT scans obtained within 24 hours of the final UK administration showed complete resolution of clots in the basal cistern and almost complete resolution of clots in the basal interhemispheric fissure and bilateral proximal sylvian fissures. Although one patient developed a transient neurological deficit, no patients manifested permanent delayed neurological deficits as a result of vasospasm. Outcome assessment according to the Glasgow Outcome Scale, no less than 3 months after GDC placement, revealed good recovery in all patients, and none developed hydrocephalus requiring a shunt procedure.

Conclusions—In patients with recently ruptured aneurysms, GDC placement followed by immediate intrathecal administration of UK from the cisterna magna may be a safe and reasonable means of preventing vasospasms and may result in improved treatment outcomes. (Stroke. 2000;31:2141-2148.)

Key Words: cerebral aneurysm ■ cisterna magna ■ embolization, therapeutic ■ urokinase ■ vasospasm

Cerebral vasospasms resulting in delayed ischemic neurological deficit occur in 17% to 40% of patients with aneurysmal subarachnoid hemorrhage (SAH) and worsen their clinical outcomes.1-7 Although the etiology of these vasospasms has not been fully established, experimental studies strongly implicate erythrocytes in the cerebrospinal fluid in their occurrence.8,9 The early obliteration of ruptured aneurysms to prevent rebleeding, followed by the early removal of subarachnoid clots to prevent delayed cerebral vasospasms, would improve these patients’ chances of complete recovery.10,11

Endovascular treatment with use of the Guglielmi detachable coil (GDC) in patients with acutely ruptured aneurysms is a well-established modality.12,13 In contrast to surgical clipping of the aneurysm, the endovascular procedure does not allow removal of the subarachnoid clot. The potential benefit of the endovascular treatment is protection from rebleeding with a minimum risk of iatrogenic morbidity. We report results that we obtained when patients with angiographically confirmed recently ruptured aneurysms first underwent embolization with the use of GDCs, followed by intermittent intrathecal injections of urokinase (UK) into the cisterna magna. This treatment eliminates the risk of early rebleeding, allows for rapid clearance of subarachnoid hematoma, and helps to prevent the occurrence of vasospasm. Our experience may lead to a new strategy for the treatment of patients with acutely ruptured aneurysms.

Subjects and Methods
The present study was reviewed and approved by the Human Subjects Review Committee of the University of Kumamoto.

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Advancement of the Microcatheter

In the supine position, the opening pressure was 5 to 10 cm H\textsubscript{2}O at the external auditory meatus. UK infusion was started within 24 hours of the ictus and placement of the GDC. After endotracheal general anesthesia was induced in the usual manner, the aneurysms were embolized almost completely by means of GDC as described by Guglielmi et al.\textsuperscript{12} A GDC tracker-10 catheter and GDC-10 coils were used in all procedures. Heparinization was begun with an intravenous bolus of 3000 IU followed by a continuous infusion of 1000 IU/h to achieve an activated clotting time of twice the normal level immediately before GDC placement. Protamine sulfate was injected to reverse the effect of heparin just before UK placement. After endotracheal general anesthesia was induced, a diagnostic transfemoral angiogram was obtained to determine appropriate GDC placement. After endotracheal general anesthesia was induced in the usual manner, the aneurysms were embolized completely by means of GDC as described by Guglielmi et al.\textsuperscript{12} A GDC tracker-10 catheter and GDC-10 coils were used in all procedures. Heparinization was begun with an intravenous bolus of 3000 IU followed by a continuous infusion of 1000 IU/h to achieve an activated clotting time of twice the normal level immediately before GDC placement. Protamine sulfate was injected to reverse the effect of heparin just before lumbar puncture. Immediately after complete embolization, the patients were returned to the lateral position, and a puncture was placed with a 14-gauge Tuohy needle at the L3–4 or L4–5 interface. Entry into the subarachnoid space was identified, and a multi–side-hole infusion microcatheter (Target Therapeutics/Boston Scientific) with a micro guidewire was introduced into the lumbar subarachnoid space under fluoroscopic guidance. The micro guidewire was advanced by the over-the-wire microcatheter technique. When the tip of the micro guidewire entered the cisterna magna, the microcatheter was advanced over it. Then the micro guidewire and the needle were withdrawn, and the microcatheter was fixed to the skin in smooth loops.

Intrathecal Thrombolytic Therapy

UK (60 000 IU in 10 mL normal saline) was administered through an infusion pump at a rate of 0.5 mL/min via the microcatheter after the removal of an identical amount of cisternal cerebrospinal fluid (CSF). The microcatheter was clamped to prevent the immediate expulsion of the UK; after 1 hour, it was reopened for spontaneous drainage. With the patient in the supine position, the opening pressure was 5 to 10 cm H\textsubscript{2}O at the external auditory meatus. UK infusion was repeated once or twice over a period of 2 to 3 days. The decision to administer 1, 2, or 3 UK injections was based on CT evidence of the status of the subarachnoid clot in the cisterns. CT scans were obtained within 24 hours of GDC placement, 2 or 3 times during and shortly after the thrombolytic therapy, and thereafter, as necessary, until the subarachnoid hematoma had disappeared. The last administration of UK was given when there was CT evidence of almost complete clearance of the clot from the basal cistern. The microcatheter was withdrawn immediately after the final UK infusion. Repeat angiograms were obtained within 24 hours of the first UK administration to confirm the complete embolization of the aneurysm and between days 6 and 14 to evaluate the degree of angiographic vasospasm.

Medical Management

Mannitol and glycerol were administered to patients with brain edema. Other medical treatments, including the intravenous administration of calcium antagonists and/or steroids, were not used. Although adequate fluid intake, including colloids of plasma and dehydrating agents such as mannitol and glycerol, was used on a case-by-case basis, prophylactic hypervolemic therapy was not used. The patients were returned to the neurological intensive care unit or neurosurgical ward, where they remained under neurosurgical care until discharge.

Clinical follow-up evaluations were performed no less than 3 months after GDC placement, and outcomes were defined according to the Glasgow Outcome Scale (GOS).\textsuperscript{16}

Results

Tables 1 and 2 provide demographic, clinical, and outcome data for each of the 15 patients. There were 6 men and 9 women; their ages ranged from 32 to 74 years (mean 57 years). These patients were divided into 2 groups according to the time lapsed between the ictus and the initial thrombolytic treatment. In group A (n=8), thrombolytic therapy was

<table>
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<tr>
<th>Patient</th>
<th>Age/Sex</th>
<th>Aneurysm Location</th>
<th>CT H &amp; H Grade</th>
<th>SAH to First UK Infusion, h</th>
<th>UK Dosage (10 000 IU)</th>
<th>Duration of Spinal Drainage, d</th>
<th>Vasospasm</th>
<th>Outcome (GOS)</th>
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<tr>
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<td>BA</td>
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<td>71</td>
<td>14</td>
<td>6</td>
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</tbody>
</table>

H & H indicates Hunt and Hess; ICA, internal carotid artery; BA, basilar artery; and —, none.

*Unruptured aneurysm.
TABLE 2. Clinical Summary of 7 Patients Who Received First UK Infusion Between 24 and 48 h After SAH

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/sex</th>
<th>Aneurysm Location</th>
<th>H &amp; H Grade</th>
<th>CT Number of Clot, HU</th>
<th>SAH to First UK Infusion, h</th>
<th>UK Dosage (10,000 IU)</th>
<th>Duration of Spinal Drainage, d</th>
<th>Vasospasm</th>
<th>Angiographic</th>
<th>Clinical</th>
<th>Outcome (GOs)</th>
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<tr>
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<td>III</td>
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<td>3</td>
<td>–</td>
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</table>

—indicates none; ±, transient.

started within 24 hours after the ictus (mean 12 hours, range 8 to 18 hours). In group B (n = 7), the interval between the insult and the first thrombolytic treatment was between 24 and 48 hours (mean 35 hours, range 28 to 44 hours). On admission, the patients were classified according to Hunt-Hess clinical grade: in group A, 5 were classified as grade III and 3 as grade IV; in group B, 5 were classified as grade III and 2 as grade IV. The site of the ruptured aneurysm was the anterior communicating artery (ACoA, n = 7), the internal carotid artery (n = 4), the middle cerebral artery (MCA, n = 2), and the basilar artery bifurcation (n = 3). Thirteen patients had 1 aneurysm, and 2 patients had 2 aneurysms. Of the latter, patient 11 had an unruptured MCA aneurysm and an ACoA aneurysm that was clearly the source of bleeding according to CT scans. The other patient with multiple aneurysms (patient 14) had a small ACoA aneurysm and a large basilar artery aneurysm. Both were embolized because the source of bleeding could not be determined on the CT scan. In all 15 patients, the microcatheter was advanced easily into the cisterna magna by the over-the-wire microcatheter technique. CT scans obtained within 24 hours after the final UK infusion disclosed complete clearance of clots from the basal cisterns and almost complete dissolution of clots in the basal interhemispheric fissure and bilateral proximal sylvian fissures. In 4 group A patients, the entire hematoma, which was in the basal cistern, the basal frontal interhemispheric fissure, and bilateral proximal sylvian fissures, was dissolved after a single UK infusion. The other 4 group A patients received 2 UK infusions, although almost complete dissolution of clots in the basal cisterns was achieved by a single injection. In contrast, 3 group B patients received 2 UK injections, and in the other 4 patients, 3 infusions were administered. Almost complete clearance of clots in the basal cisterns was noted after a single infusion or after 2 infusions. In group A, we had CT evidence of almost complete clearance of clots in the basal cisterns by the second day after the insult; in group B, almost complete clearance was achieved by day 4 after the insult at the latest. There were no complications resulting from advancing the microcatheter into the cisterna magna or from the intrathecal UK injection. In 11 patients, there was no angiographic evidence of vasospasms; mild and focal vasospasm (≤25% reduction in luminal caliber compared with pretreatment caliber) occurred in 3 patients, and 1 patient experienced moderate and diffuse vasospasm (25% to 50% reduction in luminal caliber). No severe vasospasms were noted. Although 1 patient in the case group (patient 14) developed a transient neurological deficit, none of the 15 patients manifested CT evidence of low-density areas attributable to cerebral ischemia as a result of vasospasm, and none sustained permanent delayed neurological deficits. Although a thromboembolic complication related to the GDC placement was seen in one patient in the case group (patient 3), she suffered no neurological consequences. There was no occurrence of hydrocephalus requiring CSF shunt procedure, and none of the 16 aneurysms bled again during clinical observation. Outcome assessment was based on the GOS; all 15 patients experienced good recovery, and all were able to resume their normal lives and occupations, including academic careers and household activities.

Illustrative Cases

First UK Infusion Within 24 Hours After SAH

Patient 1
A 62-year-old woman was admitted to our hospital with a severe headache within 4 hours of suffering the insult. A CT scan showed thick and diffuse hemorrhage in the basal cisterns (67 HU) and sylvian fissures. A cerebral angiogram demonstrated a ruptured ACoA aneurysm and an unruptured right MCA aneurysm. She was designated as Hunt-Hess grade III. The ruptured ACoA was completely embolized with GDC-10 coils. After the smooth introduction of the microcatheter into the cisterna magna, she received 60,000 IU of UK at 8 hours after the ictus. A CT scan obtained 20 hours after this UK treatment (within 28 hours after the ictus) showed complete lysis of the subarachnoid clots in the basal cistern and sylvian fissures, and the microcatheter was withdrawn (Figure 1). Within 5 days of the SAH, she became alert, and her headache disappeared. The unruptured right MCA aneurysm was successfully clipped 4 weeks later.

Patient 5
A 74-year-old man experienced sudden severe headache and was admitted to our clinic within 6 hours of onset. His neurological condition at the time of admission was classified as Hunt-Hess grade III. Admission CT scan showed diffuse thick and dense SAH (66 HU) and a small intracerebral hematoma in the right frontal lobe. A cerebral angiogram revealed a ruptured aneurysm of the right MCA; it was
completely embolized with GDC-10 coils. Although the patient had a deformity of the cervical spine, the microcatheter was advanced smoothly into the cisterna magna by the over-the-wire microcatheter technique. At 10 hours after the ictus, he received 60 000 IU of UK through the catheter; a second infusion of 60 000 IU was administered 24 hours later. A CT scan obtained 30 hours after SAH showed almost complete lysis of the clots in the basal cistern; however, clots in the interhemispheric fissures and sylvian fissures remained. A CT scan obtained 52 hours after the SAH demonstrated complete lysis of the subarachnoid clots; the hematoma in the right frontal lobe was almost completely dissolved (Figure 2). Within 7 days after the SAH, his neurological state returned to normal.

**First UK Infusion Between 24 and 48 Hours After SAH**

**Patient 9**

A 63-year-old woman suddenly developed a severe headache. Her neurological condition at the time of admission to our clinic 22 hours after the ictus was classified as Hunt-Hess grade III. A CT scan showed diffuse thick and dense SAH in the basal cisterns (70 HU). A cerebral angiogram showed a ruptured BA aneurysm; it was completely embolized with GDC-10 coils. The microcatheter was smoothly advanced into the cisterna magna, and she received her first infusion of 60 000 IU of UK 30 hours after the ictus. A second infusion of 60 000 IU of UK was administered 24 hours later. A CT scan obtained 18 hours after the first UK administration showed almost complete lysis of the subarachnoid clots in the basal cistern; however, the clot in the interhemispheric fissure and sylvian fissures remained. A CT scan obtained 20 hours after the second infusion, ie, within 74 hours after the ictus, showed complete lysis of the subarachnoid clots in the basal cistern and almost complete lysis in the basal frontal interhemispheric fissure and proximal sylvian fissures (Figure 3). Within 6 days after the SAH, she became alert and her neurological state returned to normal.

**Patient 14**

A 57-year-old man experienced a sudden severe headache and was unconscious when admitted to another hospital. A CT scan showed thick and diffuse hemorrhage in the basal cisterns (69 HU). The following day, within 38 hours of onset, he was transferred to our clinic. His neurological condition at the time of admission was Hunt-Hess grade IV. A cerebral angiogram showed a large ventriculoatrial aneurysm and a small ACoA aneurysm. Because the source of bleeding could not be determined on the CT scan, we first completely embolized the ventriculoatrial aneurysm and then the ACoA aneurysm with GDC-10 coils. The microcatheter was advanced smoothly into the cisterna magna, and the patient received 60 000 IU of UK at 44 hours after the ictus. Two more infusions of 60 000 IU of UK were given: the second was given 24 hours after the first, and the third was given 48 hours after the second. A CT scan obtained 22 hours after the second infusion, ie, within 90 hours after the SAH, demonstrated almost complete lysis of the clots in the basal cisterns. A CT scan obtained 5 days after the SAH demonstrated complete lysis of the hemorrhage. However, this patient developed a mild weakness of the right leg 8 days after the SAH. An angiogram was performed immediately; it showed moderate diffuse vasospasm of the left distal anterior cerebral artery (Figure 4). His symptom responded to elevation of blood pressure with resolution of deficit, and his
neurological status returned to normal within 12 days of suffering the SAH.

Discussion
The endovascular treatment of intracranial aneurysms with the GDC system was introduced in the clinical setting in 1990. The coils provide for a more controlled and safe filling of the aneurysmal sac than do balloons, and use of the coils makes it possible to obtain total occlusion of the aneurysm lumen by a combination of electrothrombosis and dense packing. Endovascular and surgical procedures have different limitations and contraindications. Endovascular therapy was initially restricted to aneurysms thought to be inoperable or difficult to manage surgically, predominantly those within the posterior circulation. The development of GDC, together with experience gained since the early 1990s, has widened these indications to include even aneurysms of the anterior circulation. Thus, endovascular treatment has become a true complement and alternative to surgery, especially when the early and controlled obliteration of a recently ruptured aneurysm is possible.

A review of the advantages and limitations of the GDC system for treating acute aneurysms indicates that GDC embolization may have some advantages over the surgical clipping of acute aneurysms. The endovascular procedure does not require the mechanical retraction of the potentially edematous and/or ischemic brain, and surgical resection or occlusion of major cortical veins is not necessary to reach the aneurysm. However, this procedure does not facilitate evacuation of subarachnoid clots, and clinical studies with longer follow-up periods are necessary to establish the long-term durability of the GDC treatment modality.

Although the etiology of cerebral vasospasms is not fully established, their incidence, distribution, and severity are correlated with the location and volume of blood clots deposited in the basal cisterns by the ruptured aneurysm. The duration of exposure to blood adjacent to the cerebral arteries may also play a role in the development of vasospasm.
The intrathecal infusion of thrombolytic agents, such as UK or recombinant tissue plasminogen activator, during or after clipping has been proposed as one means of clot evacuation, facilitating the prevention of vasospasm and resulting in an improved prognosis.20–29 Despite positive findings in experimental and clinical studies of intrathecal infusion of thrombolytic agents, this method in combination with the placement of the GDC is not widely used. Kinugasa et al30 found that endovascular cellulose acetate polymer embolization of aneurysms, combined with intrathecal retrograde infusion of tissue plasminogen activator via spinal drainage, has the potential to decrease the rate of symptomatic vasospasms. They reported that 2 patients with Hunt-Hess grade III and 6 of 7 patients with Hunt-Hess grade IV improved clinically and had a good recovery, although the 3 patients with Hunt-Hess grade V had poor outcomes. Our experience indicates that the intrathecal infusion of UK immediately after embolization of an acutely ruptured aneurysm effectively and safely prevents vasospasm. Whereas Kinugasa et al delivered the thrombolytic agent via a silicon tube, we administered the intrathecal infusion through a microcatheter. With the use of a microcatheter, the tip of the tube was easily advanced to the cisterna magna for a more anterograde infusion than is possible with the use of their method.

It is not known how the difference between the CSF circulation in an intact subarachnoid space and in a space containing a hematoma affects the diffusion of thrombolytic agents. We posit that thrombolytic agents infused into the cisterna magna spread more widely into the subarachnoid space with the help of more anterograde infusion and thus facilitate lysis of subarachnoid hematomas more rapidly than would agents infused retrogradely. Furthermore, intrathecal thrombolytic therapy after GDC embolization appeared to be more effective in lysing subarachnoid hematoma than did surgical clipping, which results in a morphologically more complicated CSF circulation that is due to the operative procedure itself, such as opening the subarachnoid membrane.

The amount of subarachnoid blood in the basal cisterns detected on the initial CT scan obtained within 3 days after the SAH is highly predictive of the risk of delayed ischemia and infarction. Therefore, previous reports have suggested that vasospasm might be prevented in humans and animals if subarachnoid blood is removed within 48 to 72 hours of the SAH. In the Canadian trial of nimodipine31 in 42 aneurysm patients with thick subarachnoid clots on admission CT, persistent basal subarachnoid clots were evident within 5- to 10-day intervals in 24 (57%) of these patients. In comparison, Kinugasa et al30 found that all but 2 patients had almost complete resolution of cisternal blood clots on CT scans within 72 hours when tissue plasminogen activator was administered within 24 hours after SAH. In the present study, group A patients received thrombolytic therapy within 24 hours of suffering the insult; group B, within 48 hours. CT scans disclosed the almost complete clearance of the clot in the basal cisterns within 2 days of the insult in group A and within 4 days even in group B. Large reductions in diffuse subarachnoid clots were generally apparent on CT scans obtained on the first posttreatment day. Rapid clearance of the subarachnoid hematoma appeared to be associated with a reduced incidence of vasospasm. Irrespective of the timing of the first UK infusion in our 15 patients, only 1 patient experienced symptomatic vasospasm and developed a transient neurological deficit.

![Figure 4. Patient 14. A, Admission CT scans revealing diffuse thick and dense SAH. B, Cervical bone x-rays. On the left, the micro guidewire advances the tip of the microcatheter (small arrow). On the right, the tip of the microcatheter (small arrow) is positioned in the cisterna magna. Note the GDC coils within the 2 aneurysmal sacs. C, CT scan obtained 90 hours after SAH showing almost complete lysis of clots in basal cisterns. D, Left internal carotid artery angiogram showing moderate diffuse vasospasm of left distal anterior cerebral artery (arrowheads).](http://stroke.ahajournals.org/DownloadedFrom)
Rapid clearance of SAH appeared to be associated with the time interval between the ictus and the initial infusion of thrombolytic agents. In our series, patients in whom thrombolytic therapy was started within 24 hours after the ictus experienced more rapid and extensive clearance than did patients in whom this therapy was started later. The shorter the interval between the ictus and the first UK infusion, the higher was the rate of clot lysis. Consequently, because thrombolytic therapy can be administered sooner after GDC placement than after direct clipping, hematoma resolution is achieved earlier in the combination GDC-UK treatment regimen.

We selected patients at high risk for vasospasm whose clots could be expected to be difficult to resolve. The 15 chosen patients had CT scores corresponding to group 3 or group 3+4 in the classification of Fisher et al. Because there can be large differences in the size of the hematoma in these groups, we also stipulated >65 HU for the hematoma.

In some reports, the incidence of symptomatic vasospasm after early embolization with GDC appeared to be similar to, or lower than, the incidence reported in the series of patients undergoing surgical clipping and cisternal drainage. Murayama et al., who recorded the incidence of symptomatic vasospasm after early endovascular treatment of acutely ruptured aneurysms in 69 patients with Hunt-Hess grades between I and III, found that it was comparable to the incidence encountered in the surgical series. In a series of 37 patients, preliminary data suggested that the incidence of cerebral vasospasm might be reduced in patients treated by endovascular therapy compared with patients who underwent direct surgical clipping. Charpentier et al. reported that symptomatic vasospasm occurred in 22.2% of surgical patients compared with 17.2% of patients who received endovascular treatment. It has been our observation that both the frequency and severity of vasospasm are decreased in patients treated by intrathecal injection of UK from the cisterna magna immediately after GDC placement because of the adequate and prompt resolution of subarachnoid clots.

We obtained repeat angiograms to confirm the complete embolization of the aneurysm because we were afraid that the intrathecal UK administration may have adversely affected the effectiveness of the GDC embolization. However, neither aneurysm recurrence nor recanalization was indicated on repeated angiograms, and none of the 16 aneurysms bled again during the period of clinical follow-up. Although they used embolic agents and infusion methods different from ours, Kinugasa et al. found that even partially thrombosed aneurysms did not show enlargement on follow-up angiograms obtained 4 to 10 days after treatment. Although we cannot exclude the possibility that the effectiveness of GDC embolization is influenced by intrathecal UK administration, we believe that fibrinolytic agents can be administered without increasing the risk of rebleeding, at least during the acute stage of SAH. Of course, incomplete GDC embolization of the aneurysm is an absolute contraindication.

It remains to be determined whether this combination therapy is appropriate in patients with huge intraventricular clots and/or huge intracerebral hematomas. Also, the dose and duration of UK infusion and the optimal mode of delivery need to be investigated further. A larger study population is required to standardize our method.

Although the population in the present study was so small that our results should be considered only preliminary, our study indicates that GDC placement in patients with recently ruptured aneurysm, followed by immediate intrathecal administration of UK from the cisterna magna, may be a safe and reasonable means in lysing subarachnoid hematomas and may prevent the occurrence of posttreatment vasospasms.

References


Microcatheter Intrathecal Urokinase Infusion Into Cisterna Magna for Prevention of Cerebral Vasospasm: Preliminary Report
Jun-ichiro Hamada, Takamasa Mizuno, Yutaka Kai, Motohiro Morioka and Yukitaka Ushio

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