

Effect on Cerebral Vasospasm of Coil Embolization Followed by Microcatheter Intrathecal Urokinase Infusion Into the Cisterna Magna

A Prospective Randomized Study

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Background and Purpose—Vasospasm remains the leading cause of death and permanent neurological disability in patients with aneurysmal subarachnoid hemorrhage (SAH). The objective of our prospective randomized trial of coil embolization followed by intrathecal urokinase infusion into the cisterna magna (ITUKI therapy) was to test its effectiveness in preventing or alleviating the severity of ischemic neurological deficits caused by vasospasm.

Methods—We enrolled 110 patients with ruptured intracranial aneurysms eligible for coil embolization and randomly assigned them to embolization with (n=57) or without (n=53) ITUKI therapy performed within 24 hours of aneurysmal SAH. The incidence of symptomatic vasospasms and the clinical outcomes, based on the Glasgow Outcome Scale, 6 months after SAH onset were assessed.

Results—There were no side effects or adverse reactions attributable to ITUKI therapy. Symptomatic vasospasm occurred in 5 patients (8.8%) with and 16 (30.2%) without ITUKI therapy; the difference was significant ($P=0.012$). Although the mortality rate did not differ between the groups, patients with ITUKI therapy had significantly better outcomes than those without ($P=0.036$).

Conclusions—Our results demonstrate that ITUKI therapy significantly reduced the occurrence of symptomatic vasospasm. Although it did not completely prevent vasospasms, ITUKI therapy resulted in a lower rate of permanent neurological deficits. (*Stroke*. 2003;34:2549-2554.)

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

Using the results of its randomized, multicenter trial to assess the safety and efficacy of endovascular coiling for ruptured aneurysms, the International Subarachnoid Trial (ISAT) group judged this method to be suitable for treating patients with ruptured intracranial aneurysms.¹ Although longer-term follow-up is vital to determine the durability of its benefit, it appears that endovascular coil treatment is significantly more likely than neurosurgery to result in survival free of disability at 1 year after the subarachnoid hemorrhage (SAH).

There is considerable clinical and experimental evidence that the severity of cerebral vasospasm is related to the volume and duration of perivascular clotting in the subarachnoid space.²⁻⁴ In contrast to surgical clipping of the aneurysm, endovascular procedure does not allow removal of the subarachnoid clot. We have reported preliminary results of Guglielmi detachable coil (GDC) placement followed by immediate intrathecal administration of urokinase from the cisterna magna (ITUKI therapy) in

patients with recently ruptured aneurysms.⁵ This treatment eliminated the risk of early rebleeding, allowed rapid clearance of subarachnoid hematomas, and helped to prevent the occurrence of vasospasm. However, our study population was small, and the trial was not randomized.

We now report results from a larger prospective randomized study of ITUKI therapy in which we tested its effectiveness in preventing or alleviating the severity of ischemic neurological deficits caused by vasospasm. Patients were recruited, treated, and followed up at 2 university centers between April 2000 and February 2002. The study protocol was approved by a clinical investigation committee at each institution.

Methods

Study Design

During the study period, all patients with primary SAH admitted to 2 university centers were evaluated as potential study candidates.

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After informed consent was obtained from all patients or their closest relative(s), all patients with ruptured aneurysms considered suitable for endovascular treatment were consecutively included, provided that they met all of the following criteria: (1) age <70 years; (2) Hunt and Hess⁶ (H&H) grade between 1 and 4; (3) initial urokinase (UK) infusion expected to be completed within 24 hours of the ictus; (4) no large hematomas and/or huge intraventricular clots necessitating surgery; (5) CT scores corresponding to those of group 3 or group 3 plus 4 in the classification of Fisher et al,² and the CT value (Hounsfield units) for hematoma in the basal cistern >60; (6) no neurological deficits before suffering the ictus; and (7) no previous surgery for the ruptured aneurysm.

Patients were not considered for inclusion in this study when diagnostic angiography revealed that (1) the neck of the aneurysm was wider than the fundus, (2) the aneurysm was fusiform or dissecting aneurysm, (3) the aneurysmal neck and its relationship to the parent vessel and adjacent branches could not be distinguished, (4) the diameter of the aneurysm was <2 mm, or (5) there were multiple aneurysms. To avoid selection bias, random assignments were performed separately for patients with H&H grades 1 to 2, 3, and 4. There were no H&H grade 5 patients in our study because in this group it was difficult to accurately diagnose the neurological deterioration caused by vasospasm. Patients who did and those who did not receive ITUKI therapy after GDC embolization received similar care in the intensive care unit.

Coil Embolization and Intrathecal Advancement of the Microcatheter Into the Cisterna Magna

We have previously detailed the procedure used.⁵ Briefly, after conventional endotracheal general anesthesia induction, the aneurysms were embolized with GDC as described by Guglielmi et al.⁷ After complete obliteration of the aneurysm sac or subtotal occlusion that left a small neck remnant, each patient was randomly designated in a double-blind manner (using sealed envelopes) to receive or not receive ITUKI therapy. Patients assigned to the ITUKI therapy group were then returned to the lateral position, and a puncture was made with a 14-gauge Touhy needle at the L3-4 or L4-5 interface. A multiside hole infusion microcatheter with a microguidewire was introduced into the lumbar subarachnoid space under fluoroscopic guidance. When the tip of the microguidewire entered the cisterna magna, the microcatheter was advanced over it. Then, the microguidewire and the needle were withdrawn, and the microcatheter was fixed to the skin in smooth loops. To treat patients in this trial, endovascular operators at each center were required to have performed at least 100 aneurysm treatment procedures previously.

ITUKI Therapy

UK (60 000 IU in 10 mL normal saline) was administered via an infusion pump at a rate of 0.5 mL/min via the microcatheter after removing an identical amount of cisternal cerebrospinal fluid (CSF). The microcatheter was clamped to prevent immediate expulsion of the UK; after 1 hour, it was reopened for spontaneous drainage. A second UK infusion was delivered 12 hours after the first, and the microcatheter was withdrawn immediately after the second UK infusion.

The primary goal of our study was the assessment of symptomatic cerebral vasospasm in ITUKI-treated and -untreated patients. All patients underwent frequent neurological examinations and daily transcranial Doppler sonographic monitoring. Vasospasm was suspected in patients with neurological deterioration and/or mean velocities in the anterior or middle cerebral arteries >120 cm/s,⁸ and they typically underwent cerebral angiography. Symptomatic vasospasm was defined as documented arterial vasospasm consistent with new neurological deficits presenting between 4 and 14 days after SAH onset that could not be attributed to other causes of neurological deterioration such as rebleeding, hydrocephalus, electrolyte disturbance, hypoxia, or seizures. Patients with angiographically confirmed vasospasm underwent mechanical and/or chemical angioplasty. Proximal vessel vasospasm was treated with intra-arterial papaverine infusion. This was repeated on daily as needed, depend-

ing on a combination of factors, including the patient's neurological status and results of transcranial Doppler sonographic monitoring.

Radiological Assessment

CT scans were obtained at a minimum just before the second UK infusion, at 48 and 72 hours, and at 6, 9, and 13 days after SAH. The intervals were shorter in patients manifesting clinical deterioration. In patients with neurological deficits attributable to vasospasm alone, angiograms were further evaluated by a neuroradiologist blinded to the patients' treatment and neurological outcome. To express the degree of vasospasm as a percentage, the diameters of the following 6 vessels on angiogram obtained before treatment and within 12 hours of deficit manifestation were compared: the supraclinoid internal carotid artery, proximal anterior cerebral artery, middle cerebral vessels distal to the bifurcation, distal anterior cerebral arteries, posterior cerebral artery, and basilar artery. The straight anteroposterior projections of the carotid and vertebral vessels were used in the actual measurements.

Assessment of Clinical Outcomes

Secondary outcome measurements included the presence of permanent clinical deficits or death attributable to vasospasm and the patient's Glasgow Outcome Scale⁹ at 6 months after SAH onset. Data on outcome were obtained from the reports submitted by the referring or treating physician or by telephone contact with the patient or a knowledgeable relative. Patients with a Glasgow Outcome Scale score of good or moderately disabled were classified as favorable outcomes. Patients who were severely disabled, in a persistent vegetative state, or dead were classified as unfavorable outcomes. Patients who died were studied separately.

Determination of Eligibility and Outcome

To ensure uniformity in this trial, a committee composed of a neurosurgeon (Y.U.), a neurologist (T.H.), and a neuroradiologist (Y.K.) and blinded to treatment made all final determinations after thoroughly reviewing each patient's complete case report, hospital chart, and all angiographic and CT studies. These data were analyzed once by blinded evaluators. The committee determined any possible violations of the eligibility requirements or study protocol, cause(s) of any neurological deficits that developed during the treatment period, and neurological status 6 months after SAH onset.

Statistical Analysis

The effects of treatment modality and of different primary clinical and anatomic factors on observed angiographic results and 6-month clinical outcome were analyzed. The χ^2 test for dichotomous discrete variables and the Mann-Whitney *U* test for continuous or ordinal scale variables were used for comparisons between ITUKI-treated and -untreated patients. Differences were considered to be statistically significant at $P < 0.05$.

Results

Baseline Characteristics

Between April 2000 and February 2002, a total of 113 consecutive patients were randomly assigned to this study. Of these, 3 were excluded because of protocol violations: In 2 patients, the initial UK infusion was not completed within 24 hours of the ictus, the other excluded patient died of unrelated causes 2 months after treatment. Of the 110 patients available for analysis, 53 did and 57 did not receive ITUKI therapy.

Comparability of the Treatment Groups

Baseline information for both treatment groups is provided in Table 1. They were remarkably similar with respect to several factors, including those thought to be important in the development of neurological deficits from angiospasm, ie, the

TABLE 1. Baseline Characteristics of SAH Patients

Characteristic	With ITUKI Therapy (n=53)	Without ITUKI Therapy (n=57)
Mean age (range), y	54 (24–75)	57 (26–73)
Sex, n(%)		
M	17 (32)	21 (37)
F	36 (68)	36 (63)
H&H grade, n (%)		
1–2	5 (9)	6 (11)
3	27 (51)	32 (56)
4	21 (40)	19 (33)
Fisher grade, n(%)		
3	6 (11)	8 (14)
3 Plus 4	47 (89)	49 (86)
CT (range), n	66 (60–72)	68 (60–74)
Aneurysm site, n (%)		
Anterior circulation	44 (83)	51 (89)
ICA*	15 (28)	17 (30)
ACA	23 (43)	28 (49)
MCA	5 (9)	6 (11)
Posterior circulation	9 (17)	6 (11)
Aneurysm size, n (%)		
Small (≤ 7 mm)	39 (74)	41 (72)
Medium (8–14 mm)	13 (25)	15 (26)
Large (15–24 mm)	1 (2)	1 (2)
Concurrent illness, n (%)		
Diabetes	2 (4)	3 (5)
Hypertension	24 (45)	19 (33)
Heart disease	5 (9)	4 (7)

ICA indicates internal carotid artery; ACA, anterior cerebral artery; and MCA, middle cerebral artery.

*This category included all aneurysms arising from the ICA, whether close to the origin of the ophthalmic artery, posterior communicating artery, or carotid bifurcation.

H&H grade and CT number in the basal cistern. They were also well matched in factors that may be important in the ability to recover from a neurological deficit, ie, age and concurrent medical illnesses. There were no significant differences in the site and size of the ruptured aneurysms.

Technical Complications of Coil Embolization or ICUKI Therapy

Mild thromboembolic complications associated with the embolization procedure were encountered in 2 patients; they had no clinical consequences and did not need therapy. There were no complications resulting from advancing the microcatheter into the cisterna magna or from the intrathecal UK. No patients developed recurrent hemorrhage during the follow-up period.

Patients With Deficits From Vasospasm

Clinical Outcomes

As shown in Table 2, symptomatic vasospasm occurred in 5 of 53 patients (9.4%) with and in 16 of 57 patients (28.1%) without ITUKI therapy; the difference was statistically significant ($P=0.012$). Favorable outcomes were achieved in 48 patients (90.6%) with and in 43 patients (75.4%) without ITUKI therapy; again, the difference was statistically significant ($P=0.036$). There was no significant difference in mortality rates: 2 patients (3.8%) with and 3 patients (5.3%) without ITUKI therapy died.

Radiological Studies

CT scans

In all patients without ITUKI therapy, CT obtained 72 hours after SAH showed clots in the basal cistern; the CT numbers for hematoma in the basal cistern exceeded 60. In contrast, in approximately half of the patients with ITUKI therapy, almost the entire hematoma in the basal cistern, the basal frontal interhemispheric fissure, or bilateral proximal sylvian fissures was dissolved after a single UK infusion (Figure 1). In most patients with ITUKI therapy, CT obtained 48 hours after SAH demonstrated the almost complete absence of clots in the basal cistern (Figure 2).

Angiograms

In symptomatic patients, the highest degree of vasospasm (smallest diameter compared with the pretreatment diameter) of 6 arteries was used for analysis. The highest degree of vasospasm was $45.6 \pm 12.9\%$ (mean \pm SD) in patients without ($n=16$) and $53.2 \pm 15.7\%$ in patients with ($n=5$) ITUKI therapy; the difference was not statistically significant.

TABLE 2. Clinical Outcome 6 Months After Coil Embolization

Parameter	With ITUKI Therapy (n=53)			Without ITUKI Therapy (n=57)		
	Good or Moderate Recovery	Severe Disability or Vegetative State	Death	Good or Moderate Recovery	Severe Disability or Vegetative State	Death
All patients	48	3	2	43	11	3
H&H grade						
1–2	5	0	0	6	0	0
3	25	1	1	27	4	1
4	18	2	1	10	7	2
Symptomatic vasospasm		5			16	
Hydrocephalus*		3			11	

*Hydrocephalus that necessitated permanent shunt creation.

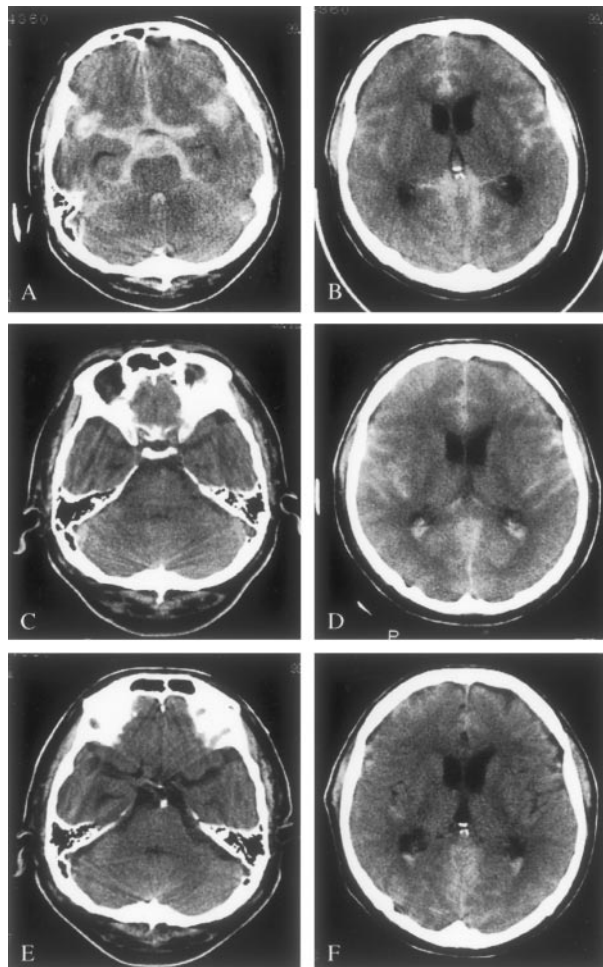


Figure 1. CT scans of patients with ruptured basilar bifurcation aneurysm who underwent ITUKI therapy. Neurological condition at the time of admission was H&H grade 3, and admission CT scan was placed in group 3 according to the classification of Fisher et al.² A, B, Admission CT scans revealing diffuse thick and dense SAH surrounding the brain stem and in the sylvian fissures. C, D, CT scans obtained just before the second UK infusion showing almost complete lysis of the subarachnoid clots in the basal cistern. However, the clot in the interhemispheric fissure and sylvian fissures remained. E, F, CT scans obtained 48 hours after the ictus showing complete lysis of subarachnoid clots in the basal cistern and almost complete lysis in the interhemispheric fissure and sylvian fissures.

Hydrocephalus

Hydrocephalus requiring permanent shunt placement occurred in 3 patients (5.7%) with and 11 patients (19.2%) without ITUKI therapy. The difference between the 2 treatment groups was statistically significant ($P=0.032$).

Discussion

There is now strong evidence that, compared with aneurysmal neck clipping, endovascular intervention with GDC can improve the chances for continued independent living in patients with ruptured intracranial aneurysms.¹ Unlike neurosurgical maneuvers, endovascular techniques do not carry the risk of morbidity resulting from iatrogenic injury to a brain already traumatized by SAH.

Although the etiology of cerebral vasospasm is not yet fully understood, their incidence, distribution, and severity

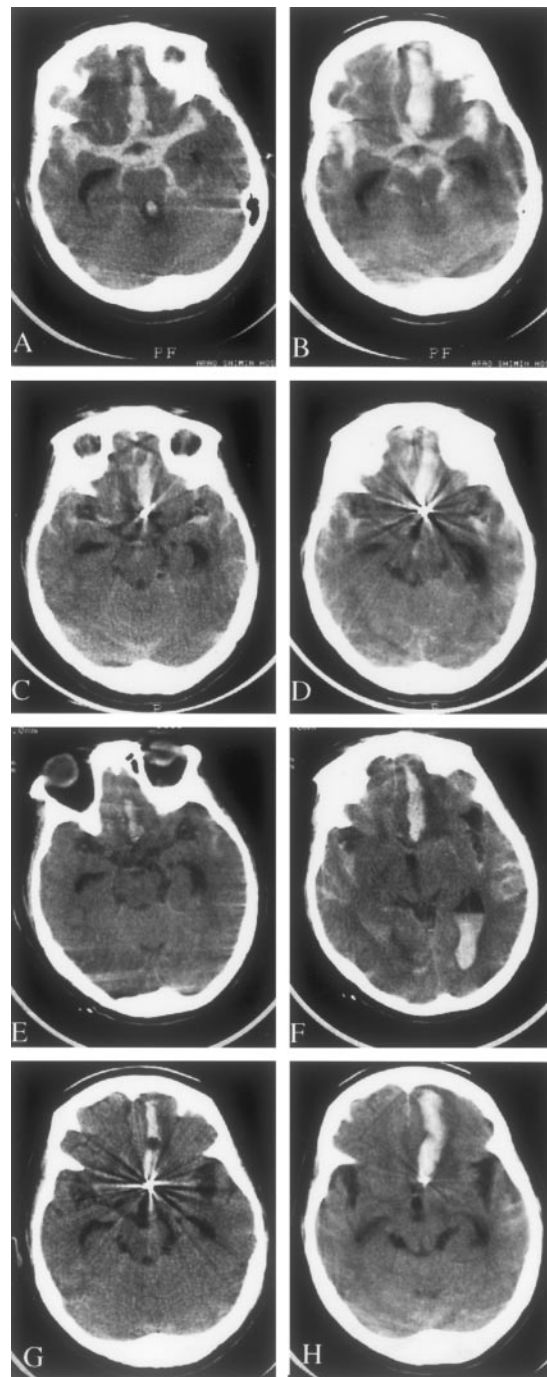


Figure 2. CT scans of patients with ruptured anterior communicating aneurysms who underwent ITUKI therapy. Neurological condition at time of admission was H&H grade 4, and admission CT scan was placed in group 3 plus 4 according to the classification of Fisher et al.² A, B, Admission CT scans revealing diffuse thick and dense SAH and small intracerebral hematoma in the left frontal base. C, D, CT scans obtained just before the second UK infusion showing almost complete lysis of the subarachnoid clots in the basal cistern. Clot in the proximal sylvian fissures remained, and slight reduction of the intracerebral hematoma is demonstrated. E, F, CT scans obtained 48 hours after the ictus showing complete lysis of the subarachnoid clots in the basal cistern and almost complete lysis of clots in the interhemispheric fissure and proximal sylvian fissures. However, subarachnoid clots in the distal sylvian fissures remained. G, H, CT scans obtained 72 hours after the ictus showing almost complete disappearance of the subarachnoid clots in the distal sylvian fissures and further resolution of the intracerebral hematoma.

are correlated with the location and volume of blood clots deposited in the basal cisterns by the ruptured aneurysm.^{10,11} The duration of exposure to blood adjacent to the cerebral arteries may also play a role in the development of vasospasm. It has been suggested that clot removal within 48 hours of SAH did prevent vasospasm but removal >48 hours after SAH did not.^{3,12}

Despite positive results in experimental and clinical studies of the intrathecal infusion of thrombolytic agents,^{13–20} this method is rarely combined with GDC placement. We have reported our preliminary results of GDC placement followed by immediate ITUKI therapy in patients with recently ruptured aneurysms.⁵ This strategy eliminates the risk of early rebleeding, allows rapid clearance of subarachnoid hematomas, and helps to prevent the occurrence of vasospasm. In our present randomized study, symptomatic vasospasm occurred in 5 of 53 patients (9.4%) who had received combined ITUKI therapy compared with 16 of 57 patients (28.1%) without ITUKI therapy. The latter is consistent with the incidence of vasospasm reported by others.^{21–23} We found that ITUKI therapy significantly reduced the occurrence of symptomatic vasospasm and significantly improved treatment outcomes, despite the fact that we selected patients at high risk for vasospasm whose clots could be expected to be difficult to resolve.

It has been shown that a marked reduction in cerebral blood flow occurred only when arterial vasoconstriction exceeded 50% of control caliber.²⁴ We observed no significant difference with respect to the highest degree of vasospasm between patients with and without ITUKI therapy, suggesting that ITUKI therapy has no direct effect on the severity of vasospasm. We also detected no association between symptomatic vasospasm and increased mortality because, in our series, overall mortality was not different between the 2 groups.

In some previously reported patients, subarachnoid blood was noted in the basal cisterns as late as 9 days after SAH.²⁵ In our patients without ITUKI therapy, CT obtained 72 hours after SAH showed clots in the basal cisterns. In contrast, most patients subjected to ITUKI therapy manifested no evidence of clots in the basal cisterns on CT scans obtained 48 hours after SAH. This suggests that rapid clearance of the subarachnoid hematoma was associated with the reduced incidence of vasospasm in ITUKI-treated patients.

It is not known how differences in the CSF circulation in an intact subarachnoid space and a space occupied by hematoma affect the diffusion of thrombolytic agents. In our experimental study, the average maximum UK concentration in the cisterna magna and the sylvian fissure was 2.5 and 6.7 times higher, respectively, when UK was infused into the cisterna magna rather than the lumbar sac.²⁶ We posit that thrombolytic agents infused into the cisterna magna diffuse more widely into the subarachnoid space with the help of anterograde infusion, thereby lysing subarachnoid hematomas more rapidly than would agents infused retrogradely. Also, ITUKI therapy after GDC embolization appeared to be more effective than surgical clipping followed by clot removal for lysing subarachnoid hematomas. Surgical intervention, because it involves opening the subarachnoid mem-

brane, results in a morphologically more complicated CSF circulation.

Significantly fewer patients with ITUKI therapy required permanent shunt placement to treat hydrocephalus (6% versus 19%). Clearance of the hematoma in the basal cisterns lowers the risk of hydrocephalus; in most ITUKI-treated patients, the entire hematoma in the basal cistern was dissolved 48 hours after SAH.

Not all patients with recently ruptured intracranial aneurysms are suitable candidates for ITUKI therapy. In patients with huge intraventricular clots and/or huge intracerebral hematomas, this therapy carries a potential risk because downward herniation may occur. It also may be inappropriate in patients with H&H grade 5. Another important factor limiting the use of ITUKI therapy is the width of the aneurysm neck. However, technical improvements, including the use of balloon remodeling to retain the coils during placement, have made possible the treatment of broader-necked aneurysms and have increased the anatomical range of aneurysms suitable for endovascular coil occlusion. Thus, as improved endovascular devices become available, the durability and safety of this procedure will be enhanced.

Although our study population was not large, our results clearly demonstrate that ITUKI therapy significantly reduced the occurrence of symptomatic vasospasm and produced better outcomes in patients with recently ruptured aneurysm. This treatment did not completely prevent the occurrence of deficits, and in efforts to improve our results, we are examining whether the UK dose was inadequate and/or whether other as-yet-unknown mechanisms were at play despite successful clot lysis. Continued studies are underway to address these issues, whose resolution may lead to the development of standardized, highly effective ITUKI therapy in patients with SAH.

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