

Urokinase Thrombolysis for Nonaneurysmal Spontaneous Intraventricular Hemorrhage

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Objective : The authors report our experience of urokinase thrombolysis in treating patients harboring nonaneurysmal spontaneous intraventricular hemorrhage (IVH) and evaluated complications, safety and feasibility of this procedure retrospectively

Methods : Fifty-three patients with nonaneurysmal IVH > 15mL without underlying structural etiology or coagulopathy were recruited. The patients with Glasgow Coma Scale (GCS) < 5 were excluded. A catheter was directed into the IVH. Hematoma aspiration was followed by instillation of urokinase at the ear level of drainage bag under intracranial pressure monitoring system. This was repeated every 6 hours until half of its initial volume. For analysis of prognostic factors, we classified the patients into two groups by Glasgow outcome scale (GOS); good (GOS ≥ 3) and bad (GOS < 3) prognosis group, and performed comparative analysis between two groups

Results : Mean age was 60.2 years. The baseline hematoma size ranged 16 to 72mL. IVH volume reduction was done by an average of 74.2%. As complications, there were 3 cases of rebleeding and 2 cases of ventriculitis. No intracranial adverse effects were observed during thrombolytic therapy. At 6 months after the procedure, 29 patients had achieved a good recovery, 15 remained vegetative, 9 patients died in hospital. The main good prognostic factors were young age, small IVH volume, and high GCS.

Conclusion : The results of this study suggest that this relatively easy and safe method of treatment will improve the prognosis. However, further clinical studies also must assess optimal thrombolytic dosage, frequency, and timing of urokinase instillation for safety and effectiveness and must include controlled comparisons of mortality, disability outcome, quality of life, time until convalescence, and cost of care in treated and untreated patients.

KEY WORDS : Intraventricular hemorrhage · Urokinase · Thrombolysis.

Introduction

Spontaneous nonaneurysmal intraventricular hemorrhage is one of the most serious types of stroke. The majority of cases are associated with arterial hypertension and/or elderly age, diabetes mellitus, and bleeding diatheses. The mortality rate for IVH is related to the amount of intraventricular blood and increases from 32.2% in cases with mild hemorrhage to 91% in cases with hemorrhage at all ventricular chambers. Most survivors are typically left severely disabled^{1,2,5,16,18,28}.

A large part of the complications seen after IVH is related to intracranial hypertension from hydrocephalus that cannot be adequately treated with standard external ventricular drainage.

The failure of ventriculostomy alone to clear IVH is frequ-

ently related to clots within or around the catheter, which obstruct attempts at therapeutic cerebrospinal fluid (CSF) drainage. Anatomic correlates of this impaired CSF outflow include compression of periventricular structures and brain stem injury. Patients initially may not have significant parenchymal injury and relief of persistent IVH may prevent subsequent significant brain damage⁴.

The authors present experience with consecutive cases of IVH treated by ventriculostomy and thrombolysis with urokinase. In this study, we attempted to assess the feasibility and safety of this treatment modality. This study was undertaken to assess the influence that adjunctive thrombolysis with urokinase has on speeding hemorrhage resolution and on outcome. The hypothesis was that this relatively simple

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therapy would improve neurological prognosis in patients presenting with IVH⁶.

Materials and Methods

From January 1999 to December 2003, 53 patients of nonaneurysmal spontaneous IVH were treated with thrombolysis of urokinase. The patients were treated according a standardized protocol as illustrated in Fig. 1. Eligibility criteria for this protocol consisted of IVH with less than 15mL of intracerebral hematoma, clinical onset <48hours before intervention, age >20years, hemorrhage volume > 15mL, GCS score ≥5 at admission, no signs of transtentorial herniation, no suspected underlying structural etiology to account for the hemorrhage, no systemic bleeding diathesis, and no severe concurrent illness.

Ventricular drainage was weaned while intracranial pressure was monitored.

A baseline CT scan was obtained with axial images at 0.5~1.0cm slice thickness and the dimensions of the hematoma were assessed. Volume of the IVH and ICH in milliliters was estimated on the methods of Steiner et al.²⁹, Intravenous contrast was administered to assess for any enhancement that would be suspicious for an underlying structural lesion. Patients aged <60years or with abnormal contrast enhancement on CT scan underwent digital subtraction angiography before hematoma aspiration and thrombolysis to exclude an underlying vascular anomaly.

Operative technique

All operations were performed under local anesthesia and intravenous sedation unless the patient was already intubated

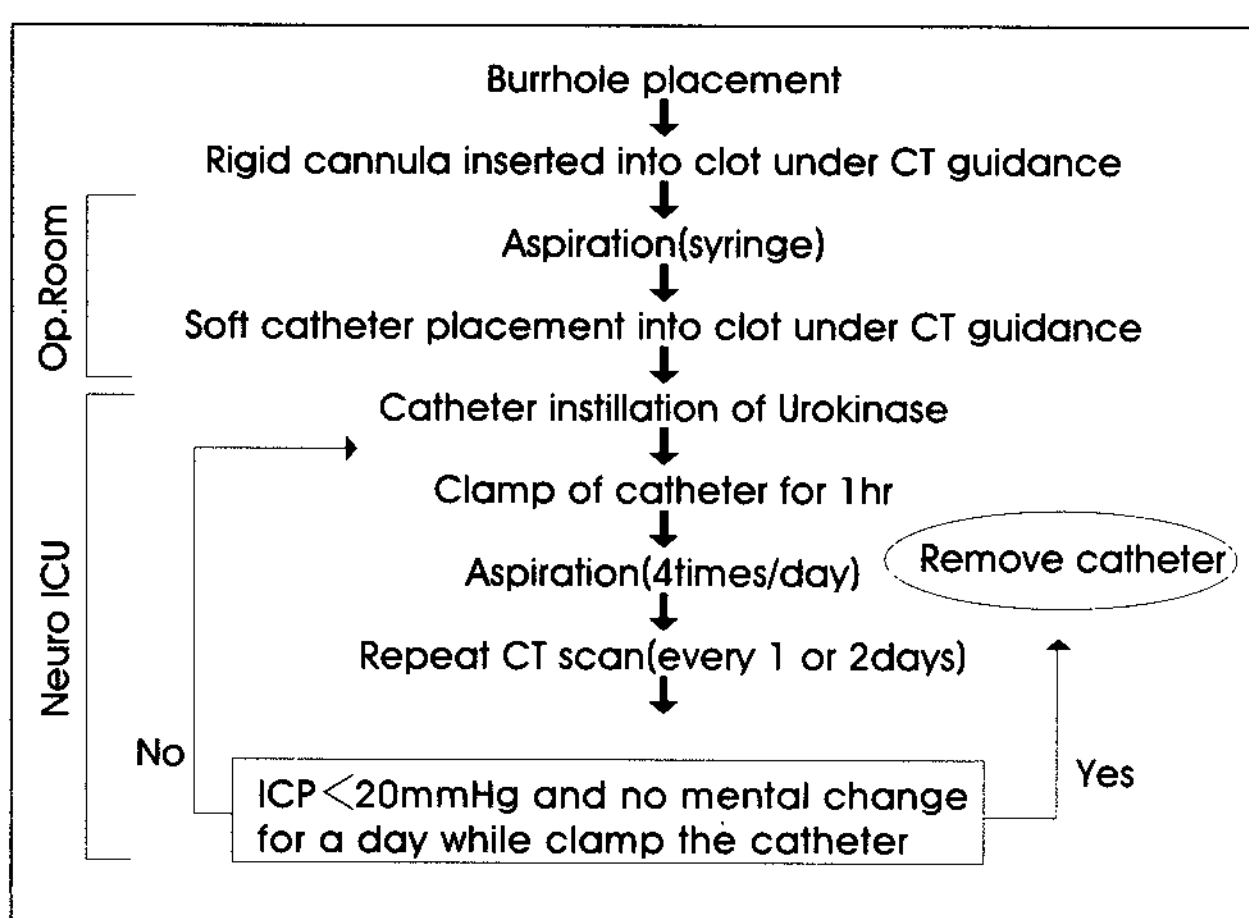


Fig. 1. Management protocol for ventriculostomy and thrombolysis. Urokinase protocol consists of catheter injection of 6000 IU preceded by hematoma aspiration every 6hours. The protocol of aspiration, computed tomography scan, and urokinase instillation is repeated as necessary until the final hematoma volume was <15mL or less than half of its initial volume. (ICU : intensive care unit).

for medical or neurological indications independent of the procedure. In this series, an ipsilateral frontal standard burr hole location(3cm lateral to mid-line and just anterior to the coronal suture) was typically used. The catheter location targeted toward ipsilateral medial epicanthus medially and tragus posteriorly. The rigid cannula was removed and replaced by a soft ventriculostomy catheter(15cm long and 1 to 2mm internal diameter). The catheter was tunneled subcutaneously and the exit site was covered with antibiotic ointment. The catheter was connected to a single port and ICP monitoring system and a sterile dressing was applied and then the drainage bag was located at the ear level. The patient was maintained on intravenous antibiotic prophylaxis until the brain catheter was removed.

All patients were managed in a dedicated neurovascular intensive care unit, where subsequent thrombolysis and hematoma aspiration were performed using sterile technique. Urokinase 6000IU(Green Cross Biotech., South Korea) in 3mL of normal saline was injected into the catheter if the CT scan revealed a residual hematoma or ventricular dilatation. The catheter was flushed with 2mL of normal saline. After clamping of catheter for 1hour, manual aspiration of lysed clot was attempted, and the aspirated volume was recorded. A CT scan was repeated at least every second aspiration. If residual hematoma remained and ventricular dilatation continued, catheter instillation of urokinase was repeated. The catheter was removed if ICP monitor ≤20mmHg and no mental change during clamp of the cap for a day, and a single suture was placed at its exit site and covered with an occlusive dressing.

Evaluation of outcome

Follow-up clinical information was obtained on all patients 6months after the procedure. Clinical outcomes were graded according to the GOS, ranging from grade 5 (good recovery) to grade 1 (dead), by a single investigator not involved in the patients' clinical management. For analysis, we classified two groups; good prognosis group (GOS grade 3, 4, 5) and bad prognosis(GOS grade 1, 2) at the time of discharge and 6months' follow-up. We performed comparative analysis between two groups in aspect of all possible relating factors of this procedure.

Unpaired Student t tests were used for the statistical analysis. The value of statistically significance means P vaule less than 0.05.

Results

Clinical outcome assessment

The Table 1 and 2 summarize clinical and radiographic data in the 53cases treated during the course of 5years. The mean

age of treated patients was 60.2years(range 38 to 82 years) and there were 28males and 25females. There were 28 right side intracerebral lesions, and 25 left side lesions with concomitant intracerebral heamtoma. A prior history of arterial hypertension was Twenty patients(37.7%), and diabetes mellitus was twenty-three patients(43.3%),and both arterial hypertension and diabetes mellitus were nine patients(16.9%). All patients had spontaneous, nontraumatic IVH. Median initial GCS score was 10 (range 5 to 15). All patients had some degree of neurological deficit such as contralateral hemiparesis, hemiplegia, and dysphasia.

The mean initial intraventricular hematoma volume was 35mL (ranging from 16 to 72mL). Hematoma aspiration via the inserted catheter was easily achieved in 50patients. In 3patients, uncomplicated repositioning of the catheter was necessary after initial placement for optimal positioning within the hematoma before thrombolysis.

The average time from symptom onset until first aspiration was 3.9hours(ranging from 2 to 7hours). The hematoma

catheter was in place for a median duration of 5days(range 2 to 8days). During this time the average number of urokinase instillations was 13(range 5 to 26times). Initial IVH volume was reduced by an average of 74.2%(range 65% to 88%) and the average final hematoma volume was 4.5mL(range 2 to 12mL).

Ventriculitis developed during procedure in 2patients, and this complication was probably related to catheter instillation for long periods. And, there were 3cases of local rebleeding in originally presented intracerebral heamtoma sites. Repeat brain CT image performed after the first urokinase instillation revealed hematoma size increased, and the patients became less responsive. In cases of rebleeding, 1patient remained severely disabled, 1patient remained vegetative, and 1patient died. However, systemic hemorrhage related to procedure was not encountered in any patient. There were no instances of late clinical deterioration from mass effect or edema associated with residual hematoma.

Nine patients(16.9%) died before hospital discharge(1 from cardiac problems and 8 from respiratory failure). At discharge, 25patients(47%) had achieved good recovery(17patients GOS 3, 6patient GOS 4, and 2patients GOS 5), and 19patient (35.8%) remained vegetative(GOS 2). At 6months' follow up, 29patients(55%) had achieved good recovery(17 patients GOS 3, 8patient GOS 4, and 4 patients GOS 5) and 15patient(28.3%) remained vegetative(GOS 2).

Table 1. Patients summary

Characteristic	Value
No. of patients	53
Mean age (year)	60.2 (38~82)
Sex (No. of Male/ Female)	28/25
Underlying disease(No.)	
HTN	20
DM	23
HTN + DM	9
Median initial GCS score	10 (5~15)
Mean initial hematoma volume(ml)	35 (16~72)
Average time to procedure(hour)	3.9 (2~7)
Average No. of urokinase instillation	13 (5~26)
Average reduction of IVH volume(%)	74.2 (65~88)
Average final hematoma volume(ml)	4.5 (2~12)
Mortality (No)	
Cardiac problem	1
Respiratory failure	8
Complications during procedure (No)	
Ventriculitis	2
Rebleeding	3

No : number, HTN : hypertension, DM : diabetes mellitus, IVH : intraventricular hemorrhage, GCS : Glasgow, Coma Scale

Table 2. Clinical outcomes

Outcome (No)	Discharge	6months
Good recovery	25 (47%)	29 (55%)
GOS 5	2	4
GOS 4	6	8
GOS 3	17	17
Bad recovery	28 (52%)	24 (45%)
GOS 2	19	15
GOS 1	9	9

No : number, GOS : Glasgow Outcome Scale

Evaluation of prognostic factors

Significant good prognostic factors were found in our study to be young age, small pre-and-postoperative volume, high GCS, absence of rebleeding, absence of underlying disease, and absence of complication of pneumonia after procedure. The other factors such as sex, time to procedure, total inst-

Table 3. Investigated prognostic factors

Prognostic factors	Mean		p-value
	*Group A	**Group B	
Sex (M/F ratio)	.58	.63	.566
Age (years)	58.1	63.5	.033
Pre vol. (ml)	25.1	45.9	.000
Post vol. (ml)	6.4	11.9	.000
Pre GCS (score)	10.9	7.7	.000
Post GCS (score)	12.8	8.1	.000
Time to procedure (hr)	4.2	3.9	.154
Total instillation vol. (ml)	81.6	82.1	.940
***Underlying disease(HTN+DM)	.19	.44	.004
***Pneumonia	.14	.50	.000

*Group A : (good prognosis group) : GOS 3, 4, 5(N=29) **Group B : (bad prognosis group) : GOS 1,2 (N=24) *** Event (+); 1 point, Event (-); 0 point Statistical analysis was performed by independent t- test. GOS : Glasgow Outcome Scale, GCS : Glasgow Coma Scale, M: male, F: female, Pre : preoperative, Post : postoperative, vol.: volume, hr : hours, HTN : hypertension, DM : diabetes mellitus, IVH : intraventricular hemorrhage

illation volume, and total number of instillation were not meaningful prognostic factors in our study (Table 3).

Discussion

Causes and natural history of IVH

Forty six to 62% of IVH result from penetration of a hypertensive or arteriosclerotic intracerebral hemorrhage into ventricle. Nineteen to 29% of IVHs are caused by rupture of cerebral aneurysm, predominantly arising from anterior communicating artery and anterior cerebral artery. Less frequent causes of IVH are periventricular arteriovenous malformations, head trauma, and tumors^{6,28}.

Intraventricular hemorrhage carries a poor prognosis. The mortality rate for IVH is related to the amount of intraventricular blood and increases from 32.2% in cases with mild hemorrhage to 91% in cases with all ventricular chambers^{4,22,28}.

Pathophysiology of IVH

The clinical course in patients with IVH is determined by different pathogenetic mechanisms which must be considered when establishing an effective therapeutic strategy. At the time of bleeding, a sudden increase of ICP occurs, which may lead to a significant decrease of cerebral perfusion and ischemic brain damage. A further raise of ICP and ventricular dilatation may occur due to obstruction of the flow of CSF at the foramen of Monro, aqueduct of Sylvius, or the fourth ventricle, depending on the amount and location of blood clots. Furthermore, intraventricular clotted blood, as well as accompanying intracerebral hemorrhage exert a direct mass effect upon adjacent brain structures. It has been shown that the prognosis in patients with IVH is directly related to the amount of intraventricular blood and the degree of ventricular dilatation on early image study. Thus, the aims of any specific therapy in severe IVH must be rapid elimination of intraventricular blood, diversion of ventricular CSF, reduction of ventricular dilatation and normalization of ICP. Obviously, this cannot be achieved by conservative medical therapy alone. Surgical blood removal through a conventional craniotomy has been advocated namely in cases with accompanying intracerebral hemorrhage. However, complete surgical removal of intraventricular blood may be hazardous or even impossible in cases in which all ventricular chambers are filled with blood. External ventricular drainage usually fails in the aim of blood elimination and normalization of ICP and ventricular size, as the catheters quickly become obstructed by clotted blood. Furthermore, ventricular drains have no effect on solid clots within the ventricles^{7-9,18,19,21}.

In the last decade, recognition of the proinflammatory role that certain blood components have on neuronal tissue led

to a growing interest in inflammation as a mechanism of secondary brain injury. A blood component identified to play a role in the development of acute and chronic brain injury as well as degeneration is thrombin^{22,32}. After first developing an animal model of IVH, Pang et al have shown that blood and its product produce inflammation and fibrosis of ependymal lining^{5,10,25-28,31}. Other previous experimental studies have shown that infusion of urokinase promotes clot lysis and restoration without producing neurotoxicity, histopathological alterations, or recurrent bleeding^{2,8,20,23,25-27,33}.

Complications

Several authors reported the rebleeding rate in CT-guided stereotactic surgery to be 3% to 16%^{12,14,17,24}. The factors contributing to recurrent hemorrhage include excessive hematoma aspiration, intraoperative or postoperative hypertension, and a bleeding tendency. Because of the rebleeding risk that could potentially be increased by early aspiration suggest not to do the stereotactic aspiration before 6 to 24hours after onset^{4,17,24}. Hondo, et al.¹³, reported a rebleeding risk of only 4% when aspiration had been carried out between 5 and 48hours after the hemorrhage. However, from our result, rebleeding after procedure seems to be not related to early aspiration. Even if the average time from symptom onset until first aspiration was 4.1hours (ranging from 2 to 7hours), the rebleeding risk cannot potentially be increased in our study(9%). Kandel, et al.¹⁴, developed a method of preventing recurrent bleeding after hematoma evacuation. After removal of the hematoma, the balloon catheter with a metal shift inside is introduced through the cannula into the cavity. Inflation continues until the pressure inside the balloon equals the pressure in the contralateral ventricle.

It is not clear whether the incidence of expanding hematoma in these above series represents any added risk from thrombolytic therapy. During the early period of time after ictus, hematoma may cause neurological deterioration as a result of an increasing mass effect caused by surrounding edema, and this mass effect may last up to 4weeks after bleeding, even with decreasing density of clot. The risk of hematoma expansion during treatment must be closely monitored in future studies, including any associated untoward clinical sequelae, but this should also be compared with the substantial risk of spontaneous hematoma expansion in the first day among untreated patients¹⁵.

In our series, three patients of rebleeding and, two patients of ventriculitis due to ventricular drainage developed. These were the only treatment related complications. No intracranial adverse effects were observed during thrombolytic therapy.

Mortality has been the primary end point of therapeutic studies in most published studies, and it has ranged from

30% to 90%^{2,6,11,15,30}). This reflects in part patient inclusion and exclusion criteria, and to a lesser extent the treatment rendered in individual studies. In our series, there was 16.9% mortality with relatively large hematoma volume (>25mL). Relative low mortality rate was because of excluding cardiac and pulmonary compromised patients and deeply comatose patients. Disability levels among surviving patients may be more relevant in assessment of management outcome. It is not clear from countless cases in published uncontrolled series whether IVH evacuation in fact enhances functional recovery. Such outcome assessment should be supplemented by documentation of quality of life domains relevant to patient and family, and these should be compared among treated and untreated cases. It may be advantageous to minimize stay in critical care unit and acute hospital settings even if eventual survival or disability level are not significantly altered by treatment. The state of consciousness is the best indicator of survival but deficit of consciousness are not always a good indicator of functional prognosis.

A pure intraventricular hemorrhage was rare, so we include intraventricular hemorrhage concomitantly with intracerebral hemorrhage. We did not consider selection bias of this problem.

Prognosis

Volume of IVH is consistently shown to be a powerful predictor of poor outcome regardless of clot location, patient age, and neurological condition^{4,5}). Most postoperative complications were seen in older patients and in those with severe neurological deficit or chronic disease. Factors contributing to poor outcome are as follows : age over 70years, large hematoma, bad neurological grading. The main prognostic factors affecting the outcome are clinical state of a patient on admission, the size of hematoma¹¹). The level of consciousness, volume of hematoma, and age are related well with bad outcome¹⁴).

Significant good prognostic factors for this procedure of IVH were found in our study to be young age, small preoperative and postoperative volume, pre-and-postoperative GCS, absence of rebleeding, absence of underlying disease, and absence of complication of pneumonia after procedure. However, the other factors such as sex, time to procedure, total instillation volume, and total number of instillation were not meaningful factors in our study

Conclusion

While this study clearly demonstrates rapid clearance of intraventricular clots, reduction of ventricular dilatation, and normalization of ICP by urokinase injection,

no conclusions regarding the clinical outcome can be made from our data, due to selection bias, lack of untreated control group, and the complex concurrence of various pathogenetic mechanisms determining the patients' outcome. Nevertheless, the results of this study suggest that this relatively easy and safe method of treatment will improve the prognosis of severe IVH, especially in those patients in whom large intraventricular volume, ventricular dilatation and impaired CSF circulation are the major determinants for the outcome. And, further clinical studies also must assess optimal thrombolytic dosage, frequency, and timing of urokinase instillation for safety and effectiveness and must include controlled comparisons of mortality, disability outcome, quality of life, time until convalescence, and cost of care in treated and untreated patients.

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