Treatment of Intraventricular Hemorrhage With Urokinase
Effects on 30-Day Survival

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Background and Purpose—Intraventricular hemorrhage (IVH) remains associated with high morbidity and mortality. Therapy with external ventricular drainage alone has not modified outcome in these patients.

Methods—Twelve pilot IVH patients who required external ventricular drainage were prospectively treated with intraventricular urokinase followed by the randomized, double-blinded allocation of 8 patients to either treatment or placebo. Observed 30-day mortality was compared with predicted 30-day mortality obtained by use of a previously validated method.

Results—Twenty patients were enrolled; admission Glasgow Coma Scale score in 11 patients was ≤8; 10 patients had pulse pressure <85 mm Hg. Mean±SD ICH volume in 16 patients was 6.21±7.53 cm³ (range 0 to 23.88 cm³), and mean±SD intraventricular hematoma volume was 44.26±31.65 cm³ (range 1.31 to 100.36 cm³). Four patients (20%) died within 30 days. Predicted mortality for these 20 patients was 68.42% (range 3% to 100%). Probability of observing ≤4 deaths among 20 patients under a 68.42% expected mortality is 0.000012.

Conclusions—Intraventricular urokinase may significantly improve 30-day survival in IVH patients. On the basis of current evidence, a double-blinded, placebo-controlled, multicenter study that uses thrombolysis to treat IVH has received funding and began January 1, 2000. (Stroke. 2000;31:841-847.)

Key Words: intraventricular hemorrhage ■ outcome ■ urokinase

Intraventricular hemorrhage (IVH) complicates subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH) in 15% and 40% of patients, respectively.1–4 When IVH is large enough to impede normal cerebrospinal fluid (CSF) circulation, acute obstructive hydrocephalus can occur. In the subacute and chronic stages of IVH, communicating hydrocephalus may develop if fibrosis of the basal leptomeninges occurs or if reabsorption of CSF becomes impaired from fibrosis of the arachnoid villus.5–8

A prevailing concept has been that the initial ventricular hemorrhage almost invariably correlates with an acute elevation of intracranial pressure (ICP). The alteration of consciousness that often develops after initial ictus and that sometimes persists during the subacute stage is thought to be the result of intracranial hypertension–induced ischemic encephalopathy. Similarly, direct compression of rostral brain stem and thalamus could play a pathogenic role.9 Several studies have identified ventricular dilation, intraventricular hematoma volume, and increased ICP to be indicators of poor prognosis in patients with IVH.10 For this reason, treatment strategies for IVH have centered on ICP management.3 Currently, use of external ventricular drainage (EVD) to accelerate recovery and reduce the risk of development of chronic hydrocephalus is widely recommended. This approach to treatment of IVH patients has become the standard of care when clinical and radiographic manifestations of acute obstructive hydrocephalus are identified. However, ICP elevations are not universally present in IVH patients who manifest acute and subacute neurological deterioration. In addition, normalization of ICP with EVD by means of intraventricular catheter (IVC) does not always lead to improvement in neurological deficits, even after an initially elevated ICP is corrected.11

Clear rationale exists in favor of the benefits of removal of IVH blood. Blood and blood derivatives have long been recognized as proinflammatory agents in neurological disease.12–15 Case studies that use thrombolysis for removal of blood components from the subarachnoid and ventricular spaces in SAH and ICH have been safely and successfully conducted.16 More recently, Tuhrim et al17 have validated that

Received November 17, 1999; final revision January 7, 2000; accepted January 20, 2000.

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IVH volume is an independent risk factor for death. In a large consecutive clinical series, Coplin et al\textsuperscript{18} demonstrated that the chance of poor outcome is 66.7% in untreated patients compared with 31.8% in urokinase-treated patients.

Outcome after ICH can be described as a function of specific clinical features that include location of the hematoma. However, analysis of functional and survival outcome has been limited by the size of the patient series, which limits the application of complex cohort outcome analysis. Furthermore, until scientifically generated therapies such as the amelioration of secondary neuronal damage are designed, mortality remains the primary end point in ICH and IVH therapy trials.

The objective of the present study is to analyze the initial experience accumulated in 4 university-based neurointensive care units (Johns Hopkins Hospital [JHH], Mount Sinai Hospital [MSH], Medical College of Virginia [MCV], and University Hospital, Innsbruck [INN]) with the use of intraventricular urokinase (UK) in the treatment of IVH and to compare the 30-day mortality found with this therapy with the predicted mortality obtained with the use of a previously validated method.\textsuperscript{19}

Subjects and Methods
This protocol-based use of UK for IVH patients was organized, standardized, and prospectively initiated as an open-label study by 1 institution (JHH) and as a novel form of therapy at 2 others (MSH and MCV) in the New Approaches to Critical Care of Acute Brain Injury (NACCABI) consortium. Seven patients from MSH, 2 from JHH, and 3 from MCV were initially treated. Subsequently, a blinded, randomized, and controlled study was initiated at all centers, with 8 patients enrolled at JHH (7) and INN (1). Randomization was in blocks of 4 patients, with a ratio of 1 control to 1 drug-treated patient.

Criteria for Patient Enrollment in the Study
All patients were screened and enrolled if an IVH with or without ICH had occurred within 48 hours before admission and was diagnosed by clinical and brain CT criteria and if an IVC was clinically required for treatment of obstructive hydrocephalus. In addition, when intracerebral aneurysms or arteriovenous malformations were suspected, they had to be excluded by appropriate diagnostic studies. Exclusion criteria were pregnancy and age <18 years.

Treatment Protocol
Patients enrolled in the present study were admitted to a Neurointensive Care Unit or Intensive Care Unit (ICU) with staff experienced in the acute care of patients with ICH and IVCs. The UK preparation was Abbokinase (Abbott Laboratories), a sterile, lyophilized preparation intended for intravascular injection. A vial of UK (immediately reverted on admission). After 1 hour of closure, the IVC was reopened with an appropriate drainage gradient. Subsequent ICP measurement and management followed routine protocols of each ICU. The study drug was administered every 12 hours until the IVC was removed based on the patient tolerance to IVC closure for 24 hours (ie, no sustained ICP elevation >20 mm Hg). Neuroradiological evaluations were performed, with head CT scans obtained on alternate days, and urgent studies were performed if an acute neurological deterioration was recognized. Intraventricular and intraparenchymal hematoma volumes were studied independently by use of standard computerized volumetric analysis following the method reported by Steiner et al.\textsuperscript{20} In addition to the radiological monitoring, clinical surveillance was performed with daily Glasgow Coma Scale (GCS) assessment and ICP, blood pressure, and CSF analysis that following the specific ICU standards. In the presence of fever without obvious source, CSF analysis was performed to investigate the possibility of bacterial or chemical ventriculitis. The JHH Internal Review Board approved this protocol.

Statistical Analysis
Predicted mortality in ICH patients with an IVH was obtained by use of the model designed by Tuhrim and coworkers.\textsuperscript{17} By use of logistic regression analysis, 30-day survival probability may be calculated with the following formula:

\[
P = \frac{1}{1 + e^{-3.125 + 2.785 \cdot \text{GCS} - 0.110 \cdot \text{ICH} - 3.832 \cdot \text{PP} - 0.957 \cdot \text{Hydro} + 0.979 \cdot \text{IVH}}}
\]

where PP (pulse pressure) can assume values of 0 (≤85 mm Hg) or 1 (>85 mm Hg); ICH is either 0 (absent) or 1 (present); GCS score can assume values of 0 (>8) or 1 (≤8); ICH (intraparenchymal hemorrhage size) is measured in cubic centimeters; Hydro is expressed as 0 if hydrocephalus is absent or 1 if present; and IVH represents the size of the intraventricular hemorrhage in cubic centimeters. After calculated mean 30-day mortality and actual mortality rate were obtained in the entire cohort, these were compared with the exact hypothesis test for binomial random variables to calculate the probability of obtaining the number of deaths observed or fewer under the predicted mortality rate. Statistical significance was accepted only if \( P < 0.05 \). Values are mean±SD.

Results
Relevant demographic, clinical, and neuroradiological characteristics of the study cohort are summarized in the Table.

Demographics
Between December 1993 and July 1998, informed consent from 20 patients was obtained in the participating university-based referral centers (JHH, 9 patients; MCV, 3 patients; MSH, 7 patients; and INN, 1 patient). Twelve patients were men, 8 were women; mean±SD age was 57±13.1 (range 35 to 80) years.

Clinical Features
In the JHH cohort, the cause of the IVH was associated with a history of hypertension in 8 patients and with warfarin anticoagulation in 1 (immediately reverted on admission). GCS on admission and before administration of intraventricular UK in the cohort was 8.7±3.89 (range 3 to 15); 11 patients had GCS ≤8, and 9 had GCS >8. Ten patients had pulse pressure <85 mm Hg on admission; the remaining 10 had pulse pressure >85 mm Hg. Throughout the study period, no clinical or laboratory evidence of meningitis or ventriculitis was detected. During the study period, only 1 patient, from the JHH group, had an IVC exchange, which
was due to presumptive ventriculitis, a diagnosis that was eventually excluded. Only 1 episode of IVC obstruction due to blood clots (MCV patient 2) occurred. Duration of IVC placement in 7 of 12 treated patients was 5.14 ± 2.27 days (range 3 to 8 days).

ICP was continuously recorded before and 1 hour after study drug administration in 2 cases. Mean ICP before administration was 7 ± 5.7 mm Hg (range 0 to 22 mm Hg). One hour after administration, mean ICP was 10.2 ± 6.5 mm Hg (range 2 to 28 mm Hg). In another 3 patients, mean ICP throughout the treatment period was 10 ± 6.1 mm Hg (range -5 to 27 mm Hg), with only 4 documented episodes of elevated ICP (20, 27, 22, and 20 mm Hg), 3 of which were in the same patient. These ICP elevations responded to hyperventilation, and CSF drainage was not required to control them.

Four deaths occurred in the entire cohort. In the JHH group, 1 patient (JHH patient 7) died from cardiac arrest. No attempt to reverse this event was made, in accordance with the patient’s “do not resuscitate” status. A second patient from the same group (JHH patient 2) and MSH patient 7 died after care was withdrawn due to patient neurological condition and preexisting medical problems complicating the neurological disease. In the MCV cohort, MCV patient 2 experienced severe ICP elevation after IVH extension, which led to death.

Laboratory Features

Laboratory evidence of bleeding diathesis was found in only 1 case (JHH patient 5) and was due to warfarin anticoagulation after left internal carotid artery angioplasty and stent placement. No other abnormalities relevant to the acute neurological disease were identified in the study cohort throughout during the study. In the prospectively controlled JHH group, baseline coagulation parameters were as follows: international normalized ratio (INR), 1.1 ± 0.4 (range 0.8 to 2.0); platelet count, 240.4 ± 77.9 × 10³/µL (range 119 to 328 × 10³/µL); and partial thromboplastin time (PTT), 23.9 ± 4.6 seconds. At the completion of the study period, INR was 0.99 ± 0.11 (n=8; range 0.8 to 1.2); platelet count, 273.0 ± 51.7 × 10³/µL (n=9; range 211 to 332 × 10³/µL); and PTT, 23.8 ± 5.1 seconds. At the completion of the study period, INR was 0.99 ± 0.11 (n=8; range 0.8 to 1.2); platelet count, 273.0 ± 51.7 × 10³/µL (n=9; range 211 to 332 × 10³/µL); and PTT, 23.8 ± 5.1 seconds. At the completion of the study period, INR was 0.99 ± 0.11 (n=8; range 0.8 to 1.2); platelet count, 273.0 ± 51.7 × 10³/µL (n=9; range 211 to 332 × 10³/µL); and PTT, 23.8 ± 5.1 seconds.

Neuroradiological Features

IVH mean volume was 44.26 ± 31.65 (range 1.31 to 100.36) cm³. An intraparenchymal component was present in 16 patients, with a mean ICH volume of 6.21 ± 7.53 (range 0 to 23.88) cm³. The treatment effect on IVH is depicted in Figures 1 and 2.
Treatment
Of the initial 12 patients treated with intraventricular UK as part of the open-label study or as a novel form of therapy, the mean number of administered doses of UK in 9 was 6.56±3.75 (range 2 to 14) doses. The dose of UK administered ranged from 5000 to 12 500 IU, depending on each center’s treatment protocol. Three patients received 10 000 IU of UK/dose, 1 received only 1 dose of 5 000 IU followed by successive doses of 10 000 IU, and 8 patients received 12 500 IU. Radiological and clinical evidence of IVH enlargement occurred in 1 case (MCV patient 2). No clinical- or laboratory-based evidence of central nervous system or sys-

Figure 1. Treatment effect. Top, Head CT scan demonstrates section from the plane of largest IVH diameter that casts the fourth, third, and left lateral ventricles in a patient (MSH patient 4) treated with intraventricular UK, which disappears after 5 days of therapy (bottom).

Figure 2. Untreated control. Top, Head CT scan shows section from the plane of largest IVH diameter that fills the fourth and lateral ventricles in a control patient treated with EVD only and matched for IVH size and location. The origin of IVH was secondary to aneurysmal SAH. This IVH persists 6 days after the initial bleeding (bottom).
ticemic bleeding was encountered in the remaining patients enrolled in the open-label or randomized study cohorts throughout the study period.

Thirty-Day Outcome
We obtained a predicted 30-day mortality of 68.42% (range 3% to 100%) for the entire cohort. Four of 20 patients died within 30 days, for an observed 30-day mortality of 20%. Probability of observing ≤4 deaths among 20 patients under a 68.42% expected mortality is 0.000012. The entire study group was divided into an open-label study/novel-therapy cohort (n=12) and a randomized study cohort (n=8) for separate analysis of 30-day outcomes.

Group 1: Open-Label Study/Novel-Therapy Cohort: Predicted 30-day mortality was 58% (range 3% to 100%), whereas observed mortality at 30 days was 25% (3 of 12 patients). Probability of observing ≤3 deaths among 12 patients under a 58% expected mortality is 0.022.

Group 2: Randomized Study Cohort: Predicted 30-day mortality in this group was 84.37% (range 4% to 100%). Only 1 case fatality occurred (JHH patient –7, who had a predicted 30-day mortality of 76%) among these 8 patients. Probability of observing 1 death among 8 patients under an 84.37% expected mortality is 0.000016.

Discussion
In this prospective study, we report a significant improvement in 30-day survival in a study cohort of 12 IVH patients treated with intraventricular UK, from a predicted 58% to an actual 25% mortality rate. Radiological and clinical evidence of worsening IVH was obtained in only 1 (6.25%) of the 16 patients treated with intraventricular UK (12 in the open-label study and 4 of 8 in the randomized arm). In addition, we did not detect infectious complications associated with the use of EVD in this group of patients.

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, as was recently independently demonstrated by Nishino and coworkers21,22 and Lee and coworkers.12–15,23,24 After first developing an animal model of IVH, Pang et al25 have shown that blood and its products produce inflammation and fibrosis of the ependymal lining.

Pang et al25,25 also demonstrated the effect of intraventricular UK in a canine model of IVH. They tested the hypothesis that intraventricular thrombolytic agents hasten the lysis of the intraventricular blood cast and accelerate the return to normal neurological status.25–27 These investigators found that clot dissolution was accelerated in the treated group (3 to 6 days) when compared with controls (38 to 65 days) without an added risk of hemorrhagic complications. The clinical correlate to this radiographic improvement was a more-rapid return to normal consciousness and a sustained reduction in ventricular size.

Although IVH is not common, a poll of referral neurointensive care units suggests that IVH is a high-morbidity condition that occurs up to several times per year in region referral centers. A large referral university hospital is anticipated to evaluate and treat 10 to 12 IVH patients per year that require EVD (JHH; unpublished data, 1999). Since 1990, 7 independent case series on the use of thrombolytic agents in IVH have been published.10,26–33 A review of these studies shows that 59 ICH and SAH patients were treated with intraventricular thrombolysis. Seventeen patients received UK and 42 received recombinant tissue plasminogen activator (rtPA). Although different thrombolytic regimens and doses were used, these studies reported intraventricular clot lysis within 4 days, no episodes of IVC obstruction, and 5 episodes of CNS infections. Good neurological outcome was reported in 42 of 59 patients. Twenty-two of 59 patients had long-term follow-up: 8 patients developed communicating hydrocephalus that required permanent CSF diversion, 5 patients developed bacterial meningitis, and no episodes of intraventricular or intraparenchymal hematoma enlargement or systemic bleeding occurred. Although these patients were retrospectively reported and did not have matched controls, the resolution process of the intraventricular clots contrasts with the clot lysis rate of untreated patients with IVH as we currently understand it.

On the basis of experimental and clinical evidence of blood and thrombin-induced neurotoxicity and the inherent mechanical injury that IVH produces on brain parenchyma either directly or through the development of acute hydrocephalus, the use of IVCs has become standard care in these patients. Traditionally, the rationale for the use of EVD has been the control of increased ICP produced by acute obstructive hydrocephalus, when present. However, several aspects of this approach deserve analysis: (1) The outcome of IVH patients treated with EVD is not improved despite corrections of ICP by means of CSF drainage.11 (2) Obstruction of the IVC by blood that leads to catheter exchange and its associated risk of brain injury often hampers the efficacy of IVCs.34,35 (3) Although EVD can correct elevated ICP, it does not accelerate the clot lysis that is necessary for restoration of normal CSF dynamics.36 (4) The duration of EVD and the presence of blood and its degradation products is probably responsible for the risk of ventriculitis and the development of delayed communicating hydrocephalus, respectively.37–39 We therefore postulate that if the lysis of intraventricular blood is accelerated, distention of the ventricular wall (and surrounding brain tissue) may decrease, better ICP control may be achieved, faster evacuation of the hematoma will take place, and the risk of catheter obstruction with blood clots will decrease or disappear. This final situation was observed only once during the present study.

In our series, 1 instance occurred of intraventricular hematoma enlargement during therapy with intraventricular UK (6.25%). Schwartz et al39 have recently reported 2 cases of worsening IVH during administration of UK for IVH; they recommended exhaustive screening of candidates for this form of therapy. It is unclear whether worsening of IVH was a complication of thrombolytic therapy, because spontaneous enlargement of the blood clot occurs in 38% of ICH patients within the first 20 hours.43 Furthermore, in a cohort of 17 IVH patients, Naff and coworkers36 reported a nearly 15% increase
in the initial clot volume in 47.1% of the patients within the initial 48 to 72 hours after hemorrhage.

In summary, our prospective pilot investigation allows us to conclude that the administration of low doses of intraventricular UK in patients with IVH is safe with careful screening. Our data strongly suggest that we can reduce the 30-day mortality of these patients. Sufficient retrospective and prospective evidence supports use of intraventricular UK or other similar thrombolytics for IVH such that a multicenter, randomized, and double-blind study has been recently funded by the US Food and Drug Administration Orphan Drug Program. The trial began patient accrual in January 2000.

**Limitations of the Study**

The small sample size in the present study limits the widespread generalization of these preliminary results to all patients with primary or secondary IVH. However, the study is large enough to produce results that strongly suggest beneficial effects of intraventricular administration of UK and to serve as positive evidence toward the design of a larger study to help establish the safety and efficacy of this intervention in the treatment of IVH.

**Addendum**

Because UK is no longer available for clinical use, rtPA was chosen for the phase II trial that started January 2000. This decision was based on experimental evidence of accelerated intraventricular clot resolution, available clinical reports of successful intraventricular administration in IVH patients, and the lack of antigenicity of rtPA as opposed to streptokinase. Although the optimal dose and administration interval of rtPA in the treatment of IVH are unknown, 3 mg of intraventricular rtPA q 12 hours was chosen for the following reasons: (1) The proposed dose is within the range of dosages reported in the clinical series previously cited. (2) The cardiology literature in coronary thrombolysis (American Hospital Formulary Service drug information) suggests an approximate efficacy ratio of 1 mg rtPA to 5000 to 10 000 IU of UK. When this ratio is applied to the indication of intraventricular thrombolysis, 3 mg of rtPA is an approximation consistent with the experience we report with 12 500 IU of UK. (3) The 12-hour dosing interval for rtPA administration remains unchanged from prior protocols. Depending on the phase II study results with rtPA, future dose-determination studies may be indicated to evaluate higher doses and shorter intervals.

**Acknowledgments**

This work was supported in part by the National Stroke Association Research Fellowship Award (N.J.N.). J.R.C. is supported in part by the David A. Dana research prize in Neurosciences Critical Care, Johns Hopkins University School of Medicine, and the Daland Fellowship for Clinical Research award from the American Philosophical Society. We wish to acknowledge the ongoing support of the US Food and Drug Administration and its Orphan Drug Program. We thank Nichol McBee and Karen Lane, CMA, for editing and assistance in preparing the manuscript.

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Stroke. 2000;31:841-847
doi: 10.1161/01.STR.31.4.841
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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