A Cohort Study of the Safety and Feasibility of Intraventricular Urokinase for Nonaneurysmal Spontaneous Intraventricular Hemorrhage

William M. Coplin, MD; Federico C. Vinas, MD; Jacob M. Agris, MD, PhD; Razvan Buciuc, MD; Daniel B. Michael, MD, PhD; Fernando G. Diaz, MD, PhD; J. Paul Muizelaar, MD, PhD

Background and Purpose—Small case series have reported potential benefit from thrombolysis after spontaneous intraventricular hemorrhage (IVH). Our objective was to review our experience using intraventricular urokinase (UK) in treating selected patients with IVH.

Methods—Using medical records, we identified all patients who received ventriculostomies for CT-confirmed nonaneurysmal nontraumatic spontaneous IVH from December 1992 through November 1996. We reviewed charts and CT images and examined the data for associations with specific outcomes.

Results—We identified 40 patients, 18 treated with ventriculostomy alone and 22 receiving adjunctive intraventricular UK. The initial Glasgow Coma Scale (GCS) scores of the two groups were similar (P=0.5). While there was a trend for patients with any intraparenchymal hemorrhage (IPH) to receive UK (P=0.07), the mean size of IPH in those who received ventriculostomy alone was larger than in those who received adjunctive UK (P=0.002). There was lower mortality in the group treated with UK (31.8 versus 66.7%; P=0.03), but there was only a trend toward an increase in favorable outcome (22.2% versus 36.4%; P=0.3). Overall, the most significant association with outcome was neurological condition at presentation (GCS >5 versus ≤5; P=0.003). Receiving UK did not increase the occurrence of complications or hospital length of stay for survivors (P=0.5).

Conclusions—Intraventricular UK remains a safe and potentially beneficial intervention. While it appeared to lower mortality, a randomized, placebo-controlled trial is needed to explore whether the therapy can increase the incidence of favorable outcomes. (Stroke. 1998;29:1573-1579.)

Key Words: intraventricular hemorrhage ■ outcome ■ thrombolysis ■ thrombolytic therapy

Spontaneous (nontraumatic) IVH, with or without other hemorrhagic lesions (eg, intraparenchymal or aneurysmal subarachnoid hemorrhage), frequently carries a grave prognosis. Associated risk factors include diabetes mellitus, bleeding diatheses, and systemic hypertension, which is the most frequent cause.1 Patient presentation ranges from headache, to confusion, to coma. A large part of the morbidity seen after IVH is related to intracranial hypertension from hydrocephalus which cannot be adequately treated with standard external ventricular drainage. The failure of ventriculostomy alone to clear IVH is frequently related to clots within or around the catheter, which obstruct attempts at therapeutic CSF drainage. Anatomic correlates of this impaired CSF outflow include compression of periventricular structures and brain stem injury.2 Patients initially may not have significant parenchymal injury, and relief of persistent IVH may prevent subsequent significant brain damage. Reported mortality from IVH is in the neighborhood of 80%, regardless of surgical interventions such as ventriculostomy or stereotactic or transcortical hematoma evacuation.2-5 CT studies6 reveal that spontaneous IVH resolution usually occurs within 3 weeks. Others have reported some improvement of outcome by speeding intraventricular thrombolysis (with hematoma resolution occurring often within a few days) with use of either UK9-15 or rt-PA.16-18

We present a retrospective cohort study of 4 years’ experience with ventriculostomy treatment of IVH, with or without adjunctive intraventricular UK administration. In this study, we attempted to examine the safety and efficacy of this treatment modality in consecutive patients who presented with spontaneous symptomatic IVH. This study was undertaken to assess the influence that adjunctive UK therapy has on speeding hematoma resolution and on outcome. The hypothesis was that this relatively simple therapy would improve neurological prognosis in patients presenting with IVH.

Subjects and Methods

Patient Population
The Wayne State University Human Investigation Committee approved these research activities. Diagnosis codes were used to...
identify all patients presenting with IVH over 4 years’ time, from December 1992 (when intraventricular UK was first used at Detroit Receiving and Grace Hospitals) through November 1996. Detailed chart abstraction was performed to confirm the diagnosis of spontaneous, nontraumatic IVH not associated with intracranial tumor, arteriovenous malformation, or cerebellar hematoma. We included all patients who were treated with ventriculostomy. We excluded those patients eventually found to have IVH secondary to an intracranial aneurysm. Patients’ charts and serial CT images were reviewed in detail to determine neurological, other clinical, demographic, comorbid, and radiographic characteristics of the patients and their treatments (with or without adjunctive intraventricular UK). An attempt was made to define the cause of IVH for all patients.

Treatment and Evaluation

All patients were managed in an ICU with ICP monitoring, aggressive hemodynamic support, and, when indicated, mechanical ventilation. Laboratory monitoring included routine coagulation studies (eg, prothrombin and partial thromboplastin times). The GCS score was recorded at admission and hourly, while in the ICU. Patients presenting with symptomatic IVH received frontal horn ventriculostomies through a frontal twist drill hole, under at least local anesthesia. Patients had CT confirmation of intraventricular location of the ventriculostomy catheter prior to the decision to administer UK.

The goals were a substantial reduction of hematoma volume and re-establishment of normal CSF flow and absorption. Ventriculostomy catheters were removed when patients no longer had symptomatic intracranial hypertension and/or CT scan did not show persistent hydrocephalus. Failing these end points, patients received implanted ventricular CSF shunts if they had symptomatic hydrocephalus.

Urokinase-Treated Group

The decision to treat an individual patient with UK was made by the senior neurosurgical resident or fellow in consultation with the attending neurosurgeon. Among the criteria used to make this decision were continued neurological deterioration despite ventriculostomy; failure of ventriculostomy to drain because of clots in or around the catheter; and dissection of blood into the brain stem (eg, from a thalamic hemorrhage). Urokinase (Abbokinase, Abbott Laboratories) is available as a lyophilized powder cake that when reconstituted with 5 mL sterile water becomes a 50 000-IU/mL solution. A dose of 10 000 U (2 mL of a 1:9 dilution of the above solution) was administered slowly through a frontal ventriculostomy catheter, every 12 hours. The catheter was then flushed with 3 mL preservative-free normal saline, closed for 1 hour, then opened to drain against a pressure gradient of 10 to 15 mm Hg (above the level of the external auditory meatus) for at least 1 hour. Patients had repeat CT scans, and drug administration was continued until the third and fourth ventricles cleared of blood on CT or until the patients fully recovered or died.

Radiographic Findings

After admission, follow-up CT images were obtained as medically indicated, at the discretion of the attending neurosurgeon. We scored CT images using a system derived from others’ previous work. The review of these images sought to delineate the ventricles involved and the degree (ie, estimated hematoma volume) of that involvement. The presence and degree (if present) of hydrocephalus and intraparenchymal and/or subarachnoid hemorrhage was also recorded. Suspicion of aneurysms or other vascular abnormalities prompted biplane contrast angiography; the findings of this study (if obtained) were also reviewed.

Outcomes

The primary outcome measure used at the time of hospital discharge was the GOS; this scale accounts for in-hospital death as a possible outcome. Because of the nature of the study, it was difficult to retrospectively apply other neurological outcome scales.

Complications

Among the complications we sought to define were death, ventriculitis (chemical or infectious), rebleeding, and the need for subsequent ventricular shunting. To screen for ventriculostomy-related infection, CSF samples were routinely sent for cell count, glucose, protein, Gram stain, and culture at least every 3 days. The presence of fever, leukocytosis, developing meningeal signs, and/or a change in the color or clarity of CSF sometimes prompted more frequent sampling from the proximal port of the closed ventricular drainage system.

Statistical Analysis

Data were entered into a computerized database (SPSS for Macintosh, Version 6.1.1, SPSS Inc.). Wayne State University computer resources were used to analyze the data. Data were presented as means, medians, and ranges. We examined these data for associations with specific outcomes. The GOS was dichotomized as poor (GOS 1 to 2) and favorable (GOS 3 to 5) outcomes for some analyses. Fisher exact (2-sided) and χ² analyses were used to calculate P values for categorical variables. Comparison of medians, for ordinal variables, was done with Wilcoxon rank sum analysis. Spearman rank correlation was used when there were more than 2 groups (eg, to assess the correlation of clinical status, such as GOS, with a variable of interest). Significant differences were assumed with P<0.05.

Results

Patient Population

We included in the data analysis 40 patients who presented with spontaneous nonaneurysmal IVH and received ventriculostomy drainage at 1 of the 2 hospitals over the 4-year study period. Thirty patients were treated at Detroit Receiving Hospital and the remaining 10 at Grace Hospital. There were 18 patients treated with ventriculostomy alone and 22 who received adjunctive intraventricular UK. The most common cause of IVH was presumed hypertensive hemorrhage; 39 patients presented with focal, lateralizing neurological signs. We included 1 patient who had associated head trauma. He fell with his ictus, but had no significant external signs of trauma or any contusion or fracture on CT scan; we presumed the cause of his fall was a spontaneous intracranial hemorrhage. We excluded from analysis 2 patients later identified as having aneurysms not initially suspected as the cause of their IVH. These 2 patients were initially managed not as patients with aneurysms but as those with nonaneurysmal IVH; however, neither received adjunctive UK.

The age range of the population was 22 to 95 years (median, 57.0 years). All patients had a history of premorbid concomitant hypertension. The range of admission GCS scores was 3 to 14. There were 6 patients (15%) with...
documented intracranial hypertension (initial ICP of >20 mm Hg) at the time of ventriculostomy placement; the incidence of intracranial hypertension was split between the two treatment groups \((P=0.36)\). There was no difference between the treatment groups in the percentage of those who were hypertensive, with a systolic blood pressure of >185 mm Hg \((P=0.71)\) or >220 mm Hg \((P=0.38)\). Demographic and initial clinical data are presented in Table 1.

### Treatment

We examined the data to ascertain if there was any relation between certain clinical factors after presentation to the emergency department and the chance of receiving adjunctive UK. Patients not treated with UK received their ventriculostomies a median of 196 minutes \((\text{range}, 70 \text{ to } 720 \text{ minutes})\) after arrival in the emergency department; those who later received UK received their ventriculostomies a median of 330 minutes \((\text{range}, 60 \text{ to } 2880 \text{ minutes})\) after arrival \((P=0.2)\). The clinical response to ventriculostomy (before any patient received UK) included 7 patients \((17.5\%)\) whose neurological condition improved and 30 patients \((75.0\%)\) whose neurological condition was similar to that before ventriculostomy. There were 3 patients \((7.5\%)\) whose clinical deterioration continued, despite ventriculostomy, before any decision was made concerning adjunctive UK therapy; all 3 received UK. A change in a patient’s GCS from the ventriculostomy was not related to later receiving UK \((P=1.0)\). The first dose of UK was given a median of 620 minutes (maximum of 8570 minutes) after ventriculostomy placement and CT confirmation of catheter tip location. Those receiving adjunctive intraventricular UK received a median of 3.0 \((\text{range}, 0.5 \text{ to } 10 \text{ days})\) of therapy.

### Radiographic Findings

Patients who received UK had significantly greater blood casting of the third ventricle and a trend that did not quite achieve significance to complete blood casting of the fourth ventricle \((P=0.002)\). The mean size of IPH in those who had ventriculostomy alone was substantially larger in those who received the adjunctive UK; however, there was a trend that did not quite achieve significance to patients having any associated IPH to receive the adjunctive UK. There was no difference between the groups in the initial CT response to ventriculostomy alone \((\text{before any patient received a dose of UK})\) \((P=0.5)\). There was no significant difference between the two treatment groups in the time required to clear any of the ventricles of blood, except in the case of the third ventricle, which cleared a median of 3.5 days sooner in patients receiving UK \((P=0.36)\).

### Outcome

Of the 18 patients treated with ventriculostomy alone, 12 \((66.7\%)\) died in the hospital. This compares with 7 deaths among the 22 patients \((31.8\%)\) treated with adjunctive UK \((P=0.03)\). We tested to see whether this improved survival translated into outcome better than vegetative state. Treatment with UK tended to reduce the chance of dying or remaining in a vegetative state from 77.8\% \((n=14/18)\) to 63.6\% \((n=14/22)\) \((P=0.3; \text{Tables 2 and 3})\).

Certain factors helped predict a favorable outcome. Patients with higher GCS scores either at admission \((P=0.001)\) of after ventriculostomy \((P=0.005)\) were more likely to have a favorable outcome. This finding was more robust for patients with higher GCS scores after ventriculostomy who then received UK versus those who did not \((P=0.03 \text{ versus } P=0.2)\). An initial change in GCS with the ventriculostomy did not otherwise influence the GOS \((P=0.5)\). Posturing at presentation \((\text{GCS motor score of } \leq 3 \text{ and total GCS score of } \leq 5)\) was predictive of having a poor outcome \((P=0.003)\) \((\text{Figure 1})\). The presence of intracranial hypertension \((\text{initial ICP of } >20 \text{ mm Hg})\) at presentation did not influence the GOS \((P=0.3)\). There was no association between the GOS and hypertension at admission \((P=0.07)\). The size of any associated IPH was not associated with having a poor outcome \((P=0.6)\).

There were 6 patients \((15\%)\) who required ventriculoperitoneal shunting. Four of these patients received UK, although receiving a permanent shunt was unrelated to having received UK \((P=0.7)\). Of survivors, 30\% were discharged from the hospital with ventriculoperitoneal shunts. For survivors, prior

### TABLE 1. Clinical Features of 40 Patients With Intraventricular Hemorrhage

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>All Patients</th>
<th>Ventriculostomy Only (n=18)</th>
<th>Adjunctive Urokinase (n=22)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>56.6 (15)</td>
<td>57.4 (15)</td>
<td>55.9 (15)</td>
<td>0.7</td>
</tr>
<tr>
<td>Female, %</td>
<td>42.5</td>
<td>27.8</td>
<td>54.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Median initial GCS score</td>
<td>5.0 (3–14)</td>
<td>5.0 (3–12)</td>
<td>5.5 (3–14)</td>
<td>0.5</td>
</tr>
<tr>
<td>Complete casting, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd ventricle</td>
<td>62.5</td>
<td>38.9</td>
<td>81.8</td>
<td>0.005</td>
</tr>
<tr>
<td>4th ventricle</td>
<td>52.5</td>
<td>38.9</td>
<td>63.6</td>
<td>0.12</td>
</tr>
<tr>
<td>IPH, %</td>
<td>70</td>
<td>56</td>
<td>82</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean size, mL</td>
<td>23.9</td>
<td>47.1</td>
<td>11.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Ventricular dilatation, %</td>
<td>79</td>
<td>75</td>
<td>82</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean initial ICP (SD), mm Hg</td>
<td>15.6 (9.7)</td>
<td>15.3 (12.7)</td>
<td>15.7 (7.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean initial SBP (SD), mm Hg</td>
<td>183.5 (36.7)</td>
<td>185.8 (37.1)</td>
<td>181.6 (37.2)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median ictus to ED (SD), min</td>
<td>240 (1350)</td>
<td>210 (175)</td>
<td>284 (1660)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; ED, Emergency Department.
to consideration of shunting, 22% of ventricular catheters required replacement because of unrelieved obstruction; only 1 of the patients requiring catheter replacement had not received UK.

There was no difference in hospital LOS between survivors who received adjunctive UK and those who did not. The median LOS for survivors treated with ventriculostomy alone was 22.5 days (range, 8 to 97 days) ($n = 6$). This compares with a median LOS of 27.0 days (range, 4 to 105) for those who were treated with adjunctive intraventricular UK and who survived ($n = 15$). This difference was not significant ($P = 0.5$). As expected, patients who died had a shorter LOS ($P = 0.0003$).

**Complications**

Complications were not clearly increased by the use of adjunctive UK (Table 4). Seven (31.8%) of the 22 patients who received UK had a complication possibly related to either treatment with ventriculostomy or the drug. No allergic reactions to UK were observed. Development of fever (core temperature of $\geq 38.5°C$) during one’s hospital course was associated neither with receiving UK ($P = 0.2$) nor with a poor outcome ($P = 0.3$). Only 1 patient underwent surgery for an intracranial hemorrhagic complication related to UK (evacuation of an enlarged IPH). No patient suffered any extracranial hemorrhagic complications.

**Discussion**

We present, to our knowledge, the largest cohort of spontaneous IVH patients yet reported in which the influence of adjunctive intraventricular chemothrombolysis on outcome can be assessed. Other series have reported a combined total of 59 patients given intraventricular thrombolytics for spontaneous IVH from either aneurysmal or presumed parenchymal rupture; of these, 17 received UK. None of these series looked at the same outcome measures we used (eg, LOS), nor did any have a sizable contemporaneous cohort managed without adjunctive thrombolytics.

**TABLE 2. Treatment and Outcome Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>All Patients (n=40)</th>
<th>No Urokinase (n=18)</th>
<th>Urokinase (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ICP (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial</td>
<td>15.6 (8.7)</td>
<td>15.3 (12.7)</td>
<td>15.7 (7.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>After 1 h</td>
<td>11.3 (6.2)</td>
<td>11.4 (7.1)</td>
<td>11.3 (5.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>After 24 h</td>
<td>13.3 (7.3)</td>
<td>14.4 (8.8)</td>
<td>12.6 (6.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Mean daily CSF drained, mL</td>
<td>127.7</td>
<td>114.7</td>
<td>137.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Clearing of ventricles</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All, %</td>
<td>25.0</td>
<td>11.1</td>
<td>36.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Median day cleared*</td>
<td>21.5</td>
<td>19.5</td>
<td>21.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Lateral, %</td>
<td>25.0</td>
<td>11.1</td>
<td>36.4</td>
<td>0.08</td>
</tr>
<tr>
<td>Median day cleared*</td>
<td>16.5</td>
<td>19.5</td>
<td>16.0</td>
<td>0.08</td>
</tr>
<tr>
<td>3rd, %</td>
<td>42.5</td>
<td>11.1</td>
<td>68.2</td>
<td>0.0003</td>
</tr>
<tr>
<td>Median day cleared*</td>
<td>7.0</td>
<td>10.5</td>
<td>7.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Ventriculoperitoneal shunt, %</td>
<td>15.0</td>
<td>11.1</td>
<td>18.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Median day performed</td>
<td>26.0 (7–94)</td>
<td>58.5 (23–94)</td>
<td>26.0 (7–36)</td>
<td>0.6</td>
</tr>
<tr>
<td>Median GOS score</td>
<td>2.0 (1–4)</td>
<td>1.0 (1–4)</td>
<td>2.0 (1–4)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

ICP indicates intracranial pressure; CSF, cerebrospinal fluid; and GOS, Glasgow Outcome Scale.

* Indicates for those who ever cleared the ventricles of blood on CT scan.

**Discussion**

We present, to our knowledge, the largest cohort of spontaneous IVH patients yet reported in which the influence of adjunctive intraventricular chemothrombolysis on outcome can be assessed. Other series have reported a combined total of 59 patients given intraventricular thrombolytics for spontaneous IVH from either aneurysmal or presumed parenchymal rupture; of these, 17 received UK. None of these series looked at the same outcome measures we used (eg, LOS), nor did any have a sizable contemporaneous cohort managed without adjunctive thrombolytics.

**TABLE 3. Glasgow Outcome Scale Scores for 40 Patients With IVH**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Poor Outcomes</th>
<th>Favorable Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (66.7%)</td>
<td>2 (11.1%)</td>
</tr>
<tr>
<td>No UK</td>
<td>14 (77.8%)</td>
<td>4 (22.2%)</td>
</tr>
<tr>
<td>UK</td>
<td>7 (31.8%)</td>
<td>7 (31.8%)</td>
</tr>
<tr>
<td></td>
<td>14 (63.6%)</td>
<td>8 (36.4%)</td>
</tr>
</tbody>
</table>

The Spearman rank correlation coefficient was used when considering 4 outcome categories; no patient in the cohort had a Glasgow Outcome Scale score of 5. The correlation coefficient was 0.28; P=0.08. Wilcoxon rank sum test was used when considering just 2 outcome categories, P=0.3. UK indicates adjunctive intraventricular urokinase therapy.

**Sensitivity = a/(a + c) = 19/28 = 68%**

**Specificity = d/(b + d) = 10/12 = 83%**

**Positive Predictive Value = a/(a + b) = 19/21 = 90%**

**Negative Predictive Value = d/(c + d) = 10/19 = 53%**

A 2 x 2 table showing prognostic performance of admission GCS score with a cut off of 5. Poor outcome is defined as being dead or vegetative (GOS score of 1 to 2).
TABLE 4. Frequency of Complications by Treatment Group

<table>
<thead>
<tr>
<th>Complication</th>
<th>No UK (n=18)</th>
<th>UK (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>1 (4.6%)</td>
</tr>
<tr>
<td>Seizure</td>
<td>1 (5.6%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Ventriculitis</td>
<td>4 (22.2%)</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>Increased IVH</td>
<td>1 (5.6%)</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Increased IPH</td>
<td>0</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>New IPH</td>
<td>0</td>
<td>1 (4.6%)</td>
</tr>
</tbody>
</table>

IVH indicates intraventricular hemorrhage; IPH, intraparenchymal hemorrhage.

Our results indicate that there was a significant increase in survival for a cohort of patients with spontaneous IVH who received adjunctive UK; however, there was only a trend toward having a favorable outcome (survival to better-than-vegetative state) with the treatment. Receiving the drug did not increase the incidence of complications or the hospital LOS for survivors. While a CT scan consistent with acute hydrocephalus was common, of interest is that only 15% of our cohort had initial intracranial pressures of >20 mm Hg. This suggests that, at least initially, CSF flow may not be impaired to a clinically significant degree, or that compensation occurred by the time of measurement. The strongest features associated with outcome were the initial neurological examination and the extent and duration of involvement of the third ventricle with IVH.

In this cohort, patients presenting with complete casting of the third ventricle but not the fourth were more likely to have subsequently received UK. There was no significant difference in the times to clear the lateral or fourth ventricles of blood; however, the third ventricles cleared a median of 3.5 days sooner in patients who received UK. This is not surprising; these mostly supine patients had frontal horn placement of their ventriculostomies. Infused UK would be expected to distribute in a dependent fashion, and the frontal horns, especially contralateral to the ventriculostomy catheter, would be expected to take longer to clear. The third ventricle, in this retrospective study, might be considered an interesting confounder, as its clearance was used to decide when to stop UK therapy. This feature of the protocol for UK administration was based on previous findings. In our cohort, clearance of the third ventricle occurred sooner in patients who received UK, and clearance of the third ventricle portended better outcome. This suggests that relief of third ventricular obstruction may be the key observation to guide successful treatment of UK therapy of IVH, and perhaps clearance of third ventricular hemorrhage should be the end point of treatment. Again, in the present cohort, the fourth ventricle never failed to clear if the third cleared.

This retrospective cohort analysis cannot account for what are likely unmeasured factors in the decision to treat some patients and not others with UK. The only clear factors we could find separating the treatment groups at presentation were those of complete casting of the third ventricle and the size of any associated IPH. Most probably, physician preference also played a role in the decision of whom to treat (other decision-making factors are listed in “Subjects and Methods”). This study does not take into account patients who never received a ventriculostomy, presumably because their hemorrhages were either too small or too large. Additionally, because the role of surgery appears quite clear, we did not include those who ultimately were diagnosed with an aneurysm or an arteriovenous malformation or those with a posterior fossa source for their IVH (eg, intraventricular rupture of a cerebellar hemorrhage). Because of the potential confounding in assessing outcome, we did not include those in whom the underlying diagnosis was a brain tumor or who had primarily traumatic hemorrhages (ie, a clear immediate history of external force to the head).

Causes and Natural History of IVH
Nontraumatic IVH in adults is a relatively rare condition. Most frequently, a hypertensive lobar, thalamic, or putaminal hematoma spontaneously ruptures into the ventricular system. The estimated incidence of IVH is approximately 3.1% of all spontaneous intracerebral hemorrhages. Additionally, there are recognized associations of nontraumatic IVH in adults with choroid plexus tumors or hamartomas, choroidal arteriovenous malformations, intraventricular aneurysms, bleeding diatheses, moyamoya disease, and hypertension. The ventricles initially are involved with the following frequency: lateral (86.2%), third (7.5%), and fourth (5.0%). These estimates likely relate to the relative ependymal surface and size of choroid plexus contained within the different ventricles.

Pathophysiology of IVH
The pathophysiology of IVH is quite variable. Hematomas can expand, producing rapid neurological deterioration and death, or they can resolve slowly. The pathogenesis of coma and early death after IVH may result from an acute rise in intraventricular pressure transmitted to the brain stem reticular formation. Milder cases present with clinical features of bilateral hemispheric dysfunction: confusion, disorientation, vomiting, hypertonic posturing, hyperthermia, and pupillary changes. Focal lateralizing signs, seen in most of our patients, may suggest an associated IPH. The presence of dienecephalic or mesencephalic signs may suggest a third ventricular hematoma. Mass effect from clots distending the ventricular walls may be the major factor responsible for the poor prognosis from IVH. Others have suggested that casting of the fourth ventricle may be the most important outcome predictor. In the present cohort, third ventricular casting appears to have been a more important factor relating to outcome; although third ventricular clearance was used as an end point for IVH treatment, fourth ventricular clearance always preceded third ventricular clearance on CT scan.

Clot lysis depends on the conversion of the plasma protein plasminogen to the active enzyme plasmin, a nonspecific proteolytic enzyme capable of digesting fibrin, fibrinogen, and other proteins. Lysis of an intraventricular clot does not necessarily depend on the fibrinolytic state of the circulation, but rather on the fibrinolytic activity of the cerebrospinal fluid, which is less effective and often referred to as incomplete. The rate of IVH clearance has not been studied.
systematically in a large number of patients. Available data suggest that these clots diminish in CT density over several weeks, becoming isodense and eventually hypodense with respect to brain tissue; however, pathologically, hematomas can persist for months.

Management by Ventriculostomy Drainage
Before the use of intraventricular chemothrombolysis, acute medical therapy of IVH was entirely supportive. Small, nonobstructing IVHs can be managed conservatively, but larger IVHs (particularly those obstructing the foramina of Monro or lower) frequently cause acute obstructive hydrocephalus and require external ventricular drainage. Ventricular drainage alone is often ineffective in managing the ventricular dilatation and intracranial hypertension resulting from large intraventricular hematomas. While a patent ventricular drain is able to divert CSF, it cannot evacuate a solid clot. External ventricular drainage alone may be of little benefit, because the catheters invariably become obstructed with clotted blood. Therein lies the rationale of adjunctive chemothrombolysis.

Development of Delayed Hydrocephalus
Impaired cerebrospinal fluid circulation is a frequent consequence of IVH. Intraventricular hematomas can produce acute obstructive hydrocephalus with quick neurological deterioration, or the proteinaceous clot lysis products can complicate recovery by producing chronic, posthemorrhagic communicating hydrocephalus. Although 15% of the patients in our cohort (30% of survivors) required ventriculoperitoneal shunting, the reported incidence of hydrocephalus after IVH ranges upward from 45% of patients surviving a severe hemorrhage; most of this information comes from neonatal IVH. Clinical studies of patients with IVH have suggested a relationship between the incidence of posthemorrhagic hydrocephalus and the quantity of intraventricular blood. Numerous theories attempt to explain the incidence of delayed, posthemorrhagic hydrocephalus. These include obstructive effects of red blood cells on the arachnoid villi, obstruction of villi by fibrin, fibrosis of the arachnoid villi, and ventricular wall injury. The goals of ventriculostomy in patients with IVH include draining CSF and intraventricular blood and measuring intracranial pressure. Ventriculostomy alone does not seem to achieve these goals for several reasons; perhaps most important, except in rare cases, the ventricular catheter is inadequate in draining the intraventricular blood. A series of 68 patients with IVH found no significant relationship between delayed hydrocephalus and the presence of a clot in the third or fourth ventricle. The prognosis for developing chronic communicating hydrocephalus may be related more to the severity of SAH associated with IVH than the amount of intraventricular blood itself. We had repeatedly experienced the problem of catheter obstruction with ventriculostomy alone; therefore, it did not appear to suffice for meeting the above goals acutely, and this protocol was undertaken.

Effect of Fibrinolytic Therapy for IVH
Compared with studies in which r-tPA was used for intraventricular lysis, there is a suggestion that UK may act more slowly in clearing the ventricles, taking as little 24 to 72 hours in at least 1 r-tPA study and 7 to 10 days in the present study. This is perhaps because UK is a nonspecific fibrinolytic agent, whereas r-tPA has a specific fibrinolytic action. There are no good animal or human comparative trials of the 2 drugs.

The early clearance of intraventricular blood seems to be important for both the relief of hydrocephalus and the clearance of blood products. Intracerebral hematomas release products (e.g., thrombin) that may be toxic to the adjacent nervous tissue; therefore, early evacuation of these products may improve outcome.

Complications
Except for 1 case, there was no significant increase in the volume of intracranial hemorrhage after UK administration, which suggests that the product is relatively safe to use. Adjuvant UK instillation did not appear to increase the incidence of any other complications, such as infection. These data need to be interpreted cautiously because of the sample size.

Prognosis
Even from the pre-CT era (with the diagnosis of IVH made by CSF sampling and/or echoencephalography), reported mortality from IVH has remained in the neighborhood of 80%, regardless of surgical interventions such as ventriculostomy or stereotactic or transcortical hematoma evacuation. While we demonstrated a decreased mortality for the UK group, there was only a trend toward improving outcome to better than vegetative state (from 22% to 36%). This result in our ventriculostomy-only group is consistent with those in other IVH studies. The lack of statistical significance may be attributable to the sample size. Another factor, although not statistically important in this study, may be the time to starting therapy. Indication bias also possibly played a role; however, intergroup differences had little impact on outcome in this, the largest reported consecutive cohort of IVH patients, 55% of whom received UK. Again, IPH size did not predict outcome, and while more patients with third ventricular casting received UK, they cleared the third ventricle more quickly and completely.

Administering fibrinolytic therapy to patients with IVH appears to offer benefit, but there are still many questions to address: which agent (e.g., UK, r-tPA, or hirudin) is the most efficacious and cost-effective; how often should what dose be used; how long should the ventriculostomy be clamped after drug administration; should third and/or fourth ventricular clearing be used to decide when to stop therapy or should the entire CT be clear of IVH; and is there a difference in outcome for patients with IVH from ruptured IPH as opposed to those with IVH in the setting of aneurysmal SAH? These are among the questions that will need to be addressed in a prospective, randomized, placebo-controlled multicenter study to establish clearly the optimal indications and ultimate value of this treatment for patients with spontaneous IVH. The hypothesis of such a trial is that more rapid clot lysis will permit more prompt and effective CSF and blood drainage. This, in turn, could shorten ICU and/or hospital LOS and
potentially decrease the incidence of posthemorrhagic hydrocephalus and improve neurological outcome. Such a protocol should aim to improve the negative predictive value of an initial low GCS (ie, presenting with hypertonic posturing) for patients without structural brain stem lesions. We are currently preparing such a trial.

Acknowledgments
This work was supported in part by the Detroit Neurotrauma Institute. We would like to acknowledge Richard Fessler, MD, Robert J. Johnson, MD, and Paul K. King, MD, for their clinical expertise in being among the attending neurosurgeons caring for the patients in this study and their continued involvement in and support of clinical research, and Mary S. Cochran, RN, CCRN, and M. Ellen St. Pierre, RN, BS, for data management support.

References
A Cohort Study of the Safety and Feasibility of Intraventricular Urokinase for Nonaneurysmal Spontaneous Intraventricular Hemorrhage
William M. Coplin, Federico C. Vinas, Jacob M. Agris, Razvan Buciuc, Daniel B. Michael, Fernando G. Diaz and J. Paul Muizelaar

*Stroke*. 1998;29:1573-1579
doi: 10.1161/01.STR.29.8.1573

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/29/8/1573

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/