Intraventricular Fibrinolysis and Lumbar Drainage for Ventricular Hemorrhage

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Background and Purpose—Both intraventricular fibrinolysis (IVF) and lumbar drainage (LD) may reduce the need for exchange of external ventricular drainage (EVD) and shunt surgery in patients with intracerebral hemorrhage and severe intraventricular hemorrhage. We investigated the feasibility and safety of IVF followed by early LD for the treatment of posthemorrhagic hydrocephalus.

Methods—This prospective study included patients with spontaneous ganglionic intracerebral hemorrhage and severe intraventricular hemorrhage with acute obstructive posthemorrhagic hydrocephalus who received an EVD (n = 32). The treatment algorithm started with IVF (4 mg recombinant tissue plasminogen activator every 12 hours) until clearance of the third and fourth ventricles from blood. Thereupon, EVD was clamped and if clamping was unsuccessful, communicating posthemorrhagic hydrocephalus was assumed and LD placed. EVD was removed if there was neither an increase of intracranial pressure nor ventricle enlargement on CT. A ventriculoperitoneal shunt was indicated if “LD weaning” was unsuccessful for 10 days. Outcome was assessed at 90 and 180 days using the modified Rankin Scale.

Results—IVF resulted in fast clearance of the third and fourth ventricles (73 ± 50 hours). However, early EVD removal was only possible in 4 patients. The remaining 28 patients developed communicating posthemorrhagic hydrocephalus. In all of these patients, early LD was capable to replace EVD. EVD exchange was not necessary and EVD duration was 105 ± 59 hours. Only one patient required a ventriculoperitoneal shunt. At 180 days, 20 (62.5%) patients had a good (modified Rankin Scale 0 to 3) outcome and 5 (15.6%) patients had died. One patient had asymptomatic ventricular rebleeding.

Conclusions—In patients with secondary intraventricular hemorrhage and posthemorrhagic hydrocephalus, the combined treatment approach of IVF and early LD is safe and feasible, avoids EVD exchange, and may markedly reduce the need for shunt surgery. (Stroke. 2009;40:3275-3280.)

Key Words: intraventricular fibrinolysis ■ intraventricular hemorrhage ■ lumbar drainage
In patients with communicating hydrocephalus, lumbar drainage (LD) may represent a simple and less invasive alternative for extracorporal CSF drainage with a lower complication profile compared with EVD.\textsuperscript{8,12} Moreover, very early CSF drainage through LD may promote the circulation of newly formed CSF from the ventricles through the subarachnoid spaces, thereby promoting fast washout of potentially harmful blood. In a retrospective analysis of patients with secondary IVH with persisting malresorptive hydrocephalus, LD was capable to replace EVD, extend the duration of extracorporal CSF drainage, and eventually reduce the need for a permanent shunt.\textsuperscript{8}

The combined approach of IVF through EVD to reopen the ventricular system followed by early LD to replace EVD and to promote CSF circulation and washout of blood may represent a promising treatment algorithm with synergistic effects for severe IVH with initial obstructive and consecutive malresorptive hydrocephalus.\textsuperscript{12} Therefore, the objective of this prospective study was to analyze the feasibility and safety of LD and its capability to replace EVD after the acute phase of IVF as soon as the third and fourth ventricles were cleared from blood and “EVD weaning” was unsuccessful.

Patients and Methods

Patient Selection
This prospective pilot study was approved by our local ethics committee. All patients with (1) spontaneous hypertensive ganglionic ICH <40 mL; (2) secondary IVH; and (3) acute obstructive hydrocephalus were included and treated according to the study protocol.

Exclusion criteria were anticoagulant therapy; international normalized ratio >1.4; coagulopathy; ICH due to trauma, tumors, or vascular malformation; infratentorial ICH; enrollment >48 hours after symptom onset; and age <18 years.

Study Protocol

Basic Management
ICH and IVH were diagnosed by cranial CT. CT angiography was performed after initial CT to exclude vascular malformation bleeding. Hydrocephalus was defined by measuring the bicaudate index, considered present if it exceeded the 95th percentile for age\textsuperscript{13} and evaluating temporal horn diameter.

All patients received standard medical treatment according to the European Stroke Initiative guidelines\textsuperscript{14} and the study protocol (Figure 1), including early intubation at Glasgow Coma Scale levels of <9, ICP was recorded hourly, and ICP increase (>20 mm Hg) was treated with 20% mannitol (4 to 6×100 to 200 mL). CSF was evaluated for infection every other day.

EVD Management
An EVD was inserted as soon as obstructive hydrocephalus was diagnosed and the position of the catheter was controlled by CT. As soon as the third and fourth ventricles were cleared from blood on CT, the EVD was clamped under continuous ICP monitoring and removed after another 24 hours when ICP remained <20 mm Hg and CT showed no enlargement of the ventricles.

Intraventricular Fibrinolysis
The first administration of 4 mg recombinant tissue plasminogen activator (rtPA; 2 mg/mL) through the EVD was initiated no sooner than 12 hours after the initial bleeding episode and at least 6 hours after EVD placement. The EVD was then clamped for 1 hour. IVF with 4 mg rtPA was continued every 12 hours until the third and the fourth ventricles were cleared from blood on CT or until a maximum cumulative dose of 20 mg rtPA was reached. The dosage and timing regimen of rtPA application was based on previous institutional experience.\textsuperscript{12,15}

LD Management
If the attempt to clamp the EVD was unsuccessful while the third and fourth ventricles had been cleared from blood, the existence of communicating hydrocephalus was assumed and extracorporeal CSF outflow was continued by LD through a silicone catheter (Codman lumbar drainage kit) inserted into the subarachnoid space at the L3 to L4 level as previously described in detail.\textsuperscript{8,12} EVD was then left closed for 24 hours. If there was no increase in ICP and no enlargement of the ventricular system on CT, the EVD was removed. Extracorporeal CSF drainage was then continued for 48 hours through the LD. LD was then clamped and left closed for 24 hours. If enlargement of the ventricles was evident on CT, LD was reopened and attempts of LD clamping were repeated every 48 hours. If no hydrocephalus was seen on CT, the lumbar catheter was removed.

The duration of catheter clamping and the interval between clamping attempts of the LD were based on previous institutional experience.\textsuperscript{8,12,15}

Management of EVD Exchange and the Permanent Shunt
If EVD replacement by LD was not feasible and prolonged external CSF outflow was necessary, the EVD was routinely exchanged between Days 7 and 10. A permanent VP shunt was indicated before insertion of a third EVD (ie, at Day 20) or if LD clamping was unsuccessful for >10 days.\textsuperscript{8,15}

Neuroimaging Data
Routine cranial CT scans were performed on admission, immediately after EVD placement, and then daily up to Day 4, on Day 7, and Day 10 after admission. During IVF, CT controls were scheduled shortly before (2±2 hours) the next scheduled rtPA application. For each time point, the site of the affected ventricles was noted using the Graeb score.\textsuperscript{16} The volume (mL) of IVH and ICH was calculated by manual tracing.
Ninety-Day and 180-Day Outcome
Patients or their relatives were interviewed by a telephone call at 90 and 180 days (±10 days). Outcome was recorded using the modified Rankin scale score (mRS)17 and Barthel Index.18 Good outcome was defined as mRS 0 to 3.

Comparison With Historical Controls
The effects of the present treatment algorithm on the incidence of EVD exchange and shunt surgery and duration of extracorporal CSF drainage were compared with previously published groups of patients who were treated with (1) EVD alone; (2) EVD combined with IVF; and (3) EVD followed by LD.8 Criteria for IVF, EVD exchange, and permanent shunting in these groups were identical to those used in the present study.

Statistical Analysis
Statistical analyses were performed using the SPSS 16.0 software package. The Shapiro-Wilk test was used to explore the distribution of the data. Normally distributed data are expressed as mean±SD and were compared using the unpaired 2-tailed t test. Other data are expressed as median and range and were compared using nonparametric tests. Correlations between volume of IVH, ICH, age, Glasgow Coma Scale, and outcome were analyzed using the Spearman correlation coefficient. A probability value of <0.05 was considered significant.

Results
Between January 2006 and July 2008, a total of 32 patients were included in the study. Median time between symptom onset and admission was 1.5 hours (range, 1 to 12 hours). Baseline characteristics of the patients are shown in the Table.

Intraventricular Fibrinolysis
IVF was initiated after 26±9 hours of symptom onset. Median rtPA dose was 12 mg (range, 4 to 20 mg). As shown in Figure 2, a rapid resolution of the total intraventricular hematoma could be observed with a clot half-life of 56±25 hours. Complete clearance of the third and fourth ventricles from blood occurred 73±50 hours after admission. Six of 32 patients needed the maximum dose of 20 mg rtPA. In this subgroup, clearance of the third and fourth ventricle from blood occurred after 150±47 hours.

Extracorporal CSF Drainage
After IVF, early weaning of EVD (ie, immediately after clearance of the third and fourth ventricles) was feasible in only 4 patients (after 100±34 hours). In the remaining 28 patients, EVD clamping was not possible indicating communicating hydrocephalus. Those 28 patients received an early LD, and replacement of EVD by LD was successful in all patients without evidence of ICP increase or ventricle enlargement on CT. As a consequence, EVD drainage time was relatively short in LD-treated patients with the mean duration being 105±59 hours. No patient needed EVD exchange.

Mean duration of LD was 120±61 hours, resulting in a total extracorporal draining duration of 219±95 hours. LD could be removed in all patients without evidence of persistent communicating hydrocephalus. Thus, none of the patients required a VP shunt until discharge. However, one patient developed delayed malresorptive hydrocephalus and underwent shunt surgery 6 weeks after discharge from the intensive care unit.

Outcome at 90 and 180 Days
Outcome after 90 and 180 days is shown in Figure 3. After 90 days, 56.3% (18 of 32) of all patients had a good outcome defined as mRS 0 to 3. Two patients (6.3%) had died due to pulmonary embolism and pneumonia.

After 180 days, 62.5% (20 of 32) of all patients had a good outcome. Mortality rate had increased to 15.6% (5 of 32; 3 additional patients had died due to internal complications). Outcome at 180 days was highly correlated with initial ICH volume (Spearman correlation; \(P=0.03\)), age (\(P=0.04\)), and Glasgow Coma Scale score (\(P<0.001\)). Interestingly, no correlation was found between the severity of IVH and

Table. Demographic, Clinical, and Radiological Characteristics of the Patient Collective (Group “EVD+IVF+LD”) and Historical Control Groups (“EVD,” “EVD+LD,” “EVD+IVF”)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Present Study</th>
<th>Historical Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EVD + IVF + LD</td>
<td>EVD (^a)</td>
</tr>
<tr>
<td>Age</td>
<td>n=32</td>
<td>n=39</td>
</tr>
<tr>
<td>61 (44–79)</td>
<td>62 (47–80)</td>
<td>64 (44–79)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>20/12</td>
<td>23/16</td>
</tr>
<tr>
<td>Glasgow Coma Scale on admission</td>
<td>10 (3–14)</td>
<td>8 (3–13)</td>
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<tr>
<td>ICH volume, mL</td>
<td>16±9</td>
<td>26±10</td>
</tr>
<tr>
<td>Graeb score on admission</td>
<td>8 (4–11)</td>
<td>7 (4–11)</td>
</tr>
<tr>
<td>rtPA dose, mg</td>
<td>12 (4–20)</td>
<td>…</td>
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</tbody>
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*Values are given in median (range) or mean±SD for normally distributed values.

Figure 2. Relative mean intraventricular hematoma volume in the course of intraventricular fibrinolysis represented as percentage of the initial hematoma volume. Error bars show the 95% CI. d0 indicates admission; d1–10, following days.
outcome when using either Graeb scoring or absolute IVH volume ($P=0.18$).

**Complications**

One patient had a rebleeding during IVF restricted to the ventricular system (Graeb score changed from 4 to 7) but without obvious clinical deterioration. Two patients had signs of ventriculitis (pleocytosis and elevated lactate levels) without detection of bacteria on Days 4 and 6, respectively (during the overlapping period of EVD and LD). The infection could be sufficiently treated with systemic antibiotics. No complications with regard to LD placement or drainage were observed.

**Comparison With Historical Groups**

We compared the efficiency of the present treatment algorithm (Group “EVD+IVF+LD”) with 3 historical groups of patients who were treated as follows (Figure 4): “EVD alone” ($n=39$), “EVD+IVF” ($n=22$), and “EVD+LD” ($n=16$). There was no significant difference among groups with regard to age, Glasgow Coma Scale on admission, IVH, and ICH volume (Table). Both LD and IVF reduced the incidence of EVD exchange and shunt surgery to a similar extent when compared with the “EVD alone” group (Figure 4). The combination therapy of the present study resulted in the lowest frequency of EVD exchange and shunts. Moreover, the present treatment regimen was associated with the shortest total extracorporeal drainage time of only 9 days.

**Discussion**

To the best of our knowledge, this is the first prospective study investigating a combined treatment approach consisting of IVF followed by early placement of a LD for the treatment of acute obstructive and consecutive communicating hydrocephalus in patients with spontaneous ganglionic ICH and severe ventricular involvement. As key findings have shown, this new treatment algorithm was safe and feasible, avoided EVD exchange in all patients, and likely reduced the need for permanent VP shunting with a short overall drainage duration.

**Intraventricular Fibrinolysis**

Because IVH is a strong and independent predictor of poor prognosis in patients with spontaneous ICH, there is a clear rationale for the benefit of fast removal of the ventricular hematoma. An external ventricular drain alone, however, has no or only little effect on hematoma clearance, because the catheter frequently obstructs by blood. Over the last years, it has been shown that IVF significantly accelerated clot resolution without major side effects. Moreover, there is now increasing evidence from numerous nonrandomized studies that IVF may reduce short-term mortality and improve functional outcome when compared with treatment with EVD alone. In the literature, a single rtPA dose varies from 1 to 8 mg and cumulative dosage from 1 to 32 mg. The results of the Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEARIVH) dose escalation trial became available after the present study has been performed. In CLEARIVH Parts A and B, a single dose of 1 mg rtPA every 8 hours and a maximum cumulative dose of 12 mg have been determined to be most appropriate considering bleeding risk under IVF and effectiveness of clot resolution. In the present study, we used a higher single dose of 4 mg rtPA every 12 hours with a maximum cumulative dose of 20 mg. IVF was initiated after exclusion of vessel malformation by CT angiography and at least 12 hours after symptom onset and 6 hours after EVD insertion to ensure stability of the source of bleeding and of the injury caused by the EVD placement. Using this approach, IVF was relatively safe despite the use of a relatively high rtPA dosage with only one IVF-associated asymptomatic bleeding and resulted in a fast IVH clearance with a clot half-life of approximately 2 days and clearance of the third and fourth ventricles after 3 days. No obstruction of the EVD catheter was observed.

**Lumbar Drainage**

In this study, clearance of the third and fourth ventricles was the main goal for IVF treatment because initial obstructive hydrocephalus is sufficiently treated and communication between inner and outer CSF spaces is restored. However, despite fast reopening of the ventricular system by IVF, normalization of CSF resorption was only achieved in 4 of 32 patients, as indicated by increasing ICP or enlargement of ventricles on CT after clamping of the EVD in the remaining 28 patients. Thus, the majority of patients still had hydrocephalus, namely communicating hydrocephalus, with requirement for further extracorporeal CSF drainage. LD was initiated as soon as communication between inner and outer CSF spaces was restored. The rationale for using LD at this
early time point was (1) to replace EVD as early as possible; and (2) to promote early washout of blood through lumbar drainage of the subarachnoid space before irreversible damage to the Pacchioni granulations by the blood has occurred. The efficacy of LD to replace EVD was confirmed because none of the 28 patients treated with LD exhibited evidence of rising ICP or enlargement of the ventricles on CT. As a consequence, EVD could be already removed after a mean duration of 5 days and no patient needed an EVD exchange. Moreover, only one patient underwent shunt surgery, supporting the hypothesis that early blood removal by LD may have beneficial effects on the development of persistent communicating hydrocephalus.

We did not observe any major side effects of LD. Evidence of ventriculitis was observed in 2 of 32 patients in the transitional period (EVD closed, LD open). Therefore, it is unlikely that the occurrence of infections was related to LD.

Combination of IVF and LD
To get first insights into the efficacy of the new treatment algorithm, we compared the combination therapy with historical groups who were treated with EVD alone, EVD and IFV, or EVD with LD. Treatment with EVD alone resulted in a high rate of EVD exchange (62%) and 33% of patients needed a shunt. The additional treatment with either IVF or LD could significantly reduce the incidence of EVD exchange (to 32% and 40%, respectively) and shunt surgery (to 18%). Similar effects on shunt incidence were reported from a prospective controlled study on patients with ICH and IVH treated with urokinase. Using the present treatment algorithm of early LD after IVF, we could remove (n=4) or replace (n=28) EVD during the first week of treatment in all patients and only one patient needed a permanent shunt (3%). The overall (EVD+LD) extracorporeal CSF drainage time was only 9 days. Thus, when comparing with historical controls, the combination therapy of IVF and early LD was most effective in replacing EVD, avoiding EVD exchange, and reducing shunt surgery with the shortest overall CSF drainage time.

Certainly, although basic medical and IVF management and the indication for EVD exchange and a VP shunt were similar among groups, the interpretation of these findings is strongly limited by the nature of comparison with historical controls. The limitation for comparison particularly applies for the EVD+LD group, in which LD was initiated considerably later (at Day 12) compared with the present study, mainly due to the longer time needed for clearance of the third and fourth ventricles without fibrinolysis. Still, this may further support the significance of early initiation of a more aggressive treatment approach, as described in the present study.

Outcome Analysis
Most importantly, the combination therapy resulted in a fairly good overall functional outcome. At 3 months, 56.3% of all patients had a favorable outcome as defined by mRS 0 to 3, and functional status further improved at 6 months with 62.5% of all patients having a mRS of 0 to 3. At this time, 40.6% of the patients were independent in daily living (mRS 0 to 2). Furthermore, a mortality rate of 15.6% was relatively low when compared with studies of patients with ganglionic ICH and ventricular extension with mortality rates often exceeding 50%. However, it is possible that the relatively small mean size of ICH (16±9 mL) and the short interval between symptom onset and admission (1.5 hours [range, 1 to 12 hours]) in our study may have also contributed to the overall good outcome.

When using the present treatment approach, IVH volume was no longer associated with outcome, whereas other well-known independent predictors of poor outcome such as initial Glasgow Coma Scale, ICH volume, and age were strongly correlated with mRS at 180 days.

This is a notable finding because IVH and the amount of ventricular blood have been consistently identified as strong predictors of poor outcome in patients with ICH. However, in these studies, a specific IVH therapy to speed up clot removal was not performed and only a minority of patients received an EVD. In our study, we aimed to treat IVH at an early stage of the disease with a specific IVH-targeted regimen. This more aggressive treatment algorithm for IVH may have contributed to an attenuation of the negative impact of ventricular hemorrhage on outcome.

The main limitations of this study are the noncontrolled design and the relatively small number of patients. Although the positive effects on avoiding EVD exchanges and VP shunts are impressive and outcome data seem to be fairly good as compared with historical patients, no definitive conclusion on the impact of this approach on clinical outcome can be drawn without a randomized, controlled design.

Possible Mechanisms
Several mechanisms may contribute to the beneficial effects of the present treatment algorithm. First, IVF induces splitting of solid fibrin clots in the ventricular system resulting in small, mobile, and soluble clot fragments that can be removed more easily from the CSF space.

Second, early CSF draining from the lumbar cistern may promote the physiological circulation of clear, newly formed CSF from the cerebral ventricles through the subarachnoid space, thereby accelerating the washout of potentially harmful blood. CSF is mainly produced in the lateral and the third ventricles, and its physiological outflow occurs through the aqueduct to the fourth ventricle and into the subarachnoid space through the foramina of Magendie and Luschka. This is followed by an ascending flow to the hemispheric subarachnoid cisterns up to the sagittal sinus, where a considerable part of the CSF is resorbed. CSF then flows downward through the foramen magnum to the lumbar cistern, where further resorption occurs. LD produces a pressure gradient by withdrawal of CSF from the last site of circulation, thereby possibly promoting physiological circulation of CSF in the upstream compartments. In contrast, drainage directly from the lateral ventricles through the EVD may inhibit or slow down normal CSF circulation and thereby contribute to stasis of the hematoma within the ventricular system with no or little effect on blood clearance.

Third, as animal studies have demonstrated, IVH causes inflammatory response in ependymal and subependymal tis-
sue layers as well as inflammation and fibrosis of the arachnoida. Therefore, fast removal of ventricular and subarachnoid blood may prevent prolonged irritation of the Pacchioni granulations and ongoing inflammatory response caused by the blood and its breakdown products possibly resulting in faster recovery of the granulations and avoidance of persistent hydrocephalus.

In conclusion, in patients with secondary IVH and hydrocephalus, the combination of IVF and early LD can avoid EVD exchange and likely reduce the need for a permanent VP shunt without major side effects. Certainly, the small sample size and the noncontrolled study design do not allow definite conclusions. Whether this approach can also improve outcome should be investigated in a randomized, controlled trial.

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Disclosures
None.

References
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