Brief Reports

Dose Effect of Intraventricular Fibrinolysis in Ventricular Hemorrhage

Dimitre Staykov, MD; Ingrid Wagner, MD; Bastian Volbers, MD; Hagen B. Huttner, MD; Arnd Doerfler, MD; Stefan Schwab, MD; Juergen Bardutzky, MD

Background and Purpose—The aim of the current study was to investigate the dose-dependent efficacy of intraventricular fibrinolysis (IVF) in patients with severe intraventricular hemorrhage (IVH).

Methods—Patients with intracerebral hemorrhage, severe IVH, and obstructive hydrocephalus with the need for external ventricular drainage were treated with IVF through external ventricular drainage. The time course of IVH resolution and the safety profile were compared between patients treated with high-dose IVF (4 mg alteplase every 12 hours, maximum 20 mg; n = 32) and low-dose IVF (1 mg alteplase every 8 hours, maximum 12 mg; n = 22). CT scans on Days 1 to 4, 7±1 and 10±1 after admission, were analyzed volumetrically. Outcome was assessed after 3 months.

Results—The overall effect of IVF dosage was not significantly different between the 2 groups (F = 1.3, P = 0.25). The course of IVH volume in the third and fourth ventricles was similar with high- and low-dose IVF. High-dose IVF resulted in lower total IVH volumes on Days 7 (4.4±4.2 mL versus 8.8±8.1 mL; P = 0.01) and 10 (1.4±2.8 mL versus 4.9±65.8 mL; P = 0.005). Total clot half-life was 78±43 hours in the low-dose and 56±25 hours in the high-dose group (P = 0.02). One asymptomatic ventricular bleeding, 2 cases of ventriculitis, and 1 death due to pulmonary embolism occurred in the high-dose group. There was no difference in outcome at 3 months.

Conclusions—Low-dose IVF (3 mg alteplase/day) has a similar effect on IVH clearance from the third and fourth ventricles and a similar safety profile when compared with high-dose IVF (8 mg alteplase/day).

Key Words: external ventricular drainage | intracerebral hemorrhage | intraventricular fibrinolysis | intraventricular hemorrhage | lumbar drainage

Intraventricular hemorrhage (IVH) is a common complication of spontaneous intracerebral hemorrhage.1 Within the recent 2 decades, intraventricular fibrinolysis (IVF), that is, the administration of fibrinolytic agents through a ventricular catheter, has been increasingly tested in patients with IVH and meanwhile a considerable body of literature on this topic has accumulated.2 However, data on the dose-related effectiveness and safety profile of IVF are scarce.

Based on institutional experience, we initially used a dosing regimen for IVF consisting of 4-mg single doses of recombinant tissue plasminogen activator (rtPA) administered every 12 hours up to a maximum cumulative dose of 20 mg.3 After the results of the Clot Lysis Evaluating Accelerated Resolution of Intraventricular Hemorrhage (CLEAR-IVH) dose finding trial have been reported,4 we changed our institutional protocol in accordance with the trial findings for the optimal IVF dosage and interval (1 mg every 8 hours, maximum cumulative dose 12 mg). The aim of the present study was to compare the effect on clot resolution and the safety profiles of the 2 IVF dosing regimens.

Methods

The present analysis was performed retrospectively on patients with hypertensive ganglionic intracerebral hemorrhage <40 mL, IVH, acute obstructive hydrocephalus, and the need for external ventricular drainage (EVD) treated with IVF using our current institutional protocol with intraventricular administration of 1 mg rtPA every 8 hours with a maximum cumulative dose of 12 mg rtPA (low-dose IVF group). Those data were compared with data from a previously published prospective study5 in which a higher single dose of 4 mg rtPA and a dosing interval of 12 hours with a maximum cumulative dose of 20 mg rtPA (high-dose IVF group) were used.

Patient selection, general management, management of ventricular catheter, lumbar drainage and shunt as well as imaging data analysis were identical for both groups and followed the study protocol, as previously described in detail.5 The decision to place 1 or bilateral EVDs was left at the discretion of the treating neurosurgeon. The only difference between the 2 groups consisted of the rtPA dose and the dosing interval used for IVF. IVF was discontinued when the third and fourth ventricles were cleared from blood on CT or the maximum cumulative IVF dose was reached.

Neuroimaging Data

CT scans were performed on admission, immediately after EVD placement, and then daily up to Day 4, on Day 7±1, and Day 10±1.
IVH volume was calculated by tracing of the ventricular hematoma using the freehand region of interest tool of the Syngo Viewer software (Siemens, Erlangen, Germany). Planimetric data were added up and multiplied by slice thickness. Clot half-life (time until removal of 50% of initial IVH volume) was calculated using the difference between IVH volume on Days 1 and 4 by first calculating the time needed for resolution of 1% of IVH for each patient and then multiplying the individual value by 50.

Complications
Incidence of IVF-associated bleeding, EVD-associated infections, and 30-day mortality were compared between the 2 groups. Significant rebleeding was defined as enlargement of the ventricular or parenchymal hematoma of >30% of initial IVH or intracerebral hemorrhage volume or also as occurrence of a new intracerebral hemorrhage.

Outcome
A telephone follow-up survey was conducted with patients or their closest relatives 90 days after admission and a standardized questionnaire was completed. Outcome was recorded using the modified Rankin Scale.

Statistical Analysis
Statistical analyses were performed using the SPSS 16.0 software package (www.spss.com). Normally distributed data were compared using the unpaired 2-tailed t test. Other data were compared using nonparametric tests. A multifactorial analysis of variance was performed for between-group and within-group comparisons of the time course of IVH resolution. Frequency distributions were compared using the χ² and Fisher exact tests. A probability value <0.05 was considered significant.

Results
Between August 2008 and March 2010, 22 patients were treated with the low-dose IVF regimen. Those patients were compared with 32 patients meeting the same inclusion criteria, who were treated with IVF in a prospective study using high-dose IVF. There were no statistically significant differences between the 2 groups considering baseline demographic, clinical, and radiological characteristics (Table).

The course of IVH volume over time is shown in the Figure. The multifactorial analysis of variance did not show significant differences when comparing total effect of IVF dosage on resolution of IVH between the 2 groups (F = 1.3, P = 0.25). However, post hoc tests revealed a significantly lower total IVH volume in the high-dose IVF group on Day 7 (4.4 ± 2.7 mL versus 8.8 ± 8.1 mL, P = 0.01) and Day 10 (1.4 ± 2.8 mL versus 4.9 ± 5.8 mL, P = 0.005; Figure A). This difference resulted only from hematoma resolution in the lateral ventricles, where similar differences were seen (Figure B). The course of IVH resolution in the third and fourth ventricles was practically identical between both groups for all time points (analysis of variance, F = 0.15, P = 0.9; Figure C). Clot half-life was shorter in the high-dose IVF group (56 ± 25 hours versus 78 ± 43 hours, P = 0.02).

There was no difference in the overall effect of high versus low-dose IVF in patients treated with a single EVD (analysis of variance, F = 2.9, P = 0.11). Similar results were seen when comparing between high- and low-dose IVF in patients treated with bilateral EVDs (analysis of variance, F = 0.59, P = 0.46). Post hoc tests showed faster clot removal in the high-dose groups at Days 7 and 10 both in patients treated with 1 EVD (trend at Day 7, P = 0.06; Day 10, P = 0.037) and in patients treated with bilateral EVDs (Day 7, P = 0.022; Day 10, P = 0.004). No differences were observed in the course of third and fourth ventricle IVH volumes between high- and low-dose IVF among patients treated with single and bilateral EVDs.

Side Effects
One IVF-associated asymptomatic IVH was observed in the high-dose IVF group after administration of 8 mg rtPA. No IVF-associated bleeding complications were seen in the low-dose IVF group. Two patients from the high-dose IVF group and 1 patient from the low-dose IVF group showed signs of ventriculitis during EVD (pleocytosis and elevated lactate levels without detection of bacteria). The infection could be sufficiently treated with systemic antibiotics. Frequency distribution analyses showed no significant differences in complication incidence between the 2 groups.

Outcome
One patient from the high-dose IVF group died of fulminant pulmonary embolism 1 week after admission. All other

<table>
<thead>
<tr>
<th>Table. Baseline Demographic, Clinical, and Radiological Characteristics, Treatment Parameters, and Complications</th>
<th>Low-Dose IVF (n = 22)</th>
<th>High-Dose IVF (n = 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>64 ± 12</td>
<td>61 ± 9</td>
<td>0.25*</td>
</tr>
<tr>
<td>Glasgow Coma Scale on admission</td>
<td>10 (3–14)</td>
<td>10 (3–14)</td>
<td>0.33‡</td>
</tr>
<tr>
<td>Male/female</td>
<td>11/11</td>
<td>20/12</td>
<td>0.40†</td>
</tr>
<tr>
<td>ICH volume, mL</td>
<td>11 ± 11</td>
<td>16 ± 9</td>
<td>0.15*</td>
</tr>
<tr>
<td>IVH volume, mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>31 ± 24</td>
<td>31 ± 23</td>
<td>0.62*</td>
</tr>
<tr>
<td>Lateral ventricles</td>
<td>26 ± 23</td>
<td>25 ± 20</td>
<td>0.50*</td>
</tr>
<tr>
<td>Third/fourth ventricle</td>
<td>6 ± 4</td>
<td>7 ± 5</td>
<td>0.53*</td>
</tr>
<tr>
<td>Graeb score</td>
<td>8 (5–11)</td>
<td>8 (4–11)</td>
<td>0.79‡</td>
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<td>Treatment</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 EVD/2 EVDs</td>
<td>16/6</td>
<td>14/18</td>
<td>0.09†</td>
</tr>
<tr>
<td>EVD duration, h</td>
<td>115 ± 63</td>
<td>105 ± 59</td>
<td>0.47*</td>
</tr>
<tr>
<td>Total rtPA dose, mg</td>
<td>3 (1–10)</td>
<td>12 (4–20)</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>No. of rtPA doses</td>
<td>3.6 ± 2.9</td>
<td>3 ± 1.3</td>
<td>0.39*</td>
</tr>
<tr>
<td>Clot half-life, h</td>
<td>78 ± 43</td>
<td>56 ± 25</td>
<td>0.02*</td>
</tr>
<tr>
<td>Opening third/fourth ventricle, h</td>
<td>43 ± 24</td>
<td>38 ± 17</td>
<td>0.41*</td>
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<tr>
<td>Clearance third/fourth ventricle, h</td>
<td>105 ± 85</td>
<td>73 ± 50</td>
<td>0.16*</td>
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<tr>
<td>Complications</td>
<td></td>
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<tr>
<td>Rebleeding</td>
<td>0</td>
<td>1</td>
<td>1.0†</td>
</tr>
<tr>
<td>Ventriculitis</td>
<td>1</td>
<td>2</td>
<td>1.0†</td>
</tr>
<tr>
<td>IVF indicates intraventricular fibrinolysis; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; EVD, external ventricular drainage; rtPA, recombinant tissue plasminogen activator.</td>
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<td>*t test.</td>
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<td>†Fisher exact test.</td>
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| ‡Mann-Whitney U.
patients survived 30 days after the initial bleeding event. At 90 days, 18 of 32 patients (56%) in the high-dose IVF group and 13 of 22 patients (59%) in the low-dose IVF group had a modified Rankin Scale 0 to 3.

Discussion
Comparing the overall effect of the IVF dose on IVH removal, we did not find statistically significant differences between the low- and the high-dose regimens. However, there was a shorter clot half-life in the high-dose IVF group (56±25 hours versus 78±43 hours, \(P=0.02\)). Moreover, at Days 7 and 10, IVH size was significantly lower in the high-dose IVF group (Figure A). Interestingly, this dose effect of IVF became recognizable at a time point when IVF had already been discontinued. At this time, the third and fourth ventricles were basically cleared from blood and only IVH in the lateral ventricles accounted for the difference observed (Figure B). The clinical implications of this effect require further research.

Blood in the third and fourth ventricles was of crucial importance, because it caused acute obstructive hydrocephalus. Comparing third and fourth ventricle opening and clearance between the 2 IVF dosage groups, we found no differences in clot resolution; moreover, the course of IVH volume was almost identical (Figure C). These findings are important, because the most severe complication of IVH, obstructive hydrocephalus, seems to be equally well treated with a lower rtPA dose.

The intraventricular administration of higher rtPA doses causes concern, because animal studies have shown a dose-dependent inflammatory damage to periventricular brain structures caused by rtPA. This aspect has not been sufficiently studied in the clinical setting. Another important issue is the concern of an increased risk of bleeding complications with higher IVF dosage, as recently reported from the dose-finding part of the CLEAR-IVH trial.4 We found only 1 asymptomatic bleeding complication (3%) under the higher rtPA dosing regimen (8 mg/day), which occurred after administration of 8 mg rtPA. No rebleeding was observed in patients who received total 12, 16, or 20 mg rtPA. The incidence of ventriculitis was also similar in both groups (Table).

Moreover, we could not detect differences in outcome and mortality between the 2 groups. However, the sample size certainly does not allow such comparisons.

Our study has clear limitations due to its retrospective design, nonconcurrent sequential epochs of dosing, and relatively small patient number (\(n=54\)). Although not statistically significant, there was an imbalance of distribution of patients treated with bilateral EVDs between the 2 IVF dosage groups with twice as frequent use of dual catheters in the high-dose cohort (Table). Despite previous reports6 revealing no differences in IVH resolution resulting from the use of single or bilateral EVDs, we cannot totally exclude that greater clearance in the high-dose cohort may have been influenced by dual catheter dosing with the higher dose. The application of high-dose IVF resulted in a higher cumulative rtPA dose. Therefore, the question if the regimen of application (single dose and dosing interval) or rather the resulting cumulative dose better explain the differences we observed remains unanswered. Despite those limitations, the patients from the low-dose IVF group were selected following the same inclusion and exclusion criteria. Furthermore, treatment followed the strict institutional protocol derived from the prospective study protocol used in the high-dose IVF group3 with the only difference of dosage and dosing interval of IVF. Thereby selection bias was minimized, and there were no differences between the 2 groups considering baseline characteristics, general management, EVD and lumbar drainage management, criteria for shunt surgery, radiological follow-up, and
clinical follow-up. However, considering the lack of a priori knowledge of the proper sample sizes needed to distinguish effects of IVF dose, dosing interval, or number of catheters on ventricular clot resolution, our results have only preliminary character and this topic requires further study.

Disclosures
None.

References
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