Intraventricular Fibrinolysis Does Not Increase Perihemorrhagic Edema After Intracerebral Hemorrhage

Bastian Volbers, MD; Ingrid Wagner, MD; Wolfgang Willfarth, MS; Arnd Doerfler, MD; Stefan Schwab, MD; Dimitre Staykov, MD

Background and Purpose—Additional intraventricular hemorrhage leads to higher mortality and worse functional outcome after intracerebral hemorrhage (ICH). Intraventricular fibrinolysis (IVF) with recombinant tissue plasminogen activator (rtPA) is an emerging treatment strategy for such patients. However, experimental studies suggest that rtPA may exert proedematous effects and lead to increased perihemorrhagic edema (PHE) after ICH. We aimed to compare the course of PHE after ICH between patients who received IVF with rtPA and controls matched for ICH volume.

Methods—Patients were identified retrospectively from our institutional ICH database. Sixty-four patients with ICH and intraventricular hemorrhage who were treated with IVF were compared with 64 controls, who did not receive IVF, matched for ICH volume. The course of PHE was assessed on computed tomography scans (day 1, days 2 and 3, days 4-6, 7-9, and 10-12) using a threshold-based semiautomatic volumetric algorithm. Relative PHE was calculated as a ratio of PHE volume and initial ICH volume.

Results—The matching algorithm resulted in similar mean ICH volumes in both groups (20.01±17.5 mL, IVF vs 20.08±17.1 mL, control). Intraventricular hemorrhage volume was larger in the IVF group (26.8±19.2 mL vs 9.2±13.4 mL). The mean total rtPA dose used for IVF was 8±6 mg. PHE increased over time in both groups until day 12. At all investigated time points, there was no significant difference in relative PHE between the IVF group and controls (F=0.39; P=0.844).

Conclusions—IVF with rtPA did not lead to a relevant increase in PHE after ICH. rtPA doses used in the current study seem to be safe regarding PHE. (Stroke. 2013;44:00-00.)

Key Words: intracerebral hemorrhage • intraventricular fibrinolysis • intraventricular hemorrhage • perihemorrhagic edema • recombinant tissue-type plasminogen activator • semiautomatic volumetry • X-ray computed tomography

Additional intraventricular hemorrhage (IVH) has been identified as a strong and independent negative prognostic predictor causing higher mortality, morbidity, and disability after spontaneous intracerebral hemorrhage (ICH). Several different pathophysiological mechanisms seem to contribute to this deleterious effect. Clotting of the aqueduct leads to the most severe complication of IVH, namely, acute obstructive hydrocephalus, which has been shown to further worsen the prognosis in such patients. Apart from this injury mechanism, ventricular blood has been shown to exert a mass effect and reduce cerebral blood flow in the periventricular brain tissue in animal models of IVH. Especially the so-caused damage of brain stem structures may explain the prognostic significance of third and fourth ventricle blood volume, demonstrated in clinical studies. Finally, blood and its breakdown products cause inflammation of the ependymal layer and the subependymal brain tissue, and also inflammation and fibrosis of the arachnoid mater, thereby leading to a delayed communicating hydrocephalus.

Considering those pathomechanisms, there seems to be a clear rationale for the fast removal of blood and blood breakdown products from the ventricular system. Intraventricular fibrinolysis (IVF), that is, the administration of fibrinolytic agents as recombinant tissue plasminogen activator (rtPA) into the ventricles, seems to be an emerging and promising treatment strategy, which is currently being investigated in a large phase III multicenter trial (Clot Lysis: Evaluating Accelerated Resolution of Intraventricular Hemorrhage [CLEAR-III]).

In the context of IVF, rtPA toxicity has been a source of concern because animal studies have shown that rtPA may exert dose-dependent proedematous and neurotoxic effects. Moreover, a recent small retrospective clinical study has indicated that there may be an increase in perihemorrhagic edema (PHE) in ICH patients treated with intraventricular rtPA. Although the influence of PHE on morbidity and mortality after ICH has not been clearly established yet, PHE may play a role as a source of additional mass effect, especially in large ICH, and thereby lead to neurological
deterioration and herniation.\textsuperscript{16,17} We aimed to investigate the effect of intraventricular rtPA on PHE evolution after ICH and compared the course of PHE in a large retrospective cohort of patients treated with IVF and controls matched for ICH volume.

**Methods**

**Patient Selection**

The study was approved by our local ethics committee. Patients treated between January 2006 and October 2011 were identified retrospectively from our institutional ICH database. The cohort treated with IVF (IVF group) consisted of patients with spontaneous ICH <40 mL and secondary IVH, initially causing acute obstructive hydrocephalus. Controls were selected among patients with spontaneous ICH and secondary IVH without obstruction of the third and fourth ventricles, who did not receive IVF (control group). For better comparison of the course of PHE between the 2 groups, control patients were matched for initial ICH volume (\(\leq 5\) mL). Spontaneous ICH was diagnosed when no other cause than hypertension or amyloid angiopathy was found. To allow sufficient evaluation of the time course of PHE in both groups, only patients who received >3 computed tomography (CT) scans covering at least the first 10 days of treatment were included in the analysis.

**Neuroimaging and Assessment of PHE and ICH Volume**

Neuroimaging was performed on a fourth-generation CT scanner (Somatom 64, Somatom AS+, Siemens Healthcare, Erlangen, Germany). Each CT scan consisted of 10 to 12 slices of 4.8 mm thickness for the skull base and 10 to 12 slices of 7.2 mm thickness for the cerebrum. CT images were acquired using the orbito-meatal plane. Absolute volumes of ICH and PHE were obtained using a semiautomatic volumetric algorithm as described elsewhere.\textsuperscript{18} The course of PHE was assessed on CT scans performed in the course of treatment. Different time points were merged to time clusters for better comparison between the 2 groups (day 1, days 2–3, 4–6, 7–9, and 10–12).

Relative PHE (rPHE) was calculated as a ratio of PHE volume and initial ICH volume.

**Intraventricular Hemorrhage**

According to our institutional protocol, IVF was performed in patients with spontaneous ICH <40 mL and obstructive hydrocephalus caused by IVH, who were treated with an external ventricular drain (EVD). IVF was started at the earliest 12 hours after symptom onset and 6 hours after EVD insertion. No patient was included with IVF starting later than 48 hours after symptom onset. Before treatment, the position of the ventricular catheter was confirmed by CT. rtPA was applied via the EVD under sterile conditions. After application of the fibrinolytic agent, the EVD was clamped for 30 to 60 minutes and then reopened. Intracranial pressure was monitored continuously during the clamping time. Until July 2008, a single dose of 4 mg rtPA and a dosing interval of 12 hours up to a maximum cumulative dose of 20 mg rtPA were used. Starting in August 2008, the dosing regimen was altered according to the preliminary results of the Clot Lysis Evaluation Accelerated Resolution of Intraventricular Hemorrhage trial (CLEAR-IVH; single dose of 1 mg rtPA, dosing interval 8 hours, maximum cumulative dose 12 mg rtPA).\textsuperscript{19} IVF was discontinued as soon as the third and fourth ventricles were no longer obstructed with ventricular blood, or if the maximum cumulative dose of rtPA was reached. During IVF, daily CT scans were performed to evaluate the resolution of IVH. Lumbar drainage (LD) was inserted as soon as the third and fourth ventricles had been cleared from blood if clamping of EVD was not possible over a period of at least 24 hours without intracranial pressure elevation, as described previously in detail.\textsuperscript{10}

**Assessment of Ventriculitis**

In all patients treated with EVD or LD, cerebrospinal fluid (CSF) was examined routinely every other day or when signs indicating an infection (eg, leukocytosis or fever of unknown origin) occurred. Ventriculitis was diagnosed according to the criteria described by Lozier et al\textsuperscript{20} if low CSF glucose level, high CSF protein, and CSF pleocytosis was found. Antibiotic therapy was started even if CSF culture was negative. Thus, a retrospective distinction between aseptic and infective ventriculitis was not sufficiently possible.

**Statistics**

Data are presented as mean\(\pm\)SD if not indicated differently. Statistical analyses were performed using the IBM SPSS Statistics 19 software package. A 2-tailed t test was used to compare differences between patient characteristics. A repeated-measure ANOVA was performed to examine the influence of IVF on rPHE at different time points. A multiple regression analysis was run to identify the impact of different patient characteristics on rPHE as well as the impact of cumulative IVF dose on rPHE. Representatively, regression and correlation analysis was performed for data of day 1, days 4–6, and days 10–12. A P value <0.05 was considered statistically significant.

**Baseline Clinical Data**

Between January 2006 and October 2011, a total of 64 patients with ICH, IVH, and obstructive hydrocephalus who were treated with IVF were identified from our institutional ICH database. Sixty-four controls were selected from the remaining 246 patients with ICH and IVH using ICH volume matching. The matching algorithm resulted in similar mean ICH volumes in both groups (IVF group: 20.01±17.5 mL; control group: 20.08±17.1 mL). Time from symptom onset to initial CT was 6.0±6.0 hours in the IVF group and 6.1±6.3 hours in the control group (P=0.89). Secondary rebleeding with hematoma expansion of >30% of the initial hematoma volume occurred in 11 patients (17.2%) of the IVF group and in 14 patients (21.9%) of the control group (P=0.51). In the IVF group, 5 patients receiving 1 mg of intraventricular rtPA per application (14.7%) and 6 patients (20%) receiving 4 mg of rtPA suffered a hematoma expansion of >30% (P=0.59). There was no relationship between cumulative dose of ventricular rtPA and the occurrence of a hematoma expansion of >30% (R\(^2\)=0.001; P=0.80). Clinical and radiological characteristics are summarized in Table 1.

**Course of PHE**

As demonstrated in Figure 1, rPHE increased significantly over time in both groups (F[1,63]=33.79; P<0.001) and showed an almost identical course in patients treated with IVF and controls (F[1,63]=0.39; P=0.844). Maximum rPHE was reached after 9.7±5.8 days after onset in the IVF group and after 9.2±5.5 days in the control group (P=0.97). Per definition, absolute PHE volume and absolute ICH volume account for rPHE. Absolute PHE volume at admission was strongly correlated with absolute ICH volume at admission (R\(^2\)=0.476; P<0.001). None of the other clinical characteristics significantly accounted for rPHE. Thus, absolute ICH volume remains an exclusive factor accounting for rPHE. IVF had no influence on rPHE at any time point (Table 2). The evolution of rPHE (changes in rPHE in correlation to rPHE at admission [Delta-rPHE]) within the examined time course was not influenced by IVF either (mean Delta-rPHE between
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No Effect of Ventricular rtPA on Edema After ICH

Influence of IVF Dosage

Thirty patients (mean ICH volume 17.45±16.65 mL) had received 4 mg intrathecal rt-PA per application (high dose group) and 34 patients (mean ICH volume 22.18±18.26 mL) 1 mg (low dose group). ICH volume did not differ significantly (P=0.339) between both subgroups. Mean cumulative intraventricularly administered rtPA was 3.79±3.43 mg in the low dose group and 11.86±5.4 mg in the high dose group. Four patients in the high dose group received <7 mg intrathecal rt-PA cumulative, and 5 patients in the low dose group >7 mg cumulative. As can be seen in Figure 2, the cumulative dose had no effect on rPHE at days 10 through 12 (R²=0.014; P=0.347). There also was no effect on rPHE at days 4 through 6 (R²=0.010; P=0.423; data not shown). Concerning the effect of a single application dose, no significant difference could be seen in the rPHE evolution between patients who received 4 mg of rtPA per application (Delta-rPHE days 10–12; 1.00±1.3) and patients who received 1 mg of rtPA per application (Delta-rPHE days 10–12; 0.54±0.83; P=0.09).

Discussion

The key finding of the present study is that patients with ICH, IVH, and obstructive hydrocephalus treated with intraventricular rtPA applied in a range of doses used in our institution (4 mg every 12 hours, up to 20 mg or 1 mg every 8 hours up to 12 mg) did not develop any detectable increase in PHE in the course of treatment compared with ICH-volume–matched controls. Furthermore, we could not find any association between the cumulative rtPA dose applied and rPHE.

Our finding is in contrast to the results of a previously published smaller study. Ducruet et al compared the evolution of PHE between 13 patients treated with intraventricular rtPA and 17 controls. The authors described significantly higher rPHE in patients treated with IVF. When comparing those results with the present study, several important differences

Table 1. Clinical, Demographic, and Radiological Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IVF Group (n=64)</th>
<th>Control Group (n=64)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>64±10.9</td>
<td>69±15.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Men (n)</td>
<td>34</td>
<td>39</td>
<td>0.38</td>
</tr>
<tr>
<td>NIHSS (median [IQR])</td>
<td>21 (24)</td>
<td>13 (15.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>GCS (median [IQR])</td>
<td>8.5 (11)</td>
<td>13 (4.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>mRS (median [IQR])</td>
<td>1 (2)</td>
<td>1 (1)</td>
<td>0.93</td>
</tr>
<tr>
<td>ICH lobar (n)</td>
<td>3</td>
<td>23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH ganglionic (n)</td>
<td>59</td>
<td>33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICH cerebellar/brain stem (n)</td>
<td>2</td>
<td>8</td>
<td>0.02</td>
</tr>
<tr>
<td>Statin use (n)</td>
<td>14</td>
<td>8</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertonia (n)</td>
<td>59</td>
<td>60</td>
<td>0.74</td>
</tr>
<tr>
<td>Warfarin use (n)</td>
<td>9</td>
<td>15</td>
<td>0.20</td>
</tr>
<tr>
<td>Aspirin use (n)</td>
<td>18</td>
<td>18</td>
<td>1.00</td>
</tr>
<tr>
<td>Aspirin + Dipyridamole use (n)</td>
<td>0</td>
<td>1</td>
<td>0.32</td>
</tr>
<tr>
<td>Osmotic therapy (Mannitol; n)</td>
<td>30</td>
<td>25</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypothermia (n)</td>
<td>11</td>
<td>9</td>
<td>0.57</td>
</tr>
<tr>
<td>Use of EVD (n)</td>
<td>64</td>
<td>31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of ventricular drainage (mean±SD), d</td>
<td>8.8±8.0</td>
<td>9.2±5.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Use of lumbar drainage (n)</td>
<td>44</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of lumbar drainage (mean±SD), d</td>
<td>7.0±5.0</td>
<td>5.8±2.6</td>
<td>0.38</td>
</tr>
<tr>
<td>Ventriculitis (n)</td>
<td>5</td>
<td>2</td>
<td>0.245</td>
</tr>
<tr>
<td>Cumulative dose of IV-rtPA (mean±SD), mg</td>
<td>8±6.01</td>
<td>0</td>
<td>...</td>
</tr>
<tr>
<td>ICH volume d1 (mean±SD), mL</td>
<td>20.01±17.5</td>
<td>20.08±17.1</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>PHE volume d1 (mean±SD), ml</td>
<td>16.7±11.4</td>
<td>18.1±15.5</td>
<td>0.46</td>
</tr>
<tr>
<td>IVH volume d1 (mean±SD), ml</td>
<td>26.8±19.2</td>
<td>9.2±13.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GRAEB score d1 (median [IQR])</td>
<td>8 (2)</td>
<td>3 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LOS days (mean±SD)</td>
<td>22±12.6</td>
<td>18±6.2</td>
<td>0.04</td>
</tr>
<tr>
<td>Intrahospital mortality (n)</td>
<td>4</td>
<td>3</td>
<td>0.70</td>
</tr>
</tbody>
</table>

d1 indicates day 1; EVD, external ventricular drain; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; IQR, interquartile range; IVF, intraventricular fibrinolysis; IVH, intraventricular hemorrhage; IV-rtPA, intraventricularly administered recombinant tissue plasminogen activator; LOS, length of stay; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and PHE, perihemorrhagic edema.

day 1 and day 12: IVF group, 0.76±1.1; control group, 0.56±0.7; P=0.459 and Delta-rPHE between day 1 and day 6: IVF group, 0.46±0.7; control group, 0.36±0.6; P=0.555).

Table 2. Evolution of Relative Perihemorrhagic Edema in Patients Treated With Intraventricular Fibrinolysis (IVF Group) Compared With Controls (Control Group)

<table>
<thead>
<tr>
<th>Relative Perihemorrhagic Edema</th>
<th>IVF Group (n=64)</th>
<th>Control Group (n=64)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1.05±0.63</td>
<td>1.16±0.67</td>
<td>0.54</td>
</tr>
<tr>
<td>Days 2–3</td>
<td>1.28±0.76</td>
<td>1.32±0.72</td>
<td>0.75</td>
</tr>
<tr>
<td>Days 4–6</td>
<td>1.52±0.99</td>
<td>1.53±0.84</td>
<td>0.92</td>
</tr>
<tr>
<td>Days 7–9</td>
<td>1.64±1.31</td>
<td>1.66±0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>Days 10–12</td>
<td>1.81±1.39</td>
<td>1.73±0.95</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Data are mean±SD.
should be considered. First, the mean ICH volume in the treatment and control group of Ducruet et al\textsuperscript{14} was larger compared with our cohort. Moreover, there was an imbalance in the ICH size between the 2 groups, although the difference was not significant. Nevertheless, considering the small sample size of this study, such a difference may have influenced the findings reported by the authors because previous studies have shown that rPHE is inversely associated with ICH volume.\textsuperscript{17,21} Second, PHE is difficult to delineate and to assess because previous studies included in this review were mainly relatively small studies, and our analysis with all consequences concerning imbalances therefore cannot exclude that statistical power may have not been sufficient to detect a possible influence. In this context, our findings support the safety of intraventricularly administered rtPA, considering its possible effect on PHE and rebleeding.

Apart from the possible influence of intraventricular rtPA on the perihemorrhagic area, animal studies have raised concerns that periventricular structures and the ependymal layer may be damaged by dose-dependent rtPA-mediated neurotoxicity, leading to edema of periventricular tissue.\textsuperscript{6,22} Furthermore, Ducruet et al\textsuperscript{14} also reported increased occurrence of aseptic meningitis in rtPA-treated patients.\textsuperscript{14} In our study, only the occurrence of ventriculitis without any further differentiation was recorded, and no significant difference was found between patients treated with IVF and controls. In light of the relatively scarce experimental and clinical data, at this time, it still remains unclear whether mechanisms of rtPA-mediated neuronal damage, as described in ischemic injury,\textsuperscript{23} play an important role in the setting of ICH with ventricular involvement. Considering the relatively low doses of rtPA used for IVF, blood breakdown products, released in higher concentrations after IVF, may be more harmful to the surrounding brain tissue than the fibrinolytic agent itself. In this context, faster and more effective drainage of IVH after lysis may be crucial to attenuate inflammatory damage.\textsuperscript{21} Of course, in the absence of experimental or histopathologic data, those interpretations remain speculative. Prospective data are necessary to possibly confirm our data and to address further questions such as influence of ventricular rtPA on periventricular matter.

Our study has several limitations that should be considered when the results are interpreted. First, this was a retrospective study; however, it was performed at a single center and, therefore, institutional protocols for management of increased intracranial pressure and severe IVH were consistent within the investigated groups. Moreover, a relatively large number of patients could be included in our analysis. Despite this, we cannot exclude that statistical power may have not been sufficient to detect small rPHE differences between both groups. Second, because of a change in our institutional protocol for IVF in 2008, 2 different dosing regimens were used for IVF.
However, the rtPA doses applied before and after the change in our treatment protocol varied within an acceptable range and were close to the doses currently investigated in the CLEAR-III trial. The 2 dosing subgroups were not matched for ICH volume, leading to a nonsignificant imbalance, which may have influenced the rPHE comparison. However, the cumulative rtPA dose had no effect on rPHE, independent from the dosing group. Third, for comparison of PHE on follow-up CTs, we merged several days to time clusters and analyzed them as single time points, thereby combining different stages of PHE evolution. Fourth, the volumetric assessment of PHE on CT is difficult, and there might be inaccuracies in delineating the PHE area. We resolved this problem by using a validated semiautomatic volumetric algorithm, as described previously. In detail. Fifth, we only analyzed PHE evolution within 10 days to 12 days after ICH, therefore, our conclusions are limited to that time period. Sixth, obstructive hydrocephalus was a selection criterion in the treatment group, and because of its characteristic appearance on neuroimaging, blinding of PHE measurement was not possible. Therefore, results could have been biased because of this fact. Seventh, there were some imbalances in the characteristics of the IVF and control group concerning age, ICH location, use of EVD and LD, originating mainly from the retrospective design of this study and the slightly different drainage management strategies depending on the severity of IVH. EVD and LD were only inserted when necessary according to an institutional protocol. Previous studies indicate that ganglionic ICH is associated with more severe IVH. This fact, as well as the more frequent need of extracorporeal CSF diversion in severe IVH, may have led to an overrepresentation of drainage use and ganglionic hemorrhage in the IVF group. Thus, we could not exclude a possible impact of those characteristics on the evolution of PHE, even if regression analysis did not show any significant influence. Although, as far as having been addressed in previous research, age, ICH location, and use of EVD and LD have not been shown to affect the evolution of PHE. However, the most important variable influencing PHE, namely ICH volume, was identical in both groups resulting from our strict matching algorithm.

In conclusion, we did not observe an effect of IVF with rtPA on CPE evolution after ICH with severe ventricular involvement.

Disclosures

None.

References


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