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Single versus bilateral external ventricular drainage for intraventricular fibrinolysis in severe ventricular hemorrhage

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ABSTRACT

Background
Intraventricular fibrinolysis (IVF) through bilateral external ventricular drains (EVD) may provide better access of the thrombolytic agent to the intraventricular clot, potentially influencing clot clearance and outcome.

Methods
Patients with spontaneous ganglionic intracerebral hemorrhage (ICH)<40ccm and intraventricular hemorrhage (IVH) with acute hydrocephalus have been treated with IVF. The decision for placement of one or two EVDs has been left to the discretion of the treating physician. CT volumetry, the effects on cerebrospinal fluid (CSF) circulation, and outcome at 3 months have been analyzed for patients with one (Group I, n=13) or two EVDs (Group II, n=14).

Results
We found no difference in clot resolution between the two groups (clot half life 2.1±1.2 versus 2.4±1.3 days). Separate analysis of the third and fourth ventricle clearance was similar (1.6±0.6 versus 1.8±0.8 days), indicating no difference in reconstitution of CSF circulation. A trend towards longer EVD duration and higher infection rate was found in the bilateral EVD group. No difference was found in outcome at 3 months.

Conclusions
Our results do not support the use of bilateral EVDs for IVF in patients with severe IVH.
INTRODUCTION

Over the last years, administration of thrombolytic agents through the external ventricular drainage (EVD) has been increasingly tested for intraventricular clot fibrinolysis (IVF), and there is growing evidence that IVF can significantly accelerate intraventricular hemorrhage (IVH) clearance without major side effects[1-6], and may also improve survival rate[4,5,7,8] and clinical outcome.[4,5,9,10]

In severe IVH and acute hydrocephalus with abundant (>50%) blood in one lateral ventricle, or involvement of both lateral ventricles and the risk of blockage of the foramen of Monro, the placement of two EVDs in each lateral ventricle is frequently considered.[3,4,11-13]

Theoretically, bilateral EVDs may also provide better access of the thrombolytic agent to the intraventricular hematoma by direct application of the agent into the blood clot of the affected ventricle[10] resulting in faster clot lysis and blood removal compared to a single EVD, which is usually placed in the lateral ventricle that is less affected. The decision for the placement of a single or bilateral EVD in such cases is usually left at the discretion of the treating physician. The aim of this study was therefore to compare the efficacy of IVF through a single versus bilateral EVD in patients with secondary IVH and acute hydrocephalus.
METHODS

Patient selection

According to an institutional protocol[14] all patients with spontaneous ganglionic ICH <40ccm and severe IVH defined as obstruction of the third and fourth ventricles resulting in acute hydrocephalus and the need for EVD were treated with IVF. The GRAEB score[15] was used for patient selection (lateral ventricles: 0:no blood; 1:trace of blood; 2:<50%; 3:>50% of ventricle filled with blood; 4:ventricle filled with blood and dilated; 3rd and 4th ventricle 1:trace of blood; 2:ventricle filled with blood and dilated; maximum score 12). Patients with (i) GRAEB score for one lateral ventricle ≥3, or (ii) with at least GRAEB ≥2 for each of both lateral ventricles received either one EVD (placed in the lateral ventricle with less blood) or bilateral EVD. Only these patients were included in the present analysis. The decision for one or two EVDs was made individually at the discretion of the treating neurosurgeon and neurologist.

Treatment algorithm

Basic management

ICH and IVH were diagnosed immediately after admission by CT. Hydrocephalus was defined by bicaudate index and temporal horn diameter[16], and immediately treated with uni- or bilateral EVD. CSF was analyzed for infection every second day.

IVF management

IVF was carried out starting 12-48h after symptom onset, with administration of 4mg rt-PA through the EVD in the single EVD group or 2mg rt-PA simultaneously through each EVD in the bilateral EVD group. The administration of rt-PA was repeated every 12h until a maximum cumulative dose of 20mg was reached. If the third and fourth ventricles were cleared from blood on CT, IVF was discontinued before the maximum dose had been reached.
**EVD management, lumbar drainage, and permanent shunt**

*Group I (single EVD)*

The EVD was clamped if ICP was <20mmHg for more than 24h and CT revealed a third and fourth ventricle cleared from blood, assuming communication between the inner and outer CSF space. EVD was removed after another 24h if ICP remained <20mmHg and CT revealed no ventricle enlargement.[3,11,14]

If the attempt to clamp the EVD was unsuccessful, extracorporeal CSF outflow was continued by lumbar drainage (LD) as previously described.[11,14] EVD was removed after 24h.

*Group II (bilateral EVD)*

Bilateral EVDs were removed following a sequential procedure: First, after clearance of the third and fourth ventricles was reached, one of the EVDs was closed for 24h and removed if ICP remained <20mmHg and CT showed no increase of ventricular size. With one EVD remaining, patients were treated as already described for the single EVD group (see above).

*Permanent VP-shunt*

When LD clamping was unsuccessful for more than 10 days, a persistent ventriculo-peritoneal shunt was indicated. If EVD-replacement by LD was not feasible, EVD was exchanged after about 10 days and ventriculo-peritoneal shunting was considered before the second EVD-exchange.[3,11]

**Imaging and data analysis**

Routine CT scans were performed on admission, after EVD placement and then daily up to day 4, on day 7 and day 10. For each time point, the site of the ventricles affected was
recorded using the GRAEB score. IVH volume was calculated by manual tracing of the hematoma. The blood volume was standardized as a percentage of the initial IVH volume.

**Outcome**

A telephone follow-up survey was conducted 3 months after symptom onset with all surviving patients and their closest relatives and outcome was assessed using the modified Rankin Scale (mRS). Good outcome was defined as mRS 0-3.

**Statistical analysis**

We performed Shapiro-Wilk test to analyse the distribution of the data. Normally distributed data are expressed as mean±standard deviation (SD) and were compared using the unpaired t-test. Other data are expressed as median and range and were compared using nonparametric tests (Wilcoxon test). A value of p ≤0.05 was considered significant.
RESULTS

Between January 2006 and April 2008 a total of 27 patients with spontaneous ganglionic ICH and ventricular extension were treated with IVF according to the protocol. Relevant demographic, clinical and neuroradiological characteristics are shown in Table 1. There was no difference between the two groups with regard to age, GCS on admission, parenchymal hematoma volume and severity of IVH.
Table 1. Demographic, clinical and neuroradiologic characteristics.

<table>
<thead>
<tr>
<th></th>
<th>single EVD (n=13)</th>
<th>bilateral EVD (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.8 ± 7.5</td>
<td>59.4 ± 9.5</td>
</tr>
<tr>
<td>GCS on admission</td>
<td>9 (3-14)</td>
<td>8 (3-14)</td>
</tr>
<tr>
<td>Graeb score on admission</td>
<td>10 (8-11)</td>
<td>9 (7-11)</td>
</tr>
<tr>
<td>ICH volume on admission (ccm)</td>
<td>17.3 ± 12.6</td>
<td>13.3 ± 8.5</td>
</tr>
<tr>
<td>IVH volume on admission (ccm)</td>
<td>31.6 ± 19.6</td>
<td>34.7 ± 11.3</td>
</tr>
<tr>
<td>Localization of ICH (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>basal ganglia</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>thalamus</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>left/right</td>
<td>6/7</td>
<td>2/12</td>
</tr>
<tr>
<td>IVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start after symptom onset (h)</td>
<td>26.5 ± 10.4</td>
<td>25.5 ± 8.2</td>
</tr>
<tr>
<td>rt-PA dose (mg)</td>
<td>13.7 ± 5.8</td>
<td>12.3 ± 3.8</td>
</tr>
<tr>
<td>Duration of EVD (d)</td>
<td>4.8 ± 1.9</td>
<td>6.4 ± 2.1</td>
</tr>
<tr>
<td>Length of stay on ICU (d)</td>
<td>19.1 ± 6.8</td>
<td>19.8 ± 6.5</td>
</tr>
<tr>
<td>mRS at 3 months</td>
<td>3 (1-5)</td>
<td>4 (1-6)</td>
</tr>
<tr>
<td>Mortality at 3 months (n)</td>
<td>0/13</td>
<td>1/14</td>
</tr>
</tbody>
</table>
Neuroradiological findings

Total intraventricular hematoma resolution

The course of total intraventricular hematoma resolution did not differ between groups, neither when using the GRAEB score, nor when using volumetric analysis (Figure 1A). Complete clearance of the ventricular system was achieved after 9.1±2 days when using a single EVD and after 8.7±2.5 days when using bilateral EVDs.

Intraventricular hematoma resolution for each ventricle

There was also no difference between groups in hematoma resolution when the third and fourth ventricles (Figure 1B) or the lateral ventricles (data not shown) were analyzed separately. Re-opening (GRAEB 0-1) and complete clearance of the third and fourth ventricle (GRAEB 0) was achieved after 1.6±0.6 and 3±1.2 days in the single EVD group compared to 1.8±0.8 and 3.6±2.6 days in the bilateral EVD group.

EVD, LD, and permanent shunt

Despite clearing of the third and fourth ventricles, early EVD removal was possible only in one patient of each group. The remaining 25 patients received LD due to persisting malresorptive hydrocephalus. Mean EVD duration was 4.8±1.9 days in group I and 6.4±2.1 days in group II (p=0.07).

No EVD exchange was necessary in both groups and weaning off of LD was successful in all patients, i.e. no patient needed a permanent shunt at discharge. The overall extracorporeal CSF drainage time (EVD+LD) was 7.8±2.4 days for group I and 9.6±3.2 days for group II.
Complications
No EVD obstruction or bleeding complications were observed in both groups. ICP course was comparable between the two groups without any episodes of increased ICP. Two patients of the bilateral EVD group had evidence of ventriculitis (pleocytosis and CSF lactate increase, without identification of bacteria), without obvious clinical consequence under systemic antibiotic therapy.

Outcome
Figure 1C shows the mRS score of the two groups at 3 months. 58% of the patients in group I and 38% of the patients in group II had a good outcome as defined by mRS≤3 (p=0.34).

Subgroup analysis: involvement of both lateral ventricles
Patients with moderate to severe involvement of both lateral ventricles (GRAEB ≥2 for each lateral ventricle (n=9 in group I; n=10 in group II) and patients with severe involvement of both lateral ventricles (GRAEB ≥3 for each lateral ventricle; n=6 in group I; n=6 in group II) were analysed separately. The course of clot resolution and the time needed for third and fourth ventricle clearance was essentially identical for group I and group II in both subgroup analyses (data not shown). There was no evidence of blockage of the foramen of Monro, as identified by asymmetric ventricle enlargement on CT, or for increase of midline shift in the single EVD group.
DISCUSSION

We investigated the use of bilateral EVDs for IVF in patients with obstruction of the third and fourth ventricles and severe involvement of one or at least moderate involvement of both lateral ventricles and did not observe any evidence in support of the use of bilateral EVDs, either radiologically or clinically.

First, the course of intraventricular hematoma resolution was essentially identical between the single and the bilateral EVD group. Particularly, the time until reopening of the third and fourth ventricles was comparable, indicating no differences in the effectiveness of treatment of occlusive hydrocephalus between uni- and bilateral EVDs. Of note, 9 out of 13 patients who were treated with a single EVD had severe involvement of both lateral ventricles with casting of both foramina of Monro. None of these patients developed asymmetrical CSF drainage or increase of ventricle size, suggesting that the risk of a foramen of Monro blockage is minimized in the setting of IVF and that treatment can be sufficiently achieved through single EVD. Moreover, none of these patients had an increase in midline shift or signs of hemiation in the unilateral EVD group.

Second, there was no difference in the frequency of EVD exchange or need for permanent shunt. This observation is not surprising, since the course of intraventricular blood resolution was basically identical between the groups. IVF lead to similarly fast clearance of the third and fourth ventricle from blood resulting in a communication between inner and outer CSF spaces. However, at this early stage, almost all patients (25/27) had malresorptive hydrocephalus since EVD clamping was not successful. Nevertheless, malresorptive hydrocephalus could be sufficiently treated with LD in all patients without the need for EVD exchange or permanent shunting.
Third, outcome analysis revealed no differences between the two treatment groups at 3 months. There was even a trend towards better outcome in the single EVD group. This finding cannot be explained by preferred inclusion of more severely ill patients in the bilateral EVD group, since clinical and radiological characteristics at admission were comparable.

There are several disadvantages of an additional ventricular catheter including additional structural brain damage, and the risk of periprocedural bleeding complications. Furthermore, the risk of more severe cognitive deficits, or symptomatic seizures may increase with bilateral frontal lesions.[17,18] Moreover, the presence of an additional EVD may promote a higher infection rate. Supporting this suggestion, we found evidence of ventriculitis in two patients in the bilateral EVD group, compared to none in the single EVD group.

Our study has several limitations mainly due to its retrospective design. The decision for one or two EVDs was left at the discretion of the treating physician. This may have produced selection bias, as physicians tend to place two EVDs in more severely ill patients. However, we only included patients with severe ventricular involvement. This selection algorithm resulted in essentially identical treatment groups with regard to known independent risk factors for ICH patients, thereby minimizing selection bias.

Since LD was equally used in both treatment groups, it is unlikely that this approach had substantial impact on the comparison of single versus bilateral EVD.
COMPETING INTERESTS AND FUNDING

None.
AUTHORS CONSENT TO PUBLICATION

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REFERENCES


FIGURE LEGENDS:

Figure 1

Course of total intraventricular blood volume for both groups using volumetric analysis by manual tracing (A). Course of relative blood volume reduction in the third and fourth ventricles (B). Values are expressed as percentage of the initial blood volume at day 1 (mean ± SD). Modified Rankin Scale scores (0-6) at 3 months (C).

d1 = admission; d2-10 = following days in correlation to d1;

EVD = external ventricular drainage.