Despite significant progress in reduction of mortality, the effective reduction of delayed cerebral ischemia (DCI) with the aim to improve functional outcome in the course of aneurysmal subarachnoid hemorrhage (SAH) remains challenging. In this respect, intracisternal fibrinolysis for therapeutic reduction of subarachnoid blood clot has been reported to have a beneficial effect for reduction of DCI and poor clinical outcome in patients experiencing SAH. Interestingly, kinetic therapy (ie, head-shaking) in addition to cisternal fibrinolysis, was reported to significantly enhance this beneficial effect. However, cisternal fibrinolysis restricted this treatment to patients undergoing surgical repair for a ruptured intracranial aneurysm. Therefore, we studied the effect of intermittent intraventricular fibrinolysis and concomitant low-frequency head-motion therapy in a randomized, phase II study in patients experiencing severe aneurysmal SAH.

**Methods**—Sixty patients experiencing subarachnoid hemorrhage were randomized into treatment with intraventricular application of recombinant tissue-type plasminogen activator and lateral rotational therapy (experimental) or treatment as usual (control). The primary end point was defined as functional outcome, measured by Glasgow Outcome Scale at discharge and at 3-month follow-up. Clot clearance rate, radiographic features of delayed cerebral ischemia, and posthemorrhagic hydrocephalus were defined as secondary end points.

**Results**—The majority of patients (78.3%) experienced severe subarachnoid hemorrhage. Although there was a higher incidence of subgaleal hematomas in the experimental group, there was no difference in the incidence of adverse or severe adverse events between the 2 groups. Despite significantly higher clot clearance rates, there was no beneficial effect on the incidence of delayed cerebral ischemia and poor functional outcome, as well as posthemorrhagic hydrocephalus after experimental treatment.

**Conclusions**—Despite the ineffectiveness on reduction of delayed cerebral ischemia or poor functional outcome, intraventricular fibrinolysis and kinetic therapy seems to be a safe and effective concept for therapeutic reduction of subarachnoid clot in a patient collective experiencing predominately severe subarachnoid hemorrhage. Therefore, future studies should investigate this treatment in a larger patient collective with a lower degree of primary brain injury and until full clot clearance on serial imaging.

**Clinical Trial Registration**—URL: http://www.controlled-trials.com. Unique identifier: ICRCTN13230264. (Stroke. 2013;44:2162-2168.)

**Key Words:** concomitant fibrinolysis and kinetic therapy ■ radiographic vasospasm ■ subarachnoid hemorrhage

**Background and Purpose**—The goal of this randomized, open-label phase II study was to investigate the effect of concomitant low-frequency head-motion therapy and intraventricular fibrinolysis in patients after surgical or endovascular treatment for aneurysmal subarachnoid hemorrhage.

**Participants**—Eligible patients were allocated into the 2 treatment groups in accordance with the randomization sequence after informed consent was obtained. Inclusion criteria were (1) aneurysmal SAH WFNS grade II to V and Fisher grade III to IV; (2) patients aged >18 years; (3) admission <24 hours after ictus; (4) no history of anticoagulative or platelet-inhibiting drugs; (5) informed consent by a legal representative; and

**Methods**—This was a randomized, prospective, open-label, treatment as usual–controlled phase II study, investigating feasibility, safety, and efficacy. The study was reviewed and approved by the local institutional ethics committee (ID#: 3062) of the Medical Faculty of the Heinrich-Heine-University, Düsseldorf, Germany. Sixty patients experiencing aneurysmal SAH, that is, World Association of Neurological Surgeons (WFNS) grade II to V and Fisher grade III to IV, were randomized into experimental or control treatment.
(6) exclusion of treatment complications because of aneurysm repair in post-treatment cranial computer tomography (CT). Exclusion criteria were (1) nonaneurysmal SAH; (2) WFNS grade I; (3) Fisher grade I SAH; (4) fusiform, mycotic, or traumatic aneurysms; (5) pregnancy; (6) admission >48 hours after SAH ictus; (7) vasospasm on initial catheter angiography (digital subtraction angiogram); (8) history of severe cardiovascular disease; (9) clotting disorders; (10) platelet count <100,000 or INR >1.4; and (11) ongoing internal bleeding. Patients with insufficient cerebral perfusion pressures (<65 mm Hg) caused by intractable primary increase in intracranial pressures on admission were not included. Furthermore, patients experiencing additional intracerebral hemorrhage were generally treated surgically for aneurysm repair and hematoma evacuation.

Randomization
The randomization sequence was generated using the PROC plan software (Statistical Analysis Software Institute, Cary, NC) and kept sealed until after patient screening and inclusion. Patients meeting the inclusion criteria were allocated to control or experimental treatment after surgical or endovascular aneurysm repair and unapparent follow-up CT 6 hours after aneurysm treatment in accordance with the randomization sequence.

Interventions
Figure 1 illustrates the study design. Control treatment was defined as treatment as usual in accordance with a standardized SAH protocol: All patients admitted to our department with a Glasgow Coma Score <13 received an external ventricular drain and remained sedated and intubated until angiographic imaging and subsequent surgical or endovascular treatment of the aneurysm. On the neurosurgical intensive care unit, all SAH patients received continuous, intravenous nimodipine (2 mg/h) for ≥10 days followed by an oral nimodipine (360 mg/d). In case of radiographic vasospasm, medical management consisted of induced hypertension and euvoolemia. In case of refractory radiographic vasospasm, rescue therapy was initiated using endovascular, intra-arterial infusion of nimodipine or balloon angioplasty (for severe proximal vasospasm refractory to intra-arterial nimodipine application).

In addition to the standard treatment regimen, experimental therapy consisted of intraventricular application of recombinant tissue-type plasminogen activator (rt-PA; Actilyse, Boehringer Ingelheim, Germany) and low-frequency rotational therapy (RotoRest, KCI, NY). The motion frequency was set to slow, with a rotation angle of 45° to each side. Rotation was applied continuously and interrupted only for nursing care or diagnostic investigations. Experimental therapy was initiated 6 hours after obliteration of the ruptured aneurysm and unremarkable postoperative or postinterventional CT scan lasting for 48 hours. For intraventricular fibrinolysis, 5 mg of rt-PA was diluted in 2 mL of NaCl and given as an intraventricular bolus every 12 hours >48 hours via the external ventricular drain. After rt-PA bolus, the external ventricular drain was locked and solely used to monitor intracranial pressure for 30 minutes to avoid premature drainage of the fibrinolytic agent. During the 48-hour period patients remained sedated using propofol with or without midazolam and sufentanil and intubated with concomitant lateral rotational therapy. In addition, a daily CT scan was performed until 1 day after cessation of rt-PA fibrinolysis to rule out hemorrhagic complications. Until removal of the external ventricular drain, daily cerebrospinal fluid samples were taken to exclude central nervous system infections.

Imaging and DCI Monitoring
In addition to a cerebral digital subtraction angiogram on admission, occurrence of DCI was monitored in every patient using perfusion CT (PCT, see below) on admission, at days 1, 3 to 4, and 9 to 11, as well as digital subtraction angiogram at day 7 after ictus or after PCT measurements indicative for DCI (see below; Figure 1). Details on our SAH PCT algorithm have been previously published. For detection of DCI and statistical analysis, only mean transit time data were used. The mean transit time values of each PCT scan and patient were pooled and dichotomized (PCT vasospasm versus no PCT vasospasm) for statistical analysis using the below-mentioned cutoff value. Incidence of new cerebral infarction because of DCI was analyzed using the latest, nonenhanced cranial CT.

Definition and Evaluation of End Points
The primary end point was functional outcome at discharge and after 3 months using the Glasgow Outcome Scale. The composite secondary end point consisted of clot clearance rate (ie, the difference of subarachnoid clot volume [mL] on CT between admission and day 4 after SAH ictus, radiographic vasospasm, new cerebral infarction, and occurrence of posthemorrhagic hydrocephalus). Functional outcome was evaluated at discharge and after 3 months. Glasgow Outcome Scale 1 to 3 was defined as poor and 4 to 5 as good functional outcome. Clot volume of cisternal and cranial CT slices was measured using a volumetric measurement software (OsiriX version 3.7.1, Pixmeo SARL, Bernex, Switzerland). Clot clearance rate was defined as the relative amount of subarachnoid blood and reduction in voxel volume (in %) within the time period from days 1 to 5 (±1–2 days). The term radiographic vasospasm concluded angiographic and PCT vasospasm. PCT vasospasm, that is, any PCT measurements indicative for DCI, was defined as a 1.5-fold prolongation of reference mean transit time values from healthy

Figure 1. Study design. Shaded boxes illustrate additional treatment and imaging performed exclusively for patients within the experimental group. cCT indicates cranial computer tomography; DSA, digital subtraction angiogram; GOS, Glasgow Outcome Score; PCT, perfusion computer tomography; rt-PA, recombinant tissue-type plasminogen activator; and SAH, subarachnoid hemorrhage.
patients, which corresponded, according to our institutional hard- and software calibration, to an absolute mean transit time threshold of 4.2 s (normal range, 2.1–3.2 s). Angiographic vasospasm was defined as narrowing of the arterial diameter >30% from baseline. New cerebral infarction was defined as the presence of cerebral infarction on CT scan within 6 weeks after SAH, or on the latest CT made before death within 6 weeks and not attributable to other causes, such as surgical clipping or endovascular treatment. Posthemorrhagic hydrocephalus was defined as the necessity for ventriculoperitoneal shunt implantation during the course of treatment. Adverse events were defined as any intracranial or subgaleal bleeding and intracranial infections (meningitis, ventriculitis). Serious adverse events were any intracranial or subgaleal bleedings or infections, requiring surgical treatment or prolonged hospitalization. The incidence of outcome events was independently analyzed by investigators blinded to treatment allocation (N.E., S.O.E., K.B., B.T.).

Sample Size Calculation
On the basis of a pilot study, investigating ventricular thrombolysis and lumboventricular irrigation in 20 patients, a risk reduction of 50% for symptomatic angiographic vasospasm and clinical features of DCI was assumed for this experimental treatment. Assuming then an incidence of symptomatic vasospasm of 30% to 40% and a risk reduction of 50%, a group size of 30 patients for the treatment group and 30 patients for the control group was calculated to achieve a power of 80% (\(\beta=0.20\)), with a level of significance of 0.05.

Statistical Analysis
Efficacy of treatment was analyzed for all patients intended to treat. For further analysis, Fisher grade IV SAH was subclassified into intraventricular and intracerebral extension. The severity of intraventricular hemorrhage was differentiated into mild (<50% blood in any ventricle), moderate (>50% blood but without obstructive hydrocephalus), and severe (>50% blood with obstructive hydrocephalus) on the basis of initial CT. The appropriate test for group comparison was chosen according to scale level. ANOVA was used to compare continuous or metric variables, whereas Fisher exact test was used for categorical data. Risk ratios and 95% confidence intervals for occurrence of new cerebral infarction from DCI and poor functional outcome at 3 months in relation to experimental versus control treatment were calculated for different subgroups. A significant difference between groups was assumed when \(P<0.05\). Statistical Product and Service Solutions software version 15.0.1 (SPSS Inc, Chicago, IL) was used for computed analysis.

Results
A total of 60 patients meeting the inclusion criteria were recruited between May 2008 and May 2011 (Figure 2). Although there were no statistically significant differences with regards to patient baseline characteristics between the 2 groups, the absolute proportion of patients with WFNS grade IV and V patients was higher in the control group (Table 1). However, there were more patients with severe intraventricular hemorrhage in the experimental group (5 versus 1). Median time from SAH diagnosis on CT to rt-PA administration was 27:01 (interquartile range, 21:37–41:34; hours:minutes). There were no significant differences in the incidence of adverse or serious adverse events between the groups (Table 2). Nevertheless, patients in the experimental group had a higher incidence (4 versus 1 in control group; \(P=0.27\)) of subgaleal hematomas following rt-PA administration after surgical aneurysm repair, whereas the incidence of external ventricular drain tract hemorrhages did not differ (2 versus 1 in control group). Functional outcome, as measured by Glasgow Outcome Scale at discharge and after 3 months, was not different between patients allocated to the experimental or control group (Table 2). Clot clearance rate differed significantly for patients allocated to experimental treatment, as compared with the control treatment for cranial \((P<0.001)\) and cisternal measurements \((P<0.001;\) Figure 3). In detail, clot clearance rate (mean±SD in %) was 83.26±17.83 for cisternal and 47.63±25.9 for cranial measurements in the experimental group, as compared with 53.50±27.82 for cisternal and 25.86±18.81 for cranial measurements in the control group. However, there was no difference on the incidence of angiographic or PCT vasospasm between the 2 groups \((P=0.438\) and \(P=1.000,\) respectively). In addition, there was no difference between the groups with regards to aneurysm occlusion rates for the endovascularly treated aneurysms on follow-up catheter angiogram on day 7. Although the incidences of new cerebral infarction related to DCI and of rescue therapy were lower in the experimental group (9 versus 12 and 9 versus 13, respectively), these differences did not reach statistical
significance (P=0.589 and P=0.422, respectively). In general, the subgroup analysis did not reveal a significant benefit in favor of experimental treatment within the subgroups. However, there was a trend for WFNS grade II to IV patients in the experimental group to have better functional outcomes at 3 months (Figure 4). Finally, there was no difference on the incidence of posthemorrhagic hydrocephalus between the 2 treatment groups (Table 2).

Discussion

The main results of our study were that, despite a significant reduction of subarachnoid blood clot in patients allocated to experimental treatment, no significant difference in neurological outcome, incidence of new cerebral infarction, and radiographic vasospasm, as well as posthemorrhagic hydrocephalus between the 2 treatment groups was detectable in a cohort of patients experiencing severe SAH.

Our results differ from previous data on the beneficial effect of fibrinolysis has on neurological outcome for patients experiencing SAH. However, the majority of these studies also differed in design, as they compared experimental with no treatment for DCI, included mainly good grade SAH patients, or investigated exclusive cisternal and urokinase application. The relation of the type of fibrinolytic agent with outcome remains incompletely understood. Despite some animal studies reporting a neurotoxic effect for rt-PA

Table 2. Incidence of End Points for Patients Allocated to Experimental or Control Treatment

<table>
<thead>
<tr>
<th>End Point</th>
<th>Experimental Group (Percentage of Treatment Group)</th>
<th>Control Group (Percentage of Treatment Group)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiographic VSP</td>
<td></td>
<td></td>
<td>0.438</td>
</tr>
<tr>
<td>Moderate/severe</td>
<td>12 (40.0)</td>
<td>16 (57.1)</td>
<td></td>
</tr>
<tr>
<td>None/light</td>
<td>18 (60.0)</td>
<td>14 (43.8)</td>
<td></td>
</tr>
<tr>
<td>PCT VSP</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>13 (43.3)</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17 (56.7)</td>
<td>17 (56.7)</td>
<td></td>
</tr>
<tr>
<td>Rescue therapy</td>
<td></td>
<td></td>
<td>0.422</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (30.0)</td>
<td>13 (43.3)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (70.0)</td>
<td>17 (56.7)</td>
<td></td>
</tr>
<tr>
<td>New cerebral infarction</td>
<td></td>
<td></td>
<td>0.589</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (42.9)</td>
<td>12 (57.1)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (57.1)</td>
<td>18 (42.6)</td>
<td></td>
</tr>
<tr>
<td>GOS d/c total</td>
<td></td>
<td></td>
<td>0.389</td>
</tr>
<tr>
<td>Good</td>
<td>11 (36.7)</td>
<td>14 (46.7)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>17 (56.7)</td>
<td>12 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>2 (6.7)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>GOS 3 mo total</td>
<td></td>
<td></td>
<td>0.648</td>
</tr>
<tr>
<td>Good</td>
<td>18 (64.3)</td>
<td>14 (53.9)</td>
<td></td>
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<tr>
<td>Poor</td>
<td>10 (35.7)</td>
<td>11 (42.3)</td>
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<tr>
<td>Dead</td>
<td>0 (3.8)</td>
<td>1 (3.8)</td>
<td></td>
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<tr>
<td>Hydrocephalus</td>
<td></td>
<td></td>
<td>0.783</td>
</tr>
<tr>
<td>Yes</td>
<td>17 (56.7)</td>
<td>17 (56.7)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11 (36.7)</td>
<td>9 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventriculitis/meningitis</td>
<td>4 (13.3)</td>
<td>4 (13.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Yes</td>
<td>26 (86.6)</td>
<td>26 (86.6)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>6 (20.0)</td>
<td>2 (6.6)</td>
<td>0.127</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Recanalization indicates the incidence of recanalized aneurysms after coiling on standard catheter angiography on day 7 after SAH ictus.
and a neuroprotective effect for urokinase, to date there is no comparative clinical trial to support these data. 15-18,19 Interestingly, a more recent study also used cerebrospinal fluid biomarkers, such as interleukin 9 and matrix metalloproteinase 9 to monitor for such a detrimental tissue reaction or inflammation. 6 Although not established for SAH, reports on more rapid IVH wash out at higher rt-PA doses were our main impetus to administer higher rt-PA doses during a shorter period of time (4× 5 mg rt-PA >48 hours) because of the necessity of prolonged sedation for concomitant kinetic therapy. 20 However, despite heterogeneous data on the effectiveness and safety in this respect, other studies also suggested lower rt-PA doses until complete blood removal in CT. 17 Nevertheless, the present study is the first randomized trial investigating the effect of intraventricular rt-PA administration to allow the inclusion of patients undergoing either surgical or endovascular repair of ruptured intracranial aneurysm after severe SAH. Despite the higher proportion of conservatively managed subgaleal hematomas in the experimental group, this less invasive and more practical application resulted in safe and highly effective clot reduction, also without altering permanent occlusion of aneurysms.

The most plausible explanation to our findings is the higher proportion of poor grade SAH patients (2/3 with WFNS grade IV and V), as compared with those from similar studies. 3,5-7,21 Thus, the extent of primary brain injury in these patients might have outbalanced any beneficial effect resulting from therapeutic clot removal. 22,23 This is also underlined by our subgroup analysis. In addition, as fibrinolysis was not continued until complete radiological removal of blood clot on CT, remaining blood clots might have still yielded DCI and poor outcome. Remaining blood clots could also explain why the incidence of hydrocephalus was not lower in the experimental group. 17 Further, the deleterious effect of subarachnoid blood might have already unfolded at the time of rt-PA application (ie, ≥24 hours after SAH onset). This is underlined by studies investigating earlier (perioperative) rt-PA administration. 3,7 Finally, it remains unclear whether the higher dosage of rt-PA could have hypothetically been detrimental for outcome. However, this is not supported by data from studies using similar or higher cumulative rt-PA doses. 17

We acknowledge several limitations of our study design. Although not statistically significant, the absolute proportion of patients with WFNS grade IV and V was higher in

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**Figure 3.** A, Clot clearance rate (%) for cranial and (B) cisternal CT measurements within the experimental and control cohort (*P<0.001).
the control group. This is most likely a sample size problem. In addition, the majority of our patients experienced severe SAH, making them more prone to poor outcome per se. However, as our experimental treatment required the application of an external ventricular drain and prolonged sedation, we refrained from inclusion of good grade SAH patients because of an unfavorable risk–benefit ratio. Nevertheless, in addition to prolonged sedation, we cannot entirely exclude detrimental effects of our increased short-term rt-PA doses, as these patients did ultimately require a longer period of recovery. Furthermore, we did not analyze the effect of concomitant low-frequency head-motion therapy and intraventricular fibrinolysis compared with sole intraventricular fibrinolysis. This was based on a larger study reporting the beneficial effect of combined fibrinolysis and kinetic therapy on outcome. In addition, our study might have still been underpowered to show a beneficial effect of our experimental treatment on clinical outcome. In this respect, more recent studies suggest cerebral infarction as a more robust and comprehensive outcome measure to study effectiveness of experimental treatment on DCI and function outcome.

In summary, concomitant intraventricular fibrinolysis and kinetic therapy effectively reduced subarachnoid clot volume, but not the incidence of DCI and poor functional outcome in patients experiencing severe SAH. Future studies on intraventricular fibrinolysis for SAH should (1) include more patients, especially with less poor grade; (2) use lower doses of fibrinolytics until complete clot removal on serial imaging; and (3) investigate whether additional kinetic therapy is actually beneficial. In addition, the treatment safety and efficacy may also be monitored using biomarkers, such as interleukin 7 and matrix metalloproteinase 9.

Conclusions

In our cohort of patients with severe SAH, concomitant intraventricular fibrinolysis and kinetic therapy did not have a significant effect on radiographic vasospasm, cerebral infarction, or neurological outcome, despite effective subarachnoid clot reduction. Our results underline data on the strong association of early brain injury and functional outcome, but also warrant future efforts to investigate modified concepts for therapeutic intraventricular fibrinolysis for reduction of secondary brain injury in patients experiencing SAH.

Acknowledgments

We thank explicitly the nursing staff of the neurointensive care unit NI04 for their unrestrained support in the execution of this study.

Disclosures

Drs Etminan and Hänggi served temporarily as consultants for KCI (NY, USA) and are scientific advisors for Edge Therapeutics Inc. The other authors have no conflict to report.

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Prospective, Randomized, Open-Label Phase II Trial on Concomitant Intraventricular Fibrinolysis and Low-Frequency Rotation After Severe Subarachnoid Hemorrhage
Nima Etminan, Kerim Beseoglu, Sven Oliver Eicker, Bernd Turowski, Hans-Jakob Steiger and Daniel Hänggi

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