Sonothrombolysis With Transcranial Color-Coded Sonography and Recombinant Tissue-Type Plasminogen Activator in Acute Middle Cerebral Artery Main Stem Occlusion

Results From a Randomized Study

Jürgen Eggers, MD; Inke R. König, PhD; Björn Koch, MD; Götz Händler, MD; Günter Seidel, MD, PhD

Background and Purpose—Sonothrombolysis is a new treatment approach in acute ischemic stroke. The results of a monocenter, randomized clinical study are presented.

Methods—Subjects with acute middle cerebral artery main stem occlusion were randomized into a target group receiving 1-hour transcranial continuous insonation using a 1.8-MHz Doppler ultrasound (US) probe or a control group. All underwent standard thrombolysis with intravenous recombinant tissue-type plasminogen activator.

Results—Thirty-seven subjects were included; 19 subjects were treated in the target (US) group and 18 in the control (no-US) group, all with no residual flow in the middle cerebral artery main stem occlusion (Thrombolysis in Brain Ischemia recanalization grade 0). Compared with the no-US group, the US group showed greater improvement in National Institutes of Health Stroke Scale values at days 1 and 4 and a higher median Thrombolysis in Brain Ischemia grade 1 hour after recombinant tissue-type plasminogen activator initiation. Recanalization (complete or partial) after 1 hour occurred in 57.9% of the US group and 22.2% of the no-US group ($P=0.045$). After 90 days, 4 subjects from the US group had a modified Rankin Score $\leq 1$ (none from the no-US group) and 8 had a Barthel Index $\geq 95$ (none from the no US group; $P=0.106$ and $P=0.003$, respectively). Three subjects from the US group (15.8%) developed a symptomatic intracranial hemorrhage as did one (5.6%) in the no-US group ($P=0.60$).

Conclusions—This small randomized study indicates a beneficial impact of transcranial ultrasound on recanalization and short-term outcome in subjects with middle cerebral artery main stem occlusion and recombinant tissue-type plasminogen activator treatment. (Stroke. 2008;39:000-000.)

Key Words: acute ischemic stroke thrombolytic therapy transcranial ultrasound

Enhancement of thrombolysis by ultrasound (US) appears to be a promising area of research in treatment of subjects with acute ischemic stroke. A phase II multicenter, randomized clinical trial using transcranial Doppler for this purpose showed encouraging results in terms of safety and end point recanalization. Additional application of microbubbles during sonothrombolysis seems to increase the effect on recanalization without increasing the bleeding rate.

In our clinical study, we used an advanced US tool, transcranial color-coded sonography (TCCS), which allowed us to visualize the occluded intracranial vessel and place the sample volume of a pulsed wave Doppler US beam for spectral analysis on the site of occlusion. TCCS has been shown to be a valid instrument in evaluating the vascular state of patients with acute stroke.

We aimed to gather information about the effect of TCCS-guided 1.8-MHz pulsed wave US on recanalization and outcome of subjects who also underwent standard thrombolytic therapy with recombinant tissue-type plasminogen activator (rt-PA). Inclusion was restricted to subjects with acute occlusion of the main stem of the middle cerebral artery (MCA-M1). Preliminary results showed a tendency toward not only a faster rate of recanalization with US application, but also an increased rate of symptomatic intracranial hemorrhage (sICH).

Methods

Study Design
This randomized clinical study was approved by the local ethics committee of the University of Lübeck. Randomization by coin toss
by a person not involved in the subject’s examination and baseline measurements was performed after written informed consent was obtained from the subject or his or her legal representative. Subjects who met all of the inclusion criteria and none of the exclusion criteria (see subsequently) were individually randomized into a target group receiving US of the occluded MCA-M1 (US group) or a control group (no-US group). From the beginning to the end of rt-PA infusion, the degree of recanalization for both groups was determined by US every 20 minutes. The subjects’ clinical course was followed up during the first 4 days after stroke onset and again after 90 days with the clinical examiners blind to the US findings. Blinding the US examiners to the subjects’ clinical state was obviously not possible, but this was partly compensated by blinded offline analysis of the stored US data.

Subjects

Subjects were drawn from the Stroke Unit of the Department of Neurology at the University Hospital of Schleswig-Holstein, Campus Lübeck. Inclusion criteria were as follows: (1) ischemic stroke in the middle cerebral artery (MCA) territory proven by clinical syndrome and/or CT within 3 hours of symptom onset; (2) early ischemic changes one third or less of the MCA territory; (3) thrombolytic therapy in accordance with the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study protocol; (4) MCA-M1 occlusion diagnosed by TCCS; and (5) written informed consent given by the subject or his or her legal representative. Exclusion criteria were as follows: (1) age <18 years or ≥80 years; (2) pregnancy or lactation; (3) premorbid modified Rankin Scale (mRS) >1; and (4) insufficient acoustic window.

Cranial CT Examinations

On admission, every subject underwent a cranial CT scan. All CT scans were evaluated by an experienced neuroradiologist, who also assessed the extension of early ischemic changes before initiation of rt-PA. A control cranial CT scan was scheduled for 24±6 hours after the start of rt-PA infusion. Results of additional CT scans performed during the first 4 days after symptom onset were included in the data analysis, including retrospective analysis of intracerebral bleeding based on CT morphology.

Intervention

Subjects who met all inclusion and no exclusion criteria were treated intravenously with Alteplase (Actilyse; Boehringer Ingelheim, Germany) 0.9 mg/kg body weight for 1 hour with a 10% intravenously with Alteplase (Actilyse; Boehringer Ingelheim, Germany) 0.9 mg/kg body weight for 1 hour with a 10% intravenous bolus injection at the beginning of treatment.

Outcome Parameters

The subjects’ clinical course during hospitalization was assessed by using the National Institutes of Health Stroke Scale (NIHSS), mRS, and Barthel Index (BI). These data were obtained before and after the 1-hour session of US as well as 24±2 hours and 4 days±6 hours after symptom onset. In cases of intubation with artificial respiration precluding neurological examination, an unfavorable clinical course (NIHSS improvement of <4) was assumed. Although the clinical examiners were blind to the US findings, as previously noted, after 1 hour, they were no longer blind to subjects’ group assignment, because the assignment became obvious by that time. After 90±7 days, the mRS and BI were determined through a telephone interview conducted by a physician who was blind to the study conditions and had not been involved in treatment or examination of the subjects during their hospitalization.

Initial CT scans were performed before randomized group assignment. Follow-up control CT scans were scheduled for 24±6 hours after symptom onset and evaluated for the occurrence of sICH (defined as parenchymal bleeding on the CT scan accompanied by NIHSS deterioration of ≥4 points). Based on CT morphology, the CT data were also retrospectively analyzed according to the type of intracerebral hemorrhage.

Statistical Analysis

Outcome variables are described here using the median and interquartile distance and the mean and SD where appropriate as well as
absolute and relative frequencies for categorical variables. To explore the outcome in the target and control groups, the Mann–Whitney U test (ordinal variables), the Fisher exact test (binary nominal variables), and the Cochran Armitage trend test (ordered categorical variables) were calculated. The exploratory 2-sided probability values are shown in the “Results” section.

The following dependent variables were statistically tested. Outcome parameters defined before the initiation of the study are indicated by an asterisk.

Primary outcome parameters:

1. mRS after 90 days (dichotomized for mRS ≤1 versus ≥2)*;
2. BI after 90 days (dichotomized for BI <95 versus ≥95)*; and
3. Death from any cause during the 3 months of follow-up.*

Secondary outcome parameters:

1. TIBI grade of recanalization (ordinal score) after 1 hour*;
2. Recanalization, partial (TIBI 2 to 3) or complete (TIBI 4 to 5) after 1 hour;
3. Improvement on the NIHSS at days 1 and 4 after symptom onset (difference from baseline and dichotomized for improvement of ≥4 points versus <4 points)*; and
4. Intracranial hemorrhage, defined as sICH (worsening of ≥4 points on the NIHSS accompanied by hemorrhage).

Table 1. Baseline Characteristics of Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>US (n=19)</th>
<th>No-US (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), years</td>
<td>61.6 (9.5)</td>
<td>59.8 (9.3)</td>
</tr>
<tr>
<td>Sex, men/women, n (%)</td>
<td>15 (78.9%)/4 (21.1%)</td>
<td>14 (77.8%)/4 (22.2%)</td>
</tr>
<tr>
<td>Cardiac embolic source, n (%)</td>
<td>7 (36.8%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>8 (42.1%)</td>
<td>9 (52.9%)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>11 (57.9%)</td>
<td>9 (50%)</td>
</tr>
<tr>
<td>Blood pressure systolic/diastolic, mean (SD)</td>
<td>143 (26)/75 (15)</td>
<td>150 (34)/79 (14)</td>
</tr>
<tr>
<td>Serum glucose, mean (SD)</td>
<td>137 (49)</td>
<td>115 (18)</td>
</tr>
<tr>
<td>NIHSS baseline, median (IQR)</td>
<td>18 (6)</td>
<td>18 (5.5)</td>
</tr>
<tr>
<td>Premorbid mRS, median (IQR)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>mRS baseline, median (IQR)</td>
<td>5 (0)</td>
<td>5 (0)</td>
</tr>
<tr>
<td>Time to rt-PA, mean (SD) minutes</td>
<td>149 (16)</td>
<td>137 (24)</td>
</tr>
<tr>
<td>EIC, n (%)</td>
<td>13 (68.4%)</td>
<td>15 (83.3%)</td>
</tr>
</tbody>
</table>

Cardiac embolic source, according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria; serum glucose (mg/dL) and blood pressure (mm Hg) were measured before rt-PA; time to US, minutes from symptom onset until start of rt-PA infusion; EIC, early ischemic changes (one third or less of MCA territory) on CT admission scan.
Table 2. Binary Outcome Parameters

<table>
<thead>
<tr>
<th></th>
<th>US (n=19)</th>
<th>No-US (n=18)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization 1 hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIBI 2 to 5, n (%)</td>
<td>11 (57.9)</td>
<td>4 (22.2)</td>
<td>0.045</td>
</tr>
<tr>
<td>TIBI 2 to 3, n (%)</td>
<td>8 (42.1)</td>
<td>2 (11.1)</td>
<td>0.067</td>
</tr>
<tr>
<td>4 to 5, n (%)</td>
<td>3 (15.8)</td>
<td>2 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Recanalization 24 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIBI 2 to 5, n (%)</td>
<td>16 (88.9)*</td>
<td>14 (82.4)*</td>
<td>1.0</td>
</tr>
<tr>
<td>TIBI 2 to 3, n (%)</td>
<td>2 (11.1)</td>
<td>6 (35.3)</td>
<td>0.149</td>
</tr>
<tr>
<td>4 to 5, n (%)</td>
<td>14 (77.8)*</td>
<td>8 (47.1)*</td>
<td></td>
</tr>
<tr>
<td>NIHSS improvement ≥4</td>
<td>At day 1, n (%)</td>
<td>10 (55.6)*</td>
<td>0.176</td>
</tr>
<tr>
<td></td>
<td>At day 4, n (%)</td>
<td>9 (52.9)†</td>
<td>0.157</td>
</tr>
<tr>
<td></td>
<td>sICH, n (%)</td>
<td>3 (15.8)</td>
<td>0.604</td>
</tr>
<tr>
<td></td>
<td>PH 2, n (%)</td>
<td>4 (21.1)</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>mRS ≥1 at 90 days, n (%)</td>
<td>4 (21.1)</td>
<td>0.106</td>
</tr>
<tr>
<td></td>
<td>mRS ≥2 at 90 days, n (%)</td>
<td>5 (26.3)</td>
<td>0.182</td>
</tr>
<tr>
<td></td>
<td>BI ≥95 at 90 days, n (%)</td>
<td>8 (42.1)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Death at 90 days, n (%)</td>
<td>3 (15.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*One subject lost to follow-up.
†Two subjects lost to follow-up.

P value, Fisher exact test; recanalization, 1 hour after start of rt-PA infusion and 24 hours after symptom onset (TIBI 2 to 5).

Results

Subjects

A total of 42 consecutive subjects met the inclusion criteria; 4 subjects (9.5%) were excluded because of an insufficient acoustic window that required an US contrast agent to detect the MCA-M1 occlusion. One subject was excluded because relatives did not provide informed consent (see supplemental Figure 1, available online at http://stroke.ahajournals.org). Of the 37 subjects included in this study, 19 (79% men, 21% women) were randomly assigned to the US group and 18 (78% men, 22% women) to the control (no-US) group. Baseline characteristics showed no differences between the US and control groups (Table 1). During the 1-hour rt-PA infusion sessions, acquisition of the US data was completed for all subjects. Two subjects (one from each group) were unavailable for TCCS examination 24 hours after symptom onset, because they had been referred to the neurosurgical department. Thirty-six subjects or their relatives were interviewed 90 days after symptom onset; one subject was lost to follow-up.

Recanalization

The ordinal TIBI values showed faster recanalization in the US group starting after 20 minutes. The TIBI results by group are presented here in the format of US versus no-US: median (interquartile range [IQR]); 2-sided exploratory probability value (Mann–Whitney U test) after 20 minutes 1 (2) versus 0 (0), P=0.003; after 40 minutes 1 (2.0) versus 0 (0), P=0.008; after 60 minutes 2 (3) versus 0 (2), P=0.013; after 24 hours (one subject from each group was lost to US follow-up after 24 hours) 5 (2) versus 3 (4), P=0.66. Recanalization (partial or complete, TIBI 2 to 5) versus no recanalization (TIBI 0 to 1) after 1 hour occurred more frequently in the US group (57.9% versus 22.2%; see Figure 1 and Table 2). When the data were categorized by degree of recanalization (no recanalization, TIBI 0 to 1; partial recanalization, TIBI 2 to 3; and complete recanalization, TIBI 4 to 5), the results after 1 hour showed only a tendency for better restitution of flow in the US group (2-sided exploratory P=0.067, Fisher exact test). Data collected 24 hours after symptom onset revealed no differences (see Table 2). No correlation was shown between prethrombolysis serum glucose level and subsequent recanalization. No reclosures occurred during the 1-hour monitoring periods. Two subjects showed a decline of one TIBI grade from the measurement at 1 hour to the follow-up measurement after 24 hours; one from TIBI 1 to 0 and the other from TIBI 2 to 1 with both being from the US group.

Tandem occlusions of the MCA and internal carotid artery were equally distributed between the groups (6 in each group).

Clinical Course During the First 4 Days

The following subjects were unavailable for clinical examination at 1 and/or 4 days after symptom onset for the following reasons. Of the 37 subjects, one (2.7%) from the US group had died on day 1 of space-occupying brain infarction and sICH. An additional 3 subjects (8.1%, one from the US group and 2 from the no-US group) were unavailable for examination at day 4; of these, one from the US group and one from the no-US group had died of space-occupying infarction and sICH; and one subject from the no-US group could not be examined due to intubation after craniotomy for treatment of space-occupying infarction. Craniotomy was performed in one subject from the US group due to space-occupying infarction in combination with sICH and in one subject from the no-US group due to space-occupying infarction alone. The subject from the no-US group could not be examined at day 4 due to intubation. Both subjects were alive at follow-up after 90 days.

The number of subjects from the US group with NIHSS improvement of ≥4 points at days 1 and 4 was approximately twice as many as that in the no-US group (see Table 2). One subject from the US group (5.6%) worsened ≥4 points on the NIHSS at day 1 and 2 subjects at day 4 (one from each group, 5.9% and 6.3%, respectively, 2-sided exploratory P=1.0 for days 1 and 4, Fisher exact test).

Compared with baseline, at day 1, the NIHSS values improved more strongly in the US group (n=18) than in the no-US group (n=18): median 10.5, IQR 12.5 versus median 15.5, IQR 7.0 (exploratory 2-sided P=0.047, Mann–Whitney U test). Also at day 4, the NIHSS values had improved more strongly in the US group (n=17) compared with the no-US group (n=16): median 14, IQR 14.0 versus median 17.5, IQR 9.5 (exploratory 2-sided P=0.025; see Figure 2).

Outcome After 90 Days

Four subjects from the US group showed a favorable outcome (defined as mRS ≤1) after 90 days compared with none from
the no-US group (2-sided exploratory \(P=0.106\), Fisher exact test; see Table 2). The median of the ordinal mRS values after 90 days was 3.0 (IQR 3.0) in the US group and 4.00 (IQR 1.0) in the no-US group (2-sided exploratory \(P=0.232\), Mann–Whitney \(U\) test). Grading based on the mRS (0 to 1, 2 to 3, 4 to 5, and 6, as in the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study)\(^1\) revealed a tendency toward less severe disability in the US group after 90 days (exact 2-sided exploratory \(P=0.126\), Cochrane Armitage trend test). For reaching a 90-day mRS of 0 to 1 rather than 2 to 3, 4 to 5, or death, respectively, the ORs (95% CI) in the US compared with the no-US group were 1.93 (0.81 to 5.30), 3.73 (0.65 to 28.06), and 7.20 (0.53 to 148.61, Cochrane Armitage trend test; see Figure 3).

Eight subjects from the US group but none from the no-US group showed a BI \(\geq 95\) (2-sided exploratory \(P=0.003\), Fisher exact test; see Table 2).

Death of any cause had occurred by the 90-day follow-up in 3 subjects from the US group and in 2 subjects from the no-US group (2-sided exploratory \(P=1.0\), Fisher exact test; see Table 2).

**Neuroradiological Findings**

According to the study protocol, all subjects had a cranial CT scan at admission and a follow-up control cranial CT scan, which was scheduled 24±6 hours after symptom onset. Three cases of sICH occurred in the US group and one case in the no-US group (2-sided exploratory \(P=0.604\), 2-sided Fisher exact test). Three subjects who had sICH showed early ischemic changes at baseline (2 from the US group and one from the no-US group); one sICH occurred in a subject without early ischemic changes at baseline (from the US group; \(P=1.0\), Fisher exact test).

Asymptomatic hemorrhages, defined as parenchymal hemorrhages without NIHSS deterioration of \(\geq 4\) points, occurred in 4 subjects from the US group and 2 from the no-US group (2-sided exploratory \(P=0.660\), 2-sided Fisher exact test). The CT data were also retrospectively analyzed in terms of the type of intracerebral hemorrhage based on CT morphology\(^1\) by an experienced neuroradiologist who was blind to the treatment group and the results of the study (see Figure 4).

Data were available from all 37 follow-up CT scans. Analogous to the results of the clinical grading in symptomatic and asymptomatic hemorrhages, there was a tendency toward more severe hemorrhagic transformations, including parenchymal hematoma (PH) 1 or PH 2, in the US group (see Figure 4). A PH 2 was found in 4 subjects from the US group and in one from the no-US group (exploratory \(P=0.340\), 2-sided Fisher exact test, OR = 4.53 [0.38 to 236.10]). In total, the number of any kind of hemorrhagic transformation (hemorrhagic infarction [HI] 1 or 2, PH 1 or 2) did not differ between the 2 groups: 8 of 19 (42.2%) in the US group versus 8 of 18 (44.4%) in the no-US group (2-sided exploratory \(P=1.0\), Fisher exact test; OR = 1.40, CI 0.14 to 18.87; see Figure 4).

No hemorrhages were found outside the infarction area.

**Discussion**

This small, randomized clinical study examines a highly selected sample of subjects with complete proximal MCA-M1 occlusions. The results show the efficacy of TCCS-guided 1.8-MHz transcranial US in recanalization and short-term clinical improvement. No differences were seen for the primary outcome parameter mRS \(\leq 1\) as well as for deaths by 90 days. Favorable functional outcome defined as BI \(\geq 95\) was more frequent in the target group. Although the BI is less valuable for measuring outcome after stroke than the mRS, this finding supports the assumption that sonothrombolysis may also have an impact on outcome after 3 months.

A greater independent sample size is required to test whether the tendency for a higher frequency of sICH and a higher number of favorable outcomes in the target group can be proven to be an effect of the US treatment.

The tendency toward an increased rate of intracerebral hemorrhage as a consequence of using TCCS for sonothrombolysis might be a result of reperfusion trauma after accelerated recanalization or an effect of the US itself.

The restriction on MCA-M1 occlusions (TIBI 0) led to a more homogenous, albeit more severely affected, sample of subjects. As shown by Labiche et al,\(^7\) even a residual flow (TIBI 1) predicts a better outcome than absent flow (TIBI 0). In the present study, we were able to assess the effect of sononation on recanalization along the whole TIBI scale from 0 to 5.

This study had several limitations. When the study was launched, no data on efficacy and safety of transcranial sononation in patients receiving thrombolysis were available, and our sample size was undefined before starting. As we now know, choosing the primary end point of mRS \(\leq 1\) made this study underpowered. Also, we did not expect an increased bleeding rate in the target group. The study was stopped by the investigators, because inclusion frequency was very low and because the strong tendency toward an increased sICH rate in the target group was confirmed by the analysis based on CT morphology. That decision was also influenced by the data of the TRUMBI study,\(^18\) which showed an increased bleeding rate. Future studies using TCCS for sonothrombolysis should select safety and recanalization as more suitable primary end points.

Because the control group did not receive sham sononation, the subjects were not blind to their group assignment; however, because we only included subjects with proximal MCA occlusions, most of them were too severely affected to be aware of their group assignment. Although the US examiners could not be blind to the subjects’ clinical course, we tried to compensate in part by performing the analysis of the recanalization data offline.

The mechanism of enhancing thrombolysis by transcranial US is not known,\(^19\) and an in vitro study could not show the effect of transcranially applied US using a 1.8-MHz commercial probe.\(^20\) However, the effect of transcranially applied US emitted by a 1-MHz commercial probe has been shown in vitro,\(^3\) and several clinical investigators have independently found such an effect as well.\(^6,12,21,22\) The additive effects of US on the endothelium could also contribute to the observed clinical results.\(^23\)

In conclusion, transcranial 1.8-MHz pulsed wave US in combination with rt-PA accelerates recanalization in acute
MCA-M1 occlusion. This finding might be associated with an elevated rate of intracerebral hemorrhage. These results, as well as the impact of this adjunct treatment on clinical outcome after 90 days, need to be confirmed in further randomized clinical studies.

Disclosures

None.

References

CONSORT Flow Chart

Assessed for eligibility
n = 3156

Excluded n = 3114
• not meeting inclusion criteria n = 3109
• refusal to participate n = 1
• insufficient acoustic window n = 4

Randomized
n = 37

Allocated to target group (rt-PA+US) n = 19
• Received allocated intervention n = 19
• Did not receive allocated intervention n = 0

Allocated to control group (rt-PA) n = 18
• Received allocated intervention n = 18
• Did not receive allocated intervention n = 0

Lost to follow up (mRS or death after 90 days) n = 0
• Discontinue intervention n = 0

Lost to follow up (mRS or death after 90 days) n = 1
• Discontinue intervention n = 0

Analyzed
n = 19
n = 17

Figure I. CONSORT flow chart.
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