Evaluation of the recombinant tissue plasminogen activator pretreatment in acute stroke patients with large vessel occlusions treated with the direct bridging approach. Is it worth the effort?

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Background and purpose: The direct bridging concept in acute stroke treatment combines intravenous thrombolysis (IVT) and endovascular treatment (EVT). The frequency and extent of reperfusion obtained already due to IVT were evaluated. Additionally undesired events and the clinical outcome were analysed.

Methods: Fifty-seven acute stroke patients treated with direct bridging were analysed for this study. The response to IVT was evaluated according to the modified Thrombolysis in Cerebral Infarction scale (m-TICI). IVT responders (m-TICI ≥2B in digital subtraction angiography) were compared with IVT non-responders (m-TICI <2B in digital subtraction angiography) with respect to clinical outcome and occurrence of undesired events.

Results: Fourteen patients (25%) got a change from TICI 0 to ≥2B due to IVT alone. There were otherwise no differences between the IVT responders and IVT non-responders.

Conclusions: Intravenous thrombolysis pretreatment in the context of the bridging approach contributes substantially to revascularization.

Introduction

The introduction of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) as a therapeutic option in the treatment of acute stroke in 1995 [1] led to a paradigm shift: for the first time the cause of the disease, the occluding clot, could be treated. Since then, IVT has established itself as the gold standard treatment of acute ischaemic stroke [2]. Although widely used, IVT has its limitations due to a narrow therapeutic window, a variety of contraindications and reduced efficacy in stroke caused by large vessel occlusions [3]. Endovascular treatment (EVT) with mechanical thrombectomy and intra-arterial thrombolysis has gained increasing attention as a therapeutic option to compensate for these limitations. Multiple papers reporting encouraging results with EVT have appeared within the past few years [4–10]. EVT can be performed either as a stand-alone treatment or in combination with IVT (bridging). The bridging concept, where IVT is given as an adjunct to EVT, has been proved to be safe in multiple trials [11–13]. In most of these trials EVT is held off until the clinical response of IVT can be assessed. In cases where no clinical improvement was seen, the treatment continued with EVT (‘rescue bridging’). Yet, this so-called rescue bridging can lead to a delay of around 60 min before EVT is started up, the time needed for rtPA infusion and subsequent patient evaluation. Since early reperfusion is crucial for a good outcome [12,13] some groups advocate continuing with EVT after IVT without waiting for a clinical response (‘direct bridging’) – the aim being to reduce time to reperfusion in cases where EVT becomes necessary. However, in the majority of tri-
als reporting on direct bridging no information about the efficacy of the initial rtPA treatment is provided [11–16]. In order to evaluate the efficacy of rtPA pretreatment in acute stroke caused by large vessel occlusions all stroke patients assigned to the direct bridging approach at the Stavanger University Hospital were retrospectively analysed. Our primary goal was to estimate the frequency and extent of revascularization already obtained due to IVT treatment. Additionally the frequency of intracerebral bleeding complications, the occurrence of undesired events and the clinical outcome were compared with previous reports.

Materials and methods

A continuous series of prospectively collected patients treated with the bridging approach between May 2009 and January 2013 were retrospectively analysed for this study. All patients arrived at the hospital within 4.5 h of symptom onset. At admission, every patient was examined with unenhanced computed tomography (CT), computed tomographic angiography (CTA) and perfusion computed tomography. An occlusion proximal to the M2 segment of the middle cerebral artery or the P2 segment of the posterior cerebral artery on CTA was considered an indication for EVT. Intracranial haemorrhage (ICH) or distinct demarcation of an infarction greater than one-third of the middle cerebral artery vessel territory on CT were considered contraindications for EVT. Perfusion computed tomography was used as an adjunct to CT and CTA in the decision making process for patient selection. In the absence of contraindications, an intravenous infusion of rtPA (Actilyse, Boehringer Ingelheim, Ingelheim, Germany) (0.9 mg/kg, maximum dose 90 mg) was started immediately after CT. The IVT infusion was continued during the EVT procedure until the full dose of rtPA was reached.

Endovascular procedures

The transfemoral approach was used for the endovascular intervention. If digital subtraction angiography (DSA) showed that the culprit occlusion had resolved, the procedure was aborted. In all other cases endovascular revascularization was attempted. Five patients were treated with IVT and intra-arterial thrombolysis, the remainder with IVT and mechanical thrombectomy. The Penumbra System (Penumbra Inc., Alameda, CA, USA) was initially used for thrombectomy; later the Solitaire FR Revascularization Device (ev3 Neurovascular, Irvine, CA, USA) became the device of first choice. The access site in the groin was in all cases closed directly after the procedure using the FemoSeal (St Jude Medical, Inc., Saint Paul, MN, USA) vascular closure device.

Efficacy evaluation

Efficacy of the treatment was determined by grading flow in the territory of the treated artery by the modified Thrombolysis in Cerebral Infarction scale (m-TICI) [17]. Successful reperfusion was defined by angiographic demonstration of m-TICI 2B or m-TICI 3.

Post-procedure imaging

Unenhanced CT or magnetic resonance imaging (MRI) was performed within 24 h of EVT. MRI scans included a diffusion weighted series and magnetic resonance angiography of the intracranial arteries in time of flight technique. The patients underwent additional imaging if deemed necessary due to unexpected changes in clinical status.

Safety evaluation

The presence of ICH on post-procedure CT or MR scans was recorded. ICH and symptomatic intracranial haemorrhage (sICH) were classified as in the European Cooperative Acute Stroke Study II (ECASS II) [18]. Data were also collected on all complications that could be attributed to EVT.

Clinical evaluation

Neurological deficit was graded on admission, on the first day after intervention and at discharge using the National Institutes of Health Stroke Scale (NIHSS) [19]. Functional status was assessed at 3 months according to the modified Rankin Scale (mRS) [20]. Good clinical outcome was defined as mRS of 2 or less.

Radiological evaluation of IVT response

The initial CTA was compared with the preliminary diagnostic cerebral angiograms (DSA) (front and side views). Reopening was graded according to the modified TICI classification. A minor thrombolytic effect was defined as a remaining TICI 0 perfusion and a minimum 5 mm distal shift in the proximal part of the thrombus. The angiograms were interpreted independently by an experienced neuroradiologist and an experienced interventional radiologist.
Time interval data
All relevant time points were recorded in the hospital files and the time intervals were calculated accordingly.

Statistical analysis
All statistical analyses were performed using SPSS Statistics version 21 (IBM Corporation, Armonk, NY, USA). Baseline variables and variable changes were examined using one-way analysis of variance (ANOVA) and Pearson’s chi-squared test as appropriate.

Ethics
Before treatment, informed consent was obtained from either the patient or their legal representative. This study was approved by the regional ethics committee.

Results
Fifty-seven patients received IVT with the intention of progressing to EVT. After the preliminary DSA was obtained, EVT was aborted in 10 of these patients (18%). In nine of them IVT led to complete recanalization (16%) and in one patient a change from a proximal to a distal M1 occlusion was misinterpreted as a complete reperfusion. Forty-seven patients (82%) proceeded further to EVT.

The demographic data of all patients, subdivided into two groups according to IVT response, are shown in Table 1. There were no statistically significant differences comparing baseline demographic variables or incidence of cerebrovascular risk factors between the groups.

Radiological IVT response evaluation
Between CTA and DSA in 14 patients (25%) a change from TICI 0 to ≥2B could be seen and in nine of them (16%) no additional treatment was needed. In five patients (9%) DSA showed remaining central thrombotic material; these patients proceeded further to EVT to prevent early reocclusion. The sites of the occlusions are shown in Table 2.

In the IVT non-responders one patient improved between CTA and DSA to a TICI 1 score. In another eight patients (14%) a minor thrombolytic effect without a change in the TICI score was found. This minor thrombolytic effect was not associated with a shorter intervention time ($P = 0.41$) or a better clinical outcome ($P = 0.68$).

Safety evaluation
Twenty-four hours after treatment ICH was found in 24 patients (42%) (Table 3): 10 patients (17%) had a mild ICH (H1, H2) or local subarachnoid haemorrhage, 14 patients (25%) had a severe ICH (PH1, PH2 or severe subarachnoid haemorrhage) of whom six patients (11%) had an sICH. There was no sICH in the group of patients treated with IVT alone whilst one IVT responder proceeding with EVT developed an sICH.

The patients not recanalised experienced a higher number of ICH [7 (50%) vs. 17 (39.5%), $P = 0.49$] and more severe ICH [6 (43%) vs. 8 (19%), $P = 0.067$] compared with the recanalised patients.

Intra-procedural complications occurred in four patients in the IVT non-responder group. One patient got a severe subarachnoid haemorrhage and died the first post-procedural day. Two patients got an embolization to the anterior cerebral artery territory as the solitaire stent was retrieved. One patient got an iatro-

| Table 1 Demographic and baseline features of the patients |
|---------------------------------|----------------|----------------|----------------|
| IVT responders | IVT non-responders | $P$ value |
| Patients | 14 | 43 | |
| Median age (years) | 77.5 ± 15.3 | 70.0 ± 13.1 | 0.34 |
| >80 years | 6 (42.9) | 10 (23.3) | 0.16 |
| Male | 8 (57.1) | 26 (60.5) | 0.83 |
| Mean NIHSS at admission | 17.6 ± 5.5 | 18.0 ± 5.3*2 | 0.81 |
| Previous coronary heart disease | 2 (14.3) | 3 (7.0) | 0.40 |
| Previous cerebral stroke | 3 (21.4) | 6 (14) | 0.51 |
| Arterial hypertension | 8 (57.1) | 28 (65.1) | 0.59 |
| Diabetes | 3 (21.4) | 6 (14.0) | 0.51 |
| Atrial fibrillation | 2 (14.3) | 18 (41.9) | 0.06 |

IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale. Values represent number of patients (%), ±SD. *Number missing.

| Table 2 Site of arterial occlusion |
|---------------------------------|----------------|----------------|
| MCA segment M1 | 13 (92.9) | 24 (55.8) |
| MCA + ICA tandem | 0 | 7 (16.3) |
| Carotid T | 0 | 4 (9.3) |
| ICA alone | 1 (7.1) | 1 (2.3) |
| Basilar artery | 0 | 7 (16.3) |
| Total (%) | 14 (100) | 43 (100) |

IVT, intravenous thrombolysis; MCA, middle cerebral artery; ICA, internal carotid artery. Values represent number of patients (%).
Table 3 Clinical and radiological outcome

<table>
<thead>
<tr>
<th></th>
<th>IVT responders</th>
<th>IVT non-responders</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>14</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Mean NIHSS after treatment</td>
<td>11.9 ± 6.3*2</td>
<td>11.9 ± 8.4*4</td>
<td>0.99</td>
</tr>
<tr>
<td>Mean NIHSS change pre/post treatment</td>
<td>6.6 ± 7.4*2</td>
<td>5.9 ± 8.2*4</td>
<td>0.8</td>
</tr>
<tr>
<td>Confirmed TICI ≥2B after treatment</td>
<td>14 (100)</td>
<td>29 (67.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>Per-procedure complications</td>
<td>0</td>
<td>4 (9.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Intracranial haemorrhage in total</td>
<td>6 (42.9)</td>
<td>18 (41.9)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mild (HI1, HI2 or local SAH)</td>
<td>4 (28.6)</td>
<td>6 (14.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>Severe (PH1, PH2 or severe SAH)</td>
<td>2 (14.3)</td>
<td>12 (27.9)</td>
<td>0.30</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1 (7.1)</td>
<td>5 (11.6)</td>
<td>0.64</td>
</tr>
<tr>
<td>mRS ≤ 2 at 90 days</td>
<td>7 (50.0)</td>
<td>18 (41.9)</td>
<td>0.59</td>
</tr>
<tr>
<td>Mortality at 90 days</td>
<td>3 (21.4)</td>
<td>12 (27.9)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

IVT, intravenous thrombolysis; NIHSS, National Institutes of Health Stroke Scale; TICI, Thrombolysis in Cerebral Infarction scale; HI, haemorrhagic infarction; SAH, subarachnoid haemorrhage; PH, parenchymal haemorrhage; ICH, intracranial haemorrhage; mRS, modified Rankin Scale. Values represent numbers of patients (%), ±SD.

*Number of missing data.

In this study it was found that rtPA pretreatment in patients with acute stroke caused by large vessel occlusions reopened the previously occluded vessel in 25% of all cases and rendered EVT superfluous in 16% of the patients. The desired clinical goal was achieved without exposing them to the inherent risks of EVT. None of the patients who received IVT alone developed sICH or exhibited complications as a result of DSA imaging.

In acute stroke patients with large vessel occlusions, the reperfusion rate due to IVT alone is reported to be limited to 4.4%–5.9% at the terminal internal carotid artery and around 30% at the proximal middle cerebral artery M1 segment [3,21]. In total 14 of our patients (25%) achieved a reopening of the target vessel (from TICI 0 to ≥2B) due to IVT alone; in nine patients the reperfusion was complete and in five patients remaining central thrombotic material led to EVT. These IVT reperfusion figures appear to be in line with the results reported in IVT trials [3,21], yet they are significantly higher than the 5.6% reported in the only direct bridging trial reporting these data [22].

Most IVT alone reperusions will occur within 1 h after IVT initiation, and reperfusion after 1 h is reported to be rare [23]. Although focusing on rapid initiation of EVT, the time from IVT to groin puncture was in our study a mean of 1 h 15 min after IVT; at
this point in time practically all reperfusions due to IVT alone should have been achieved. An IVT to EVT time range from 0:42 to 2:02 is reported in direct bridging trials reporting these data [11, 12, 15, 16, 24].

Besides complete early recanalization in some cases, a further advantage of IVT pretreatment in the context of the bridging approach could be the interaction of rtPA with the occluding thrombus. This can be attributed either to the achievement of partial recanalization or to helping to facilitate mechanical thrombectomy in the EVT procedure. The EMS Bridging Trial [24] indicated a positive interaction between the IVT pretreatment and the subsequent intra-arterial thrombolysis. In our cohort, in addition to the nine patients exhibiting complete reperfusion and the five patients with a TICI score ≥2B proceeding to EVT, another eight patients demonstrated a minor thrombolytic effect without a change in the TICI score. In comparison, only one of 22 patients directly treated with EVT (not admitted to the bridging approach) showed a comparable minor change in the thrombus location (data not shown). However, the clot formation change seen in our patients had no correlation to improved clinical outcome (P = 0.73) or shortened intervention time (P = 0.43) compared with the patients without signs of any thrombus effect. Yet, as our sample size is too small to draw conclusions, future studies are warranted to investigate this possibility.

Whilst none of the patients treated with IVT alone developed sICH or exhibited intra-procedural complications, one patient in the IVT responder group treated with EVT developed an sICH. In the IVT non-responders the incidences of sICH and intra-arterial complications were 12% and 9%, respectively. These figures are in line with the literature [5, 15, 24]. The safety of IVT pretreatment is to be expected and has been shown in earlier studies [11–13]. The lack of sICH in the group treated with IVT alone is probably influenced by the earlier reperfusion in these cases and the absence of mechanical manipulation in intracranial vessels. Because of the low number of patients this result should be interpreted with caution.

Four patients (7%) treated with EVT got a severe per-procedure complication. The number of reported per-procedure complications varies between 0% and 7% and seems to some extent to be related to the device used [25]. Embolization to new territory found in two of our patients (3.5%) seems to be more frequent with the use of stent retrievers [6, 8, 9]. In the TREVO 2 trial [9] 7% of the patients experienced embolization to new territory.

Compared with EVT alone the bridging concept has the advantage that an earlier treatment due to IVT is provided. An invaluable advantage of the direct bridging concept is that those patients not responding sufficiently to IVT proceed to EVT without delay. Most patients treated by the ‘rescue bridging’ approach will experience a substantial additional time delay of at least 60 min. This time delay reduces the likelihood of a good outcome by about 20% [12, 13].

In total 25 patients (43%) had a good clinical outcome (mRS ≤ 2) at the 3 months follow-up, which is in line with a recent published review and a meta-analysis encompassing 15 studies [26]. There was no statistical difference in outcome comparing IVT responders with IVT non-responders or patients only treated with IVT with patients treated additionally with EVT. The incapability of demonstrating a better clinical outcome in patients with recanalization already due to IVT may be influenced by the somewhat higher age and comorbidity in this patient group (Table 1).

Fifteen patients (26%) died within 90 days after receiving treatment and there was no difference between IVT responders and non-responders (P = 0.63). This number is higher than the 17.9% reported in a meta-analysis [26], yet lower than the 32% of a comparable series of patients [27]. As age is one of the most important predictors for mortality [28], the high mean age in our patient sample with a high number of octogenarians (28%) may be an important contributor to the higher mortality rate compared with the meta-analysis.

The retrospective nature of our study and the relatively low number of patients included are limitations. Yet, the efficacy and safety of the IVT pretreatment can be unequivocally demonstrated and it is hoped that our study will stimulate similar investigations of the direct bridging approach.

In summary, it is shown that IVT pretreatment in the context of the direct bridging approach is safe and leads to a considerable number of early revascularizations in acute stroke caused by large vessel occlusions. Additionally, compared with rescue bridging, direct bridging saves time in cases of IVT failure. Thus it is concluded that this approach is most definitely worth the effort. It is advocated that more studies state the numbers of revascularizations due to IVT alone as these numbers seem to be under-reported and underrated in studies using the direct bridging concept.

**Acknowledgement**

None.

**Disclosure of conflicts of interest**

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References


