Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke
A Meta-Analysis of Individual Patient Data

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Background and Purpose—The safety and efficacy of thrombolysis in cervical artery dissection (CAD) are controversial. The aim of this meta-analysis was to pool all individual patient data and provide a valid estimate of safety and outcome of thrombolysis in CAD.

Methods—We performed a systematic literature search on intravenous and intra-arterial thrombolysis in CAD. We calculated the rates of pooled symptomatic intracranial hemorrhage and mortality and indirectly compared them with matched controls from the Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register. We applied multivariate regression models to identify predictors of excellent (modified Rankin Scale=0 to 1) and favorable (modified Rankin Scale=0 to 2) outcome.

Results—We obtained individual patient data of 180 patients from 14 retrospective series and 22 case reports. Patients were predominantly female (68%), with a mean±SD age of 46±11 years. Most patients presented with severe stroke (median National Institutes of Health Stroke Scale score=16). Treatment was intravenous thrombolysis in 67% and intra-arterial thrombolysis in 33%. Median follow-up was 3 months. The pooled symptomatic intracranial hemorrhage rate was 3.1% (95% CI, 1.3 to 7.2). Overall mortality was 8.1% (95% CI, 4.9 to 13.2), and 41.0% (95% CI, 31.4 to 51.4) had an excellent outcome. Stroke severity was a strong predictor of outcome. Overlapping confidence intervals of end points indicated no relevant differences with matched controls from the Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register.

Conclusions—Safety and outcome of thrombolysis in patients with CAD-related stroke appear similar to those for stroke from all causes. Based on our findings, thrombolysis should not be withheld in patients with CAD. (Stroke. 2011;42:2515-2520.)

Key Words: carotid artery ■ cerebral infarct ■ dissection ■ outcome ■ thrombolysis ■ safety

Approximately 2% of all ischemic strokes are caused by cervical artery dissection (CAD). In patients <50 years of age, CAD accounts for 10% to 25% of all ischemic strokes.1,2 CAD is characterized by the presence of an intramural hematoma due to an intimal tear in the carotid or vertebral artery wall. Subsequent ischemic stroke is believed to be caused by thromboembolism in most cases rather than by hemodynamic factors.3 Randomized controlled trials to investigate thrombolysis in acute ischemic stroke did not exclude patients with CAD.4 However, safety and efficacy have not been investigated for this particular group in these randomized controlled trials. Therefore, it remains unknown whether thrombolysis can be given in acute ischemic stroke attributable to CAD.

The most serious complication of thrombolysis is symptomatic intracranial hemorrhage (SICH), which occurs in 2% to 9%.4 In patients with CAD, an additional concern is the risk of enlargement of the intramural hematoma. Small retrospective case series suggested that thrombolysis in CAD patients is safe.5,6 The aim of the current meta-analysis was to...
pool all available case reports and series using individual patient data (IPD) and thus provide a valid estimate of safety and outcome of thrombolysis in patients with CAD-related stroke. In addition, predictors of outcome after thrombolysis in CAD patients were evaluated.

Methods

Study Selection

We systematically searched the PubMed and EMBASE database up to March 2010 for publications on thrombolysis in patients with CAD-related ischemic stroke by using the following combination of variables: “[dissection]” AND “[carotid” or “vertebral” or “cervical” or “extracranial” or “stroke” or “brain ischemia” or “brain infarction”] AND [“thrombolysis” or “recombinant tissue plasminogen activator” or “rTPA” or “tissue plasminogen activator” or “tPA” or “urokinase” or “pro-urokinase”]. In addition, we searched for relevant studies in the Cochrane Library and Cochrane Central Register of Controlled Trials and hand-searched citations from the retrieved studies. Finally, experts in the field were consulted.

We included studies that investigated thrombolysis in patients with CAD-related stroke, either as the main focus of research or as a subgroup analysis. Because the number of publications on this topic is scarce, we did not set a minimum to the number of patients per study. We included publications written in English, German, French, and other languages if an abstract in English, German, or French was available. Patients with a dissection limited to the intracranial part of the vessel(s) only or with an aortic dissection extending into the cervical arteries were excluded. The diagnosis of CAD needed to be confirmed with appropriate imaging tests: color duplex sonography, computed tomography angiography, magnetic resonance angiography, or conventional angiography. Confirmation of the dissection before or after thrombolysis was allowed. Because most studies did not systematically assess the degree of both extracranial and intracranial stenosis before and after treatment, recanalization was not included in our analysis. We analyzed 2 treatment groups: intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT). IAT was defined as treatment with IAT only, IVT followed by IAT, or IAT in combination with any endovascular procedure, such as mechanical thrombectomy or stent placement. Thrombolytic therapy had to be administered within 24 hours after stroke symptom onset. The subgroups of patients treated within 3 hours and within 4.5 hours were analyzed separately.

Data Extraction

We collected the following baseline characteristics: sex, age, preceding trauma, stroke severity at presentation as assessed on the National Institutes of Health Stroke Scale (NIHSS), location of the dissected artery (carotid or vertebral), vessel occlusion before treatment, intracranial extension, time from symptom onset to treatment, treatment type (IVT or IAT), and duration of follow-up.

As safety variables, we analyzed SICH, mortality, and recurrent stroke. For the present study, we defined SICH as any intracranial bleeding documented on computed tomography or magnetic resonance imaging that was temporally related to deterioration in the patients’ clinical condition. In the included studies, different definitions were used for clinical deterioration. Additional adverse events as reported by the authors were collected and described. We assessed functional outcome by means of the level of dependency at follow-up. Excellent functional outcome was defined as 0 to 1 on the modified Rankin Scale (mRS), and favorable functional outcome, as an mRS score of 0 to 2. Finally, we performed a subgroup analysis to investigate whether patients with carotid or vertebral artery occlusion had a higher risk of poor functional outcome (mRS=3 to 6).

Two independent observers (S.Z., P.N.) extracted all data. Disagreements were resolved by consensus. When the mRS was unavailable, the same observers reconstructed the score if this could clearly be deducted from the case description, according to the mRS criteria.²

Individual Patient Data

We sent a uniform datasheet to the authors of all case series with aggregated data only. To prevent double counting of patients who were reported in case series, only the IPD were used for analysis. Authors of case reports were contacted only when the IPD needed for the analysis were incompletely described in the manuscript.

Statistical Analyses

We used the IPD to construct mixed models with the lme4 package of R.⁴ We adjusted for the heterogeneity across studies by including a random intercept per study in these models. Pooled proportions were calculated for SICH and mortality, for recurrent stroke and for excellent and favorable outcome. SICH and mortality rates were calculated for the subgroup treated within 3 and within 4.5 hours according to IVT guidelines. These proportions were also calculated for all patients treated with IVT. The following variables were included in univariate models as predictors of excellent and favorable outcome: sex, age, preceding trauma, location of dissected artery, onset-to-treatment time, stroke severity (NIHSS score), and treatment modality. Onset-to-treatment time was analyzed as both a continuous and categorical variable, the latter based on empirically defined cutoff values (<120 minutes, 120 to 180 minutes, and >180 minutes). In the multivariate analyses, we adjusted for predictors that were significantly (P<0.05) associated with excellent and favorable outcomes in the univariate analyses. A subgroup analysis was performed after excluding data from the case reports.

Comparison With SITS-ISTR

We compared our findings with the results of the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR), an ongoing, prospective, international stroke register of patients treated with IVT.⁵ Our pooled rates for SICH and functional outcome (including mortality) were indirectly compared with the same end points of selected controls from SITS-ISTR; that is, matched for age and stroke severity (NIHSS score). When a complete match did not exist (allowing a deviation of 1 year or 1 point on the NIHSS score), a control patient was recorded as missing. In SITS-ISTR, SICH was reported according to the definition of both the National Institute of Neurological Diseases and Stroke (any hemorrhage with any neurologic deterioration <7 days after symp- tom onset) and the European-Australian Acute Stroke Study II (any hemorrhage with a ≥4-point increase on the NIHSS and likely to be the cause of the clinical deterioration). Functional outcome (mRS) in SITS-ISTR was assessed at 3 months, whereas follow-up duration in our meta-analysis differed among studies. From our IPD, we therefore selected only patients with outcome assessed within 3 months of follow-up.

Results

Studies

Our search strategy yielded 186 citations; 36 publications about 190 patients fulfilled our predefined criteria. All studies were retrospective series or single case reports; no randomized controlled trials were identified. Fourteen case series (160 patients) presented data on thrombolysis in dissection-related stroke.⁵,⁶,¹⁰–²¹ Nine series used data from stroke registries¹⁰,¹⁴,¹⁸,²¹ or thrombolysis registries,⁵,¹¹,¹⁶,²² and 1 was based on a nondefined hospital registry.¹⁵ Of these, 3 studies were multicenter studies.⁵,¹⁰,²² Supplemental Table I (http://stroke.ahajournals.org) gives an overview of the study characteristics of the case series. In addition, 22 case reports were retrieved describing another 24 patients;²³–⁴⁴ IPD were available from 33 publications (72 patients). IPD from 108 patients were provided by the authors from the remaining 3 publications that contained aggregated data of 118 patients.
Table 1. Baseline Characteristics of All Included Cervical Artery Dissection Patients: Individual Patient Data

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>IPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>180</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>57  (32)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>46±11</td>
</tr>
<tr>
<td>Preceding trauma, n (%)</td>
<td>31  (17)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
</tr>
<tr>
<td>Presenting NIHSS score, mean±SD (range)</td>
<td>15.8±6.9 (1–36)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>16  (11–20)</td>
</tr>
<tr>
<td>Mild stroke (NIHSS score 1–7), n (%)</td>
<td>21  (15)</td>
</tr>
<tr>
<td>Moderate stroke (NIHSS score 8–14), n (%)</td>
<td>42  (25)</td>
</tr>
<tr>
<td>Severe stroke (NIHSS score ≥15), n (%)</td>
<td>86  (60)</td>
</tr>
<tr>
<td>Location of dissection</td>
<td></td>
</tr>
<tr>
<td>Carotid artery, n (%)</td>
<td>131 (73)</td>
</tr>
<tr>
<td>Vertebral artery, n (%)</td>
<td>48  (27)</td>
</tr>
<tr>
<td>Both, n (%)</td>
<td>1   (1)</td>
</tr>
<tr>
<td>Occlusion before treatment, n (%)</td>
<td>107 (83)</td>
</tr>
<tr>
<td>Intracranial extension, n (%)</td>
<td>16  (10)</td>
</tr>
<tr>
<td>Onset-to-treatment time, mean±SD, min</td>
<td>195±123</td>
</tr>
<tr>
<td>Onset-to-treatment time, median (IQR)</td>
<td>165 (125–225)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>IVT, n (%)</td>
<td>121 (67)</td>
</tr>
<tr>
<td>IAT, n (%)</td>
<td>59  (33)</td>
</tr>
<tr>
<td>Median duration of follow-up (mo) (range)</td>
<td>3.0 (0.2–18)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IQR, interquartile range; IVT, intravenous thrombolysis; IAT, intra-arterial thrombolysis; IPD, individual patient data; SD, standard deviation.

Table 2. Safety and Outcome in Cervical Artery Dissection Patients Treated With Thrombolytic Therapy (N=180)

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion</th>
<th>Crude Estimates, % (95% CI)</th>
<th>Adjusted for Heterogeneity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>8/180</td>
<td>4.4 (2.1–8.7)</td>
<td>3.1 (1.3–7.2)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>3/98</td>
<td>3.0 (0.7–9.0)</td>
<td>3.1 (0.1–9.1)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>5/137</td>
<td>3.7 (1.3–8.5)</td>
<td>3.6 (1.5–8.5)</td>
</tr>
<tr>
<td>Mortality</td>
<td>14/173</td>
<td>8.1 (4.8–13.1)</td>
<td>8.1 (4.9–13.2)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>8/96</td>
<td>8.3 (4.1–15.8)</td>
<td>8.3 (4.2–15.8)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>9/135</td>
<td>6.7 (3.4–12.3)</td>
<td>6.7 (3.5–12.3)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>8/177</td>
<td>4.5 (2.2–8.8)</td>
<td>4.5 (2.3–8.7)</td>
</tr>
<tr>
<td>mRS=0–1</td>
<td>63/173</td>
<td>36.4 (29.6–43.8)</td>
<td>41.0 (31.4–51.4)</td>
</tr>
<tr>
<td>mRS=0–2</td>
<td>103/173</td>
<td>59.5 (52.1–66.6)</td>
<td>59.5 (52.1–66.6)</td>
</tr>
</tbody>
</table>

SICH indicates symptomatic intracranial hemorrhage; mRS, modified Rankin Scale score; CI, confidence interval.

*Minutes from symptom onset to thrombolytic treatment.

Table 3. Adverse Events and Outcome in Cervical Artery Dissection Patients Treated With Intravenous Thrombolysis (n=121)

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion</th>
<th>Crude Estimates, % (95% CI)</th>
<th>Adjusted for Heterogeneity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>4/121</td>
<td>3.3 (1.0–8.5)</td>
<td>3.3 (1.2–8.5)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>2/87</td>
<td>2.3 (0.1–8.5)</td>
<td>2.3 (0.6–8.7)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>3/110</td>
<td>2.7 (0.6–8.6)</td>
<td>2.7 (0.9–8.1)</td>
</tr>
<tr>
<td>Mortality</td>
<td>8/120</td>
<td>6.7 (2.2–11.1)</td>
<td>6.7 (3.4–13.8)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>6/86</td>
<td>7.0 (3.0–14.7)</td>
<td>7.0 (3.2–14.7)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>6/109</td>
<td>5.5 (2.3–11.7)</td>
<td>5.5 (2.5–11.7)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>8/118</td>
<td>6.8 (3.3–13.0)</td>
<td>6.8 (3.4–13.0)</td>
</tr>
<tr>
<td>mRS=0–1</td>
<td>40/120</td>
<td>33.3 (25.5–42.2)</td>
<td>33.3 (25.5–42.2)</td>
</tr>
<tr>
<td>mRS=0–2</td>
<td>73/120</td>
<td>60.8 (51.9–69.1)</td>
<td>60.8 (51.8–69.1)</td>
</tr>
</tbody>
</table>

SICH indicates symptomatic intracranial hemorrhage; mRS, modified Rankin Scale score; CI, confidence interval.

*Minutes from symptom onset to thrombolytic treatment.

Safety

The pooled mortality was 8.1% (95% CI, 4.9 to 13.2). However, in 7 patients (4%), survival status was unavailable. Pooled mortality in 121 patients treated with IVT was 6.7% (95% CI, 3.4 to 13.8). SICH occurred in 8 of 180 patients (3.1%; 95% CI, 1.3 to 7.2), of which 2 occurrences were fatal. In the IVT group, 4 patients experienced SICH (3.3%; 95% CI, 1.2 to 8.5). Recurrent stroke occurred in 4.5% (95% CI, 2.3 to 8.7) and in 6.8% (95% CI 3.4 to 13.0) of the patients treated with IVT (Tables 2 and 3).

Other complications after thrombolytic treatment were asymptomatic ICH in 26 patients. One patient with right vertebral artery dissection treated with IVT experienced hematoma expansion (unpublished data), with excellent recovery (mRS score=1 at 3 months). Pseudoaneurysm at follow-up was reported in 8 of the 133 patients for whom this information was available. One asymptomatic subarachnoid bleeding event occurred. Progression of the infarct defined as worsening of the NIHSS score with intracranial hemorrhage excluded on imaging was reported in 13 of 161 patients.

Functional Outcome

The mRS score was available for 156 patients. In 17 cases, the mRS score could be reliably deduced from the description of functional status. In total, 41.0% (95% CI, 31.4 to 51.4) made an excellent recovery (mRS score=0 to 1), and 59.5% (95% CI, 52.1 to 66.6) had a favorable outcome (mRS score=0 to 2). In the IVT group, 33.3% (95% CI, 25.5 to 42.2) had an excellent outcome, and 60.8% (95% CI, 51.8 to 69.1) had a favorable outcome (Tables 2 and 3).

Median follow-up was 3 months (range, 5 days to 18 months), but 137 patients had their functional outcome and from unpublished cases. In total, IPD from 180 patients, all treated with IVT or IAT, were available for the analysis.

Baseline Characteristics

Patients were predominantly female (68%) with a mean±SD age of 46±11 years. The median NIHSS score was 16 (interquartile range, 11 to 20), and most patients (60%) presented with severe stroke symptoms (NIHSS score ≥15). Median onset-to-treatment time was 165 minutes (interquartile range, 125 to 225). Treatment was IVT in 67% and IAT in 33%. Six percent of the IVT patients were treated beyond the therapeutic window of 4.5 hours after symptom onset. Baseline characteristics are summarized in Table 1.
assessments at 3 months exactly. Proportions per follow-up period are reported in Supplemental Table II.

The odds ratio (OR) for poor functional outcome (mRS = 3 to 6) for the subgroup of patients with proven carotid artery occlusion (n = 79) was 1.47 (95% CI, 0.41 to 5.51) for patients with vertebral artery occlusion (n = 28), this OR was 1.57 (95% CI, 0.19 to 15.41). The small numbers precluded a valid or meaningful multivariate analysis.

Regression Models
Predictors of excellent (mRS score = 0 to 1) and favorable (mRS score = 0 to 2) outcome are presented in Supplemental Table III. In the univariate analyses, only stroke severity (NIHSS score on admission) was inversely associated with both excellent and favorable outcome. The OR for excellent outcome was 0.9 (95% CI, 0.8 to 0.9) for each 1-point increase on the NIHSS. For favorable outcome, this OR was also 0.9 (95% CI, 0.8 to 0.9). Vertebral artery dissection was significantly associated with excellent outcome compared with carotid artery dissection (OR = 2.6; 95% CI, 1.2 to 5.6) but not with favorable outcome (univariate analysis). Other variables were not associated with outcome. In the multivariate models, we adjusted for stroke severity only. In these models, vertebral artery dissection remained associated with an excellent outcome (OR = 3.9; 95% CI, 1.4 to 11.1). None of the other variables examined were associated with outcome.

Publication Bias
Leaving out the data from case reports did not alter the main findings. Apparently, there was no publication bias in favor of case reports compared with the results of the larger studies.

Comparison With SITS-ISTR
Selection of controls from SITS-ISTR, matched for age and stroke severity, resulted in 170 eligible cases. Point estimates for the main outcomes of our study compared with SITS-ISTR are shown in Table 4. Overlapping CIs indicated no relevant differences in SICH rates, mortality, and functional outcome.

Discussion
This meta-analysis of IPD comprises the largest published number of CAD patients treated with thrombolysis to date and suggests that thrombolysis in acute ischemic stroke due to CAD is safe. The pooled SICH rate of 3% and overall mortality of 8% (3% and 7%, respectively, in IVT) in CAD patients are apparently similar to those of stroke from all causes. In particular, the indirect comparison between our population and matched controls from SITS-ISTR did not show relevant differences for these important end points. We did not perform statistical testing of differences between our population and SITS-ISTR, as both studies were not designed beforehand to be compared. We therefore present this comparison only in a descriptive way. However, because placebo-controlled trials on thrombolysis in patients with CAD-related stroke may not be ethical anymore, the presented data may be the best available evidence for clinical guidelines to date.

Expansion of the intramural hematoma during thrombolysis seems to be a rather theoretical concern. In our study, only 1 patient with an intramural hematoma expansion was described but had an excellent outcome. We realize that most studies did not systematically report on this direct complication. However, given the overall safety end points and functional outcome, direct bleeding complications from thrombolysis are apparently not a major issue.

In our population, 31% of all CAD patients had an excellent outcome (mRS = 0 to 1), compared with 37% in SITS-ISTR. However, a favorable outcome seemed slightly higher in our population (58%, versus 52% in SITS-ISTR). For both outcome measures, the CIs largely overlapped. Therefore, given the fact that we can only make an indirect comparison, the outcome after IVT in patients with stroke due to CAD is in the same range as observed in IVT after stroke from all causes. The subgroup of patients with a priori proven carotid or vertebral artery occlusion may have a higher risk for poor outcome. Because of the small numbers and wide CIs, we could not prove this, and the possible association was not significant. If a higher risk would be found in a larger study in the future, this could imply a different and possibly

<p>| Table 4. Indirect Comparison of Thrombolysis in Patients With Cervical Artery Dissection–Related Stroke (Current Meta-Analysis) With Matched* Patients With Stroke From All Causes Treated With IVT (Data From SITS-ISTR)* |</p>
<table>
<thead>
<tr>
<th>All Patients</th>
<th>IVT</th>
<th>Stroke From All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/n</td>
<td>% (95% CI)</td>
<td>n</td>
</tr>
<tr>
<td><strong>End point: SICH</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180</td>
<td>3.1 (1.3–7.2)</td>
<td>121</td>
</tr>
<tr>
<td><strong>Mortality at ≤3 mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>9.0 (5.3–14.9)</td>
<td>110</td>
</tr>
<tr>
<td><strong>mRS=0–1 at ≤3 mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>31.2 (24.2–39.3)</td>
<td>110</td>
</tr>
<tr>
<td><strong>mRS=0–2 at ≤3 mo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>55.6 (47.4–63.5)</td>
<td>110</td>
</tr>
</tbody>
</table>

IVT indicates intravenous thrombolysis; SITS-ISTR, Safety Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register; SICH, symptomatic intracranial hemorrhage; NINDS, National Institutes of Neurological Disorders and Stroke definition; ECASS II, European-Australian Acute Stroke Study II; mRS, modified Rankin Scale score; CI, confidence interval.

*Controls were matched for age and stroke severity.
†Any hemorrhage plus any neurologic deterioration.
‡Any hemorrhage plus ≥4-point increase on the National Institutes of Health Stroke Scale.
more aggressive therapeutic approach in this particular subgroup. This still needs to be investigated.

Our study has some limitations. First, no randomized trials were available for this meta-analysis. The pooled estimates are based on retrospective and mostly uncontrolled series and case reports only. Although leaving out the case reports did not change our findings, the possibility of publication bias in included series cannot be excluded and might still have influenced the results of this meta-analysis. Another limitation is that we used a pragmatic instead of a strict definition of SICH because the criteria for SICH in the studies contributing to our meta-analysis were heterogeneous. This makes a comparison with SICH rates in other studies difficult. However, our rate with mixed definitions of SICH falls within the rates from SITS-ISTR according to the National Institute of Neurological Diseases and Stroke and European-Australian Acute Stroke Study II definitions. This strongly suggests that the risk of SICH is not increased in patients with CAD-related stroke.

Another point of concern in this study is diagnostic uncertainty in patients with presumed CAD. However, the largest published series included in our analysis excluded patients with “possible” CAD, thereby reducing the diagnostic uncertainty. The type of antithrombotic agents used after thrombolysis was not assessed, which might influence the rate of SICH as well as the outcome. One could argue that thrombolysis was not assessed, which might influence the results of this meta-analysis. Another limitation is that we used a pragmatic instead of a strict definition of SICH because the criteria for SICH in the studies contributing to our meta-analysis were heterogeneous. This makes a comparison with SICH rates in other studies difficult. However, our rate with mixed definitions of SICH falls within the rates from SITS-ISTR according to the National Institute of Neurological Diseases and Stroke and European-Australian Acute Stroke Study II definitions. This strongly suggests that the risk of SICH is not increased in patients with CAD-related stroke.

Conclusions

In conclusion, thrombolysis appears to be safe in acute ischemic stroke due to CAD. Mortality and SICH rate, as well as outcome, after thrombolysis in these patients appear to be similar to the rates in stroke patients from all causes treated with thrombolysis. Although our analysis is based on retrospective data with small numbers of patients, our results give no evidence that thrombolysis should be withheld in patients with ischemic stroke caused by CAD.

Acknowledgments

We gratefully acknowledge the final comments of Prof J. Stam, Department of Neurology, Academic Medical Centre, University of Amsterdam, the Netherlands.

Source of Funding

M.D.I.V. is financially supported by a grant from the Netherlands Thrombosis Foundation, the Netherlands (2010-4).

Disclosures

None.

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case of basilar artery occlusion of traumatic vertebral artery dissection
successfully managed by endovascular treatment. *No Shinkei Geka*. 2003;
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deafness as a prodromal symptom of basilar artery occlusion. *J Neurol
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therapy for acute extracranial artery dissection: report of two cases. *Arq
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Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke: A Meta-Analysis of Individual Patient Data


*Stroke*. 2011;42:2515-2520; originally published online July 28, 2011; doi: 10.1161/STROKEAHA.111.617282

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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ONLINE SUPPLEMENT

Safety and functional outcome of thrombolysis in dissection-related ischemic stroke: a meta-analysis of individual patient data

Zinkstok et al.

Supplemental Tables: 4
### Supplemental Tables

#### S1. Characteristics of included series (case-reports are not listed)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>No. of patients included in meta-analysis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelter et al. (2010)</td>
<td>retrospective, multicenter</td>
<td>55 consecutive patients with stroke due to cervical artery dissection treated with IVT</td>
<td>55</td>
<td>IVT</td>
</tr>
<tr>
<td>Vergouwen et al. (2009)</td>
<td>retrospective, single centre</td>
<td>8 consecutive patients with stroke due to extracranial artery dissection</td>
<td>6</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Putaala et al. (2009)</td>
<td>retrospective, single centre</td>
<td>48 consecutive patients with stroke aged 16-49 treated with IVT</td>
<td>12</td>
<td>IVT</td>
</tr>
<tr>
<td>Huang et al. (2009)</td>
<td>retrospective, single centre</td>
<td>73 patients with cervicocranial arterial dissection</td>
<td>1</td>
<td>IAT</td>
</tr>
<tr>
<td>Cerrato et al. (2008)</td>
<td>retrospective, single centre</td>
<td>3 patients with vertebral artery dissection and basilar artery occlusion treated with IAT</td>
<td>3</td>
<td>IAT</td>
</tr>
<tr>
<td>Baumgartner et al. (2008)</td>
<td>retrospective, single centre</td>
<td>18 consecutive patients with internal carotid artery dissection and a symptomatic middle cerebral artery occlusion</td>
<td>18</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Lavallée et al. (2007)</td>
<td>retrospective, single centre</td>
<td>10 patients with tandem internal carotid and middle cerebral artery occlusion with internal carotid dissection</td>
<td>5</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Dabitz et al. (2007)</td>
<td>retrospective, single centre</td>
<td>10 consecutive patients with cerebral ischemia associated with proximal carotid artery occlusion</td>
<td>3</td>
<td>IAT</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Description</td>
<td>N</td>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------------</td>
<td>----------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>----</td>
<td>-----------</td>
</tr>
<tr>
<td>Georgiadis et al. (2005)⁹</td>
<td>retrospective, multicentre</td>
<td>33 consecutive patients with stroke due to spontaneous carotid dissection treated with IVT</td>
<td>33</td>
<td>IVT</td>
</tr>
<tr>
<td>Arnold et al. (2002)¹⁰</td>
<td>retrospective, single centre</td>
<td>9 patients with cervical artery dissection treated with thrombolysis</td>
<td>9</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Bin Saeed et al. (2000)¹¹</td>
<td>retrospective, single centre</td>
<td>26 patients with vertebral artery dissection</td>
<td>2</td>
<td>IAT</td>
</tr>
<tr>
<td>Derex et al. (2000)¹²</td>
<td>retrospective, single centre</td>
<td>11 consecutive patients with acute ischemic stroke related to internal carotid artery dissection treated with IVT</td>
<td>11</td>
<td>IVT</td>
</tr>
<tr>
<td>Ahmad et al. (1999)¹³</td>
<td>retrospective, multicentre</td>
<td>18 patients with cervicocerebral artery dissections</td>
<td>2</td>
<td>IAT</td>
</tr>
<tr>
<td>Rudolf et al. (1999)¹⁴</td>
<td>retrospective, single centre</td>
<td>15 consecutive patients with internal carotid artery occlusion treated with IVT</td>
<td>6</td>
<td>IVT</td>
</tr>
</tbody>
</table>

IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis
### S2. Functional outcome per time period of follow-up

<table>
<thead>
<tr>
<th>Follow-up duration</th>
<th>All patients (n=180)</th>
<th>IVT (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mRS 0-1</td>
</tr>
<tr>
<td>0 - ≤10 days</td>
<td>4</td>
<td>2/4</td>
</tr>
<tr>
<td>&gt; 10 days - ≤1 month</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>&gt; 1 months - ≤3 months</td>
<td>139</td>
<td>42/139</td>
</tr>
<tr>
<td>3 months exactly</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td>&gt; 3 months - ≤12 months</td>
<td>22</td>
<td>15/22</td>
</tr>
<tr>
<td>&gt;12 months - ≤18 months</td>
<td>3</td>
<td>1/3</td>
</tr>
<tr>
<td>Follow-up period or outcome unknown</td>
<td>11</td>
<td>--</td>
</tr>
</tbody>
</table>

mRS = modified Rankin Score; IVT = intravenous thrombolysis; CI = confidence interval
S3. Univariable and multivariable analysis. Odds for excellent and favourable outcome, multivariate analysis is adjusted for stroke severity by means of the NIHSS before start of treatment.

<table>
<thead>
<tr>
<th>Variables</th>
<th>mRS 0 - 1 Univariate</th>
<th>mRS 0 - 1 Adjusted for stroke severity</th>
<th>mRS 0 - 2 Univariate</th>
<th>mRS 0 - 2 Adjusted for stroke severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>Gender [female]</td>
<td>0.73 (0.37-1.43)</td>
<td>0.35</td>
<td>0.51 (0.22-1.15)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98-1.04)</td>
<td>0.91</td>
<td>1.00 (0.96-1.04)</td>
<td>0.99</td>
</tr>
<tr>
<td>Preceding trauma</td>
<td>1.79 (0.67-4.77)</td>
<td>0.24</td>
<td>0.43 (0.09-2.03)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dissected artery [vertebral artery]</td>
<td>2.64 (1.24-5.62)</td>
<td>0.01</td>
<td>3.94 (1.40-11.12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Onset to treatment time</td>
<td>Continuous reference</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
<td>1.00 (1.00-1.00)</td>
</tr>
<tr>
<td></td>
<td>&lt; 120 minutes</td>
<td>0.72</td>
<td>1.00 (0.99-1.00)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>120-180 minutes</td>
<td>0.44</td>
<td>0.74 (0.32-1.71)</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>&gt;180 minutes</td>
<td>0.52</td>
<td>0.27 (0.03-2.83)</td>
<td>0.27</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.88 (0.82-0.93)</td>
<td>&lt;0.001</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Treatment</td>
<td>IVT</td>
<td>reference 1.66 (0.80-3.43)</td>
<td>0.17</td>
<td>2.36 (0.86-6.53)</td>
</tr>
<tr>
<td></td>
<td>IAT</td>
<td>reference 0.88 (0.45-1.70)</td>
<td>0.70</td>
<td>1.45 (0.61-3.45)</td>
</tr>
</tbody>
</table>

mRS = modified Rankin Score; OR = odds ratio; CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale; IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis
### S4. Overview of centers providing individual patient data

<table>
<thead>
<tr>
<th>Centre</th>
<th>No of patients with individual patient data (per treatment modality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Hospital Lausanne, Switzerland</td>
<td>27 patients (22 IVT, 5 IAT)</td>
</tr>
<tr>
<td>University Hospital Bern, Switzerland</td>
<td>25 patients (9 IVT, 16 IAT)</td>
</tr>
<tr>
<td>University Hospital Zürich, Switzerland</td>
<td>24 patients (21 IVT, 3 IAT)</td>
</tr>
<tr>
<td>University Hospital Basel, Switzerland</td>
<td>22 patients (20 IVT, 2 IAT)</td>
</tr>
<tr>
<td>University Hospital Helsinki, Finland</td>
<td>12 patients (12 IVT)</td>
</tr>
<tr>
<td>UniversitätsMedizin Mannheim, Germany</td>
<td>7 patients (7 IVT)</td>
</tr>
<tr>
<td>Academic Medical Centre, University of Amsterdam, the Netherlands</td>
<td>6 patients (4 IVT, 2 IAT)</td>
</tr>
</tbody>
</table>

IVT = intravenous thrombolysis only, IAT = intra-arterial thrombolysis only
References


表4 顔面神経障害に関係した脳卒中患者（本メタアナリシス）と，IVTを実施したあらゆる原因による脳卒中患者（本患者群と条件を一致させた*SITS-ISTRのデータ）における血栓溶解療法の間接比較

<table>
<thead>
<tr>
<th>評価項目</th>
<th>全患者</th>
<th>IVT症例</th>
<th>一致させた対照群（SITS-ISTR）</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>例数</td>
<td>% (95% CI)</td>
<td>例数</td>
</tr>
<tr>
<td>評価項目：SICH</td>
<td>180</td>
<td>3.1 (1.3 ~ 7.9)</td>
<td>121</td>
</tr>
<tr>
<td>3カ月以内の死亡率</td>
<td>144</td>
<td>9.0 (5.3 ~ 14.0)</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>31.2 (24.2 ~ 39.3)</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>55.6 (47.4 ~ 63.5)</td>
<td>110</td>
</tr>
</tbody>
</table>

IVT：静注血栓溶解療法。SITS-ISTR：Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register。SICH：虚血性脳頭蓋内出血。
NINDS：米国国立神経疾患・脳卒中研究所の基準。
ECASSⅡ：European-Australian Acute Stroke Study II。
mRS：改変Rankin尺度スコア。
* 一致させた対照群は年齢および脳卒中重症度を患者群と一致させた。
† あらゆる出血+虚血性脳卒中。
* あらゆる出血+NINDSスコアが4点以上上昇。
Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke
A Meta-Analysis of Individual Patient Data

Sanne M. Zinkstok, MD; Mervyn D.I. Vergouwen, MD; Stefan T. Engelter, MD; Philippe A. Lyrer, MD; Leo H. Bonati, MD; Marcel Arnold, MD; Heinrich P. Mattle, MD; Urs Fischer, MD; Hakan Sarikaya, MD; Ralf W. Baumgartner, MD; Dimitrios Georgiadiis, MD; Céline Odier, MD; Patrik Michel, MD; Jukka Putaala, MD; Martin Gribe, MD; Nils Wahlgren, MD; Niaz Ahmed, MD; Nan van Geloven, MSc; Rob J. de Haan, PhD; Paul J. Nederkoorn, MD

(Stroke. 2011;42:2515-2520.)

Key Words: carotid artery ■ cerebral infarct ■ dissection ■ outcome ■ thrombolysis ■ safety

배경과 목적: 경부동맥기와(cervical artery dissection, CAD)에서 혈전응해술(thrombolysis)의 안전성 및 효능에 대하여 논란이 많다. 본 메타분석은 모든 개별환자자료를 통합하여 CAD 환자에서 혈전응해술의 안전성과 결과에 대한 타당한 평가를 제공하고자 하였다.

방법: 저자들은 CAD에서 정맥내(intravenous), 동맥내(intra-arterial) 혈전응해술에 대한 체계적 문헌 검색을 시행하였다. 동족(pooled) 증상성두께내출혈(symptomatic intracranial hemorrhage) 발생률과 사망률을 계산하고 SITS–ISTR (Safe Implementation of Thrombolysis in Stoke–International Stroke Thrombolysis Register) 연구로부터 확자는 대조군과 간접 비교를 하였다. 탑퇴한 결과(수정Rankin적도(modified Rankin Scale, mRS)=0~1)와 양호한 결과(mRS=0~2)의 예측인자 찾기 위해 다변량 회귀 모델을 적용하였다.

결과: 14개의 후속 연구와 22개의 증례 보고에서 180명의 개별환자자료를 얻었다. 환자들은 여성이 많았고(68%), 평균 연령은 46±11세였다. 대부분의 환자들이 증상 뇌졸중(NIH뇌졸증적도 점수 중앙값=10)을 보였다. 환자들의 67%가 정맥내 혈전응해술, 33%가 동맥내 혈전응해술을 받았다. 추적 기간 중앙값은 3개월이었다. 동통 증상성두께내출혈 발생률은 3.1% (95% CI, 1.3~7.2)였다. 전체 사망률은 8.1% (95% CI, 4.9~13.2)였고, 41.0% (95% CI, 31.4~51.4)의 환자들이 탑퇴한 결과를 보였다. 뇌졸중 중증도는 강력한 결과 예측인자였다. 종말점(end point)의 신뢰구간이 겹치는 SITS–ISTR 연구로부터 확자는 대조군과는 유의한 차이가 없었다.

결론: CAD 관련 뇌졸중 환자에서 혈전응해술의 안전성과 결과는 모든 원인에 의한 뇌졸중 환자의 안전성 및 결과와 유사하였다. 저자들의 결과에 근거할 때, CAD 환자에서 혈전응해술을 보유하여서는 안된다.
전체 혈혈뇌출혈(ischemic stroke)의 약 2%는 경부동맥 박리(cervical artery dissection, CAD)에 의하여 발생한다. 50세 미만의 환자에서 CAD는 전체 혈혈뇌출혈의 10~25% 정도를 차지한다. 1,2 CAD는 경동맥 혹은 칩추동맥의 내막 파열에 의한 백내혈증(intramural hematoma) 특징이다. CAD에 의한 혈혈뇌출혈은 대부분 헌혈역학적 요인보다는 혈전색소(thrombocytopenia)에 의하여 발생하는 것으로 여겨진다. 1 급성 혈혈뇌출혈에서 혈전암해(thrombolysis)를 연구한 무작위대조시험들에서 CAD 환자를 제외하지는 않았다. 1,2 그러나 이 무작위대조시험들에서 CAD 환자에 대하여 별도로 혈전암해의 안전성과 결과를 연구하는 것은 어렵다. 따라서 CAD에 의한 급성 혈혈뇌출혈에서 혈전암해의 시행 여부는 아직 알려져 있지 않다.

혈전암해의 가장 심각한 합병증은 증상성두개내출혈(symptomatic intracranial hemorrhage, SICH)로, 2~9%에서 발생한다. 1,2,3 CAD 환자에서는 백내혈증의 확대 위험에 대한 추가가 유의하다. 작은 규모의 후향 중재 연구들에서 CAD 환자에서의 혈전암해는 안전한 것으로 제시되었다. 4,5 본 메타분석의 목적은 연을 수 있는 모든 증례 보고(case report)와 중재 연구(case series)들의 개별환자자료(individual patient data)를 통합하여 CAD 관련 뇼출증 환자에서 혈전암해의 안전성과 결과에 대한 타당한 평가를 제공하는 것이다. 추가적으로 혈전암해의 결과 예측인자도 평가하였다.

방법

환자 선택

저작들은 PubMed와 EMBASE 데이터베이스에서 [‘dissection’] AND [‘carotid’ or ‘vertebral’ or ‘cervical’ or ‘extracranial’ or ‘stroke’ or ‘brain ischemia’ or ‘brain infarction’] AND [‘thrombolysis’ or ‘recombinant tissue plasminogen activator’ or rtPA or ‘tissue plasminogen activator’ or ‘tPA’ or ‘urokinase’ or ‘pro-urokinase’] 변수들을 조합하여 2010년 3월까지 출판된 CAD 관련 뇼출증 환자에 대한 연구들을 통합적으로 검색하였다. 또한 Cochrane Library, 혹은 Cochrane Central Register of Controlled Trials에서 기준에 일치하는 연구들을 찾았고, 찾은 연구들과 수치로 인용 문헌들을 조사하였 다. 마지막으로 이 분야 전문가들에게 자문을 얻었다.

저작들은 CAD 관련 뇼출증에서 혈전암해를 주목적으로 연구하였지만, 이들에 대한 하위 집단 분석을 한 연구들은 포함시켰다. 이 수치에 대한 연구가 드물기 때문에 각 연구당 최소 환자 수 기준을 정하지는 않았다. 영어, 독일어, 프랑스어로 출판된 연구를 포함하였고, 다른 언어라도 초록이 이들 언어로 쓰여진 경우는 포함하였다. 두개내 혈관에 국한된 혈관박리, 혹은 대동맥박리(aortic dissection)가 경부동맥까지 확장된 경우는 제외하였다. CAD의 진단은 컴퓨터단층활영(CD, computed tomography angiography), 자기공명혈관조영술(magnetic resonance angiography) 또는 고식적 혈관조영술을 통해 확인한 경우였다. 혈전암해 시행 전 혹은 후의 혈관박리 확인을 모두 인정하였다. 대부분의 연구에서 치료 전과 치료 후 두개내 혈관 혈착에 대하여 체계적으로 평가하지 않기 때문에 세개동 영역은 분석에서 제외하였다. 저작들은 2개 치료군(경동맥 혈전암해[intravenous thrombolysis, IVT]과 두개내 혈전암해[intra-arterial thrombolysis, IAT])으로 나누어 분석하였다. IAT는 IAT만 시행한 경우, IVT 이후 IAT를 시행한 경우, 또는 IAT가 기계적 혈전거제술 혹은 스텐트술과 같은 혈관내 시술을 병행한 경우로 정의하였다.

혈전암해는 증상 발생 이후 24시간 이내에 시행되어야 했다. 3시간 이내와 4.5시간 이내에 치료받은 환자들을 구분하여 하위 집단 분석을 하였다.

자료 추출

저작들은 성별, 연령, 성형 외상학, NIH뇌출증척도(National Institutes of Health Stroke Scale)로 평가한 내원 시 뇼출 증 중증도, 혈관박리의 위치(경동맥 또는 칩추동맥), 치료 전 혈관 폐쇄, 두개내 집중 여부, 증상 발생 후 치료까지 소요 시간, 치료 종류(IVT 또는 IAT) 및 추적 관찰 기간에 대한 정보를 수집하였다.

안전성 변수로 SICH, 사망률 및 뇼출증 재발을 평가하였다. SICH는 환자의 임상적 악화와 시간적 연관성을 가지면서 컴퓨터단층활영, 혹은 자기공명영상상에서 확인된 모든 두개내 출혈로 정의하였다. 포함된 연구들에서 임상적 악화에 대한 정의는 다양하였다. 저작들이 보고한 추가적인 부작용은 자료에 수집하여 기술하였다. 기능적 결과는 추적 기간 중 기능적 독립성의 정도로 평가하였다. 탁월한 기능적 결과는 수행Rankin척도(modified Rankin Scale, mRS)가 0~1인 경우로, 양호한 기능적 결과는 mRS 2~3로 정의하였다. 마지막으로 경추동맥 혹은 경동맥 폐쇄 중에서 어느 것이 더 불량한 결과(mRS =3~6)를 보이는지에 대하여 하위 집단 분석을 시행하였다.

두 명의 독립적인 관찰자(S.Z., P.N.)이 모든 자료를 추출하였다. 의견이 일치하지 않는 경우에는 합의에 의해 해결하였 다. mRS 정보가 없는 경우에는, 증례 기술을 통해 명확히 유추할 수 있는 경우에 동일한 관찰자가 mRS 판단 기준에 따라 재구성하였다. 6

개별환자자료

저작들은 모든 중재 연구 저작들에 수집된 자료만 포함된 동일한 데이터 시트를 보았다. 중재 연구에 보고된 환자들의
통계 분석

R Ime4 레지오로 개별환자자료를 이용한 통합 모형을 만들었다. 이 모델에서는 각 연구들의 무작위 절편(random intercept)을 포함함으로써 연구들의 어절성을 보정하였다. SICH, 사망률, 뇌졸중 재발, 타цикл한 결과 및 양호한 결과에 대한 통합 비율(pooled proportion)을 계산하였다. SICH와 사망률은 IVT 가이드라인에 따라 3시간 이내와 4.5시간 이내의 하위 집단으로 나누어 계산하였고, IVT 치료를 받은 모든 환자들에 대하여서도 계산하였다. 타цикл한 결과나 양호한 결과의 예측인자들 보기 위한 단변량 모델에 신별, 나이, 선행 외상, 혈관벽의 위치, 증상 발생-치료 시간, 뇌졸중 중증도(NIH뇌졸중척도 점수), 치료 종류를 변수로 포함하였다. 증상 발생-치료 시간은 연속 변수와 범주형 변수로 분석하였는데, 범주형 변수 분석에서 범주 구분을 위한 차단값(cutoff value)은 경험적으로 120분 미만, 120~180분 및 180분 초과의 경우로 나누었다.

SITS-ISTR과의 비교

저자들은 분석 결과를 현재 진행 중인 IVT 치료를 받은 환자들의 전산적 국제적 뇌졸중 등록 체계인 SITS-ISTR(Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register)의 결과와 비교하였다. 연구에서 얻은 SICH의 사망률을 포함한 가능성을 통합 비율(pooled rate)을 SITS-ISTR에서 연구한 뇌졸중 중증도를 기준으로 선택한 대조군의 같은 통합결과 비교하였다. 판별한 확률 기가 이루어지지 않을 경우(나이 1년 죽은 NIH뇌졸중척도 점수 1점 이내의 페어는 랜덤), 대조 환자는 균질성을 기록되었다. SITS-ISTR에서 SICH는 National Institute of Neurological Diseases and Stroke (증상 발생 7일 이내 어떠한 신경학적 악화와 연관된 모든 출혈) 및 European–Australian Acute Stroke Study II (NIH뇌졸중척도 점수 4점 이상의 신경학적 악화와 연관되며 임상적 악화의 원인으로 판단되는 모든 출혈) 정의에 따라 보고되었다. SITS-ISTR에서는 3개월에 가능적이며 결과(mRS)를 평가한 반면, 본 메타분석에서의 주적 관찰 기간은 연구마다 달랐다. 따라서 저자들의 개별환자자료에서 3개월 이내에 예후가 평가되었던 환자들만을 선택하였다.

결론

연구

검색 결과 186개의 인용을 찾았고, 36건의 출판물에서 190명의 환자들이 본 연구에 정의된 기준을 충족하였다. 모든 연구들은 후향 보고, 혹은 단일 증례 보고였으며, 무작위대조시험은 없었다. 14개의 증례 연구들(환자 160명)에서 혈관벽 관련 뇌졸중에서의 혈전용해술에 대한 자료를 제시하였다. 5,6,10-21 9개의 증례 연구는 뇌졸중 등록 체계, 5,10,11,12,21 혈관용해술 등록 체계의 자료를 이용하였으며, 1개 연구는 특별히 정 의하지 않은 병원 등록 체계를 이용하였다. 13-15 3개는 다기관 연구었다. 5,10,22 연구의 개요와 증례 연구들의 특정을 Table 1에 제시하였다(http://stroke.ahajournals.org). 추가로 24명의 환자를 보고한 22개의 증례 보고를 얻었다. 23-44 33개의 출판물에서 72명 환자들의 개별환자자료를 얻었다. 118명의 환자 자료가 포함된 나머지 3개의 출판물은 출판되지 않은 증례에서 108명 환자들의 개별환자자료를 저자로부터 제공받았다. 총 180명의 IVT 혹은 IAT를 받은 환자들로부터 얻은 개별환자자료가 본 논문에 이용되었다.

기본 특성

환자들은 주로 여성이었고(68%), 평균 연령은 ۶۶±۱۱세였다. NIH뇌졸중척도 점수 중앙값은 16점(사분위수 범위: 11~۲۰)이었으며, 60%가 중증의 뇌졸중 증상이 보였다(NIH뇌졸중척도 점수 15점 이상). 증상 발생-치료 시간의 중앙값은 165분(사분위수 범위: 11~۲۰)이었다.
위수 범위: 125~225)이었다. 67%에서 IVT, 33%에서 IAT 치료를 받았다. IVT 환자 중 6%가 증상 발생 후 4.5시간 이후에 치료를 받았다. Table 1에 환자들의 기본 특성이 요약되어 있다.

안전성

통합 사망률은 8.1% (95% CI, 4.9~13.2)이었다. 그러나 7명 (4%)의 사망 여부는 확인할 수 없었다. IVT를 받은 121명에서 통합 사망률은 6.7% (95% CI, 3.4~13.8)이었다. 180명 중 8명 (3.1%; 95% CI, 1.3~7.2)에서 SICH가 발생하였으며, 이 중 2명이 사망하였다. IVT군에서 4명(3.3%; 95% CI, 1.2~8.5)에서 SICH가 발생하였다. 뇌졸중 재발은 4.5% (95% CI, 2.3~8.7)였고, IVT 치료 환자 중 6.8% (95% CI, 3.4~13.0)에서 있었다(Table 2, 3).

혈전용해 후 다른 혈행중으로 무증상두뇌출혈이 26명에 서 있었다. 우측 적추동맥 تلك IVT를 받은 환자 중 혈증의 증가가 있었으나(비용출 자료), 탁월한 회복을 보였다(3개월 mRS=1). 자료를 얻을 수 있는 133명 중 8명에서 추적 관찰 중 경제적맥류(pseudoeurysm)가 발생하였다. 한 명에서 무증 상기비막혈출이 발생하였다. 뇌영역의 정점은 영상 감사에 서 두개내출혈 없이 신경학적 악화를 보이는 경우로 정의하였는데, 161명 중 13명에서 보고되었다.

기능적 결과

156명의 환자에서 mRS를 얻을 수 있었다. 17명에서 기능적 상태에 대한 기술을 통해 신뢰성 있는 mRS를 추정하였다. 전체 환자 중 41.0% (95% CI, 31.4~51.4)에서 탁월한 회복(mRS=0~1)을 보였고, 59.5% (95% CI, 52.1~66.6)에서 양호한 결과(mRS=0~2)를 보였다. IVT군에서는 33.3% (95% CI, 23.5~42.2)가 탁월한 결과를, 60.8% (95% CI, 51.8~69.1)가 양호한 결과를 보였다(Table 3).

추적 관찰 중의 3개월(5일~18개월)이었으나, 3개월째 정확한 기능적 결과 평가가 된 환자는 137명이었다. 추적 관찰 기간별 비율은 부록 Table II에 있다.

불량한 기능적 결과(mRS=3~6)에 대한 교차비(odds ratio, OR)는 정동맥 복사 환자(79명)에서 1.17 (95% CI, 0.84~1.65)이었고, 적추동맥 복사 환자에서는 1.57 (95% CI, 1.09~2.21)이었다. 습자가 작고 타당한 혹은 유의한 다변량 분석은 시행 할 수 없었다.

회귀 모델

탁월한 결과(mRS=0~1)와 양호한 결과(mRS=0~2)에 대한 예측인자는 부록 Table III에 제시되어 있다. 단변량 분석에서 뇌졸중 증증도(입원 시 NIH뇌졸증지수 점수)만 탁월한 결과 및 양호한 결과와 역의 연관관계가 있었다. NIH뇌졸증지수 점수가 1점 증가 시 탁월한 결과에 대한 OR는 0.9 (95% CI, 0.8~0.99)었고, 양호한 결과에 대한 OR 역시 0.9 (95% CI, 0.8~0.99)였다. 정동맥막막과 비교 시 적추동맥막막은 탁월한 결과와 유의하게 연관성을 보였으나(OR=2.6; 95% CI, 1.2~5.6), 양호한 결과와의 연관이 없었다(단변량 분석). 다른 변수들간의 결과와 연관이 없었다. 각각들은 다변량 모델에서 뇌졸중 증증도만을 보정하였다. 이 모델에서 적추동맥막막은 탁월한 결과와 연관성이 있었다(OR=3.9; 95% CI, 1.4~11.1). 나머지 다른 변수들은 결과와 연관이 없었다.
Table 4. Indirect Comparison of Thrombolysis in Patients With Cervical Artery Dissection-Related Stroke (Current Meta-Analysis) With Matched* Patients With Stroke From All Causes Treated With IVT (Data From SITS-ISTR+)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>IVT</th>
<th>Stroke From All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>N/n</td>
<td>(95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>End point: SICH</td>
<td>180</td>
<td>3.1 (1.3–7.2)</td>
<td>121</td>
</tr>
<tr>
<td>Mortality at ≤3 mo</td>
<td>144</td>
<td>9.0 (5.3–14.9)</td>
<td>110</td>
</tr>
<tr>
<td>mRS=0–1 at ≤3 mo</td>
<td>144</td>
<td>31.2 (24.2–39.3)</td>
<td>110</td>
</tr>
<tr>
<td>mRS=0–2 at ≤3 mo</td>
<td>144</td>
<td>55.6 (47.4–63.5)</td>
<td>110</td>
</tr>
<tr>
<td>SICH per NINDS†</td>
<td>170</td>
<td>5.9 (3.0–10.9)</td>
<td>170</td>
</tr>
<tr>
<td>SICH per ECASSII‡</td>
<td>160</td>
<td>8.8 (5.1–14.5)</td>
<td>159</td>
</tr>
</tbody>
</table>

ItalianITT indicates intravenous thrombolysis; SITS-ISTR, Safety implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register; SICH, symptomatic intracranial hemorrhage; NINDS, National Institutes of Neurological Disorders and Stroke definition; ECASS II, European-Australian Acute Stroke Study II; mRS, modified Rankin Scale score; CI, confidence interval.

*Controls were matched for age and stroke severity.
†Any hemorrhage plus any neurologic deterioration.
‡Any hemorrhage plus ≥4-point increase on the National Institutes of Health Stroke Scale.

결론

해협혈술을 이용한 본 메타분석은 현재까지 출판된 혈
전용혈술 치료를 받은 CAD 환자들을 가장 많이 포함하였고,
CAD에 의한 급성 혈절뇌출혈에서 혈전용혈술이 안전하다는
것을 제시한다. CAD 환자에서 3%의 환자 중 8%의 SICH 발생률과 8%의
전체 사망률(IVT에서는 각각 3%, 7%)은 모든 환자에서 인
한 뇌출혈에서의 결과와 비슷하였다. 특히 본 연구의 환자들과
SITS-ISTR로부터 측정한 타조군과의 간격적인 비교에 여러
한 주요 종양점에 대한 차이는 유의하지 않았다. 본 연구와
SITS-ISTR 연구는 사전에 비교가 가능하도록 설계된 것은
아니기 때문에, 두 연구들의 차이에 대한 통계적 검증은 시행
하지 않았다. 따라서 저자들은 두 연구에 대한 비교를 기술적
으로만 제시하였다. 그러나 CAD 관련 뇌출혈 환자에 대한 혈
전용혈술의 속임사이익연구는 더 이상 윤리적이지 않기 때문
에, 본 자료는 현재까지의 가이드라인에 대한 가장 최신의 증
거가 될 수 있다.

혈전용혈술 중 뇌내혈중의 확자는 아시아적으로 상당한 우려
가 될 수 있다. 본 연구에서 한 명에서만 뇌내혈중의 확장이 보
고되었고, 이 환자는 또한 탐원한 결과를 보였다. 저자들은 대부분
의 연구결과에서 이러한 직접적 합병증에 대한 체계적인 보고
가 없음을 실감하였다. 그러나 전반적인 안전성과 가능적 결과를
고려한 때 혈전용혈술로 인한 직접적인 출혈 합병증은 분명히
주요 죽병 사항이 아니다.

본 연구에서 모든 CAD 환자 중 31%가, SITS-ISTR에서는
37%가 탐원한 결과(mRS=0–1)를 보였다. 그러나 양호한 결
과를 보인 경우에는 본 연구에서 조금 더 많은 숫자 있었다(58% vs.
52% in SITS-ISTR). 두 가지 결과 모두에 대한 신뢰구간
이 크게 점차졌다. 그러나 두 연구의 간격적 비교는 가능했
다는 고려하여 CAD로 인한 뇌출혈 환자들에서 IVT의 결과는
모든 원인으로 인하여 발생한 뇌출혈 환자들에서 관찰된 IVT
치료의 결과와 같이 범위 내에 있다. 추정적으로 확인된 정도
막 혹은 첫추중막 페식을 가진 환자들만 뇌내혈중의 합병증이
더 높을 수 있다. 환자 수가 적고 신뢰구간이 넓어 저자들은 이
를 인정할 수 없었으며 상관성도 유의하지는 않았다. 추후 더
큰 규모의 연구에서 고위험군을 확인할 수 있다. 이러한 하
위 집단 환자들에게는, 아마도 더 적극적인 치료가 필요
함을 의미할 수 있다.

본 연구는 몇 가지 한계점을 가지고 있다. 첫째, 무작위대조
시험 자료가 없어 본 메타분석에 포함되지 않았다. 통합 추정
치는 후향적 대조연구와 중재 보고에 근거한 것이다. 중재
보고 자료를 제외하여도 연구 결과가 변하지는 않았으나 출판
지침의 가능성은 배제할 수 없어 이로 인하여 메타분석 결과가
영향을 받았을 수 있다. 또한 본 메타분석에 포함된 연구가

Disclosures

References

Acknowledgments
We gratefully acknowledge the final comments of Prof J. Stam, Department of Neurology, Academic Medical Centre, University of Amsterdam, the Netherlands.

Source of Funding
M.D.I.V. is financially supported by a grant from the Netherlands Thrombosis Foundation, the Netherlands (2010-4).


