Association of Early National Institutes of Health Stroke Scale Improvement With Vessel Recanalization and Functional Outcome After Intravenous Thrombolysis in Ischemic Stroke

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Background and Purpose—Early neurological improvement (ENI) after thrombolytic therapy of acute stroke has been linked with recanalization and favorable outcome, although its definition shows considerable variation. We tested the ability of ENI, as defined in previous publications, to predict vessel recanalization and 3-month functional outcome after intravenous thrombolysis recorded in an extensive patient cohort in the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR).

Methods—Of 21,534 patients registered between December 2002 and December 2008, 798 patients (3.7%) had CT- or MR angiography-documented baseline vessel occlusion and also angiography data at 22 to 36 hours post-treatment. ENI definitions assessed at 2 hours and 24 hours post-treatment were (1) National Institutes of Health Stroke Scale (NIHSS) score improvement $\geq$ 4 points from baseline; (2) NIHSS 0, 1, or improvement $\geq$ 8; (3) NIHSS $\leq$ 3 or improvement $\geq$ 10; (4) improvement by 20%; (5) 40% from baseline; or (6) NIHSS score 0 to 1. Receiver operating curve analysis and multiple logistic regression were performed to evaluate the association of ENI with vessel recanalization and favorable functional outcome (modified Rankin Scale score 0 to 2 at 3 months).

Results—ENI at 2 hours had fair accuracy to diagnose recanalization as derived from receiver operating curve analysis. Definitions of improvement based on percent of NIHSS score change from baseline demonstrate better accuracy to diagnose recanalization at 2 hours and 24 hours than the definitions based on NIHSS cutoffs (the best performance at 2 hours was area under the curve 0.633, sensitivity 58%, specificity 69%, positive predictive value 68%, and negative predictive value 59% for 20% improvement; and area under the curve 0.692, sensitivity 69%, specificity 70%, positive predictive value 70%, and negative predictive value 62% for 40% improvement at 24 hours). ENI-predicted functional outcome with OR 2.8 to 6.0 independently from recanalization in the angiography cohort (n=695) and with OR of 6.9 to 9.7 in the whole cohort (n=18181).

Conclusions—Early 20% neurological improvement at 2 hours was the best predictor of 3-month functional outcome and recanalization after thrombolysis, although fairly accurate, and may serve as a surrogate marker of recanalization if only imaging evaluation of vessel status is not available. If recanalization status is required after intravenous thrombolysis, vascular imaging is recommended despite ENI. (Stroke. 2011;42:1638-1643.)

Key Words: early neurological improvement $\rightarrow$ recanalization $\rightarrow$ stroke $\rightarrow$ thrombolysis $\rightarrow$ vessel occlusion

Early neurological improvement (ENI) after thrombolytic therapy of acute stroke has been shown to be a favorable prognostic sign,1-5 because ENI is usually associated with recanalization of previously occluded vessels6-11 and good functional outcome.1,12,13 Clinical improvement is considered a consequence of successful recanalization, which is the aim of acute stroke treatment.12,14 Because it was shown that ENI may follow the recanalization pattern very closely, ENI may be regarded by a clinician as an indicator of effective thrombolytic therapy.1,8-10,15

In clinical practice of stroke centers, ENI after intravenous thrombolysis is regarded as a favorable sign and may prevent...
additional intraarterial interventions even in patients with cerebral artery occlusion documented on baseline imaging.16–19 Such interventions are currently increasingly used in clinical practice,20 although regarded by many as a developing therapy. Moreover, a significant ENI before intravenous thrombolysis is a contraindication for treatment according to existing recommendations.21–22

Although ENI may appear as a useful predictor of recanalization and favorable functional outcome, the optimal definition of ENI remains elusive. Various definitions of ENI have been proposed either from clinical expertise23–26 or from studies with assessment of vessel patency.1,4,8 Most of which are based on changes or absolute values of National Institutes of Health Stroke Scale (NIHSS) scores. It still remains unclear, however, which definition is most useful. Moreover, some studies of ENI are based on comparisons between baseline and a time point far beyond the hyperacute phase, when the information is needed for decisions on therapeutic interventions.4,23,25,26

Given the importance of acute assessment of vessel status after intravenous thrombolysis for indication of additional interventional therapies, the present study was performed to explore ENI in the largest cohort of patients with stroke evaluated within 2 hours, and also within 24 hours, from initiation of recombinant tissue plasminogen activator in this population, we aimed to evaluate the predictive value of different definitions of ENI for vessel recanalization and for functional outcome at 3-month follow-up.

Methods

Data from the present analysis are a part of the Safe Implementation of Treatment in Stroke–International Stroke Thrombolysis Register (SITS-ISTR). The aims of the register, collection of data, and structure of the database were described elsewhere.27 The database version used for the present study contains records of patients with acute ischemic stroke treated with intravenous thrombolysis registered from December 2002 to December 2008. Patients included into the register were adults >18 years old who received 0.9 mg/kg intravenous alteplase (Actilyse; Boehringer-Ingelheim GMBH), but not exceeding 90 mg, according to the conventional guidelines. Data collected at the baseline included age, sex, weight, time form stroke onset to treatment, medical history (hypertension, hyperlipidemia, smoking, atrial fibrillation, congestive heart failure, history of previous stroke, pre-existing disability assessed by modified Rankin Scale), intake of medications (antiplatelet, anticoagulant, and anti-hypertensive therapy), blood glucose, and pretreatment blood pressure. CT scan was performed in all patients before treatment; in addition, results of optional imaging technique were increasingly available, including CT or MR angiography. Only patients with confirmed baseline data and admission CT were included in the analysis. NIHSS scores were calculated at baseline, at 2 hours after the start of recombinant tissue plasminogen activator infusion, and at 24 hours. Follow-up imaging, including plain CT scan or MRI and, as an option, CT or MR angiography (CTA/MRA), was performed between 22 and 36 hours after thrombolysis or earlier in case of clinical necessity. All imaging scans and large vessel occlusion on CTA/MRA were evaluated by local neuroradiologists. Outcome was assessed at 3 months by modified Rankin Scale; the main outcome measure for the present study was independence, defined as modified Rankin Scale 0 to 2 on Day 90.

We searched for the previously reported cutoff values of NIHSS score used to describe ENI in the literature using the MEDLINE database and key words “neurological improvement,” “early neurological improvement,” and “NIHSS improvement.” The following cutoff levels were identified: (1) NIHSS improvement ≥4 points from baseline (the “National Institutes of Neurological Disorders and Stroke definition”),25 (2) NIHSS 0 or 1 on follow-up or improvement ≥8 from baseline (major neurological improvement);26 (3) NIHSS ≤3 on follow-up or improvement ≥10 from baseline (dramatic neurological improvement);24 (4) improvement by 20%; and (5) improvement by 40% from baseline NIHSS score. In addition, we used the concept of (6) complete neurological improvement, which was defined as NIHSS score 0 or 1 on follow-up.

For the analysis of ENI definitions and association of ENI with vessel recanalization, we identified the patients with baseline cerebral artery occlusion documented either by CTA or MRA who had undergone a follow-up angiographic imaging between 22 and 36 hours after thrombolysis. Recanalization at follow-up was defined as absence of vessel occlusion on follow-up 22 to 36 hours CTA/MRA. If data of follow-up imaging were missing, the case was not included into the analysis. In this data set, the NIHSS score cutoff values described were assessed at 2 hours and 24 hours and correlated with results of 22- to 36-hour CTA/MRA and 3-month functional outcome.

Additionally, for the analysis of association between ENI and functional outcome, all patients from the SITS database registered between December 2002 and December 2008 with confirmed baseline data and modified Rankin Scale at Day 90 were recruited.

Statistical Analysis

To evaluate the ability of neurological improvement, defined in various ways, to diagnose recanalization of the previously occluded vessel, we calculated the area under the curve by receiver operating characteristic analysis and sensitivity, specificity, and positive and negative predictive values of neurological improvement at 2 hours and 24 hours according to each of the given definitions described previously. To evaluate the ability of ENI to predict recanalization assessed at 22 to 36 hours, we calculated unadjusted ORs (independently from baseline variables) for each given definition checked at 2 hours and 24 hours.

To validate 2-hour ENI as an independent predictor of favorable outcome in the general population of patients treated with thrombolysis, we analyzed the entire study cohort irrespective of the availability of the angiography data. A multivariable logistic regression models were used to adjust for those factors that were significantly (P<0.05) associated with favorable and unfavorable outcomes in univariate analysis; after that, those factors that were not significant in the initial model were removed from the multivariable analysis. Final adjustment for reported ORs was made for the following predictors of functional outcome: age, baseline NIHSS score, and recanalization at 24 hours (if data available). Because adjustment for recanalization could not be made in the general population, we show results both adjusted and unadjusted for recanalization in the cohort with available CTA/MRA results.

For the comparison of groups in univariate testing, χ² (with Yates correction for 2×2 tables or Fisher exact test, when appropriate) was used for proportions; Mann-Whitney U test for scores and nonparametrically distributed numeric data. Estimation of percentage was based only on those cases in which data were known, excluding missing cases. Multiple logistic regression was used to calculate the ORs for 2-hour ENI to predict vessel recanalization at 22 to 36 hours and independence at Day 90. We set the significance level for all tests at P<0.05.

Results

A total of 21 534 patients were enrolled in the SITS register between December 2002 and December 2008: mean age was 67±12 years, 12 593 (58%) were males, and median baseline NIHSS score was 12 (interquartile range, 8 to 17). Of these, 798 (3.7%) patients had CTA/MRA data available both at baseline and on follow-up. Mean age of the patients with CTA/MRA was 65±14 years; 439 (55%) were male 439 and median baseline NIHSS score was 14 (interquartile range, 9 to 18). Recanalization at 24 hours occurred in 50.4% (402 of
Table 1. Comparison of Early Neurological Improvement Definitions Assessed at 2 Hours and 24 Hours and Their Association With Recanalization at 22 to 36 Hours

<table>
<thead>
<tr>
<th>Definition</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>OR (95% CI) for Recanalization at 22 to 36 H</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>OR (95% CI) for Recanalization at 22 to 36 H</th>
</tr>
</thead>
<tbody>
<tr>
<td>20% NIH from baseline</td>
<td>58%</td>
<td>69%</td>
<td>68%</td>
<td>59%</td>
<td>0.633</td>
<td>3.0 (2.2–4.1)</td>
<td>80%</td>
<td>56%</td>
<td>65%</td>
<td>67%</td>
<td>0.684</td>
<td>5.3 (3.8–7.4)</td>
</tr>
<tr>
<td>NINDS NI</td>
<td>42%</td>
<td>75%</td>
<td>66%</td>
<td>53%</td>
<td>0.583</td>
<td>2.1 (1.5–3.0)</td>
<td>70%</td>
<td>64%</td>
<td>67%</td>
<td>62%</td>
<td>0.674</td>
<td>4.3 (3.2–5.9)</td>
</tr>
<tr>
<td>40% NIH from baseline</td>
<td>39%</td>
<td>82%</td>
<td>72%</td>
<td>54%</td>
<td>0.607</td>
<td>3.0 (2.1–4.2)</td>
<td>69%</td>
<td>70%</td>
<td>70%</td>
<td>62%</td>
<td>0.692</td>
<td>5.0 (3.7–6.9)</td>
</tr>
<tr>
<td>DNI</td>
<td>27%</td>
<td>87%</td>
<td>70%</td>
<td>51%</td>
<td>0.567</td>
<td>2.4 (1.6–3.5)</td>
<td>57%</td>
<td>76%</td>
<td>72%</td>
<td>57%</td>
<td>0.669</td>
<td>4.3 (3.1–6.0)</td>
</tr>
<tr>
<td>MNI</td>
<td>24%</td>
<td>90%</td>
<td>73%</td>
<td>51%</td>
<td>0.570</td>
<td>2.8 (1.8–4.3)</td>
<td>55%</td>
<td>82%</td>
<td>75%</td>
<td>58%</td>
<td>0.684</td>
<td>5.4 (3.9–7.7)</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>7%</td>
<td>97%</td>
<td>71%</td>
<td>47%</td>
<td>0.519</td>
<td>2.2 (1.1–4.6)</td>
<td>25%</td>
<td>92%</td>
<td>75%</td>
<td>49%</td>
<td>0.583</td>
<td>3.6 (2.3–5.7)</td>
</tr>
</tbody>
</table>

ENI indicates early neurological improvement; NIHSS, National Institutes of Health Stroke Scale; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating curve; NINDS NI, National Institute of Neurological Disorders and Stroke Improvement ≥4 points from baseline; DNI, dramatic neurological improvement, NIHSS ≥ on follow-up, or improvement ≥10 from baseline; MNI, major neurological improvement, NIHSS 0 or 1 on follow-up, or improvement ≥8 from baseline.

Discussion

Our study demonstrated the association of early neurological improvement as measured by NIHSS score at 2 hours and 24 hours with vessel recanalization at 22 to 36 hours and functional independence at 3 months. We explored various definitions of ENI after intravenous thrombolysis in a comparatively large population of patients with stroke and evaluated the strength of the association between ENI and vessel recanalization and functional outcome. Different definitions of ENI can be used as a surrogate marker of vessel recanalization, but all of them have demonstrated fair accuracy in predicting recanalization. Change of NIHSS score at 24 hours predicted recanalization better than that of 2-hour assessment, but 24-hour assessment is too late to influence any clinical decisions. Based on the balance among sensitivity, specificity, area under the curve, and number of actually recanalized patients yielded that the definition of 40% NIHSS score improvement at 2 hours/24 hours from baseline, 20% NIHSS score improvement at 2 hours/24 hours from baseline, and major neurological improvement after intravenous thrombolysis than the other 3 definitions. Some definitions such as complete recovery are very specific for recanalization, but only very few patients achieve complete recovery and therefore such definitions are not helpful in most clinical situations.

Our study shows that approximately 30% of patients, who had vessel occlusion at baseline, will have persisting occlusion after thrombolysis even if they achieve a substantial amount of ENI. Therefore, we suggest that vessel status is evaluated by CTA, MRA, or transcranial Doppler in all cases with previously documented large vessel occlusion. CTA,
The present study has several limitations. Data were collected through prospective clinical register; hence, the study holds all the drawbacks of observational design. Imaging data were read by local radiologists, who could not be blinded to clinical information. The structure of the database does not require specifying which vessel was occluded and blinded to clinical information. The presentation of recanalization was not provided by the database. Furthermore, the assessment of recanalization was not available (such as interventional treatment). Because outcome at 3 months was predicted by ENI independently from recanalization, the other aspect of our finding is that effect of treatment may be influenced by other biological factors such as collateral blood supply and/or retrograde flow of thrombolytic agent through previously occluded smaller vessels. Based on these results, we hypothesize that augmenting collateral or retrograde flow would improve outcome. However, partial recanalization (misdiagnosed as persistent occlusion) may be another factor responsible for ENI. Therefore, further studies of stroke thrombolysis under control of vascular imaging are needed to estimate the interaction between ENI and vessel recanalization and the impact of these factors taken together on final outcome.

The second most important finding of our study is that ENI is a positive predictor of outcome at 3 months in a very large cohort of patients irrespective of CTA/MRA-verified recanalization. The positive association between ENI of various definitions with clinical outcome assessed by ENI may serve as a surrogate marker of thrombolytic treatment effect if objective evaluation of vessel status is not possible. The important aspect is that assessment of ENI is a simple, inexpensive, and easily available and repeatable test as compared with angiography or ultrasound.

MRA, or transcranial Doppler is not, however, available in many hospitals. Our study shows that recanalization can be diagnosed with fair accuracy using ENI (area under the curve, 0.58 to 0.69); most importantly, ENI is still associated with a favorable functional outcome at 3 months. For this reason, clinical examination assessed by ENI may serve as a surrogate marker of thrombolytic treatment effect if objective evaluation of vessel status is not possible. The important aspect is that assessment of ENI is a simple, inexpensive, and easily available and repeatable test as compared with angiography or ultrasound.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Se</th>
<th>Sp</th>
<th>PPV</th>
<th>NPV</th>
<th>AUC</th>
<th>OR (95% CI) for Independence (mRS 0 to 2) at 3 Mo in a Cohort With 22- to 36-H CTA/MRA Available*</th>
<th>OR (95% CI) for Independence (mRS 0 to 2) at 3 Mo in a Cohort With 22- to 36-H CTA/MRA Available†</th>
<th>OR (95% CI) for Independence (mRS 0 to 2) at 3 Mo in the Whole SITS Register Population†</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENI based on baseline to 2-h NIHSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20% NI from baseline: 61% 74% 73% 62% 0.674 2.8 (1.8–4.1) 4.0 (2.8–5.8) 6.5 (6.0–7.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS NI</td>
<td>44%</td>
<td>78%</td>
<td>71%</td>
<td>54%</td>
<td>0.613</td>
<td>2.8 (1.8–4.2) 3.9 (2.6–5.7) 6.9 (6.3–7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% NI from baseline</td>
<td>42%</td>
<td>87%</td>
<td>79%</td>
<td>56%</td>
<td>0.647</td>
<td>2.8 (1.8–4.5) 4.2 (2.8–6.5) 7.7 (7.1–8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNI</td>
<td>32%</td>
<td>95%</td>
<td>88%</td>
<td>54%</td>
<td>0.634</td>
<td>6.0 (3.2–11.3) 7.3 (4.1–13.3) 8.1 (7.3–9.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNI</td>
<td>28%</td>
<td>93%</td>
<td>83%</td>
<td>53%</td>
<td>0.608</td>
<td>5.6 (3.1–10.4) 7.7 (4.4–13.5) 9.7 (8.7–10.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete recovery</td>
<td>9%</td>
<td>99%</td>
<td>89%</td>
<td>48%</td>
<td>0.540</td>
<td>3.8 (1.2–12.3) 4.1 (1.4–12.4) 7.5 (6.1–9.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENI based on baseline to 24-h NIHSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20% NI from baseline: 65% 66% 74% 79% 0.753 7.3 (4.7–11.5) 10.9 (7.2–16.4) 16.3 (14.9–17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NINDS NI</td>
<td>72%</td>
<td>69%</td>
<td>73%</td>
<td>68%</td>
<td>0.707</td>
<td>6.3 (4.0–9.8) 9.5 (6.3–14.4) 14.7 (13.4–16.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40% NI from baseline</td>
<td>74%</td>
<td>80%</td>
<td>81%</td>
<td>73%</td>
<td>0.773</td>
<td>8.4 (5.4–13.0) 12.0 (8.0–18.0) 16.7 (15.3–18.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNI</td>
<td>66%</td>
<td>90%</td>
<td>89%</td>
<td>70%</td>
<td>0.782</td>
<td>15.3 (9.2–25.4) 20.3 (12.5–32.9) 16.2 (14.7–17.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MNI</td>
<td>58%</td>
<td>87%</td>
<td>84%</td>
<td>64%</td>
<td>0.724</td>
<td>12.0 (7.1–20.4) 16.1 (9.9–26.1) 17.2 (15.5–19.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete recovery</td>
<td>29%</td>
<td>99%</td>
<td>96%</td>
<td>54%</td>
<td>0.638</td>
<td>14.4 (5.0–41.3) 19.7 (7.0–55.1) 14.8 (12.5–17.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Se indicates sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating curve; mRS, modified Rankin Scale; CTA/MRA, CT angiography/MR angiography; SITS, Safe Implementation of Thrombolysis in Stroke; ENI, early neurological improvement; NIHSS, National Institutes of Health Stroke Scale; NINDS NI, National Institute of Neurological Disorders and Stroke improvement ≥4 points from baseline; DNI, dramatic neurological improvement, NIHSS ≥3 on follow-up, or improvement ≥4 from baseline; MNI, major neurological improvement, NIHSS 0 or 1 on follow-up, or improvement ≥8 from baseline.

*Adjusted for age, baseline NIHSS score, recanalization at 22 to 36 h.
†Adjusted for age, baseline NIHSS score.
Table 3. Rates (%) of Functional Independence (Modified Rankin Scale Score 0 to 2 at 3 Months) in Patients With Early Neurological Improvement (ENI) Compared With Non-ENI for the Whole Study Population (N=18181)

<table>
<thead>
<tr>
<th>NIHSS Change</th>
<th>At 2 H</th>
<th>At 24 H</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENI</td>
<td>Non-ENI</td>
<td>P</td>
</tr>
<tr>
<td>Improvement from baseline</td>
<td>40%</td>
<td>4234</td>
</tr>
<tr>
<td>MNI</td>
<td>2543</td>
<td>6306</td>
</tr>
<tr>
<td>DNI</td>
<td>3344</td>
<td>5505</td>
</tr>
<tr>
<td>20% improvement from baseline</td>
<td>76%</td>
<td>3052</td>
</tr>
<tr>
<td>NINDS NI</td>
<td>4146</td>
<td>4708</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>92%</td>
<td>7682</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; MNI, major neurological improvement, NIHSS 0 or 1 on follow-up, or improvement ≥8 from baseline; DNI, dramatic neurological improvement, NIHSS ≥3 on follow-up, or improvement ≥10 from baseline; NINDS NI, Neurological Institute of Neurological Disorders and Stroke improvement ≥4 points from baseline.

SITS population. Furthermore, vessel recanalization was assessed as late as 22 to 36 hours, whereas neurological improvement was defined not only at the same time space (24 hours post-treatment), but also at 2 hours, when no data of vessel status were available. Therefore, some patients may have had reocclusion between 2 hours and 22 to 36 hours, and these patients increase the proportion of those who are nonrecanlized at follow-up CTA/MRA despite an ENI. However, the fact that ENI at 2 hours was strongly associated to the recanalization assessed at 24 hours suggests that most of the recanalizations had occurred already when 2-hour assessment of ENI was performed. This result is in accordance with the reports from studies using transcranial Doppler monitoring showing that recanalization in intravenous thrombolysis predominantly occurs in the first hours after initiation of treatment. Finally, the clinical diagnosis of ENI can be too late for indication of interventional treatment if assessed at 2 hours after intravenous thrombolysis. However, based on our data and other publications, the earlier ENI occurs, the higher specificity and the lower sensitivity in general. Therefore, if ENI occurs very early after the start of intravenous thrombolysis, it can be considered at least as good an indicator of recanalization as if it occurs at 2 hours.

Conclusions

Our data based on a relatively large study population not only demonstrated the association of early neurological improve-
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Early NIHSS Improvement After Stroke Thrombolysis  

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Supplemental material

Title page

Full title

Association of early NIHSS improvement with vessel recanalization and functional outcome after intravenous thrombolysis in ischemic stroke

Cover title:

Significance of early NIHSS improvement in stroke thrombolysis

Supplemental table S1. Association of excellent functional outcome (mRS 0-1 at 3 months) in improved patients and non-responders at 2h and 24 in the whole SITS population, by various definitions of improvement.
Supplemental table S1.

Association of excellent functional outcome (mRS 0-1 at 3 months) in improved patients and non-responders at 2h and 24 in the whole SITS population, by various definitions of improvement.

<table>
<thead>
<tr>
<th>Definition</th>
<th>OR (95% CI) for excellent outcome (mRS 0-1) at 3 months, in cohort with 22-36h CTA/MRA available *</th>
<th>OR (95% CI) for excellent outcome (mRS 0-1) at 3 months, in cohort with 22-36h CTA/MRA available †</th>
<th>OR (95% CI) for excellent outcome (mRS 0-1) at 3 months in whole SITS register population †</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENI based on baseline to 2 h NIHSS</td>
<td>2.7 (1.9-4.0)</td>
<td>3.7 (2.6-5.2)</td>
<td>5.7 (5.2-6.1)</td>
</tr>
<tr>
<td>20% NI from baseline</td>
<td>3.1 (2.1-4.7)</td>
<td>4.0 (2.7-5.7)</td>
<td>5.9 (5.4-6.4)</td>
</tr>
<tr>
<td>NINDS NI</td>
<td>3.0 (2.0-4.5)</td>
<td>4.0 (2.7-5.8)</td>
<td>6.3 (5.8-6.8)</td>
</tr>
<tr>
<td>DNI</td>
<td>4.2 (2.6-6.8)</td>
<td>4.7 (3.0-7.4)</td>
<td>6.1 (5.6-6.7)</td>
</tr>
<tr>
<td>MNI</td>
<td>6.1 (3.6-10.2)</td>
<td>7.7 (4.7-12.5)</td>
<td>8.0 (7.2-8.8)</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>5.9 (2.2-15.8)</td>
<td>6.0 (2.4-14.9)</td>
<td>7.2 (6.1-8.5)</td>
</tr>
<tr>
<td>ENI based on baseline to 24 h NIHSS</td>
<td>7.1 (4.3-11.8)</td>
<td>9.5 (6.0-15.0)</td>
<td>15.1 (13.7-16.7)</td>
</tr>
<tr>
<td>20% NI from baseline</td>
<td>4.6 (3.0-7.1)</td>
<td>6.2 (4.2-9.2)</td>
<td>10.6 (9.7-11.6)</td>
</tr>
<tr>
<td>NINDS NI</td>
<td>6.5 (4.3-9.9)</td>
<td>8.2 (5.6-12.0)</td>
<td>13.1 (12.1-14.3)</td>
</tr>
<tr>
<td>DNI</td>
<td>9.9 (6.5-15.0)</td>
<td>12.1 (8.2-18.0)</td>
<td>12.0 (11.1-13.0)</td>
</tr>
<tr>
<td>MNI</td>
<td>9.1 (5.8-14.2)</td>
<td>10.9 (7.2-16.5)</td>
<td>12.3 (11.2-13.5)</td>
</tr>
<tr>
<td>Complete recovery</td>
<td>11.2 (5.7-21.8)</td>
<td>12.9 (6.9-24.0)</td>
<td>11.9 (10.6-13.3)</td>
</tr>
</tbody>
</table>

*Adjusted for age, baseline NIHSS score, recanalization at 22-36h
† Adjusted for age, baseline NIHSS score
해혈뇌졸중 환자에서 정맥내 혈전용해제 투여 이후 조기 NIHSS 점수의 호전과 혈관재개통 및 기능적 예후에 대한 연관성

Association of Early National Institutes of Health Stroke Scale Improvement With Vessel Recanalization and Functional Outcome After Intravenous Thrombolysis in Ischemic Stroke

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Key Words: early neurological improvement ■ recanalization ■ stroke ■ thrombolysis ■ vessel occlusion

배경과 목적
급성 뇌졸중의 혈전용해요법 이후 조기 신경학적 호전(early neurological improvement, ENI)에 대하여 다양한 점을 사용하고 있으나, ENI의 경우 혈관의 재개통 및 기능적 결과와 연관이 있는 것으로 보고되고 있다. 저자들은 이전 보고에 따라 정의된 ENI가 정맥내 혈전용해제 투여 이후 혈관재개통 및 3개월 기능적 예후를 얼마나 예측할 수 있는가, SITS-ISTR (Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Register)의 대규모 코호트 기록을 이용하여 조사하였다.

방법
2002년 12월부터 2008년 12월까지, 21,534명의 환자를 중 798명(3.7%)에서 CT 혹은 MR 혈관조영에서의 초기 폐색과 치료 이후 22-36시간의 혈관조영 데이터를 확인할 수 있었다. 치료 이후 2시간내와 24시간내에 ENI를 평가하였고, 다음과 같이 각각 정의하였다. (1) NIHSS (National Institutes of Health Stroke Scale) 점수가 초기에 비해 4점 이상 호전된 경우, (2) NIHSS 점수가 0, 1 혹은 8점 이상 호전된 경우, (3) NIHSS 점수가 3점 이하 혹은 10점 이상 호전된 경우, (4) NIHSS 점수가 초기에 비해 20% 이상 호전된 경우, (5) NIHSS 점수가 초기에 비해 40% 호전된 경우, (6) NIHSS 점수가 0 또는 1인 경우, ENI와 혈관재개통 및 양호한 기능적 결과(3개월 수정란킨도[modified Rankin Scale] 점수 0-2)의 연관성을 평가하기 위하여 ROC (receiver operating curve) 곡선 분석 및 다중 로지스틱 회귀 분석이 사용되었다.

결과
치료 결과 2시간내의 ENI는 ROC 곡선 분석에 따라 재관류를 진단하는 데 있어 양호한 정확성을 보였다. 초기로부터의 NIHSS 점수 변화의 분율에 기반한 ENI의 정의가 NIHSS 재판정(cutoff)에 기반한 정의에 비해 2시간, 24시간의 재관류를 진단하는 데 있어 더 좋은 정확도를 보이는 것으로 조사되었다(2시간내 NIHSS 점수 20% 이상에 대한 최상의 결과에 대한 AUC [area under the curve]=0.633, 민감도 58%, 특이도 69%, 양성 예측도 68%, 음성 예측도 59%: 24시간내 NIHSS 점수 20% 이상에 대한 최상의 결과에 대한 AUC=0.692, 민감도 69%, 특이도 70%, 양성 예측도 70%, 음성 예측도 62%). ENI는 혈관조영 코호트(605명)에서는 재개통 여부와는 독립적으로 2.8에서 6.0의 교차비(OR)로 기능적 예후를 예측할 수 있었고, 전체 코호트(18,181명)에서는 6.9에서 9.7의 교차비로 기능적 예후를 예측할 수 있었다.

결론
2시간내의 조기 20% NIHSS 점수의 호전이 3개월내의 기능적 결과 및 혈전용해요법 이후의 재개통에 대한 가장 적극적인 예측 인자였다. 혈관 상태에 대한 영상 검사가 이루어질 수 없는 경우에 정확하게 ENI가 혈관재개통의 대비 효과로서의 역할을 할 수도 있다. 그러나 정맥내 혈전용해 이후 재관류에 대한 평가가 필요한 경우에는 ENI 외에 혈관 영상진단이 추천된다.