The Types of Neurological Deficits Might Not Justify
Withholding Treatment in Patients With Low Total National
Institutes of Health Stroke Scale Scores

Enrique C. Leira, MD, MS; Bryan R. Ludwig, MD; M. Edip Gurol, MD;
James C. Torner, MS, PhD; Harold P. Adams, Jr, MD

Background and Purpose—There is controversy regarding the threshold for treating patients with mild strokes. Physicians often are confronted with the dilemma of excluding patients with low baseline National Institutes of Health Stroke Scale (NIHSS) score and long-term outcome among patients with a low total NIHSS score.

Methods—We performed a secondary analysis on those patients enrolled in the Trial of ORG 10172 in Acute Stroke Treatment that presented within 4.5 hours of symptom onset and had a baseline NIHSS score ≤6 (n=194). We performed multivariate logistic regression analyses using very favorable outcome at 3 months as the outcome variable and each of the individual items of the baseline NIHSS examination and syndromic combinations of NIHSS scores as predictors. The analyses were adjusted for potential confounders with and without adjusting for total NIHSS score.

Results—Baseline total NIHSS scores were inversely associated with very favorable outcome at 3 months. No individual NIHSS item, or syndromic combination of NIHSS scores, was independently associated with very favorable outcome in a consistent manner after accounting for confounders and collinearity.

Conclusions—The types of neurological deficits in the baseline NIHSS are not independent predictors of long-term prognosis for patients with mild stroke. These exploratory findings argue against the practice of withholding reperfusion treatment in patients with mild stroke when the types of baseline NIHSS deficits are perceived to be nondisabling. (Stroke. 2012;43:782-786.)

Key Words: acute stroke ■ mild stroke ■ NIH Stroke Scale ■ outcomes ■ prognosis ■ scales

See editorial, p 625.

Approximately half of the patients with an acute stroke have a clinical syndrome that could be categorized as mild.1 Physicians often are confronted with the dilemma of deciding which patients with mild symptoms need to be treated with reperfusion therapies. Withholding treatment may be problematic because patients with mild deficits initially may have unfavorable long-term outcomes.2 The types of neurological deficits are often considered when deciding about acute treatment. Physicians may favor treating patients with language or visual deficits and withhold reperfusion treatment when they perceive the symptoms are not likely disabling.3 Unfortunately, physicians are known to disagree about the functional significance of neurological symptoms in the acute stroke setting.4 Furthermore, there is a lack of consensus about what constitutes a “minor” stroke syndrome.5 In this study, we evaluated the appropriateness of the practice of excluding patients with low baseline National Institutes of Health Stroke Scale (NIHSS) scores for treatment based on the perception that some symptoms are not significantly disabling.3 We analyzed the relationship between specific neurological deficits in the NIHSS score and long-term outcome among patients with a low total NIHSS score. We hypothesized that, among patients with low baseline NIHSS scores, the presence of aphasia or visual deficits would independently predict a worse functional outcome.

Materials and Methods

The study methodology is shown in Figure 1. We tested our hypothesis through a retrospective analysis of a large stroke trial, Trial ORG 10172 in Acute Stroke Treatment (TOAST), which enrolled patients with a wide range of stroke syndromes, including numerous patients with relatively mild neurological impairment. The trial evaluated the effects of danaparoid, a low-molecular-weight heparinoid, administered within 24 hours of onset of acute ischemic stroke in 1281 patients at 37 centers in the United States.6 The specific methods and results are published elsewhere.6 The study was...
authorized by the University of Iowa Institutional Review Board. Because the studied intervention did not show differences in outcome, for the purpose of this analysis, we joined both arms of the trial. Data collected prospectively included the patients’ age, sex, side of the lesion, temperature, systolic blood pressure, blood glucose level, and baseline neurological impairments as rated on the NIHSS.

Each NIHSS item was categorized as either normal (score=0) or abnormal (score>0). Right and left arm scores were combined as “arm motor,” and right and left leg scores were combined as “leg motor.” Items graded as 9 (“untestable”) were considered as “missing” responses for analysis. We also created 8 different combinations of NIHSS responses that replicate clinical syndromes used in clinical practice. These syndromes included “pure motor syndrome” (abnormal NIHSS responses for only arm motor and leg motor, with or without dysarthria or facial weakness, with normal remaining NIHSS items), “pure sensory syndrome” (abnormal sensory examination with normal remaining NIHSS items), “aphasia–hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal language), “neglect–hemiparesis” (abnormal ipsilateral motor arm and leg and neglect), “hemianopsia & hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal visual fields), “lethargic hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal level of consciousness); “brachial pattern of weakness” (motor arm score greater than ipsilateral motor leg score), and “ataxic hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal coordination). Functional outcomes at 3 months were determined by a prespecified algorithm using the Glasgow Outcome Scale and the modified Barthel Index. Patients who had a Glasgow Outcome Scale score of 1 and a Barthel Index score of 19 to 20 (95–100 in the usual scoring system) were categorized as having a “very favorable outcome” (VFO).

Figure 1. Study hypothesis and research methodology.

Results

We identified a total of 194 patients with a baseline NIHSS score of ≤6 who presented to the emergency department within 4.5 hours of symptom onset. Forty-eight percent arrived in the 0- to 2-hour time window, 24% in the 2- to 3-hour window, and 28% in the 3- to 4.5-hour window. Of those patients, 65% were men. The mean age was 65.8 years (SD 11.7). Ninety-seven patients had a left-sided ischemic lesion, 87 had a lesion on the right, and 10 were classified as “other.” The mean and median baseline NIHSS score for this target population was 4.22 and 4, respectively (SD 1.47). Figure 2 shows the distribution of total NIHSS scores among those patients, 65% were men. The mean age was 65.8 years (SD 11.7). Ninety-seven patients had a left-sided ischemic lesion, 87 had a lesion on the right, and 10 were classified as “other.” The mean and median baseline NIHSS score for this target population was 4.22 and 4, respectively (SD 1.47).

Figure 2. Distribution of NIHSS scores among 194 patients with a total NIHSS score ≤6 who presented within 4.5 hours of symptom onset. NIHSS indicates National Institutes of Health Stroke Scale.

Our target population was those patients who presented to the emergency department within 4.5 hours of symptom onset and had a baseline NIHSS score ≤6. We analyzed baseline characteristics and performed an analysis of the prevalence of abnormal individual baseline NIHSS items among those patients. We then performed multivariate logistic regression analyses using VFO as the outcome variable. In all logistic regression analyses, we included each of the individual items of baseline NIHSS examination as independent predictors. All these analyses were adjusted for age, sex, side of the lesion, time from symptom onset to emergency department arrival, temperature, systolic blood pressure, blood glucose level, and treatment group assignment (ORG 10172 versus placebo). To evaluate for potential collinearity (the total NIHSS score and the stroke syndromes are the result of combining individual NIHSS items), we performed 4 separate logistic analyses to combine these additional covariates. The main analysis did not include any additional covariates. In 1 of those analyses, total NIHSS score was added as a covariate. In another analysis, stroke syndromes were added as covariates. In a third analysis, both total NIHSS score and stroke syndromes were added. All statistical analyses were done using SAS Version 9.2 (SAS Institute Inc, Cary, NC).

Each NIHSS item was categorized as either normal (score=0) or abnormal (score>0). Right and left arm scores were combined as “arm motor,” and right and left leg scores were combined as “leg motor.” Items graded as 9 (“untestable”) were considered as “missing” responses for analysis. We also created 8 different combinations of NIHSS responses that replicate clinical syndromes used in clinical practice. These syndromes included “pure motor syndrome” (abnormal NIHSS responses for only arm motor and leg motor, with or without dysarthria or facial weakness, with normal remaining NIHSS items), “pure sensory syndrome” (abnormal sensory examination with normal remaining NIHSS items), “aphasia–hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal language), “neglect–hemiparesis” (abnormal ipsilateral motor arm and leg and neglect), “hemianopsia & hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal visual fields), “lethargic hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal level of consciousness); “brachial pattern of weakness” (motor arm score greater than ipsilateral motor leg score), and “ataxic hemiparesis” (abnormal ipsilateral motor arm and leg and abnormal coordination). Functional outcomes at 3 months were determined by a prespecified algorithm using the Glasgow Outcome Scale and the modified Barthel Index. Patients who had a Glasgow Outcome Scale score of 1 and a Barthel Index score of 19 to 20 (95–100 in the usual scoring system) were categorized as having a “very favorable outcome” (VFO).
Table 1. Prevalence of “Abnormal” Individual NIHSS Items and Stroke Syndromes Among 194 Patients With a Total NIHSS Score ≤6

<table>
<thead>
<tr>
<th>NIHSS Item</th>
<th>Percent of Patients With Abnormal NIHSS Item</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of consciousness</td>
<td>3.1</td>
</tr>
<tr>
<td>Orientation questions</td>
<td>6.2</td>
</tr>
<tr>
<td>Command questions</td>
<td>0.0</td>
</tr>
<tr>
<td>Horizontal gaze</td>
<td>4.6</td>
</tr>
<tr>
<td>Visual fields</td>
<td>9.8</td>
</tr>
<tr>
<td>Facial motility</td>
<td>63.0</td>
</tr>
<tr>
<td>Arm weakness</td>
<td>35.0</td>
</tr>
<tr>
<td>Leg weakness</td>
<td>22.7</td>
</tr>
<tr>
<td>Limb ataxia</td>
<td>38.1</td>
</tr>
<tr>
<td>Sensory loss</td>
<td>37.1</td>
</tr>
<tr>
<td>Best language</td>
<td>14.5</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>42.3</td>
</tr>
<tr>
<td>Hemineglect</td>
<td>11.3</td>
</tr>
</tbody>
</table>

Stroke Syndrome (NIHSS Combinations) | Percent of Patients With Syndrome |
-------------------------------------|----------------------------------|
| Pure motor syndrome               | 4.1                              |
| Pure sensory syndrome             | 0.5                              |
| Aphasia–hemiparesis               | 0.0                              |
| Hemineglect–hemiparesis           | 3.1                              |
| Hemianopsia & hemiparesis         | 0.5                              |
| Lethargic hemiparesis             | 0.0                              |
| Brachial pattern of weakness      | 18.0                             |
| Ataxic–hemiparesis                | 9.8                              |

NIHSS indicates National Institutes of Health Stroke Scale.

symptom onset. Table 2 shows the significant variables in the 4 separate logistic regression analyses modeled after a higher probability of VFO at 3 months. Higher total NIHSS scores were consistently associated with a lower chance of a VFO at 3 months. Higher glucose levels on admission had a borderline association with a lower chance of VFO.

No single NIHSS item was independently and consistently associated with VFO at 3 months. The main logistic regression model (Table 2, “no additional covariates”) showed no independent association between NIHSS items and outcome. NIHSS items that show statistical significance only when total NIHSS score or stroke syndromes are included in the model reflect collinearity, an artifact of logistic regression, rather than a true association. For example, ataxia–hemiparesis was associated with a lower chance of VFO, but that association disappeared when adjusting for total NIHSS score. This can be explained by collinearity with the total NIHSS score, because all 19 patients with ataxia–hemiparesis had higher total NIHSS scores. Similarly, hemineglect was associated with a better outcome at 3 months only when total NIHSS was added to the logistic model and stroke syndromes were excluded. Univariate analysis confirmed that this finding was also due to collinearity with the NIHSS score: a VFO was achieved by 16 of 19 (84%) patients with hemineglect and higher (4–6) NIHSS scores as compared with 2 of 3 (67%) of patients with hemineglect and lower (1–3) NIHSS scores. A similar situation occurred with limb ataxia, which was associated with a better 3-month outcome only if total NIHSS scores were added to the logistic model. This finding was also due to collinearity with lower NIHSS scores: VFO was achieved by 11 of 12 (92%) patients with limb ataxia and lower total NIHSS scores as compared with 43 of 62 (69%) patients with limb ataxia and higher NIHSS scores. This was also the case for facial weakness, which was only associated with better outcomes if both total NIHSS score and stroke syndromes were also present as covariates.

Discussion

Physicians face dilemmas deciding whether to treat patients with mild ischemic strokes with recombinant tissue plasminogen activator (rtPA). This is an important public health issue because over half of the strokes in the United States have a NIHSS ≤5.1 Physicians do not want to expose patients with low NIHSS scores to the hemorrhagic risks of rtPA because they are likely to have a favorable outcome despite any intervention.10 However, data suggest that the long-term outcome of patients with mild strokes might not be benign.11,12 Of particular concern are the limitations of the NIHSS to transmit the severity of certain stroke syndromes13 such as the posterior circulation strokes.14 For example, patients with vertebrobasilar symptoms such as the relatively common lateral medullary syndrome of Wallenberg often have potentially disabling abnormalities in gait or swallowing that are not measured by the NIHSS. In addition, the risk of hemorrhagic transformation after rtPA may correlate with the size of the infarction,15 implying that patients with milder strokes may have a lower bleeding risk,16 which could support the treatment of milder cases.

The dilemma for treating milder cases is not unequivocally clarified by the available guidelines. The American Heart
Association guidelines suggest that a patient is eligible for rtPA unless the neurological signs are “minor and isolated.”17 This recommendation can be confusing, particularly because “minor stroke” remains an ill-defined entity.5 Attempts have been made to define “minor stroke” quantitatively based on the total NIHSS score.5,18 Unfortunately, any cutoff for defining this entity is arbitrary given the linear relationship between total NIHSS score and outcome.10 The practice advisory of the American Academy of Neurology added some qualitative statements to the concept of mild stroke. It suggests avoiding thrombolytic therapy in patients “with isolated mild neurological deficits, such as ataxia alone, sensory loss alone, dysarthria alone, or minimal weakness.”19 This recommendation is inspired by the National Institute of Neurological Disorders and Stroke (NINDS) rtPA trial, which excluded patients with isolated sensory stroke, isolated ataxia, isolated dysarthria, or isolated facial weakness.9 Because the risk/benefit of rtPA remains unknown in these patients, it seems reasonable to exclude them from such treatment. However, patients with such isolated symptoms can only sum very low total scores (1–2) in the NIHSS and represent a small fraction of the total patients. Unfortunately, the guidelines do not specify what to do in the most common scenario of a combination of those or other minor symptoms.

Attempts have also been made to define “minor stroke” qualitatively.18 A secondary analysis of the NINDS rtPA trial retrospectively categorized subjects into 5 definitions for minor stroke that were based on the total NIHSS score and qualitative aspects of the symptoms.18 One of these categories specifically included patients with a combination of motor, coordination, and sensory deficits without deficits in the sphere of language, level of consciousness, extinction/neglect, horizontal eye movements, or visual fields.18 Those patients with “lacunar” findings experienced favorable outcomes with rtPA.18 Patients with mild “nonlacunar” neurological findings were excluded from that analysis, so it is uncertain whether they would have benefited differently from rtPA than the “lacunar” counterparts. Another secondary analysis of the NINDS rtPA trial attempted to better categorize the neurological findings of those patients who had minor symptoms (total NIHSS score ≤5). They analyzed the prevalence and outcomes of 16 different clinical syndromes based on combinations of baseline NIHSS scores. This exploratory study provides some reassurance about the favorable outcomes with rtPA for patients with minor symptoms.16 However, the study had a small number of subjects with minor symptoms (n=58), which limits the ability to draw conclusions regarding the outcome of the different clinical syndromes.16

We found that the type of neurological deficits, as detected by the NIHSS examination, does not independently predict poor outcome among patients with a low baseline NIHSS score. The associations observed are not consistent and reflect collinearity with the total NIHSS score. The lack of a consistent and independent association between baseline NIHSS deficits, or syndromic combination of those deficits, and a favorable 3-month outcome argues against the current practice of withholding reperfusion treatment in mild patients who have deficits perceived to be nondisabling.3 Therefore, the decision for considering treatment should not depend on which specific items are abnormal on the initial baseline NIHSS. Our negative findings seem counterintuitive at first. After all, the pattern of neurological deficits is a function of the location of the brain lesion, which in turn has been associated with neurological outcome.20 It is important to understand, however, that we are focusing on a selective group of patients with stroke who have a low score in the NIHSS. The NIHSS scores tend to be higher in patients with supratentorial lesions14 and dominant hemispheric lesions.21 As such, the population of patients with a low total NIHSS scores is biased toward milder subcortical strokes.22 This may explain the low percentage of patients with language and visual dysfunction in this target population. Our findings do not contradict the overall relationship between lesion location and outcome. It just suggests that such an association is not observed among the particular array of neurological deficits seen in patients with milder symptoms. The strength of our study is that it includes a representative large cohort with low baseline NIHSS scores with data systematically and reliably collected.6 The TOAST trial is unique because, unlike most acute stroke trials, it allowed a large number of patients with mild symptoms.

We also recognize the limitations of this study. There is always a risk of selection bias in patients participating in clinical trials. This can raise concerns about generalizability to other settings such as the population of patients considered for rtPA in clinical practice. This concern is particularly valid because patients in the TOAST trial were not treated with rtPA. For that reason we have selected only those patients in TOAST who presented to the emergency department within 4.5 hours of symptom onset.8 Also, the TOAST study is now more than a decade old. Ancillary care, which influences outcome, has improved. However, in this study, we were interested in NIHSS items as predictors of outcome rather than in the absolute outcomes of patients. We consider it unlikely that improvements in ancillary care would have resulted in differentially improved outcomes for different baseline NIHSS deficits. We also recognize that the stroke outcome measure used in this study (VFO) could lack sensitivity to detect prognosis differentially in patients with mild strokes, including the ability to detect mild but significant language and visual deficits. On the other hand, these outcome measures are standard in clinical trials as well as clinical practice. Lastly, we recognize that the absence of an observed association does not eliminate the possibility that such association in fact exists. We retrospectively estimated the power we had to detect an association for the different NIHSS items. This estimation ranged from 76% to 10%. This raises the possibility that we might have been underpowered to detect an effect on those NIHSS items that are less prevalent among patients with low total scores.

In summary, there is uncertainty about the choice of an appropriate NIHSS cutoff for acute thrombolytic treatment in patients with mild symptoms. Future trials are needed to better define the risk/benefit of acute interventions in patients with milder symptoms.16 In the meantime, our findings suggest that the types of neurological deficits are not independent predictors of long-term prognosis for patients with
mild stroke and should not be used to justify withholding reperfusion treatment. These data, in conjunction with other recent studies, suggest that the current rtPA guidelines might be unnecessarily restrictive for treating patients with mild strokes.

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**Disclosures**

None.

**References**

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神経脱落徵候の種類は総 NIHSS スコアが低い患者の治療保留の根拠とはならない

The Types of Neurological Deficits Might Not Justify Withholding Treatment in Patients With Low Total National Institutes of Health Stroke Scale Scores

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背景および目的: 軽度脳卒中患者に対する治療の閾値に関しては異論が多い。症状が大きな障害をもたらすものではないと判断される場合は、急性期の治療を保留する医師も多い。本研究では、NIHSS スコアによって示される特定の神経脱落徵候と、総 NIHSS スコアの低い患者の長期的転帰の関係を分析し、治療を保留することの適否を検証した。

方法: Trial of ORG 10172 in Acute Stroke Treatment 試験の被験者のうち、症状発現から 4.5 時間以内に受診し、ベースラインの NIHSS スコアが 6 以下であった患者 (194例) を対象に二次分析を実施した。3カ月時の非常良好な転帰を転帰変数とし、ベースラインの NIHSS 検査の各項目および症候群的な NIHSS スコアの組み合わせを予測因子とする多変量ロジスティック回帰分析を行った。潜在的交絡因子について補正を行い、総 NIHSS スコアについて補正した場合と補正しなかった場合の分析を行った。

結果: ベースラインの総 NIHSS スコアと3カ月時の非常良好な転帰の間には負の関連が認められた。交絡因子および共線性に関する補正を行った結果、個々の NIHSS の項目または症候群的な NIHSS スコアの組み合わせと非常良好な転帰の間に、独立した関連が一貫して認められることはなかった。

結論: ベースラインの NIHSS によって示される神経脱落徵候の種類は、軽度脳卒中患者の長期的予後の独立した予測因子とはならない。上記の探索研究の所見が示すように、ベースラインの NIHSS による脱落徵候の種類が障害をもたらすものではないと判断されたとしても、軽度脳卒中患者の再灌流治療を保留するのは適切ではない。

表2 3カ月時の「非常に良好な転帰」の確率上昇をモデル化したロジスティック回帰分析における有意な変数 *

<table>
<thead>
<tr>
<th>モデルに追加した共変量</th>
<th>有意な変数</th>
<th>OR (95% CI)</th>
<th>p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>共変量追加なし (主モデル)</td>
<td>血糖値</td>
<td>0.99 (0.99 〜 1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>脳卒中症候群</td>
<td>運動失調−不全片麻痺</td>
<td>0.08 (0.01 〜 0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>総 NIHSS スコア</td>
<td>口舌の運動失調 (NIHSS)</td>
<td>4.64 (1.09 〜 19.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>脳卒中症候群および総 NIHSS スコア</td>
<td>黒的運動失調 (NIHSS)</td>
<td>4.89 (1.05 〜 7.95)</td>
<td>0.04</td>
</tr>
<tr>
<td>総 NIHSS スコア</td>
<td>四肢の運動失調 (NIHSS)</td>
<td>4.08 (1.37 〜 12.08)</td>
<td>0.01</td>
</tr>
<tr>
<td>运動失調−不全片麻痺</td>
<td>0.11 (0.01 〜 0.95)</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

NIHSS: 米国国立衛生研究所脳卒中スケール。
* すべてのモデルにおいて NIHSS の各項目を予測因子として用い、年齢、性別、病変の有無を共変量とした。