Identifying Patients at High Risk for Poor Outcome After Intra-Arterial Therapy for Acute Ischemic Stroke

Hen Hallevi, MD; Andrew D. Barreto, MD; David S. Liebeskind, MD; Miriam M. Morales, BS; Sheryl B. Martin-Schild, MD, PhD; Anitha T. Abraham, MD; Jignesh Gadia, MD; Jeffrey L. Saver, MD; the UCLA Intra-Arterial Therapy Investigators; James C. Grotta, MD; Sean I. Savitz, MD

**Background and Purpose**—Intra-arterial recanalization therapy (IAT) is increasingly used for acute stroke. Despite high rates of recanalization, the outcome is variable. We attempted to identify predictors of outcome that will enable better patient selection for IAT.

**Methods**—All patients who underwent IAT at the University of Texas Houston Stroke Center were reviewed. Poor outcome was defined as modified Rankin Scale score 4 to 6 on hospital discharge. Findings were validated in an independent data set of 175 patients from the University of California at Los Angeles Stroke Center.

**Results**—One hundred ninety patients were identified. Mean age was 62 years and median baseline National Institutes of Health Stroke Scale score was 0.18. Recanalization rate was 75%, symptomatic hemorrhage rate was 6%, and poor outcome rate was 66%. Variables associated with poor outcome were: age, baseline National Institutes of Health Stroke Scale, admission glucose, diabetes, heart disease, previous stroke, and the absence of mismatch on the pretreatment MRI. Logistic regression identified 3 variables independently associated with poor outcome: age (P=0.049; OR, 1.028), National Institutes of Health Stroke Scale (P=0.013; OR, 1.084), and admission glucose (P=0.031; OR, 1.011). Using these data, we devised the Houston IAT score: 1 point for age >75 years; 1 for National Institutes of Health Stroke Scale score >18, and 1 point for glucose >150 mg/dL (range, 0 to 3 mg/dL). The percentage of poor outcome by Houston IAT score was: score of 0, 44%; 1, 67%; 2, 97%; and 3, 100%. Recanalization rates were similar across the scores (P=0.4). Applying Houston IAT to the external cohort showed comparable trends in outcome and nearly identical rates in the Houston IAT therapy 3 tier.

**Conclusions**—The Houston IAT score estimates the chances of poor outcome after IAT, even with recanalization. It may be useful in comparing cohorts of patients and when assessing the results of clinical trials. (Stroke. 2009;40:1780-1785.)

**Key Words:** acute care ■ acute stroke ■ interventional neuroradiology ■ thrombolysis

Intra-arterial therapy (IAT) is increasingly used in the treatment of acute stroke either as the primary modality for patients presenting 3 to 8 hours from symptom onset or as an adjuvant measure in patients treated with intravenous tissue plasminogen activator (IV tPA) who do not improve in a timely fashion. Primary IAT has been shown to be improve clinical outcome when administered 3 to 6 hours from symptom onset using intra-arterial thrombolytics\(^1\)-\(^2\) and is approved up to 8 hours using mechanical clot retrieval (Merci Retriever) or suction thrombectomy (Penumbra System).\(^3\)\(^4\)

Adjuvant IAT has been studied in Phase I and II trials\(^5\) and 2 randomized trials are ongoing.\(^6\) The primary goal of IAT is recanalization of the occluded artery and reperfusion of the ischemic territory. Recanalization has been shown to correlate with a better outcome in patients with stroke\(^7\); however, this correlation may be confounded by several factors, including the time from symptom onset to recanalization and the degree of collateral circulation to the ischemic region\(^8\) and the extent of infarct before recanalization.\(^9\) Therefore, it is not surprising that despite high rates of recanalization with IAT, the rate of functional independence is reported to be only 40% to 50%.\(^4\)\(^10\)-\(^12\) A recent meta-analysis of uncontrolled IAT cohort studies failed to detect a benefit compared with a model predicting outcome without IAT,\(^13\) suggesting a need for more rigorous evaluation of the efficacy and safety of this approach. IAT is invasive, frequently requiring intubation and admission to an intensive care unit. IAT is also a very time- and resource-intensive procedure requiring a trained and dedicated interventional team. It may therefore be important both clinically and economically to improve patient...
selection for IAT. Important predictors of outcome in IAT have already been identified. In a post hoc analyses of the PROlyse in Acute Cerebral Thromboembolism (PROACT II) trial, the investigators identified age and the National Institutes of Health Stroke Scale (NIHSS) and the Alberta Stroke Program Early CT (ASPECT) score (a semiquantitative measure of early ischemic changes in the middle cerebral artery territory on admission CT) as independent predictors of outcome. Those predictors were used to evaluate the treatment effect of prourokinase in middle cerebral artery strokes and may not be applicable to current IAT techniques, thrombolytics, and devices. Older patients have also been previously shown to benefit less from IAT in a single-center series of 114 patients. Based on these data, we hypothesized that patients with severe strokes, advanced age, and comorbidities are less likely to benefit from IAT. The purpose of this study was therefore to determine, in patients with stroke subjected to IAT in routine clinical practice, admission criteria that will identify patients who are not likely to benefit from IAT.

Methods

Study Population

Patients undergoing IAT were identified using the University of Texas at Houston (UTH) prospective stroke registry from 1998 to 2007. In our institution, the criteria for considering IAT are: ischemic stroke within 6 hours of time first evaluated by the stroke team, disabling symptoms, large vessel occlusion (suspected or documented), and less than one third of the middle cerebral artery territory showing hypodensity on the admission CT. For patients eligible for IV tPA, the same criteria are applied after IAT is given if the patients do not recanalize (by transcranial Doppler, CT angiography, or MR angiography) and show no clinical improvement at the end of the infusion. Patients were excluded from this study if they were treated >8 hours from symptom onset or participating in a clinical trial.

Measurements

MRI was obtained before IAT depending on the availability of the MRI machine. At our institution, candidates for IAT are routinely intubated before the procedure. In addition, follow-up imaging with either CT or MRI and clinical assessment using NIHSS are routinely obtained as close as possible to 24 hours after IV tPA or IAT. We reviewed the records and neuroimaging of all patients taken to IAT from 1998 to 2007. Clinical data points included demographics, medical history, symptom onset time, baseline NIHSS, laboratory values, IV tPA treatment, symptomatic intracerebral hemorrhage (defined as a parenchymal hematoma Grade 2 associated with worsening neurological status thought to be related to the hematoma), and functional outcome on discharge as measured by the modified Rankin Scale. Poor outcome was defined as modified Rankin Scale 4 to 6 on hospital discharge. Radiological data points included pre-IAT MRI if performed (including diffusion-weighted imaging lesion volume and presence of mismatch) and post-IAT CTs or MRIs. “Malignant” lesion was defined as diffusion-weighted imaging infarct volume >100 mL on pre-IAT MRI. Mismatch was defined as >20% difference between the diffusion-weighted imaging lesion and perfusion deficit (by eyeballing the lesion) on pre-IAT MRI. Angiography data included IAT duration (defined from groin puncture to the time of the last angiogram), responsible vessel, degree of occlusion, thrombolytic used, mechanical device used, and degree of recanalization at the end of the procedure. For recanalization, we used Thrombolysis in Cerebral Infarction (TICI) score. Recanalization (partial and complete) was defined as TICI 2b or higher because this was previously shown to better correlate with good outcome.

The study was approved by the Institutional Review Board.

Table 1. Baseline Characteristics and Outcome

<table>
<thead>
<tr>
<th>Cohort</th>
<th>UTH (n=190)</th>
<th>UCLA (n=175)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD</td>
<td>62±14</td>
<td>70±17</td>
<td>&lt;0.001 (TT)</td>
</tr>
<tr>
<td>Admission NIHSS, median (IQR)</td>
<td>19 (16.5–22.5)</td>
<td>17 (12–22)</td>
<td>0.126 (MW)</td>
</tr>
<tr>
<td>Admission glucose, mg/dL, mean±SD</td>
<td>144±55</td>
<td>136±56</td>
<td>0.181 (TT)</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>42 (22.1)</td>
<td>29 (16.6)</td>
<td>0.182 (CS)</td>
</tr>
<tr>
<td>Poor outcome, %</td>
<td>126 (66)</td>
<td>84 (48)</td>
<td>&lt;0.001 (CS)</td>
</tr>
</tbody>
</table>

IAT indicates interquartile range; TT, t test; CS, χ² test; MW, Mann–Whitney test.

Validation Cohort

For the validation data set, we used a cohort of consecutive patients treated with IAT within 8 hours of symptom onset at the University of California at Los Angeles (UCLA) stroke center between July 1992 and December 2007.

Statistical Analysis

The analysis was carried out using SPSS for Windows version 15 (SPSS Inc, Chicago, III). We conducted a univariate analysis using χ² for categorical variables and logistic regression for continuous variables to identify potential predictors of poor outcome. To reduce the likelihood of Type I error, we prespecified the following variables to be tested: age, admission NIHSS, admission glucose, presence of mismatch on pretreatment MRI, presence of a malignant lesion on pretreatment MRI, comorbidities (hypertension, coronary artery disease, diabetes, previous stroke), and time from symptom onset to IAT (this was included because in most cases, this time can be estimated in the emergency room). Variables from univariate analysis resulting in probability values of <0.2 were entered into the multivariate logistic regression model using the forced entry method. At the multiple regression level, variables with a probability value >0.05 were excluded. The Hosmer-Lemeshow goodness-of-fit statistics were used to assess the final model. We also tested the association of procedure-related variables (recanalization and IAT duration) to outcome; however, because the primary goal of the study was predicting IAT outcome before the procedure, these were not used in the multivariate model.

The independent predictors identified in the multivariate analysis were used to create a score. Continuous variables were dichotomized at the median or the 75th percentile where appropriate. Spearman’s correlation explored how well the final score correlated with discharge modified Rankin Scale.

Receiver operator characteristics curves were used to explore agreement between the predictive score and outcomes in the original and validation cohorts. χ² test was used to compare the proportion of poor outcome of each tier of the Houston IAT (HIAT) score between the UTH and UCLA cohorts.

Results

We identified 190 patients undergoing IAT in the UTH data set. Seventy-four (38.9%) underwent primary IAT and 116 (61.1%) adjuvant IAT. Forty-one (21.6%) had pre-IAT MRI. The IAT techniques used were as follows: intra-arterial thrombolytics, only 30.5% (58 of 190); intra-arterial thrombolytics with guidewire clot disruption, 48.9% (93 of 190); guidewire clot disruption, only 2.1% (4 of 190); and MERCI clot retriever, 18.5% (35 of 190). The stroke was in the dominant hemisphere in 94 patients (49.5%). Symptomatic intracerebral hemorrhage occurred in 13 patients (6.8%) and the rate of recanalization was 75.6%. Table 1 shows the main baseline and outcome characteristics.
Pre-IAT Predictors of Outcome and Score Development

The results of univariate analysis in the derivation cohort for all variables are listed in Table 2. The following predictors of poor outcome were identified in univariate analysis and entered into the multivariate analysis: age, NIHSS, admission glucose, history of coronary artery disease, history of diabetes mellitus, and previous stroke. Presence of a nonmalignant diffusion-weighted imaging lesion or mismatch on the pre-IAT MRI was associated with a favorable outcome. After logistic regression, only age (Wald $= 3.9$, $P = 0.049$; OR, 1.028), NIHSS (Wald $= 6.1$, $P = 0.013$; OR, 1.084), and admission glucose (Wald $= 4.7$, $P = 0.031$; OR, 1.011) remained as significant predictors of poor outcome. We then proceeded to dichotomize the predictors according to our primary hypothesis: age and admission glucose at the 75th percentile and admission NIHSS at the median. We scored 1 point for each variable as follows: age $> 75$ years; NIHSS $> 18$; and admission glucose $> 150$ mg/dL. The sum of points resulted in a score we named the UTH IAT (HIAT) score. HIAT score ranges from 0 to 3.

Procedural Outcomes

Table 2 also shows the association between the prespecified procedural outcomes and clinical outcomes in the univariate analysis. Recanalization was associated with favorable outcome and IAT duration with poor outcome. There was no association between the time from symptom onset to IAT and outcome. Also, there was no association between the rates of recanalization and the presence of mismatch on MRI ($P = 0.15$). Table 3 shows the procedural and clinical outcomes according to the occluded artery, IAT technique used, and whether IV tPA was given before IAT.

Exploring Clinical and Procedural Outcomes Using the HIAT Score

We next plotted the percentage of patients with the various study end points by the HIAT score (Table 4). The HIAT score demonstrated an increase in the proportion of poor outcome up to 100% in patients with HIAT of 3. A similar pattern was observed when we looked at mortality and symptomatic intracerebral hemorrhage. There was no difference in the time from symptom onset to IAT and the rates of recanalization across scores; however, IAT duration was significantly increased in the HIAT 2 and 3 groups. The time from symptom onset to recanalization was likewise increased; however, this was not statistically significant (Table 4).

Table 2. Univariate Analysis of Outcome Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Good Outcome (mRS 0–3)</th>
<th>Poor Outcome (mRS 4–6)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-IAT variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median NIHSS (range)</td>
<td>16 (5–29)</td>
<td>20 (3–39)</td>
<td>$&lt;0.001$ (MW)</td>
</tr>
<tr>
<td>Mean age±SD</td>
<td>59±12</td>
<td>63.6±14.5</td>
<td>0.032 (TT)</td>
</tr>
<tr>
<td>Mean glucose±SD</td>
<td>12.6±37</td>
<td>153±61</td>
<td>0.001 (TT)</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>11 (17)</td>
<td>31 (26)</td>
<td>0.16 (CS)</td>
</tr>
<tr>
<td>PVD, %</td>
<td>1 (2)</td>
<td>4 (4)</td>
<td>0.42 (CS)</td>
</tr>
<tr>
<td>CHF, %</td>
<td>3 (5)</td>
<td>10 (10)</td>
<td>0.27 (CS)</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>126.4±36.6</td>
<td>153±60.6</td>
<td>0.37 (CS)</td>
</tr>
<tr>
<td>CAD, %</td>
<td>12 (19)</td>
<td>36 (30)</td>
<td>0.092 (CS)</td>
</tr>
<tr>
<td>Previous stroke, %</td>
<td>6 (9)</td>
<td>21 (18)</td>
<td>0.116 (CS)</td>
</tr>
<tr>
<td>Malignant pattern on MRI, %</td>
<td>1 (2)</td>
<td>5 (4)</td>
<td>0.37 (CS)</td>
</tr>
<tr>
<td>Nonmalignant pattern or mismatch pattern on MRI, %</td>
<td>16 (25)</td>
<td>15 (12)</td>
<td>0.021 (CS)</td>
</tr>
<tr>
<td>IAT variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean onset to IAT time, minutes, ±SD</td>
<td>266±80</td>
<td>282±83</td>
<td>0.28 (TT)</td>
</tr>
<tr>
<td>Mean IAT duration, minutes, ±SD</td>
<td>82±45</td>
<td>104±44</td>
<td>0.002 (TT)</td>
</tr>
<tr>
<td>Mean onset to recanalization time, minutes, ±SD</td>
<td>348±91</td>
<td>387±94</td>
<td>0.029 (TT)</td>
</tr>
<tr>
<td>Recanalization, %</td>
<td>50 (85)</td>
<td>76 (70)</td>
<td>0.042 (CS)</td>
</tr>
</tbody>
</table>

mRS indicates modified Rankin Scale; PVD, peripheral vascular disease; CHF, chronic heart failure; CAD, coronary artery disease; TT, t test; CS, $\chi^2$ test; MW, Mann-Whitney test.

Table 3. Procedural and Clinical Outcomes by Arterial Co-Occlusion, IAT Technique, and Combination Therapy

<table>
<thead>
<tr>
<th></th>
<th>pICA</th>
<th>tICA</th>
<th>M1</th>
<th>M2</th>
<th>BA</th>
<th>IA, IAL</th>
<th>IA, IAL+M</th>
<th>MERCI</th>
<th>MERCI+IAL</th>
<th>pIAT</th>
<th>aIAT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization, %</td>
<td>14 (67)</td>
<td>14 (74)</td>
<td>48 (74)</td>
<td>28 (78)</td>
<td>21 (84)</td>
<td>0.7</td>
<td>38 (73)</td>
<td>61 (71)</td>
<td>6 (100)</td>
<td>19 (86)</td>
<td>0.2</td>
<td>50 (71)</td>
</tr>
<tr>
<td>sICH, %</td>
<td>2 (10)</td>
<td>2 (10)</td>
<td>4 (6)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>0.6</td>
<td>3 (5)</td>
<td>4 (4)</td>
<td>0 (0)</td>
<td>5 (17)</td>
<td>0.08</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>8 (38)</td>
<td>4 (20)</td>
<td>12 (17)</td>
<td>3 (8)</td>
<td>12 (48)</td>
<td>0.002</td>
<td>12 (21)</td>
<td>17 (18)</td>
<td>2 (33)</td>
<td>10 (35)</td>
<td>0.3</td>
<td>21 (28)</td>
</tr>
</tbody>
</table>

pICA indicates proximal ICA; tICA, terminal ICA; BA, basilar artery; IAL, intra-arterial thrombolitics; M, mechanical clot disruption; MERCI, MERCI retriever; pIAT, primary IAT; aIAT, adjuvant IAT; sICH, symptomatic intracranial hemorrhage.
HIAT Score Validation

The UCLA cohort consisted of 175 patients. Receiver operator characteristic curve analysis of the HIAT score showed that the score performed equally well in both cohorts (Figure 1). The rates of poor outcome and mortality were comparable in the HIAT 3 tier; however, in the lower tiers of 0, 1, and 2, there were lower rates of poor outcome and mortality in the UCLA cohort (Figure 2).

Discussion

Patients with stroke with a large vessel occlusion are often screened for IAT if they present in extended time windows to a comprehensive stroke center. Our work introduces a novel score consisting of 3 clinical variables: age, admission glucose, and admission NIHSS. These variables were assessed to aid in the process of decision-making before IAT. Older patients have been shown to benefit from thrombolytic therapy (both IV and intra-arterial)16,20; however, they have worse outcomes and lower rates of recovery. Older people also may have reduced physiological reserves rendering them more susceptible to complications from intubation and sedation that frequently accompany IAT.21 NIHSS measures stroke severity and is a powerful predictor of outcome14; and admission hyperglycemia has been shown22 to be associated with poor outcome after ischemic stroke. It is, thus, not surprising that these 3 variables were identified in our cohort as independent predictors of outcome. The HIAT score is unique in incorporating the 3 variables into a unifying score and providing an assessment of poor outcome after IAT. In both cohorts studied, we observed an increase in the rate of poor outcome and mortality with increasing HIAT scores. Although these rates were variable among centers in the lower tiers (HIAT 0, 1, 2), the rate of poor outcome and mortality is uniformly high in the HIAT 3 tier. The outcome of any treatment is always a tradeoff between the potential benefits and harms of the intervention.
benefits versus the risks. In the HIAT 3 tier, the balance appears heavily weighted toward the latter. This result is likely due to the severity of the stroke combined with a poor metabolic state aggravating the ischemic injury and possibly reducing the benefit of recanalization combined with decreased functional reserve of older patients.

The decision to proceed to IAT is determined individually using clinical judgment and family discussions. Until prospective data from randomized trials are available, the HIAT score could be useful to provide prognostic data and to adjust expectations of outcome. It is also possible that patients with a HIAT of 2 or 3 may benefit from additional studies such as penumbral imaging to select those who may be harmed by recanalization therapies. Most importantly, HIAT 2 and 3 groups could serve as a means of stratifying patients in future IAT trials. The poor outcome of these groups from 2 separate centers supports the need to enroll such patients into prospective, randomized trials such as Interventional Management of Stroke (IMS-3) and MR and REcanalization of Stroke Clots Using Embolectomy (MR RESCUE).

Our work is in agreement with previous studies that identified recanalization as an important predictor of outcome. However, recanalization rates were evenly distributed among the 4 HIAT groups implying that the HIAT score predicts outcome in both recanalizers and nonrecanalizers. An interesting finding in our work is the increased duration of IAT and the resultant increase in the time from symptom onset to recanalization in the HIAT 2 and 3 tiers. This may be related to a more difficult access and navigation of the intraarterial catheter in older patients with atherosclerotic vessels. It is possible that this delay in recanalization contributed to the poor outcome in these patients.

Imaging is being used to select patients who may benefit from reperfusion therapy in extended time windows. We showed that a nonmalignant pattern or mismatch pattern correlated with a favorable outcome. The imaging results did not, however, predict outcome independently; most likely this is due to the small percentage of patients undergoing MRI in our cohort of patients. We are accumulating more patients with pre-IAT imaging data and will reanalyze our prediction score after sufficient numbers of patients are collected.

This work has several limitations. It is retrospective and as such needs to be validated prospectively. We have used both primary IAT and adjuvant IAT cohorts to create the HIAT score. It is possible that there are subtle differences between groups that may bias the results. Our study spans across 8 years. During that time, there have been advancements in IAT techniques, notably the introduction of the Multi mechanical Embolus Removal in Cerebral Ischemia (MERCI) retriever. As a result, there is lack of uniformity in our IAT methods. It is possible that newer techniques may alter the pattern of outcome observed in our study. Our patients were routinely intubated per institutional protocol. This may contribute significantly to IAT morbidity (especially in older patients). Although the HIAT score performed equally well in the independent UCLA validation cohort that is derived from another academic stroke center, the reduced rates of poor outcome in this cohort in the HIAT 0, 1, and 2 tiers may indicate important differences in patient population, patient selection, or techniques. For instance, at UCLA, intubation is not done routinely before IAT. This study was not designed to explore these differences. Whether the HIAT score may apply at nonuniversity-based hospitals remains to be proven. Finally, our clinical end point only includes hospital discharge, but patients continue to recover over time and therefore our results must be interpreted with caution.

In summary, the HIAT score may provide useful information to clinicians who are considering IAT options for patients with acute ischemic stroke in extended windows after symptom onset. The score may help in treatment decisions when evidence from randomized trials is still lacking and the pursuit of IAT is made based on clinical judgment alone. At the very least, the concordance of our treated cohort data across 2 separate stroke centers showing poor outcome in patients in HIAT 3 supports the need to enroll patients into prospective, randomized IAT trials such as IMS-3 and MR RESCUE.

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Disclosures

None.

References


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