Transfer Delay Is a Major Factor Limiting the Use of Intra-Arterial Treatment in Acute Ischemic Stroke

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Background and Purpose—The development of comprehensive stroke centers within hub-and-spoke stroke networks offers the opportunity to increase the proportion of acute ischemic stroke patients treated with intra-arterial therapies (IAT). Interhospital transfer delays will be critical in evaluating the success of this strategy.

Methods—We collected data on consecutive patients who were transferred to our institution for possible IAT. We defined transfer time as time elapsed from initial transfer call to arrival at our hospital and assessed whether transfer time was a predictor of emergent angiography using multivariable logistic regression.

Results—Among 132 patients referred for IAT, 53 (40.2%) were excluded on clinical grounds. The remaining 79 (59.8%) patients (mean age, 61 years; median National Institutes of Health Stroke Scale score, 18; 49.4% male) were analyzed. Sixty-one of 79 (77%) patients underwent emergent angiography for IAT. The median hospital-to-hospital distance was 14.7 (interquartile range, 8.5–21.9) miles and median transfer time was 104 (interquartile range, 80–135) minutes. Transfer time was 33% lower among those who underwent emergent angiography (100.6 versus 149.0 minutes; P<0.001). Adjusting for relevant covariates, transfer time remained an independent predictor of emergent angiography (OR, 0.975; 95% CI, 0.956–0.995; P=0.014). The odds of treatment decrease by 2.5% for every minute of transfer time.

Conclusions—Delay in hospital-to-hospital transfer is a common reason that acute ischemic stroke patients are excluded from interventional therapy. The likelihood of receiving IAT decreases rapidly by increasing transfer time. Specific goals for transfer time should be considered in future quality standards for hub-and-spoke–organized stroke networks. (Stroke. 2011; 42:00-00.)

Key Words: comprehensive stroke center ■ health care access ■ medical transportation ■ revascularization ■ stroke systems

Timely revascularization through intravenous or intra-arterial approaches remains a mainstay of acute ischemic stroke (AIS) management. However, only 1% to 2% of AIS patients are treated with intravenous (IV) tissue plasminogen activator (tPA) in the United States.1–3 The most common exclusion is arrival >3 hours from symptom onset.4 Recent advances in stroke medicine including an extended IV tPA window and intra-arterial therapies (IAT) such as embolectomy may allow more patients to be considered for revascularization therapies up to 8 hours from stroke symptom onset.5–8

The development of comprehensive stroke centers (CSC) within hub-and-spoke stroke networks has been recommended to improve stroke care and increase the utilization of approved therapies.9 Within these networks, eligible patients from community or primary stroke center hospitals could be transferred to CSC for acute interventional management. A critical factor, however, is the facilitation of rapid hospital-to-hospital transfers. Efforts to reduce treatment delays related to hospital-to-hospital transportation times will likely allow more patients to benefit from approved therapies and may improve outcomes.

We therefore assessed transfer times from regional hospitals to our institution among eligible AIS patients referred for possible IAT. We hypothesized that hospital-to-hospital transfer delay would exclude eligible patients from IAT because of elapsed time window for treatment and attempted to quantify its impact on treatment decisions.

Subjects and Methods

Study Participants

From a prospective registry of confirmed stroke patients admitted to our institution, we reviewed consecutive patients with AIS trans...
ferred from regional hospitals for possible IAT between August 1, 2006 and July 31, 2010. We excluded patients transferred beyond 12 hours from symptom onset and those in whom treatment decisions were based on perfusion imaging. The study was approved by the Institutional Review Board at our hospital.

**Data Collection**
Prospective data were collected for the following: demographics (age, sex, and race), previous medical history (hypertension, diabetes mellitus, dyslipidemia, current smoking, atrial fibrillation, coronary artery disease, congestive heart failure, and previous stroke), symptom onset time, initial request for transfer time, transportation mode, referring hospital location, arrival time, start of angiography time, complications, and in-hospital outcomes.

Transfer time was defined as time of initial call from the referring hospital to time of arrival at our hospital. From August 2006 to November 2007, time of initial call was captured manually at time of call (n = 6); since November 2007, an automated monthly phone log provided the exact times (n = 73). Time of arrival was defined as time of admission (entered electronically on arrival and registration at our institution).

**Intra-Arterial Treatment Protocol**
Using a standardized approach, patients were considered eligible for IAT if: (1) initiation of therapy could be accomplished within 8 hours of onset for anterior circulation or 12 hours of onset for posterior circulation ischemic strokes; (2) NIHSS score was ≥ 8 on evaluation at our institution; and (3) initial CT of the head excluded hemorrhage or hypodensity more than one-third middle cerebral artery territory. Repeat brain imaging was performed before angiography only if there was clinical deterioration. Use of mechanical and/or pharmacological treatments remained at the discretion of the treating interventionalist and stroke neurologist.

**Statistical Analysis**
We compared transfer times between those who underwent emergent angiography for IAT versus those who did not using χ² or Fisher exact tests, Student t tests, and Mann-Whitney U tests as appropriate. We also performed correlational statistics among relevant continuous variables. We considered variables with P < 0.15 on univariable testing (ie, any variable associated with transfer delay or decision to proceed with emergent angiography) for entry into a multivariable logistic regression model with emergent angiography as the dependent variable. Odds ratios and 95% confidence intervals were estimated for predictors of emergent angiography. We used goodness-of-fit (Hosmer-Lemeshow) tests to evaluate logistic regression models. P < 0.05 was considered significant in the final model. All statistical analyses were performed using SPSS 14.0 (Chicago, IL).

**Results**
Between August 1, 2006 and July 31, 2010, 132 patients with AIS were transferred from 33 regional hospitals for possible endovascular revascularization therapy (Figure 1). Of these, 53 (40.2%) were excluded on clinical grounds, irrespective of time from symptom onset. Eighteen (13.6%) were excluded because of delayed transfer and elapsed treatment time window on arrival at our institution. Of the 61 patients who had emergent angiography performed, 52 underwent IAT and 9 were not offered IAT because of angiographic recanalization (spontaneous or after tPA) or inadequate access.

### Table 1. Baseline Characteristics of Transferred Patients Eligible for Intra-Arterial Therapies

<table>
<thead>
<tr>
<th>Eligible Cohort (n = 79)</th>
<th>Age (y), mean (SD)</th>
<th>61.2 (16.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, (%)</td>
<td>39 (49.4)</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity, (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>32 (40.5)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>36 (45.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>11 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Current smoking, (%)</td>
<td>13 (16.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, (%)</td>
<td>64 (81.0)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, (%)</td>
<td>18 (22.8)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation, (%)</td>
<td>20 (25.3)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease, (%)</td>
<td>22 (28.8)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure, (%)</td>
<td>12 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia, (%)</td>
<td>28 (35.4)</td>
<td></td>
</tr>
<tr>
<td>Previous stroke, (%)</td>
<td>5 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Onset to initial call time (min), median (IQR)</td>
<td>176.0 (137.0–252.0)</td>
<td></td>
</tr>
<tr>
<td>Intravenous tPA, (%)</td>
<td>27 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Land transport, (%)</td>
<td>72 (81.1)</td>
<td></td>
</tr>
<tr>
<td>Distance (miles), median (IQR)</td>
<td>14.7 (8.5–21.9)</td>
<td></td>
</tr>
<tr>
<td>Transfer time (min), median (IQR)</td>
<td>104.0 (80.0–135.0)</td>
<td></td>
</tr>
<tr>
<td>Onset to arrival time (min), median (IQR)</td>
<td>296.0 (237.0–357.0)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score on arrival, median (IQR)</td>
<td>18 (15–22)</td>
<td></td>
</tr>
<tr>
<td>Anterior circulation, (%)</td>
<td>69 (87.3)</td>
<td></td>
</tr>
<tr>
<td>Emergent angiography performed, (%)</td>
<td>61 (77.2)</td>
<td></td>
</tr>
<tr>
<td>Onset-to-angiography time (min), median (IQR)*</td>
<td>338 (290–414)</td>
<td></td>
</tr>
</tbody>
</table>

IQR indicates interquartile range; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation; tPA, tissue plasminogen activator.

*Includes only those who underwent emergent angiography (n = 61).
administered to 27 patients (34.2%) before transfer in a “drip and ship” protocol. The median hospital-to-hospital distance was 14.7 (range, 1.9–81.0) miles. Mode of transportation was land ambulance in a majority of patients (91.1%). Median transfer time was 104 (interquartile range, 80–135) minutes and time from symptom onset to arrival was 296 (interquartile range, 237 to 357) minutes. Median NIHSS score was 18 (interquartile range, 15–22) on arrival at our institution.

On univariable analyses, transfer time was directly correlated with hospital-to-hospital distance ($r_s=0.267; P=0.017$) and inversely correlated with NIHSS score ($r_s=-0.223; P=0.048$). In addition, transfer time was slightly longer in those who received IV tPA before transfer (122.6 versus 105.9 minutes; $P=0.127$). There was no association between mode of transportation and transfer time ($P=0.443$), although distances were greater in patients transported by air versus land (36.9 versus 12.9 miles; $P<0.001$). Transfer times were not longer on weekends ($P=0.645$) or at night ($P=0.648$). Time from onset to initial call was also not correlated with transfer time ($r_s=-0.011; P=0.927$). No other demographic or clinical factors were associated with transfer time. Transfer time did not improve over the study period ($r_s=-0.110; P=0.340$).

Transfer time was 33% lower in those who underwent emergent angiography compared to those who were excluded (100.6 versus 149.0 minutes; $P<0.001$). There were no differences by age, sex, race, onset-to-initial call time, time of day, day of week, mode of transport, distance, or medical history, with the following exceptions: those with atrial fibrillation were more likely (95.0% versus 71.2%; $P=0.028$) whereas those with heart failure were less likely (58.3% versus 80.6%; $P=0.090$) to undergo emergent angiography than those without these conditions. In addition, NIHSS score was higher among those who underwent attempted IAT than those who were excluded (19 versus 16; $P=0.031$).

In univariable logistic regression analysis (Figure 2), the odds of emergent angiography decreased by 3% (unadjusted OR, 0.970) per minute of delay beyond 46 minutes (the lowest limit in our series). In a multivariable logistic regression model (Table 2) including age, NIHSS score, atrial fibrillation, congestive heart failure, IV tPA use, transfer time, and distance, transfer time remained independently associated with emergent angiography (adjusted OR, 0.975; 95% CI, 0.956–0.995; $P=0.014$). The Hosmer-Lemeshow test suggested good model fitness ($\chi^2=5.26; P=0.730$).

### Table 2. Multivariable Logistic Regression Model Evaluating Predictors of Emergent Angiography After Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfer time (per min)</td>
<td>0.975</td>
<td>0.956–0.995</td>
<td>0.014</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16.7</td>
<td>1.4–197.3</td>
<td>0.026</td>
</tr>
<tr>
<td>Age (per y)</td>
<td>0.995</td>
<td>0.990–1.004</td>
<td>0.073</td>
</tr>
<tr>
<td>NIHSS score (per point)</td>
<td>1.13</td>
<td>0.980–1.299</td>
<td>0.094</td>
</tr>
<tr>
<td>Intravenous tPA</td>
<td>1.95</td>
<td>0.469–8.085</td>
<td>0.358</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.867</td>
<td>0.148–5.079</td>
<td>0.874</td>
</tr>
<tr>
<td>Distance (per mile)</td>
<td>0.996</td>
<td>0.949–1.046</td>
<td>0.884</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; tPA, tissue plasminogen activator.

### Discussion

In a metropolitan hub-and-spoke system, the median transfer time for AIS patients in need of IAT was 104 minutes despite relatively short distances (average 14.7 miles) between referring hospitals and our comprehensive stroke center. After clinical exclusions (40%), transfer delay resulting in elapsed treatment time window was the second most common reason patients were excluded from IAT (14%). In our study, each minute of delay beyond a minimum of 46 minutes reduces the odds of attempted IAT by 3%.

It is well-established that outcomes after IV tPA for AIS are strongly time-dependent. Among those patients reperfused using IAT, the probability of good clinical outcomes also decreases with time such that the benefit is no longer significant after ~6 hours. The median onset-to-angiography time was nearly 6 hours in our study, with transfer time accounting for 100 minutes (30%) of the overall time. Our results, therefore, suggest that transfer delay not only excludes many patients from IAT but also could negatively impact on the efficacy of IAT in those achieving delayed recanalization beyond 6 hours.

The establishment of stroke centers and organized stroke systems of care aims to counter the obstacles impeding widespread delivery of highly efficacious but time-sensitive stroke treatments. There is mounting evidence of the benefits of preferential triage of acute stroke patients to primary stroke centers, related mostly to increased utilization of IV tPA. However, access to primary stroke centers remains limited nationwide and the subset of patients who require endovascular treatment or who do not respond to IV tPA alone may benefit from further specialized care at CSC.

Figure 2. Graph shows predicted probability of attempted intra-arterial therapies (IAT) (red line) with 95% confidence bands (black lines) as a function of transfer time.
Given the scarcity of neuro-interventionalists and CSC nationwide, regions will also need to develop systems to transport or divert eligible AIS patients to the nearest center capable of providing endovascular services. Specifically, protocols for expedited transportation and strategies to minimize transfer delays need to be devised. In rural areas where distances extend hundreds of miles from the nearest CSC, air ambulance services need to be considered. When distances are >10 miles, helicopter transportation is associated with faster transfer times compared to land transportation. Despite the increased costs with helicopter transport, its time-saving benefits in acute stroke patients eligible for revascularization therapies greatly offset these costs.

Using these strategies, some integrated stroke networks in a hub-and-spoke model have demonstrated increased utilization of acute stroke therapies, rapid transfer and initiation of IAT, and improved clinical outcomes. Another solution may be selective triage of suspected acute stroke patients by emergency medical services directly to CSC, thereby bypassing community hospitals and primary stroke centers. For instance, those presenting outside of the IV tPA window (>4.5 hours) may be identified in the field for selective triage to the closest CSC. Not surprisingly, time delay to IAT has been shown to be less with direct referral to a CSC by emergency medical services compared to referral from community hospitals. To assist in these efforts, prehospital screening also can be modified with high sensitivity and specificity for detection of patients with persistent large artery occlusions who might benefit most from preferential triage to CSC.

Although less well-studied than primary stroke centers, quality and outcome measures for CSC are only emerging. Our results argue for time-based metrics such as interhospital transfer and door-to-angiography times to be included along with procedural quality standards. Efforts to develop formal hospital-to-hospital transfer arrangements and to provide dedicated 24-hour on-site land and air ambulance services should be considered requirements for CSC.

Although our study has limitations and needs replication in larger multicenter cohorts, we are the first to our knowledge to focus on a critical issue that has implications for the development of stroke networks. Future studies should also examine elements of transfer delay, including bed procurement, administrative steps, contacting ambulances, travel time, and traffic patterns. Although we utilized a time-based approach to patient selection, imaging-based approaches (ie, perfusion imaging) may obviate some, but not all, of the impact that time delays have on outcomes after stroke. Our protocol did yield similar proportions of patients included and excluded from IAT as reported in the literature, suggesting comparability to standard practice. Finally, although expansion of the acute revascularization treatment window is appealing and holds promise, it should be emphasized that it may increase the proportion of eligible AIS patients only marginally. Public education regarding reducing prehospital patient-related delays in symptom recognition, emergency medical services activation, and early hospital arrival remains paramount. Notwithstanding these limitations, addressing hospital-based processes that delay or prevent timely administration of approved treatments should remain a major component of any comprehensive plan to improve acute stroke care.

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Disclosures
None.

References


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