Extending Tissue Plasminogen Activator Use to Community and Rural Stroke Patients

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Background and Purpose—Guidelines for intravenous tissue plasminogen activator (tPA) use in stroke emphasize the importance of limiting its use to facilities with imaging capabilities and stroke expertise. This prospective case series set out to evaluate the safety of tPA use in patients referred from rural communities to a tertiary center.

Methods—Prospective data of 82 consecutive patients treated with tPA in London, Ontario, were reviewed.

Results—Twenty-three patients were transferred to London from a rural hospital (non-London patients); 49 were first evaluated in a London emergency room (London ER); and 10 were inpatients in a London hospital at the time of stroke onset. Mean transfer time and distance to London for non-London patients were 89 minutes and 41 miles. Although symptom onset to London ER times were longer for non-London than for London ER patients (123 versus 53 minutes), the door to needle times were significantly shorter for the former (49 versus 95 minutes, \(P<0.005\)). Imaging to needle times were longer for London inpatients compared with London ER patients (55 versus 36 minutes, \(P=0.16\)). The proportion of patients with >4-point improvement on the NIH Stroke Scale or cure at 24 hours was 57%, with no difference among groups (\(P=0.46\)). The overall symptomatic hemorrhage rate at 36 hours was 2%. No significant differences in outcomes were observed at 3 months.

Conclusions—This prospective study suggests that it is feasible and safe to treat rural patients referred to a tertiary care center with tPA, thus extending the benefits of thrombolysis for acute stroke to a wider population. (Stroke. 2002;33: 141-146.)

Key Words: Canada ■ stroke, acute ■ stroke management ■ thrombolytic therapy ■ tissue plasminogen activator

The National Institute of Neurological Disorders and Stroke (NINDS) tPA Stroke Study Group showed in 1995 that intravenous tissue plasminogen activator (tPA) was an efficacious treatment for acute ischemic stroke. Since its approval by the FDA in 1996, tPA has been used safely and effectively in routine clinical practice in urban academic medical centers and in community hospitals. Strategies to extend thrombolysis to rural community hospitals with imaging and intensive care facilities but with limited stroke expertise and referral protocols for urban community hospitals that have limited access to imaging facilities have been implemented successfully.

Guidelines have been developed to ensure safety in the use of tPA for acute ischemic stroke. Routine tPA use is currently restricted to those patients who can be treated within 3 hours of symptom onset. All the guidelines emphasize the importance of involving physicians with expertise in the diagnosis of stroke and in the interpretation of CT scans and restrict treatment to facilities that have the ability to handle hemorrhagic complications. Many hospitals, particularly outside the United States, lack the staff or the facilities required to meet these criteria.

In February 1999, the Health Protection Branch of Canada granted a conditional license for the use of tPA in acute ischemic stroke. However, as in many other countries, access to imaging and intensive care facilities in Canada is limited. Given the short time window within which tPA can be safely used, travel times to these facilities limit the application of tPA in acute stroke. However, 78% of the Canadian population lives within 40 miles (or 90 minutes) of a medical center identified as having the capability of providing tPA. Coordinated stroke strategies that can facilitate transfer of patients from rural communities to these centers would ensure that new interventions for stroke would become available to a
larger segment of the population. This prospective case series set out to evaluate whether intravenous tPA can be safely given in a tertiary care center to patients referred from rural communities (those with <35,000 inhabitants and lack of around-the-clock availability of some or all of the following: CT scanner, intensive care, laboratory facilities, and stroke expertise).

Subjects and Methods
Community and Patients
London, with a population of 325,646 inhabitants (398,616 in the metropolitan area), is the largest city in southwestern Ontario. It has 2 academic medical centers, both with independent stroke teams and 24-hour access to CT and MRI [London Health Sciences Center (LHSC) and St Joseph’s Hospital]. The academic hospitals in London are referral centers for a large part of Ontario. In addition to serving the local population, LHSC receives acute stroke referrals from 33 rural hospitals16 from 7 counties. This catchment area covers 7800 square miles and serves 1,167,755 inhabitants. In southwestern Ontario, only 8 hospitals outside London have a CT scanner; not all of them are available 24 hours a day. Most rural hospitals that refer acute stroke patients to London lack intensive care facilities, CT scanners, and emergency access to physicians with stroke expertise. A coordinated stroke strategy has been set up so that physicians from rural community hospitals can contact the stroke team at LHSC and, when appropriate, transfer acute stroke patients to London for evaluation and treatment. If patients are not treated with tPA and if they are thought to be stable after evaluation, they can be transferred back to the referring hospital for further care. The stroke team at LHSC supports these centers through educational activities that emphasize the acute management of stroke and the importance of rapid referral and transfer of patients who could benefit from treatment with tPA. Several stroke candidates, a variable number of fellows (3 to 7), and 4 research nurses make up the stroke team. One consultant, 1 fellow, and 1 nurse are always on call. At St Joseph’s Hospital Center, 2 consultants share call and are assisted by a research nurse.

Clinical Assessment and Treatment
When patients in London have onset of symptoms suggestive of acute stroke, they are transported by emergency medical services (EMS) to 1 of the 2 academic medical centers. EMS does not notify the hospital or the stroke team when transporting a patient with stroke. On arrival at the emergency room (ER), an emergency physician makes a preliminary assessment and, if indicated, contacts the stroke team. The stroke fellow or stroke consultant in consultation with a neuroradiologist examines and arranges for a noncontrast CT or, in some cases, MRI (including diffusion-weighted imaging) to be performed. Through arrangements with the radiology department and the laboratory, tPA candidates are given priority for imaging and analysis of blood samples. When a stroke occurs in a hospital inpatient, the treating physician or the floor nurse contacts the stroke team. The workup and treatment process is similar for both inpatients and outpatients.

When a patient with an acute ischemic stroke presents to a rural hospital, the emergency physician arranges transfer to London after contacting the stroke fellow. Only patients who can be expected to arrive in London within 3 hours of symptom onset are transferred. When possible, blood is drawn at the community hospital before transfer, and the results are faxed to LHSC. The stroke fellow meets the patient on arrival at the emergency room and accompanies the patient through every step of the workup.

The decision to treat with tPA is made by the stroke fellow in consultation with a stroke consultant. Inclusion and exclusion criteria from the NINDS study1 are used, with 1 major difference: Patients are excluded if involvement of more than one third of the middle cerebral artery territory is noted on the initial CT scan. Treatment can be initiated in the CT scan room, the ER, or the stroke unit. Patients are treated with 0.9 mg/kg; 10% is given as a bolus and the rest is infused over 1 hour. Management after infusion adheres to published guidelines.12 After treatment, patients are admitted for 24 hours to an acute stroke unit with at most a 3:1 ratio of patients to nurse.

Data Collection and Statistical Analysis
Data of patients treated with tPA at both academic medical centers in London were collected prospectively between December 1, 1998, and November 30, 2000. Data of patients with suspected ischemic stroke who were seen within 3 hours of symptom onset at LHSC between February 1, 2000, and November 30, 2000, were also collected prospectively. Demographic variables, evaluation and treatment times, admission and 24-hour National Institute of Health Stroke Scale (NIHSS) scores, and outcomes were entered into the database by a stroke fellows. For all patients, time of symptom onset was considered the time they were last seen to be well. The time of symptom onset to arrival in London ER, the time from ER arrival to imaging study, and the time from imaging study to tPA administration were recorded for all patients who were seen in a London ER. The door to needle and symptom onset to tPA times were calculated from these data. In addition, for patients transferred from other communities, the time from symptom onset to arrival in the local community hospital and the transfer time from the community hospital to the London ER were recorded. Travel distances for these patients were calculated by use of the Free Trip Internet Travel Planner.11 For patients who had onset of symptoms as inpatients in a London hospital, the time from symptom detection to imaging study was recorded and considered equivalent to the ER to imaging time.

Outcomes were measured at 24 hours and 3 months. An outcome was considered positive at 24 hours when there was an improvement of ≥4 points in the NIHSS score or an NIHSS score of 0. The stroke fellow or stroke consultant in consultation with a neuroradiologist determined the presence of hemorrhage. With the use of the Prolyse in Acute Cerebral Thromboembolism (PROACT) criteria,13 a hemorrhage was defined as symptomatic when it led to a 1-point decrease in the level of consciousness or a >4-point increase in the total NIHSS. At the 3-month follow-up visit, an NIHSS and a modified Rankin scale were performed.

Student’s t test was used to compare the London and non-London groups for continuous variables. A χ² test or Fisher’s exact test was used when the variables were discrete. Probability values of P<0.05 were considered statistically significant.

Results
Demographics and Baseline Characteristics
Eighty-two patients were treated with intravenous tPA in London, Ontario, between December 1, 1998, and November 30, 2000. Twenty-three (28%) were transferred to London from a rural hospital (non-London patients), 49 (60%) were first evaluated in a London emergency room (London ER patients), and 10 (12%) were inpatients in a London hospital at the time of stroke onset (London IP patients). Of the non-London patients, 1 had onset of symptoms while he was an inpatient in a rural hospital. Because the protocol used for transfer to and management in London was the same as for other non-London patients, he is analyzed as part of that larger group. Initial median NIHSS scores were 14, 13, and 18 in the non-London, London ER, and London IP groups, respectively. Eighty-two patients were originally evaluated with CT; 2 were assessed with MRI. No patients were lost to follow-up. Baseline variables are shown in Table 1.

Time to Arrival in a London Hospital and Door to Needle Times
Patients who were transferred to London from a rural hospital presented to their local emergency room within 36 minutes of
symptom onset (range, 7 to 75 minutes, excluding the patient who had onset of symptoms as an inpatient). Average transfer time to London for non-London patients was 89 minutes (range, 46 to 138 minutes), and the mean transfer distance was 41 miles (range, 11 to 80 miles) (Figure 1). All patients were transferred by ambulance. The mean time from symptom onset to arrival in the London ER was 123 minutes (range, 76 to 168 minutes). This was significantly higher than that of London patients (53 minutes; range, 4 to 111 minutes; \( P<0.0001 \)). The overall time from symptom onset to arrival in the London ER was 75 minutes (range, 4 to 168 minutes). In the overall sample, only 4% of patients were treated within 90 minutes of stroke onset, and 10% were treated \( >3 \) hours after onset of symptoms (2% of the London ER, 26% of the non-London, and 10% of the London IP groups). The range of symptom to needle times for patients who were treated beyond 3 hours was 189 to 203 minutes.

Table 2 presents mean times to workup and treatment for non-London and London ER patients. The door to imaging, imaging to needle, and door to needle times were significantly shorter for non-London than for London ER patients (all at \( P<0.005 \)). Time from symptom onset to imaging for the London IP group was similar to the ER arrival to imaging time for London ER patients (66 versus 59 minutes, \( P=0.487 \)). However, the imaging to needle time was significantly longer for the former group (55 versus 36 minutes, \( P=0.016 \)).

There was an inverse relationship between symptom onset to London ER arrival time and door to needle times (Figure 2). For every 10-minute delay in arrival, door to needle times decreased by \( \approx 3 \) minutes in the case of the London ER patients and by \( \approx 5 \) minutes in the case of non-London patients (\( P=0.52 \)).

Outcomes

The median NIHSS score at 24 hours for all 82 patients was 7 (interquartile range, 2 to 14). The overall proportion of patients with \( >4 \)-point improvement on the NIHSS or cure at 24 hours was 57%. The difference among groups was not statistically significant (\( P=0.46 \)). The overall asymptomatic and symptomatic hemorrhage rates at 36 hours were 12% and 2%, respectively. The admission NIHSS scores for patients with symptomatic hemorrhage were 27 and 13. Both symptomatic hemorrhages were fatal. NIHSS scores and hemorrhage rates sorted by patients group are presented in Table 3. Compared with those treated within 180 minutes of symptom onset, the asymptomatic hemorrhage rate was higher for patients treated beyond 3 hours (12% versus 37.5%, \( P=0.055 \)). The 2 symptomatic hemorrhages occurred in patients treated within the time stipulated by the guidelines; both patients were from the London ER group.

Three-month follow-up data are available for all patients. Overall, 62 patients (76%) had an improvement of \( >4 \) points or cure as measured by the NIHSS. The rates of improvement were 78%, 76%, and 50% in the non-London, London ER, and London IP patients, respectively. The difference among groups was not statistically significant. Eleven patients (13%) were dead at 3 months. The death rate was 10% in the non-London, 12% in the London ER, and 20% in the London IP groups (\( P=0.8 \)). Overall, 34%, 29%, and 23% of patients had modified Rankin scores of 0 to 1, 2 to 3, and 4 to 5, respectively. The breakdown of 3-month Rankin scores by patient group is given in Figure 3.

Patients Not Treated With tPA

Between February 1, 2000, and November 30, 2000, 82 patients with suspected ischemic stroke were seen within 3
hours of symptom onset in LHSC. The reasons for not treating these patients are detailed in Table 4. For comparison, during that time period, 15 non-London patients and 37 London ER and London IP patients were treated.

**Discussion**

The results of this prospective study suggest that it is feasible and safe to treat patients referred from rural hospitals to a tertiary center with tPA, thus extending the benefits of thrombolysis for acute stroke to a wider population than has traditionally been possible. The outcomes in our patients are comparable with those of the NINDS trial, and they contribute to the growing number of studies that have demonstrated the safety and effectiveness of tPA when used in routine clinical practice.

Given the geographic location of London, the demographic characteristics of southwestern Ontario, and the fiscal constraints of the Canadian health system, our stroke team must provide stroke care coverage to a large geographical area. Other centers have reported successes with the use of tPA in rural settings or in settings where access to neurologists and imaging facilities is limited. In central Illinois, by providing stroke expertise to small community hospitals, the Order of St Francis Stroke Network has extended the benefits of tPA to inhabitants of rural communities. However, because the community hospitals in their network have CT scanners, patients are treated with tPA locally and then transferred to a tertiary center for further management. The stroke teams in Köln, Germany, and Vancouver, British Columbia, have demonstrated the feasibility of using tPA in patients with acute ischemic stroke who are referred from urban community hospitals with limited access to neurologists or imaging facilities. To the best of our knowledge, our series is the first to explore the use of tPA in rural communities where there are no imaging facilities and where patients must be transferred before treatment can be instituted. These conditions refer to most countries outside the United States.

Using Geographic Information System analysis, which combines digital population data and cartographic information, Scott et al calculated that 67.3%, 78.2%, and 85.3% of the Canadian population lives within 20, 40, and 65 miles, respectively, of a hospital with the capability of providing tPA. They estimated that these distances represent 60, 90, and 120 minutes of traveling time and advocated a coordinated emergency medical service for stroke to maximize coverage. Our study confirms that it is feasible to treat patients with tPA when they are first seen in a rural hospital up to 80 miles away.

The door to needle times for our patients are comparable to those reported in other series, and those for patients transferred from rural hospitals were within the 1 hour recommended by guidelines. This was significantly shorter than times for patients who presented directly to a London hospital. A key difference in the management of both groups of patients was that the stroke team knew in advance that a patient was coming to the hospital and could arrange the imaging study before the patient’s arrival. In addition, advance notification gave the stroke fellow time to get to the ER and to meet the patients at the door. This means that no time was lost in triage and ER evaluation before neurological

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**TABLE 2. Times to Evaluation and Treatment for Patients Who Were First Evaluated in a Community Hospital and Those Who Were Initially Evaluated in a London ER**

<table>
<thead>
<tr>
<th>Mean Time (minutes)</th>
<th>Non-London</th>
<th>London ER</th>
<th>Difference of Means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom onset to London ER</td>
<td>123 (76–168)</td>
<td>53 (4–111)</td>
<td>−70 (−82—59)</td>
</tr>
<tr>
<td>ER arrival to imaging study</td>
<td>28 (9–48)</td>
<td>59 (19–106)</td>
<td>32 (22–41)</td>
</tr>
<tr>
<td>Imaging to tPA</td>
<td>22 (1–56)</td>
<td>36 (5–89)</td>
<td>14 (4–24)</td>
</tr>
<tr>
<td>Door to needle</td>
<td>49 (21–81)</td>
<td>95 (42–174)</td>
<td>46 (34–58)</td>
</tr>
<tr>
<td>Symptom onset to tPA</td>
<td>172 (135–203)</td>
<td>148 (69–191)</td>
<td>−24 (−37—12)</td>
</tr>
</tbody>
</table>

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**Figure 2. Scatterplot of door to needle times by symptom (Sx) to ER times. For London ER patients, the regression equation is y=112−0.334x and r²=0.08. For non-London patients, the regression equation is y=106−0.461x and r²=0.468.**
examination and imaging studies were performed. In Vancouver, advanced warning of transfer also led to shorter door to needle times.7 Our findings support the argument that EMS should notify the hospital and the stroke team whenever an acute stroke patient is being transported.2 Because patients referred from outside hospitals arrived at the ER later, the shorter door to needle time could be a reflection of a phenomenon previously reported in the Standard Treatment With Alteplase to Reverse Stroke (STARS) study: The symptom to ER time and the door to needle time are inversely related.4

Patients in rural areas arrived at their local ER more rapidly than London patients (36 versus 53 minutes). This difference is probably due to selection bias because patients who arrived later at their local hospitals would be likely to arrive in London within 3 hours of symptom onset and thus would not be transferred. A larger percentage of the non-London patients were treated beyond 3 hours (26%). This figure is much higher than the 10% to 15% reported by other centers.2,4,5 The reasons for this are not clear; it may represent a willingness to assume a higher risk of hemorrhage on the part of the family or the treating physician when the patient has traveled a long distance to get to the hospital. Patients who are transferred to London have already been told about tPA, which may make them more willing to assume the risk. The rate of asymptomatic hemorrhage was higher in patients treated beyond 3 hours (38%) than in under 180 minutes (12%). However, there were no symptomatic or fatal hemorrhages in the late treatment (38%) than in under 180 minutes (12%). However, there were no symptomatic or fatal hemorrhages in the late treatment group. In our center, we exclude patients with early involvement of more than one third of the middle cerebral artery territory." This may account for the low symptomatic and fatal hemorrhage rate.

Our series was prospective, and no patients were lost to follow-up. Despite this, some weaknesses remain. We do not know how many patients with acute stroke were actually evaluated in the referring centers, and we are unable to assess the true tPA treatment rate. A selection bias may be responsible for the positive outcomes in patients who were transferred from rural areas. It is unlikely that severely impaired patients or patients who arrived late at the community hospital were referred to the stroke team in London. Although we were able to offer a safe and efficacious treatment to some patients with acute stroke, we do not know how many still do not benefit from this important therapeutic intervention. Our numbers are small, and as such, our results must be viewed with caution.9 However, they add to the findings of numerous other series that corroborate the safety of this treatment in daily clinical practice.

Acknowledgments

Dr Merino is the recipient of the Fisher Family/Heart and Stroke Foundation of Ontario Research Fellowship. Dr Silver is the recipient of the Fisher Family Fellowship in Stroke. Drs Foell and Demaerschalk are supported by Heart and Stroke Foundation of Canada Research Fellowships. Members of the Southwestern Ontario Stroke Program were Bart Demaerschalk, Connie Frank, Jane Finan, Vladimir Hachinski, Andrew Kertesz, Cheryl Mayer, Mary McGaggart, Joseph G. Merino, Darlyn Morlog, Christina O’Callaghan, Fali Poncha, Brian Silver, J. David Spence, Arturo Tamayo, Blaine Foell, G. Bryan Young, and Edward Wong.

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Stroke. 2002;33:141-146
doi: 10.1161/hs0102.100481

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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