A Telestroke Network Enhances Recruitment into Acute Stroke Clinical Trials

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Background and Purpose—Acute stroke clinical trials are conducted primarily at academic medical centers. As a result, patients living in rural areas are excluded from participation, results may not be generalizable to nonacademic settings, and studies may be slow to recruit subjects. Telemedicine can provide rural patients with emergency neurovascular consultation. We sought to determine whether telemedicine facilitates enrollment into acute stroke trials.

Methods—We have an established rural “hub and spoke” telestroke network. From 2005 to 2009, we participated in 2 time-sensitive acute stroke trials: Factor Seven for Acute Hemorrhagic Stroke and Minocycline to Improve Neurological Outcome. Candidates for the 2 trials could be identified at either the hub or at the spokes, with patients presenting to the latter transferred to the hub for enrollment. We analyzed the times from symptom onset to consultation via telemedicine, arrival at the hub, and to initiation of a study drug to determine the impact of telemedicine on study enrollment.

Results—Nineteen of 28 subjects enrolled in the 2 trials were identified initially at an outside facility via a telemedicine link. An additional 9 candidates identified by telemedicine could not be enrolled because of transportation time. Arrival at the hub was 127 minutes later (median, 207 [95% CI, 145 to 255] versus 80 [95% CI, 55 to 142]; P=0.0002), and study drug was started 74 minutes later (median, 298 [95% CI, 218 to 352] versus 225 [95% CI, 147 to 330]; P=0.05) for subjects who were identified via telemedicine and required transport to the hub compared with local subjects who presented directly to the hub.

Conclusions—Telemedicine can enhance enrollment into time-sensitive acute stroke trials. However, transfer of subjects to the hub results in delays in study initiation for some and precludes enrollment for others similar to the weaknesses of “ship and drip” thrombolytic strategies. To save time, efforts are needed to enroll clinical trial subjects and begin the research drug at the remote site under telemedicine guidance.

Key Words: telemedicine ■ stroke ■ clinical trials

Recruitment for acute stroke clinical trials is inefficient. Among 32 large acute ischemic stroke trials published since 1990, the average recruitment rate of individual centers in these trials was only 0.79 subjects enrolled per month, and only 0.57 in North American centers.1 Some of this may be related to the concentration of investigators within academic centers in urban areas. Stroke patients in rural communities either do not present to academic centers involved in acute stroke trials, or delays in transportation to these centers have largely exempted them from study participation. In addition, therapies that have been shown in controlled trials to be effective may not be used in nonacademic hospitals, and new therapies may be slow to disseminate into the community. A case in point is the National Institute of Neurological Disorders and Stroke tissue plasminogen activator (tPA) trial that was conducted primarily at 8 academic medical centers.2 Despite approval of intravenous tPA in 1996, use remains very low. In fact, a recent review of Medicare Provider Analysis and Review data of eligible hospital discharges noted that 64% of US hospitals did not report a single tPA use for a Medicare recipient for acute ischemic stroke over a 2-year period, from 2005 to 2007.3

Telestroke, the combination of neurovascular expertise and telemedicine, can overcome geographic barriers to acute stroke therapy.4 IV tPA administration in rural and community emergency departments (EDs) using telestroke systems is safe and feasible and improves therapeutic decision making compared with simple telephone consultation.5–8 At the Medical College of Georgia (MCG) in Augusta, we developed a rural and community telestroke network designed to facilitate thrombolytic therapy for acute ischemic stroke patients presenting to hospitals that lack neurological expertise.5–12 In this report, we examine the impact of our telestroke network on enrollment of subjects in acute, time-sensitive stroke trials.
Methods

The MCG telestroke network was established in 2003. The network currently consists of 12 hospitals in Georgia that lack acute neurology consultants. Ten of these hospitals are located in rural areas between 37 and 127 miles from MCG and serve as spokes in a hub and spoke network. These hospitals have between 10 and 72 beds and lack intensive care units. Details of the Remote Evaluation of Acute Ischemic Stroke (REACH) telestroke system have been described previously.9-12 Key components include a web-based telestroke system allowing for a 2-way audio–video link, transmission of Digital Imaging and Communications in Medicine (DICOM) images for review of CT scans, drop-down menus for recording the National Institutes of Health Stroke Scale, decision support tools, and the ability to document the encounter in a SOAP (subjective, objective, assessment, and plan) note. A telestroke consultation is initiated by an ED physician who suspects an acute stroke presenting within 5 hours of symptom onset. The stroke specialist interacts with local physician(s) and nurses, patient, and family. After the consultation, patients needing intensive care unit monitoring or inpatient neurological follow-up are transferred to the hub hospital.

In addition, MCG is a telephone-only stroke hub (because of state licensure requirements) for 4 rural hospitals in South Carolina located 26 to 65 miles from MCG. The need for stroke consultation is determined by the local ED physician, and subsequent transfer to MCG is based on the potential for IV tPA, intervention, or surgery. From 2005 through 2009, MCG participated in 2 time-sensitive, acute stroke trials: Factor Seven for Acute Hemorrhagic Stroke (FAST) and Minocycline to Improve Neurological Outcome in Stroke (MINO).13 FAST was a multicenter randomized clinical trial to determine whether recombinant Factor VIIa would improve functional outcome in intracerebral hemorrhage. Patients were randomized no more than 4 hours after symptom onset and no more than 1 hour after baseline CT scan. The baseline CT had to be performed at the enrolling center. MINO is an ongoing pilot clinical trial of intravenous minocycline in acute ischemic stroke. Patients are enrolled within 6 hours of symptom onset.

Time of symptom onset, arrival at MCG, enrollment and initiation of study drug, and demographic data were collected prospectively in each clinical trial. In addition, data were collected on whether enrolled subjects were initially identified at a REACH spoke site and subsequently transferred to MCG. Screening logs for both trials noted whether patients excluded from participation were first identified via the REACH system. For all patients evaluated using the REACH system, system, onset, ED arrival, time of consultation, and demographics are recorded.

A test of a single proportion of the total number of enrolled subjects (assuming a hypothesized proportion of 0.50) was done for subjects enrolled who were first evaluated by REACH and for those who presented directly to MCG. Descriptive statistics were calculated for the time from symptom onset to the initiation of a telestroke consult (for all potentially eligible candidates identified via REACH, and from symptom onset to arrival at the hub hospital, from arrival at the hub to the initiation of study drug infusion, and from symptom onset to the initiation of study drug infusion for all study subjects enrolled in FAST and Minocycline to Improve Neurological Outcome. Wilcoxon rank sum tests were performed to examine whether onset to the initiation of a telestroke consult for patients identified via REACH was different between patients who were enrolled in each of the 2 clinical trials compared with those who were not enrolled. We also compared the onset to arrival at the hub hospital, hub to the initiation of study drug infusion, and symptom onset to the initiation of study drug infusion times between the REACH-identified subjects, and those who presented directly to MCG. Statistical significance was assessed using an α level of 0.05, and all statistical analyses were performed using NCSS 2007.

Results

A total of 28 patients were enrolled in the 2 trials. Of these, 19 (68%) were identified via REACH, and 9 (32%) presented directly to MCG. An additional 9 otherwise-qualified patients were identified via REACH but could not be enrolled because of arrival at MCG beyond the enrollment window (9 of 28; 32% of all qualified patients identified via REACH). During the respective study periods, 9 intracerebral hemorrhage and 9 ischemic stroke patients were admitted to MCG after transfer from a South Carolina hospital. None of these patients were enrolled in a clinical trial on arrival. Four patients presented within the time window for eligibility in the South Carolina ED but arrived at MCG too late for inclusion.

Seven different REACH spokes contributed subjects for the 2 trials. Age, sex, and race were similar among subjects who presented directly to MCG and those who were transferred after a telestroke consult (Table 1). Enrolled patients identified via the REACH system came to MCG from a median distance of 55 (range 37 to 62) miles in FAST and 62 (range 45 to 127) miles in MINO, whereas those who arrived at MCG beyond the study window came from a median distance of 53.5 (range 45 to 62) and 76 (range 7 to 127) miles, respectively (Table 2). The onset to the initiation of a telestroke consult via REACH was shorter for patients who were successfully enrolled in FAST (63 [range 45 to 91] compared with 142 [range 99 to 185] minutes; \(P = 0.05\); Table 2) than those who were transferred too late but similar in MINOS (99 [range 43 to 176] compared with 137 [range 46 to 320] minutes; \(P = 0.45\); Table 2). In addition, the median onset to arrival at the hub hospital and symptom onset to the initiation of study drug infusion were longer for patients transferred to MCG than those who presented directly to MCG (Table 1). Conversely, median hub to the initiation of study drug infusion was shorter for subjects initially identified via REACH compared with those who were initially evaluated at MCG (Table 1).

An in-person 90-day follow-up clinical examination was obtained in all subjects recruited from rural telestroke spoke hospitals. For 4 subjects, this required the investigator trav-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Telestroke</th>
<th>Direct</th>
<th>(P)</th>
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</thead>
<tbody>
<tr>
<td>Subjects, No. (percentage, 95% CI)</td>
<td>19 (68%; 48, 84)</td>
<td>9 (32%; 16, 52)</td>
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<tr>
<td>Age, y (median, 95% CI)</td>
<td>70 (50, 76)</td>
<td>63 (51, 80)</td>
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<tr>
<td>Male</td>
<td>58%</td>
<td>67%</td>
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<tr>
<td>Black</td>
<td>42%</td>
<td>56%</td>
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<tr>
<td>OTH, min (median, 95% CI)</td>
<td>207 (145, 255)</td>
<td>80 (55, 142)</td>
<td>0.0002</td>
</tr>
<tr>
<td>HLT, min (median, 95% CI)</td>
<td>71 (62, 104)</td>
<td>140 (94, 188)</td>
<td>0.002</td>
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<tr>
<td>OTL, min (median, 95% CI)</td>
<td>298 (218, 352)</td>
<td>225 (147, 330)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

A test of a single proportion of total enrolled subjects (assuming a hypothesized proportion of 0.50) was done for subjects enrolled via telestroke and for those who presented directly to MCG. Groups are compared using Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables.

OTH indicates the time from symptom onset to arrival at the hub hospital; HLT, time from arrival at the hub to the start of study drug infusion; OTL, time from symptom onset to the start of study drug infusion.
eling to the subject’s residence. The REACH system was not used for 90-day follow-up assessments.

Discussion

Telestroke facilitated enrollment of patients into acute stroke treatment trials at our center. However, patients enrolled after a transfer from a spoke hospital received the study therapy later than patients who presented directly to our ED, and for some patients, the delays in transfer precluded participation in clinical research. In addition, despite the distances between our hospital and each subject’s hometown, follow-up was achieved; although in 4 cases, this required the study physician to travel to the respective subject’s residence.

Interestingly, the time from arrival at MCG to the start of study drug infusion was shorter when subjects were initially evaluated via REACH than when they presented directly to MCG. This may be attributable to the advanced warning that REACH provides for transfers and study candidates. Enrolling physicians and coordinators receive a heads-up on potential participants, and if at home (after hours or on weekends), they can go to the hospital and arrive before the subject(s). In addition, early notification to the pharmacy of a potential study subject may prevent delays in study drug preparation. Finally, informed consent discussions are initiated remotely using REACH so that by the time the patient(s) or family arrives at MCG, they have already made a decision regarding clinical trial participation.

Whether similar results could have been accomplished using only telephone consultations to identify research candidates is not clear. However, MCG is a telephone-only stroke hub for 4 rural hospitals in South Carolina, and no patients from any of these hospitals were enrolled in the 2 acute stroke trials despite potential eligibility. The telestroke system allows the consultant to perform a modified neurological examination, review neuroimaging studies, and begin discussions with patients and family regarding possible study participation. On 2 occasions, the informed consent document was faxed to the spoke hospital, signed by a legally authorized representative, and transported with the patient to the hub to be cosigned by the investigator. Because the family members often must travel to the hub separately from the patient, this prevented delays in waiting for their arrival for the consent.

Short times from symptom onset to initiation of a telestroke consult are probably necessary to successfully enroll candidates after a transfer using telestroke systems. Because intracerebral hemorrhages tend to present to the ED sooner than ischemic strokes, there may be more opportunity to enroll these subjects in spite of interhospital transfer. However, for intracerebral hemorrhage and ischemic stroke, time lost in transportation to the hub results in delays to enrollment and limits participation analogous to what was seen clinically in the ship and drip paradigm of tPA delivery for acute ischemic stroke patients in remote EDs. This could be overcome by enrolling patients at the spokes and initiating research protocols before arriving at the hub. Although not all therapies would be feasible in this scenario, administration of a putative neuroprotectant may be possible. Obstacles would include obtaining an informed consent remotely and lack of research experience at the spokes.

Validation of key process measures required in acute stroke clinical trials (onset to enrollment time, informed consent, serum biomarker collection, study drug administration, and long-term follow-up) may be needed to determine the feasibility and reliability of data and documentation and to establish the safety of conducting research in these settings. Depending on the capabilities of the spokes, different tiers of participation in clinical research trials may be possible. Whereas smaller spokes might enroll, treat, and then ship a subject to a hub for further management, larger spokes could keep subjects, and subsequent in-hospital research visits could be conducted remotely using telemedicine. Finally, audiovisual recording of the neurological examination could allow centralized analysis of the National Institutes of Health Stroke Scale and modified Rankin Scale, reducing interobserver variability and improving the reliability and accuracy of entry and outcome data.

Disclosures


References


