Feasibility of Acute Clinical Trials During Aerial Interhospital Transfer

Enrique C. Leira, MD; Diane L. Lamb, RN, BSN; Andrew S. Nugent, MD; Azeemuddin Ahmed, MD; Karla J. Grimsman, RN; William R. Clarke, PhD; Harold P. Adams, Jr, MD

Background and Purpose—In rural America, patients are often first seen at a small community hospital and then transferred to a tertiary care center by helicopter for further care. If acute clinical research were feasible during the aerial interhospital transport, more patients might be enrolled in trials at a critical earlier stage.

Methods—Prospective data were collected for all aerial transfers of a university-based helicopter service from April 2005 to January 2006. Flight nurses were educated about stroke research and offered certification and participation. Data collected included patient characteristics and the availability of relatives to provide surrogate consent.

Results—All 12 flight nurses completed the institutional review board certification requirements and collected data on 215 transfers. Sixty-one patients had acute stroke or myocardial events (MIs). The median time from symptom onset to helicopter arrival at an outside hospital was 213 minutes (range, 90 to 2135) for ischemic stroke (n = 12), 186 (45 to 1332) for intracranial hemorrhage (n = 28), and 157 (47 to 1044) for MI (n = 21). A relative was available in >74% of those transfers. A trial with a 4-hour window would permit enrollment of 67% of the ischemic strokes, 82% of intracranial hemorrhage cases, and 76% of MI patients.

Conclusions—Clinical trials are feasible during aerial interhospital transport of patients. Flight nurses became successful investigators in clinical research and were exposed to potentially eligible patients with the ability to consent either directly or through surrogates. This approach could improve current clinical trial recruitment in rural areas, as well as permit testing of inflight ancillary interventions to improve outcome during patient transport. (Stroke. 2006;37: 2504-2507.)

Key Words: air ambulances ■ clinical trials ■ delivery of health care ■ emergency medical services ■ rural population

Time is a crucial variable when testing new interventions for treatment of acute stroke. The odds for an improved neurological outcome are inversely proportional to the delay in starting treatment.1 Consequently, a major goal for acute stroke trials is to find strategies that could facilitate early patient enrollment. One approach is having ambulance paramedics recruit patients in the field.2 This tactic may work well for metropolitan-based trials.3 Unfortunately, patients enrolled in the field do not have neuroimaging studies available at the time of randomization, which limits the use of therapies to restore perfusion that have potential bleeding side effects. Another problem is the generalizability to nonurban settings, where patients are first transported by ambulance services to a community hospital emergency department (ED). Although treatment could be implemented at these sites, perhaps with the assistance of large cadres of paramedics or physicians trained as coinvestigators, this approach would be logistically complicated given the multiplicity and dispersion of resources in rural settings. A telemedicine network4 might eventually allow for remote clinical trial recruitment, but this strategy would need to overcome likely legal and regulatory hurdles first. Because patients in rural America with stroke or myocardial infarction (MI) often are transferred to a tertiary care center by helicopter for further care,5–8 one option is to have the patient enrolled at the local ED by those tertiary care center–based aerial medical personnel (potential coinvestigators) when they arrive at the site. There are reports of clinical trials in aerially evacuated trauma patients,9 but to our knowledge, such an approach has not been used for either stroke or MI. If clinical research were feasible during that early aerial interhospital transport, patients might be enrolled at a critical earlier stage. In addition, because neuroimaging studies and basic laboratory tests could already be performed in the local ED before arrival of the air crew, this approach might allow for patient enrollment in a large number of stroke research protocols.
of coverage and traveling distance from Iowa City is shown in Figure 1. The AMCCS flight nurses were approached in March 2005 about exploring clinical research in stroke and MI patients. This recruitment included a single audiovisual presentation about the project during their monthly meeting as well as reminders through E-mail fliers. Those nurses interested in participating were offered directions on how to obtain institutional review board (IRB) certification to conduct clinical research. After successfully completing the IRB certification, flight nurses were asked to participate in the prospective data collection. This involved completing a study form during each flight mission. The IRB waived consent from patients because no specific intervention was tested and no key identifying patient information was included.

Data collected included the time when the transfer was requested, time when the helicopter left the base, and time of arrival to the outside ED. The time of onset of symptoms (or last time seen normal) was recorded on arrival at the outside ED. It also included the patient’s demographic data, ED location, diagnosis, neurological characteristics of the patient, and availability of relatives/surrogates who could have provided informed consent. The local physician’s diagnosis was used to categorize the type of event. Descriptive statistics were used to analyze data. To assess the availability of patients for clinical research depending on their time window from symptom onset to aircrew arrival, we plotted the percentage of patients who would qualify for different time cutoff points. After determining the nonnormal distribution of data through a Kolmogorov-Smirnov test, comparisons of times between the different diagnoses were performed through a Kruskal-Wallis test with a 5% level of significance. All statistical analyses were completed with SAS version 9.1 (SAS Institute Inc). The study was previously authorized by the University of Iowa IRB.

Results

All 12 flight nurses from the AMCCS agreed to participate in this study, and they successfully completed mandatory IRB training. A total of 318 aerial transfers were logged by AMCCS in the 9-month duration of the study, and data forms were collected by investigators for 215 flights (overall capture rate was 68%, 95% capture for stroke cases, and 62% for MI). Those patients were transferred to the University of Iowa from 38 different hospitals/EDs in Iowa, Illinois, and Wisconsin (median distance, 104 km; range, 36 to 248), as well as from 20 field locations (trauma cases only). Of those 215, 40 (19%) were strokes (28 intracranial hemorrhages [ICHs] and 12 infarctions), and 21 (10%) had an MI. All of the transferring hospitals/EDs are equipped with computed tomography scanners and basic laboratory tests. Table 1 compares the times from symptom onset to AMCCS activation, helicopter departure, and arrival at the outside ED for the different diagnoses. Each of these times was significantly different between diagnoses ($P<0.001$). Table 1 also shows the time delays from crew activation to helicopter departure and outbound flight travel time for the different diagnoses. There were no differences among these 2 times among the different diagnoses. Demographic characteristics of the patients and capability to provide eventual informed consent are shown in Table 2. A relative who could have provided consent was available for >74% of the stroke/MI transfers. Figure 2 shows the percentage of stroke, ICH, and MI patients who could be considered for a clinical trial depending on the trial’s time window of inclusion from symptom onset to AMCCS crew arrival at the outside ED (the additional time required for screening and informed consent is not included).

### Methods

This study consisted of a prospective data collection of all consecutive aerial transfers to the University of Iowa Hospitals and Clinics (UIHC) by the Air and Mobile Critical Care Services (AMCCS) at the University of Iowa from April 2005 to January 2006. The AMCCS is a university-owned service that captures 50% of the incoming aerial transfers to UIHC. AMCCS operates a Eurocopter EC-130 helicopter based at UIHC. The EC-130 has a range of 640 km and a cruising speed of 235 km/h and carries 2 registered flight nurses trained and equipped to provide critical life support. The area of coverage and traveling distance from Iowa City is shown in Figure 1. The AMCCS flight nurses were approached in March 2005 about exploring clinical research in stroke and MI patients. This recruitment included a single audiovisual presentation about the project during their monthly meeting as well as reminders through E-mail fliers. Those nurses interested in participating were offered directions on how to obtain institutional review board (IRB) certification to conduct clinical research. After successfully completing the IRB certification, flight nurses were asked to participate in the prospective data collection. This involved completing a study form during each flight mission. The IRB waived consent from patients because no specific intervention was tested and no key identifying patient information was included.

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### Table 1. Times From Symptom Onset to AMCCS Notification, Departure From Base, and Arrival at an Outside ED for Different Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Time From Symptom Onset to Air Base Notification, min</th>
<th>Delay for Helicopter Departure, min</th>
<th>Time From Symptom Onset to Helicopter Departure, min</th>
<th>Flight Time to Destination, min</th>
<th>Time From Symptom Onset to Arrival at Outside ED, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH (n=28)</td>
<td>150 (25–1247)</td>
<td>9 (1–29)</td>
<td>171 (29–1251)</td>
<td>24 (11–81)</td>
<td>186 (45–1332)</td>
</tr>
<tr>
<td>Ischemic stroke (n=12)</td>
<td>184 (55–2076)</td>
<td>9 (3–17)</td>
<td>187 (64–2085)</td>
<td>30 (12–50)</td>
<td>213 (90–2135)</td>
</tr>
<tr>
<td>MI (n=21)</td>
<td>120 (20–968)</td>
<td>9 (5–30)</td>
<td>127 (30–979)</td>
<td>27 (14–65)</td>
<td>157 (47–1044)</td>
</tr>
<tr>
<td>Other medical (n=60)</td>
<td>123 (18–985)</td>
<td>6.5 (1–23)</td>
<td>131 (24–998)</td>
<td>28.5 (6–163)</td>
<td>166 (44–1040)</td>
</tr>
<tr>
<td>Trauma (n=94)</td>
<td>52 (3–577)</td>
<td>7 (1–60)</td>
<td>61 (5–582)</td>
<td>24 (6–73)</td>
<td>84 (17–608)</td>
</tr>
</tbody>
</table>

Values are presented as median and (range). The delays from base notification and helicopter departure and flight times to destination are also shown. Missing data <30% (<20% stroke cases).
A trial with a 4-hour window would permit enrollment of 67% of the ischemic strokes, 82% of ICH cases, and 76% of MIs.

**Discussion**

The feasibility to perform clinical trials during aerial interhospital transport of patients depends on two crucial factors. One is the level of motivation and skill of the aerial transport team members, as research would likely increase their already-busy workload. The other factor is the availability of eligible patients who could provide consent in that setting directly or through surrogate family members.

This study has shown an encouraging response without compensation from the university-based flight nurses, with 100% becoming IRB certified within 1 month and therefore eligible to join a clinical research protocol. This degree of spontaneous enthusiasm, which is further corroborated by the ability to record data in aerial transfers in 9 months with a moderate amount of missing data, is commendable. Although this research involved a prospective cohort that did not require recruitment or randomization procedures, this preliminary response is very encouraging for eventually pursuing clinical trials in this setting.

The other critical factor for performing any clinical trial in this setting would be the availability of eligible patients. Although the response times for stroke were longer than for trauma, we have shown that the flight crew arrived at stroke and MI patient locations at a reasonably early stage, and some of these persons could be considered for enrollment into clinical trials (Figure 2). Unlike the patients recruited from the field, these patients have already been seen by an ED physician, have had basic laboratory tests, ECGs, and a computed tomography scan. This preliminary work-up would likely make them eligible to be safely enrolled in protocols that require blood tests and neuroimaging before randomization.

The ability to obtain informed consent is crucial for participating in an acute stroke intervention trial. Unlike trauma field trials, where informed consent may be waived, ethical and legal regulations are likely to require such consent for a population of stroke patients already admitted to local hospitals. Many of the stroke and MI patients in this study appeared awake and sufficiently coherent to be able to legally sign a consent form. Still, other patients will not be able to give consent because of aphasia, decreased level of consciousness, or intubation. Fortunately, we found that a majority of patients had a relative at the bedside in the outside ED who could provide surrogate consent for entry into a trial. These findings are encouraging for pursuing clinical trials in this previously unexplored setting for clinical research.

Performing clinical trials during an aerial interhospital transfer of patients has obvious advantages for advancing research and acute patient care in rural America. First, it would enable investigators to randomize more patients and at an earlier stage in the current acute stroke or MI protocols. In this proposed strategy, patients would be enrolled in clinical trials at the rural ED, just before aerial interhospital aerial transport. Once the AMCCS helicopter crew arrived to pick up a patient at a local ED, the care of that patient would be legally transferred to the Department of Emergency Medicine of our institution. Any clinical research from then on would be the sole responsibility of our tertiary care ED, and the university-based flight nurses or physicians would be the only investigators legally required for such a trial. This eliminates the need to train a large number of paramedics or local ED investigators or to obtain approval from each of the EDs in range of the helicopter system. Patients would be randomized at the outside ED, and the intervention could be administered aboard the emergency medical service helicopter.

In addition to regular stroke trials, this proposed strategy would permit clinical trials of specific ancillary interventions...
while aboard the helicopter. At present, inflight management is limited to maintaining adequate vital signs and monitoring neurological status because there are no known effective interventions to promote neurological recovery aboard a helicopter. This is unfortunate, because the helicopter crews have access to patients at a critical stage when early management could be instituted. The proven feasibility of clinical research in this setting will likely open the door for trials to test inflight interventions to avoid complications and foster recovery.

Limitations of this study include questions about the generalizability to other nonuniversity-based helicopter systems and the reliability of diagnosis classification. Although the amount of missing data were reasonably low for stroke cases, considering that this was the first uncompensated study, we are aware of the need to minimize missing data collection in subsequent studies. We are also aware of other challenges that lie ahead before clinical trials can be safely implemented in this setting, including the accuracy of preliminary diagnosis, the ability of performing research scales in this setting, and the difficulties in obtaining informed consent in such a time-restrictive environment. Another limitation is the narrower range of neurological deficit seen in these patients. Understandably, a population of helicopter-transported patients is biased toward more severe strokes, including ICH. Depending on the inclusion criteria, this could disqualify some patients for a clinical trial. The strength of this study is to have prospectively collected data to specifically explore the feasibility of research in this new setting as the first step to improve stroke/MI clinical trial recruitment in rural areas, as well as permit testing of inflight ancillary interventions to improve outcome during patient transport.

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Disclosures
None.

References
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