Feasibility of Neuroprotective Agent Administration by Prehospital Personnel in an Urban Setting

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Background and Purpose—Studies have demonstrated the importance of early stroke treatment. If a neuroprotective agent (NA) clinical trial is successful, the greatest benefit might be attained with early prehospital administration. This study determined the potential reduction in time to treatment of stroke patients when NAs were administered in the prehospital setting.

Methods—Twenty-three urban emergency medical services (EMS) agencies participated in this study. Prehospital personnel completed a stroke assessment checklist on any potential stroke victim. The checklist collected clinical inclusion/exclusion criteria for NA administration and event/decision times. Patients meeting the hypothetical clinical inclusion criteria were enrolled into this study. Time data included scene arrival/departure, emergency department (ED) arrival, and estimated time of theoretical NA administration. The reduction in time to stroke treatment was calculated as the difference between the time of ED arrival and the reported time of NA administration. The t test and simple linear regression were used to probe for differences in treatment time reduction between selected subgroups. EMS personnel’s ability to obtain informed consent for theoretical NA administration was calculated.

Results—Two hundred twenty-two patients were enrolled in this study; of these, 75 were deemed eligible for hypothetical NA administration and had complete time data. On average, EMS personnel documented the theoretical time of NA administration at 12.04±2.07 minutes before arrival at the ED (17.06±1.74 minutes when the NA was given on scene [n=43]; 6.65±1.14 minutes when the NA was given en route [n=32]).

Conclusions—Prehospital NA administration can potentially significantly reduce the time to first intervention in stroke patients. (Stroke. 2003;34:1918-1922.)

Key Words: emergency medical services • neuroprotection • stroke

Studies have documented the important role of rapid transport offered by emergency medical services (EMS) systems in the care of acute stroke patients.1,2 Furthermore, EMS personnel are the first medical contact for 35% to 70% of stroke patients.1,3,4 This offers EMS personnel an opportunity to provide early stroke recognition, assessment, and treatment. Because there is no reliable way to differentiate hemorrhagic strokes from ischemic strokes in the prehospital environment, administration of tissue plasminogen activator (tPA) must be deferred until a CT scan of the brain is obtained after hospital arrival. However, use of an effective neuroprotective agent (NA) that can be safely administered in all types of stroke and that can be administered in the field by trained EMS personnel might significantly increase stroke patients’ chances of improved outcome.

Subjects and Methods
Twenty-three EMS agencies were voluntarily recruited to participate in this study. Before the start of this study, all participating EMS agencies received an educational seminar by a member of the Greater Cincinnati/Northern Kentucky Stroke Team. The educational seminars were 2 hours long and discussed the pathophysiology, identification, treatment, and management of stroke. EMS personnel were educated on the proper methods for determining the appropriate time of symptom onset (including the management of patients whose symptoms were present on wakening from sleep).

EMS personnel in the participating agencies were instructed to enroll any patient whom they considered to be a potential stroke victim during the period June 20, 2000, to June 19, 2001. Enrollment in this study included completion of a Prehospital Stroke Assessment Checklist (Figure 1). The data sheet consisted of 4 separate sections: patient demographic information, inclusion and exclusion criteria evaluation, NA utilization determination, and physical examination/time-interval assessments.

The first section (patient demographic information) collected data relating to the patient and the EMS provider. The second section included a series of hypothetical inclusion and exclusion criteria that EMS personnel used in their patient evaluations. The inclusion criteria incorporated time limitations used in previous NA clinical studies,5–7 as well as an out-of-hospital stroke scale. The exclusion criteria consisted of multiple clinical conditions that might mimic an...
acute stroke and warrant patient elimination from the study. Based on the inclusion and exclusion criteria, the third part of the Prehospital Stroke Assessment Checklist prompted EMS personnel for a final decision regarding the use of an NA. If the inclusion criteria were met and the exclusion criteria were not, the EMS personnel were asked whether or not they would prepare to administer an NA. In the event that EMS personnel would administer an NA, the time of this decision was documented. EMS personnel were not instructed as to when NA eligibility should be determined within the sequence of events in a patient’s prehospital course. One of the elements of this research protocol was to determine at which phase in prehospital care the theoretical NA would be administered. Therefore, EMS personnel were simply instructed to determine patient eligibility to receive the theoretical NA and to document the time at which this decision was made. EMS personnel were also queried on the availability of any individuals capable of providing informed consent at the time these patient management decisions were being made. The final section of the Prehospital Stroke Assessment Sheet collected information pertaining to the time intervals during the EMS response, as well as the patients’ neurologic assessments over time.

**Statistical Analysis**

Data from the completed Prehospital Stroke Assessment Checklists were entered into a Microsoft Access database, JMP 4.0 software (SAS Institute) was used for data analysis. Potential reduction in time to NA administration was calculated by taking the difference between the time of arrival at the emergency department (ED) and the reported time of the theoretical NA administration by EMS personnel. Before further analyses, a Shapiro-Wilks W test was performed on the distribution of the treatment time reduction variable to check the extent to which it met the assumptions of normality. Any evidence of a skewed distribution was corrected through data transformations to increase the validity of further statistical test results. The mean treatment time reduction was calculated for the entire group of participants. A subgroup analysis of treatment time reduction was performed on male versus female patients to assess for any gender influence. A second subgroup analysis of treatment time reduction was performed on patients who would have received the theoretical NA while EMS was on scene versus en route to the hospital. Individuals for whom EMS departure time was equal to NA administration time were analyzed in the “treatment given on scene” subgroup. Equal variances were assumed when the Levene statistic was not significant. Simple linear regression was used to examine any association between years of EMS experience and treatment time reduction. An α = 0.05 was chosen as the significance level. Descriptive statistics were calculated for the type and availability of individuals present in the prehospital setting able to give informed consent for NA administration.

**Results**

Data were available for 75 patients for whom EMS personnel reported that they would administer an NA (Figure 2). Males constituted 53% of the patient population, and the mean age was 74.35 years. An initial Shapiro-Wilks test of the distribution demonstrated slight departure from normality within the distribution of the treatment time reduction variable. Consequently, a square root data transformation was conducted, yielding a distribution that met the assumptions of normality (W=0.96, P=0.20).

The overall, average treatment time reduction for all 75 individuals was 12.04 ± 2.07 minutes. Subgroup analysis revealed that 43 individuals (57.3% of total) would have received the NA while EMS personnel were on the scene, and 32 (42.7%) would have received the NA en route to the hospital. There were only 8 individuals whose EMS departure time equaled their NA administration time. Individuals in the...
“on-scene NA administration group” had an average time reduction that was 10.41 minutes greater than those in the “en route NA administration group” (Figure 3). Placing individuals whose treatment time was equal to their EMS departure time within the on-scene group did not change the overall results. When these 8 individuals were placed in the en route NA administration group, the resulting average treatment time reduction difference between the 2 groups would still have been 13.56 minutes in favor of the on-scene NA administration group.

The mean NA treatment time reduction was slightly larger for males when compared with that of females; however, this result was not statistically significant (12.81 versus 11.16 minutes; \( P=0.4643 \)). No association was found between years of EMS experience and estimated treatment time reduction (\( P=0.5027 \)). The most commonly reported reasons for not administering an NA included patient’s having met the exclusion criteria, EMS did not think the patient was having a stroke, and inadequate airway.

Among the 75 patients for whom EMS personnel said they would administered an NA, in 75% of cases, either someone was present and able (usually a family member) to give informed consent or the patient would have been able to provide it themselves. The estimated time for which informed consent could be acquired was not requested by the investigators. Instead, only the presence or absence of an appropriate decision maker for informed consent was solicited. Informed consent was more likely to be acquired among patients who would have received an NA on scene (81.3%) compared with patients who would have received an NA en route (66%; Figure 2).

**Discussion**

Stroke costs the United States billions of dollars every year because of its significant morbidity and mortality. In 1998 alone, $3.6 billion in Medicare benefits were paid to care for stroke survivors. Although 50% to 70% of stroke patients regain functional independence, 15% to 30% remain permanently disabled.\(^{10}\) Despite this bleak prognosis, early treatment with tPA has been shown to increase functional recovery in stroke patients.\(^{11-13}\)

Time to treatment has been shown to be critical to maximize benefit in many disease processes. Just as there is a “golden hour” in trauma, during which treatment is critical, time to tPA administration is also critical for stroke recovery. Intravenous tPA can be beneficial to a subgroup of acute stroke patients up to 180 minutes from the time of symptomatic onset.\(^{11}\) Unfortunately, this narrow therapeutic window renders many stroke patients ineligible to receive tPA. Often, patients do not recognize the symptoms of stroke early enough, and especially in rural areas, long travel times to the hospital can extend the time from stroke onset beyond the 180-minute therapeutic window.

Further complicating matters is the fact that field administration of tPA by EMS personnel is proscribed, because hemorrhagic stroke patients cannot receive tPA and this diagnosis is not possible without a CT scan of the brain. This situation has stimulated the search to discover other treatments for stroke patients, including NAs that protect the brain against the physiologic mechanisms that cause cellular death.

Numerous NAs have been developed and shown to have a favorable effect in animal models of stroke, but none have been found to be effective in phase III clinical trials in humans. Of 178 controlled, acute stroke trials identified in a recent study,\(^{14}\) 114 involved NAs, and none met the conventional criteria for a positive outcome. These NAs have included N-methyl-D-aspartate antagonists, calcium channel blockers, sodium cell channel blockers, free-radical scavengers, and promoters of cell membrane repair.\(^{15-22}\) Only 29 of the 178 studies limited patient enrollment to within 6 hours of symptom onset, and only 3 studies limited enrollment to < 3 hours. The prolonged window of patient enrollment might be 1 reason why there have been such failures in so many clinical studies. Another explanation for this failure might be due to the fact that these NAs were used to target only a single component of ischemic injury and the subsequent physiologic cascade. Therefore, in the larger clinical trials, the benefit might be seen only in a small patient cohort, and the effects were lost in the multiple mechanisms of damage that occur in human patients. This explanation suggests that combination therapy might be key to the discovery of an effective NA. Such therapy has been shown to be beneficial in animals.\(^{23}\)

One such study examined the influence of magnesium and tirilazad in a rat model of ischemic infarct.\(^{24}\) In this study, combination therapy decreased stroke volume infarct by 59%, which was substantially better than either MgCl\(_2\) (25%) or tirilazad (48%) alone. A combination therapy involving human clinical trials tested the combination of lubeluzole and rPA in the treatment of ischemic stroke. Although the study was prematurely terminated after no efficacious link between lubeluzole alone and stroke therapy was established, there were no significant safety concerns found.\(^{25}\)

Discovery of an NA that could be safely administered to all stroke patients regardless of etiology would be a significant advancement in the acute treatment of stroke. This type of safety profile would enable prehospital administration of an NA either on scene or en route to the hospital. Thus, even if the window of opportunity with tPA were exceeded, an NA could still be given with the hope that some functional salvage could be achieved. In our study, patients who would
have received an NA on scene would have received, on average, their first stroke intervention 17 minutes earlier (7 minutes for those receiving an NA en route) versus having to wait until arrival at the ED and physician evaluation to receive treatment. Although 17 minutes of time savings might initially seem trivial, it represents nearly 10% of the total therapeutic window for tPA. Additionally, these savings estimates are conservative because they were calculated by using time of ED arrival instead of time to physician evaluation and treatment. Although we did not examine time to physician evaluation and treatment in the present study, a previous investigation found that EMS patients presenting with stroke symptoms saw an ED physician an average of 10 minutes after arrival. Consequently, the true treatment time savings are most likely to be even higher than the estimates reported. Because of the time sensitivity in stroke patient management, one should not dismiss the significance of this degree of earlier intervention. Some authors have even theorized that NAs given in the prehospital setting could extend the tPA treatment window. This, however, remains to be proven.

Another practical consideration regarding the feasibility of prehospital NA administration is whether such administration would delay arrival to the hospital sufficiently long enough to make tPA candidates ineligible to receive thrombolytic therapy. In our study, there was no significant difference between the on-scene time of patients for whom EMS personnel would have administered an NA compared with patients in whom EMS personnel would not have administered an NA (16.446 versus 17.966 minutes, respectively), although the actual time involved in such NA administration is not yet known.

The ability of EMS to affect the early treatment and recovery of patients in the prehospital setting has clear precedent in the treatment of trauma and cardiac patients. EMS personnel provide early stabilization, aspirin, nitroglycerin, and life-and-limb saving interventions in the field, as well as the early alert that is critical to the receiving facility for the mobilization of necessary personnel and equipment to treat these patients properly. Essentially, an NA would be analogous to aspirin and nitroglycerin administration in the prehospital treatment of the heart attack patient.

One question stemming from the issue of prehospital NA stroke treatment is the extent to which EMS personnel can accurately identify patients experiencing a stroke. Our study used just 1 prospectively validated prehospital stroke scale, the Cincinnati Prehospital Stroke Scale. Primary ICD-9 codes for 66 of the 75 individuals allowed us to determine EMS accuracy of stroke diagnosis. Secondary ICD-9 codes were not reviewed. Of these 66 patients, 30 (45%) were determined to have a final primary discharge diagnosis of stroke. Although this level of EMS accuracy is lower than that found in previous studies, it likely results from our study protocol that instructed prehospital personnel to consider enrollment of any potential stroke patient. Additionally, the focus of this study was to ascertain new insights into prehospital time management of stroke patients rather than EMS accuracy in stroke recognition. Numerous other studies have been conducted to assess the accuracy of EMS personnel in identifying stroke patients by using a variety of prehospital stroke scales. One previous publication found that EMS personnel were >90% accurate in identifying stroke patients when the Los Angeles Prehospital Stroke Screen was used.

Using prehospital stroke scales and/or educational seminars on the topic, EMS personnel have also demonstrated a high sensitivity in detecting patients with stroke symptoms. Treatment of stroke in the prehospital setting with an NA does not decrease the need for accurate use of screening tools and exams by EMS personnel and early activation of the receiving facility. Stroke team mobilization, early CT, and early administration of tPA are (and will remain) critical steps in reducing the morbidity caused by stroke.

Informed consent is another very important consideration when discussing the feasible administration of drugs that are new, not widely used, and unfamiliar to the public and many practitioners. In the present study, we found that 81.3% of stroke patients were able to give informed consent or had someone with them who could give consent on scene. Often, family members will not arrive at the ED before many interventions are started or need to be started to improve patient outcome. These problems are decreased when family members are on scene with the patient and EMS can obtain consent.

There are several limitations of this study that warrant further discussion. One limitation of this study is its execution in EMS systems that are well trained, well established, and administered by full-time EMS personnel. Similar results cannot necessarily be expected in EMS systems that employ volunteer personnel or in EMS systems that evaluate few stroke patients on an annual basis. Furthermore, it is reasonable to expect that EMS performance would be different in other regions of the country where stroke education is less frequent. Another important limitation is the primary time interval that was evaluated in our study. Time-interval documentation concluded on the arrival of EMS at the ED. As discussed, this feature underestimated the true time savings of prehospital stroke intervention by virtue of the numerous additional tasks that must still occur within the ED itself. These include triage, physician evaluation, decision making, and drug administration. Our study is also limited by the theoretical nature of NA administration. Providing an NA to patients on a theoretical basis is a different issue than its actual administration. This issue, however, beckons the future research endeavor of comparing these results with time data acquired in a study that includes prehospital placebo administration. Finally, an important question includes the willingness of family members to formally give consent for NA administration and the effect that this would have on total prehospital time savings. Again, this is a logical next step in investigating the role that NAs might play in the future prehospital management of stroke patients.

Conclusion
This study has shown that prehospital NA administration could significantly reduce time to first intervention in stroke patients. This time reduction is not influenced by patient gender or EMS personnel experience. Our study has also demonstrated the high incidence of informed consent that could be obtained in the prehospital setting. Additional
studies on this topic are warranted to characterize this issue further.

Acknowledgments

The authors would like to acknowledge the following EMS agencies from the Greater Cincinnati area that participated in the study: Anderson, Colerain, Deer Park/Silverton, Delhi, Forest Park, Green Hills, Green Township, Loveland-Symmes, Madeira/Indian Hill, Mariemont, Mason, Miami Township–Clermont County, Montgomery, Norwood, North College Hill, Reading, Sharonville, Springdale, Springfield Township, Sycamore, Union Township Fire Department–Clermont County, West Joint Ambulance District, and Wyoming.

References

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Stroke. 2003;34:1918-1922; originally published online July 3, 2003;
doi: 10.1161/01.STR.0000080943.59701.0D
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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