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Enrollment Yield and Reasons for Screen Failure in a Large Prehospital Stroke Trial

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Abstract

Background and purpose—The enrollment yield and reasons for screen failure in prehospital stroke trials have not been well delineated.

Methods—The Field Administration of Stroke Therapy – Magnesium (FAST-MAG) trial identified patients for enrollment using a two stage screening process - paramedics in person followed by physician-investigators by cellphone. Outcomes of consecutive screening calls from paramedics to enrolling physician-investigators were prospectively recorded.

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Disclosures

None.

Results—From 2005 to 2012, 4,458 phone calls were made by paramedics to physician-investigators, an average of one call per vehicle every 135.7 days. A total of 1,700 (38.1%) calls resulted in enrollments. The rate of enrollment of stroke mimics was 3.9%. Among the 2,758 patients not enrolled, 3,140 reasons for screen failure were documented. The most common reasons for non-enrollment were: more than 2 hours from last known well (17.2%), having a prestroke condition causing disability (16.1%), and absence of a consent provider (9.5%). Novel barriers for phone informed consent specific to the prehospital setting were infrequent, but included: cellphone connection difficulties (3.2%), patient being hard of hearing (1.4%), insufficient time to complete consent (1.3%) or severely dysarthric (1.3%).

Conclusions—In this large, multicenter prehospital trial, nearly 40% of every calls from the field to physician-investigators resulted in trial enrollments. The most common reasons for non-enrollment were out of window last known well time, prestroke confounding medical condition, and absence of a consent provider.

Clinical Trial Registration—URL—http://www.clinicaltrials.gov. Unique identifier: NCT00059332. Barrier to completion of prehospital phone informed consent

Keywords

Prehospital trial; Enrollment yield; clinical trial; ambulance; neuroprotection

Introduction

In acute focal ischemic and hemorrhagic stroke, neuronal injury progresses rapidly after first onset of ischemia or hemorrhage.[1] Stroke trialists are beginning to test novel therapies in the prehospital setting, evaluating neuroprotective agents that may be administered by paramedics without requiring brain imaging and thrombolytic treatment ordered by physicians in ambulances equipped with mobile CT scanners.[2]

Many aspects of stroke trials conducted in the prehospital setting differ from traditional hospital-based trials. Enrollment yield and the reasons for screen failure may be expected to be quite different for prehospital than for Emergency Department acute stroke trials.

The Field Administration of Stroke Therapy–Magnesium (FAST-MAG) was the first large, prehospital pivotal stroke trial to employ physicians elicited informed consent by cellphone immediately after screening by paramedics in stroke patients within 2 hours of symptom onset.[3] This study was undertaken to delineate the enrollment yield and reasons for non-enrollment in the FAST-MAG study.

Methods

FAST-MAG was a pivotal, placebo-controlled, randomized clinical trial of field-initiated magnesium sulfate in acute stroke with enrollment taking place in Los Angeles and Orange Counties in the United States between January 2005 and December 2012.[3] The great preponderance (more than 98%) of patients in FAST-MAG were enrolled using explicit, written, informed consent procedures, with a very small proportion enrolled using exception from informed consent in emergency circumstances.

The FAST-MAG trial employed a two stage screening process for patient enrollment.[3–6] In the first step, paramedics identified potentially study-eligible patients and called to the responding physician. In the second step, physician-investigators performed the final study eligibility determination, based on paramedic report and discussion with the patient and/or on-scene legally authorized representatives (LARs).

Initially, in addition to the modified Los Angeles Prehospital Stroke Screen (mLAPSS), 4 inclusion criteria were developed with evaluation of all 10 study exclusion criteria left for the phone-enrolling physician-investigator.[4, 5] Over the course of the study, three revisions to the screening form were made, adding several exclusion criteria elements for paramedic performance (Table 1). Two of these revisions aimed to reduce non-enrollment calls, and exclusion of blood pressure > 220mmHg aimed to reduce the proportion of hemorrhage patients enrolled, as the study hypothesized treatment benefit in ischemia and neutral effect in hemorrhage.

For all calls from paramedics not resulting in an enrollment, physician-investigators recorded the reason for non-enrollment. Details of methods and main results of the trial have been reported previously with the final paramedic screening form and exclusion criteria.[3–6]

Results

Over the 8-year study period, 4,458 potential subjects were screened by enrolling physicians from paramedic phone calls. Among the 315 ambulances that participated in the trial, the median duration of active screening in the trial was 64 months (IQR 24-81). Accordingly, the average ambulance made 1 screening call to an enrolling physician every 135.7 days and yielded one study enrollment every 355.7 days. Among these, 1,700 patients (38.1%) were enrolled.

Among enrolled patients, final diagnoses of the qualifying event were cerebral ischemia in 73.3%, intracranial hemorrhage in 22.8%, and cerebrovascular disease mimic in 3.9%.

Among 2,758 non-enrolled patients (61.9%), a total of 3,140 reasons for non-enrollment were documented (Table 2). The most common reasons for non-enrollment were: being more than 2 hours from last known well time (17.2%), having a pre-existing condition causing disability (16.1%), and patient being not competent with no LARs on scene to provide consent (9.5%).

Aspects of the presenting neurologic deficit making the diagnosis of acute stroke insecure accounted for 29.8% of the non-enrollment reasons, including last known well time more than 2 hours (17.2%), rapidly improving deficit (7.6%), absence of any arm or face motor deficit (2.8%), presence of bilateral weakness (1.5%), and coma (0.7%).

Barriers to completion of prehospital phone informed consent process accounted for 20.8% of the non-enrollment reasons, including absence of a consent provider on scene (9.5%), patient not fluent in the English or Spanish languages (4.3%), phone connection difficulties (3.2%), patient or LARs too hard of hearing to understand physician-investigator over the phone (1.4%), etc (Table 2).

Informed non-consent (informed decision to decline participation in the study) accounted for 6.7% of non-enrollment reasons, including declinations by patients (3.8%) and declinations by LARs (2.9%).

Changes in the screening form were not associated with a reduction, and actually associated with an increase, in the proportion of calls that were non-enrollments (p=0.009) (Table 1). Before addition of initial SBP > 220mmHg exclusion criteria, the rate of hemorrhage enrollment was 24.3% (190/782) and after 21.5% (197/918), (p = 0.16). There was a correlation between calendar date of enrollment (by quarter) and rate of hemorrhage enrollment was 0.50 (p=0.004, Spearman's test for correlation) (Supplemental Table 1).

Discussion

This study's findings highlight that the two stage screening method in FAST-MAG, involving paramedics and then physician-investigators, was important to assure stringent patient selection. Overall, the low rate of mimics (3.9%) entered into FAST-MAG using the two stage screening process contrasts favorable with the higher rates of mimics enrolled in smaller prehospital stroke trials using one stage, paramedic screening (7–13%),[7–9] or less formal two-stage processes (24%).[10] Time since onset longer than target, an exclusion criteria available to paramedics, was the most common reason for physician exclusion of patients. Enrolling physicians were able to exclude cases where there was uncertainty of onset of unfamiliarity with the strict definition of last known well time. It is possible that paramedics erred on the side of calling physicians in cases with uncertain time of onset, knowing that the trial would be more greatly set back by missing an eligible patient than by physician screening of an uncertainly eligible patient. Pre-existing disability prior to onset of the current stroke was the second most common reason for non-enrollment and is a difficult variable to assess for individuals who are not experienced stroke trialists

The enrollment yield of this prehospital study (38.1%) is similar to that (37.3%) of a recent multicenter neuroprotective trial using in-hospital recruitment,[11] but the spectrum of reasons for non-enrollment differ. First, noncompetent patients were frequently not accompanied by a LARs in the field who could provide consent. The longer enrollment time window in Emergency Department-based trials often permits LARs to arrive or be contacted by phone. Exception from informed consent-enrolling was permitted at most sites when no LARs was available, but the requirement of a person who knew the patients well and could provide a reliable prestroke medical history limited its enrollment yield. Second, cellphone connection difficulties did occur as a reason for non-enrollment in FAST-MAG, but at a low (3%) rate, indicating that incorporation of cellphone processes into enrollment mechanisms is feasible in the current cellular broadband environment. Thirdly, noncognitive communication barriers included presbyacusis, preventing consent providers from hearing physicians over the phone, and severe dysarthria, preventing physician-investigators from understanding patients. These would usually be able to be overcome with more time to interact and the availability of nonverbal modes of complementary messaging with in person-consenting in hospital.

As the prehospital setting might be inherently coercive, and patients and LARs in the prehospital setting are not in a position to make an unforced decision, the informed declination rate would be lower in a prehospital than a hospital-based hyperacute trial. However, the rate of declination in FAST-MAG was substantially higher (6.7% of non-enrollment reasons) than that in contemporaneous trials of in-hospital neuroprotective (1.9%) and endovascular (2.5%) acute stroke treatment.[11, 12] These findings suggest that the prehospital setting and brief time window for decision-making actually somewhat influenced consent-providers against rather than towards participation.

Screening form changes to reduce screen failure call were paradoxically associated with an increase, rather than decrease, in non-enrollment calls. This increase likely reflects the countervailing influences of: 1) increased paramedic awareness of and enthusiasm for the trial as the study progressed, leading to call even when exclusion criteria were present just to be sure not to miss an enrollable patient, and 2) more stringent application of exclusion criteria by physician-investigator as the study progressed, to enroll the most informative cohort once it was clear that study would be proceeding to completion.

Also over the course of the trial, a goal was to reduce the rate of enrollment of hemorrhagic versus ischemic stroke patients, as the study hypothesized treatment benefit in ischemia and neutral effect in hemorrhage. Exclusion of the cases with systolic blood pressure > 220mmHg on first measurement by paramedics was associated with a nominal decrease in hemorrhage enrollments that did not reach statistical significance. However, over the entire course of the study, a statistical significant decline in hemorrhage enrollments did occur, likely as a combined result of the screening form change and of increased enrolling-investigator stringency in assessing exclusion criteria in patients with presentations suggestive of hemorrhage.

The findings of this study will be useful to planning of future prehospital stroke trials. Studies of paramedic-delivered prehospital therapies for acute stroke should take into account that the enrollment yield from paramedic calls to off-scene enrolling physicians will be about 40%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Impact of exclusion criteria changes on screen failure and enrollment rate

	1st period (January 2005~ January 2007)	2nd period (February 2007 ~ June 2009)	3rd period (July 2009 ~ October 2011)	4th period (November 2011 ~ December 2012)	P-value
Addition of exclusion criteria		A prisoner, homeless, on dialysis or residing in a nursing home	Initial systolic blood pressure <90 or >220mmHg	Dementia or Alzheimer's disease and receiving chemotherapy	
Screen failure rate (%)	57.3 (351/613)	61.8 (840/1360)	61.5(982/1596)	65.8(585/889)	0.009

Table 2

General enrollment yield and reasons of exclusion after central phone screen in FAST-MAG

	Number (%)
Number of phone calls by paramedics	4,458
Number of enrollment	1,700
Number of screen failure	2,758
Patients with single reason	2,388 (86.6%)
Patients with two or more reasons	370 (13.4%)
Reasons for exclusion	3,140
Presenting neurologic deficit associated with acute stroke	
Last known well > 2 hours	539 (17.2%)
Rapid improving neurologic deficit	240 (7.6%)
No arm/face weakness	87 (2.8%)
Bilateral arm/face weakness	46 (1.5%)
Coma	22 (0.7%)
Pre-existing and current medical diseases or conditions	
Pre-existing neurologic, psychiatric, or advanced systemic condition	505 (16.1%)
Systolic blood pressure <90 mmHg or >220 mmHg	196 (6.3%)
Age <40 years	51 (1.6%)
Cerebrovascular disease mimic	49 (1.5%)
Recent stroke within 30 days	45 (1.4%)
History of seizures	43 (1.3%)
Known severe renal dysfunction (eg. Creatinine above 3.0)	40 (1.2%)
Blood glucose <60 or > 400 mg/dL	21 (0.7%)
Barrier to completion of prehospital phone informed consent	
Patients unable give informed consent and no proxy available	298 (9.5%)
Patient not English or Spanish speaking	135 (4.3%)
Phone connection difficulties in field	99 (3.2%)
Hard of hearing	43 (1.4%)
Not enough time for consent prior to arrival	40 (1.3%)
Severe dysarthria	40 (1.3%)
Informed non-consent	
Patient competent and declined participation	119 (3.8%)
Patient not competent and representative declined participation	90 (2.9%)
Being transported to a non-enrolling hospital	139 (4.4%)
Paramedics could not start IV	21 (0.6%)
Other	232 (7.4%)