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METHODOLOGY OF THE FIELD ADMINISTRATION OF STROKE THERAPY - MAGNESIUM (FAST-MAG) PHASE 3 TRIAL:

PART 1: RATIONALE AND GENERAL METHODS

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Abstract

Rationale—Prehospital initiation by paramedics may enable delivery of neuroprotective therapies to stroke patients in the hyperacute period when they are most effective in preclinical studies. Magnesium is neuroprotective in experimental stroke models and has been shown to be safe with signals of potential efficacy when started early after onset of human cerebral ischemia.

Aims—1) To demonstrate that paramedic initiation of the neuroprotective agent magnesium sulfate in the field is an efficacious and safe treatment for acute stroke; 2) To demonstrate that field enrollment of acute stroke patients is a practical and feasible strategy for phase 3 stroke trials, permitting enrollment of greater numbers of patients in hyperacute time windows.

Design—Multicenter, randomized, double-blinded, placebo-controlled, pivotal clinical trial.

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Conflicts of Interest: None declared

Study Procedures—The study is enrolling 1700 patients (850 in each arm) with likely acute stroke, including both cerebral infarction and intracerebral hemorrhage patients. Inclusion criteria are: 1) likely stroke as identified by the modified Los Angeles Prehospital Stroke Screen (mLAPSS), 2) age 40–95, 3) symptom onset within 2 hours of treatment initiation, and 4) deficit present ≥ 15 minutes. Paramedics administer a loading dose of magnesium sulfate (Mg) or matched placebo in the field, 4 grams over 15 minutes. In the Emergency Department, a maintenance infusion follows, 16 grams Mg or matched placebo over 24 hours.

Outcomes—The primary endpoint is the modified Rankin Scale measure of global disability, assessed using the Rankin Focused Assessment, 90 days after treatment. Secondary efficacy endpoints include the NIHSS (neurologic deficit), Barthel Index (activities of daily living), and the Stroke Impact Scale (quality of life).

Keywords

Magnesium; paramedic; ambulance; neuroprotection; clinical trial; prehospital

This paper describes the rationale and general clinical trial design methodology of the Field Administration of Stroke Therapy - Magnesium (FAST-MAG) Phase 3 Trial. A companion paper describes in detail select aspects of the prehospital trial methodology employed in the FAST-MAG Phase 3 trial.

Rationale

Stroke is the second leading cause of death and a leading cause of adult disability worldwide. Unfortunately, currently available therapies for acute ischemic stroke, all focused on reperfusion, are of only modest effectiveness.[1] Tissue plasminogen activator (TPA), the only regulatory agency-approved pharmacologic treatment for acute ischemic stroke, achieves early reperfusion in less than half of treated patients, carries significant bleeding risks, can be started only after neuroimaging has ruled out intracerebral hemorrhage, and is used in only 2–7% of acute ischemic stroke patients in the US.[2] Mechanical thrombectomy devices are cleared for the technical indication of removing acute thrombi from the cerebral vasculature, but have not been demonstrated to improve patient outcome and are employed in only a small fraction of stroke patients nationally.[3–5] New, effective, widely applicable treatments for acute ischemic stroke are urgently needed.

Neuroprotection is a promising treatment strategy, complementary to reperfusion. Neuroprotective agents interrupt the cellular, biochemical, and metabolic processes that mediate cerebral tissue injury during or following exposure to ischemia. Since they are typically safe and potentially beneficial in hemorrhagic as well as ischemic stroke, neuroprotective agents can in principle be given prior to brain imaging, including in the prehospital setting, to stabilize threatened tissues until definitive rescue by therapeutic or spontaneous reperfusion. In past studies, more than 70 neuroprotective agents were tested in randomized controlled clinical trials in acute ischemic stroke and none were found unequivocally beneficial in definitive phase 3 trials .[6] However, the crucial factor of delayed time to treatment hindered all trials. Although it is in the first 2 hours that neuroprotective agents are most beneficial in rodent and primate focal stroke models, no prior human clinical

neuroprotective agent trial has enrolled any substantial cohort of patients in this time window.[6, 7]

The ideal neuroprotective agent for stroke would be inexpensive, readily available, easy to administer, have few adverse side effects, and safe and potentially beneficial in both ischemic and hemorrhagic stroke. Intravenous magnesium sulfate offers promise as just such an agent. Magnesium sulfate is reliably cerebroprotective in diverse animal stroke models, exerting both vasodilatory and direct neuroprotective and glioprotective effects.[8–10] In human clinical trials, magnesium has shown signals of potential neuroprotective efficacy if administered early, including when given prior to ischemia onset among patients undergoing cardiac bypass surgery and carotid endarterectomy,[11, 12] and shortly after start of global ischemia in patients resuscitated from cardiac arrest.[13] Moreover, magnesium is economical, widely available, simple to administer, and has a long established safety and tolerability profile in myocardial infarction and eclampsia, as well as in initial human focal stroke studies.[9, 14] Unlike many synthetic neuroprotective compounds, parenteral magnesium has no major adverse effects in doses that achieve serum levels in the range of preclinical neuroprotective concentrations.

One phase 3 clinical trial of magnesium sulfate for acute ischemic stroke has been performed, using a traditional, post-hospital arrival design, the Intravenous Magnesium Efficacy in Stroke (IMAGES) Trial.[15] The IMAGES trial overall had a neutral result, but trial data suggest that the nonpositive outcome may have been due to late administration of study agent, with start of infusion permitted up to 12 hours after stroke onset. In the small subset of under 3 hour patients in IMAGES, the point estimate for averting death or unfavorable recovery suggested benefit of magnesium, 0.66 (95%CI 0.25–1.70).[15]

Initiating experimental neuroprotective therapies more quickly is critical if the substantial benefits of neuroprotective agents evident in the laboratory are to be achieved in human stroke victims. Enrolling patients in the field is a highly promising approach to the challenge of testing neuroprotective agents in hyperacute time epochs. The FAST-MAG pilot trial demonstrated that prehospital initiation of magnesium sulfate was feasible, generally safe, and accelerated start of study agent by 2 hours compared with in hospital initiation.[16] Several additional recent trials in stroke and other neuroemergency conditions have confirmed the feasibility and potential advantages of the prehospital treatment approach.[17–20] The FAST-MAG Phase 3 trial is the first prehospital pivotal trial of a pharmacologic agent in focal stroke.

Methods

Objectives

The central aim of this study is to demonstrate that paramedic initiation of the neuroprotective agent magnesium sulfate in the field is an efficacious and safe treatment for acute stroke. An additional core objective is to show that field enrollment and treatment of acute stroke patients is a practical and feasible strategy for phase 3 stroke trials, permitting enrollment of greater numbers of patients in hyperacute time windows.

Design

FAST-MAG Phase 3 is a multicenter, randomized (1:1), double-blinded, placebo-controlled, pivotal clinical trial, using intention to treat analysis, of magnesium sulfate among ambulance-transported patients with acute stroke, with study agent initiated in all individuals within two hours of stroke onset.

Patient Population

All ambulance-transported patients are potentially eligible if they are within 2 hours of last known well time and have a likely stroke identified by the modified Los Angeles Prehospital Stroke Screen (mLAPSS). Detailed study inclusion and exclusion criteria are shown in Table 1. The mLAPSS used in the trial differs from the original LAPSS in having a lower age threshold of 40 or older, rather than 45 or older, increasing screen sensitivity. The use of the mLAPSS as an inclusion criterion ensures that all patients have motor deficits on entry.

The rationale for key exclusion criteria are as follows. Patients with known advanced renal dysfunction are excluded because magnesium sulfate is cleared renally. The total 24 hour study dose could theoretically produce potentially toxic magnesium serum levels in these patients. The loading dose alone is anticipated to be safe even in anuric patients. Consequently the rare patient with new onset renal failure that is not discovered until hospital arrival will not be adversely affected by trial enrollment, as trial procedures dictate the immediate cessation of the maintenance dose when creatinine is discovered to exceed 3.0. Patients with severe respiratory distress are excluded lest subclinical effects of magnesium sulfate on neuromuscular transmission and muscle strength reduce respiratory effort. Including this exclusion criteria is an extremely conservative measure, as magnesium sulfate at trial doses exerts no clinical effect or documented subclinical effect on muscle strength. Patients with known unprotected second or third degree heart block are excluded because, at high serum levels, magnesium inhibits the cardiac conduction system and could worsen heart block. Patients with recent strokes in the past 30 days are excluded because they may have not yet recovered to a stable baseline from their prior stroke, and evolution of the old deficit will confound interpretation of study agent effect on evolution of the new deficit. Pre-existing diseases that would confound trial outcome evaluations include any condition or combination of conditions that made the patient’s prestroke modified Rankin Scale score 3 or higher.

Randomization

Randomization allocation is 1:1 to magnesium sulfate or placebo, using permuted block randomization sequences stratified by enrolling ambulance. Each ambulance is stocked with one study kit at a time, containing the next allocation in its permuted block sequence. A patient is considered enrolled in the trial once the first drop of study agent has been infused.

Treatment

Magnesium sulfate (Mg) or matching placebo are administered intravenously with a 15 minute bolus load followed by a 24 hour maintenance infusion. In the active treatment arm, the bolus-loading dose contains 4 grams Mg in 54 ml normal saline infused over 15 minutes; the maintenance infusion contains 16 grams Mg diluted in 240 ml 0.9% normal saline,

infused at 10 ml/hr for 24 hours. Paramedics in the field initiate the bolus-loading dose, administered at 216 ml/hr over 15 minutes through a fixed-lumen size infusion tubing that automatically implements rate-control of gravity driven infusion. Nurses start the maintenance infusion in the ED immediately upon completion of the loading dose, using electronic infusion pumps.

The 24 hour study infusion is to be completed in full both in patients found on arrival imaging to have acute ischemic stroke and patients found to have acute intracranial hemorrhage. Patients with transient ischemic attacks (TIAs) receive the full 24 hour infusion if they are admitted for a period of 24 hours or longer. However, if a TIA patient is discharged to home prior to 24 hours, the maintenance infusion may be discontinued early. If a definitive diagnosis of a non-cerebrovascular disease condition (stroke mimic) is made during the first 24 hours after arrival, the maintenance infusion is stopped early, when the stroke mimic diagnosis is rendered. All patients, including stroke mimic patients, are followed for adverse events and 90 day final clinical outcomes.

Concomitant therapy follows national practice guidelines from the American Heart Association / Stroke Association Stroke Council. Ischemic stroke patients may be treated with IV TPA up to 3 to 4.5 hours after last known well and with FDA-cleared thrombectomy devices. Intracerebral hemorrhage patients may undergo ventriculostomy and hematoma evacuation procedures at the discretion of the attending neurosurgeon.

Primary Outcome

The primary outcome is global disability as assessed by the modified Rankin Scale three months poststroke. For the primary analysis, categorical shifts in outcome over all seven levels of the modified Rankin Scale will be analyzed. To ensure reliable scoring of the modified Rankin Scale, raters employ the Rankin Focused Assessment.[21]

Secondary Outcomes

Secondary efficacy measures, asertained at 90 days, include the Barthel Index of Activities of Daily Living (instrumental activities of daily living), the National Institute of Health Stroke Scale (neurologic deficit), and the Stroke Impact Scale (stroke-specific quality of life).

Secondary safety endpoints include all-cause mortality, symptomatic intracranial hemorrhage, and all serious adverse events.

Data and Safety Monitoring

To ensure that appropriate ethical consideration is given to the welfare of the patients enrolled in the study, the National Institute of Neurological Diseases and Stroke appointed a Data and Safety Monitoring Board (DSMB), consisting of two vascular neurologists, a neurologist-neurointensivist, an emergeny physician, and a biostatistician. The DSMB meets every 6–12 months during the study, reviews trial group data in partially unblinded fashion (comparing group A with group B, with power to fully unblind as needed), and performs the trial formal interim analyses. Additionaly, an independent and experienced stroke

neurologist was appointed as the trial Medical Safety Monitor. The Medical Safety Monitor reviews all serious adverse events, adjudicates their relatedness to study drug or procedures, and monitors for signal events that would cause any safety concerns between formal DSMB meetings.

Sample Size

Sample size calculations projected that beneficial effects of magnesium sulfate would vary among three enrolled patient groups:

1. In acute cerebral ischemia patients with ischemic stroke not treated with TPA, the distribution of 3 month modified Rankin Scale (mRS) scores in the placebo group was estimated based on observations of placebo outcomes among under 3 hour patients in 4 prior trials. Modified Rankin Scale score distribution in the magnesium sulfate group was then projected at approximately 70% of the effect size observed in a meta-analysis of 4 phase 2 randomized controlled trials of magnesium for focal stroke.
2. In patients with acute cerebral ischemia treated with TPA, it was expected that this effect size would be modified by two factors: a) better outcome in placebo treated patients due to the administration of TPA, and b) lesser effect size of magnesium sulfate as some tissue at risk would already be salvaged by TPA. For TPA treated patients, distribution of modified Rankin Scale scores at 3 months in the FAST-MAG placebo group were based on observations from the TPA-treated groups in the 2 NINDS-TPA trials. Distribution of mRS scores in the magnesium group was projected at 80% of the effect projected for non-TPA treated patients. The proportion of enrolled patients treated with TPA was anticipated to be 20%.
3. In patients with intracranial hemorrhage and in patients with final nonstroke diagnoses, the effect size was set at nil.

Sample size calculations also took into account the three planned interim data analyses. The primary analysis is to be executed on the intent to treat principle and include all enrolled and randomized patients, regardless of their final diagnosis.

Initial sample size calculations projected that 95% of enrollees would have acute cerebrovascular disease, including 80% with acute cerebral ischemia and 15% with acute intracerebral hemorrhage, and 5% would have stroke-mimicking conditions. In actual implementation, the trial was noted to enroll the expected rate of stroke mimic patients, but a modestly higher proportion of intracerebral hemorrhage (ICH) patients than originally anticipated, 25% instead of 15%. As a result, the proportion of enrolled patients with acute cerebral ischemia was approximately 70% instead of 80%. Consequently, in January 2010, an adjustment to study sample size was made, from the original 1298 patients (649 in each arm) to 1700 patients (850 in each arm). The sample size adjustment was made with the concurrence of the trial Steering Committee, the DSMB, the Food and Drug Administration (FDA), and the NIH-NINDS, based solely upon the difference in baseline patient features

from initial sample size projections, and not upon any analysis of post-randomization patient outcomes.

The reasons for the modestly higher than anticipated rate of enrollment of intracerebral hemorrhages are straightforward. In the United States, among focal stroke syndrome patients (ischemic stroke and intracerebral hemorrhage (ICH), but not subarachnoid hemorrhage), 90% of strokes are cerebral infarctions and 10% are intracerebral hemorrhages.[22] When transient ischemic attacks are added, the rate of ICH among acute focal cerebrovascular syndromes drops to 6–9%. However, intracerebral hemorrhage patients are disproportionately represented among early 911 system activating patients, because intracerebral hemorrhages are associated with headaches and more severe deficits, and occur more often in younger individuals, prompting more rapid accessing of the emergency medical system. For these reasons, the FAST-MAG investigators anticipated, and incorporated into original study power projections, a higher rate of ICH enrollments than in population-based studies. However, data were not available at the time of study design to gauge precisely the degree to which ICH patients would be over-represented, as FAST-MAG is the first-ever large clinical trial to be performed in stroke patients in the hyperacute period and prehospital setting. In sample size projections, we anticipated an approximate doubling of ICH rates in the study population over population-based rates, from 6–9% to 15%. Initial enrolling experience, however, demonstrated this projection underestimated the actual rate, in which the representation of ICH patients was tripled or quadrupled to 24%.

Statistical analyses

For the primary efficacy analysis, data will be analyzed to test the null hypothesis that the distribution of scores on the modified Rankin Scale at Day 90 is identical in the magnesium sulfate and placebo groups, versus the one-sided alternative that the distribution of scores is shifted lower in the active magnesium sulfate therapy group. The statistic used to test the primary hypothesis will be the Cochran-Mantel-Haenszel test statistic performed on the rank scores and stratified by transport vehicle. The criterion for statistical significance will be set at an alpha level of 0.05. Three efficacy interim analyses were performed, after enrollment of 325, 650, and 1275 patients, resulting in a total of 0.0025 alpha used before the final analysis, leaving 0.0475 alpha for the final analysis. The planned sample size has 80% power to detect the projected treatment effect.

In addition to the efficacy interim analyses, safety interim analyses tested the null hypothesis that the distribution of scores on the modified Rankin Scale at Day 90 is identical in the magnesium sulfate and placebo groups versus the one-sided alternative that the distribution of scores is shifted lower in the placebo group. This test was performed at the 1% alpha level at each interim analysis. This analysis was conducted to ensure that patients are not being harmed by assignment to the magnesium sulfate group during the course of the trial. As this pure safety, one-sided analysis did not overlap with the final efficacy analysis (evaluating whether patients are benefitted by treatment with magnesium sulfate), it did not enter into the efficacy alpha spending function.

Predefined subgroups for analysis of treatment heterogeneity are:

- patients with acute cerebral ischemia
- patients with intracerebral hemorrhage
- patients with acute cerebral ischemia treated with conventional intravenous tissue plasminogen activator
- patients with acute cerebral ischemia not treated with conventional intravenous tissue plasminogen activator
- patients with acute cerebral ischemia treated within 60 minutes of onset
- patients with acute cerebral ischemia treated within 61–120 minutes of onset

Study Organization and Funding

The FAST-MAG Phase 3 trial is funded as a collaborative U01 trial by the NIH-NINDS. The performance centers include 40 Emergency Medical Services Provider Agencies, 315 rescue ambulances, and 60 receiving hospitals in Los Angeles and Orange Counties. The Clinical Coordinating Center and the Core Imaging Laboratory are at the University of California, Los Angeles, the Statistical Management Center is at Mt. Tam Data Analysis with an affiliation with Stanford University, and the Data Management Center is at InClin, Inc. Drug kits are specially prepared for the study by McGuff Pharmacy, a certified research pharmacy with extensive experience in preparation of agents for IND clinical trials.

Summary

The goals of this NIH-funded, phase 3, randomized, multicenter, placebo-controlled trial are to demonstrate that paramedic initiation of the neuroprotective agent magnesium sulfate in the field is an efficacious and safe treatment for acute stroke, and that field enrollment of acute stroke patients is a practical and feasible strategy for phase 3 stroke trials, permitting enrollment of greater numbers of patients in hyperacute time windows. The study is enrolling prehospital patients with suspected acute stroke with unilateral motor deficits within 2 hours of last known well time. The trial is organized as a regional consortium, with participation by all EMS provider agencies, ambulances, and stroke centers in Los Angeles and Orange Counties. Trial enrollment began in January 2005.

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Table 1

Study Entry Criteria

Inclusion Criteria	
1	Suspected stroke identified by the modified Los Angeles Prehospital Stroke Screen (Age ≥ 40; History of seizures or epilepsy absent; At prestroke baseline, patient not wheelchair-bound or bedridden; Blood glucose between 60 and 400; Unilateral face, arm, and/or grip weakness)
2	Age 40–95, inclusive
3	Last known well time within 2 hours of treatment initiation
4	Deficit present for > 15 minutes
Exclusion Criteria	
1	Coma
2	Rapidly improving neurologic deficit
3	Pre-existing neurologic, psychiatric, or advanced systemic disease that would confound the neurological or functional outcome evaluations
4	SBP < 90 or > 220
5	Known severe renal dysfunction (on dialysis or known chronic creatinine > 3.0)
6	Severe respiratory distress (O2 sat < 90% or respiratory rate < 12 or > 24)
7	Known second or third degree heart block with no pacemaker in place
8	Major head trauma in the last 24 hours
9	Recent stroke within prior 30 days
10	Patient unable to give informed consent and no available legally authorized representative to provide informed consent and enrollment under exception from explicit consent not yet approved in catchment area