ORIGINAL ARTICLE

Prehospital Use of Magnesium Sulfate as Neuroprotection in Acute Stroke

Jeffrey L. Saver, M.D., Sidney Starkman, M.D., Marc Eckstein, M.D., Samuel J. Stratton, M.D., Franklin D. Pratt, M.D., M.P.H.T.M., Scott Hamilton, Ph.D., Robin Conwit, M.D., David S. Liebeskind, M.D., Gene Sung, M.D., Ian Kramer, M.D., Gary Moreau, M.D., Robert Goldweber, M.D., and Nerses Sanossian, M.D., for the FAST-MAG Investigators and Coordinators*

ABSTRACT

BACKGROUND

Magnesium sulfate is neuroprotective in preclinical models of stroke and has shown signals of potential efficacy with an acceptable safety profile when delivered early after stroke onset in humans. Delayed initiation of neuroprotective agents has hindered earlier phase 3 trials of neuroprotective agents.

METHODS

We randomly assigned patients with suspected stroke to receive either intravenous magnesium sulfate or placebo, beginning within 2 hours after symptom onset. A loading dose was initiated by paramedics before the patient arrived at the hospital, and a 24-hour maintenance infusion was started on the patient's arrival at the hospital. The primary outcome was the degree of disability at 90 days, as measured by scores on the modified Rankin scale (range, 0 to 6, with higher scores indicating greater disability).

RESULTS

Among the 1700 enrolled patients (857 in the magnesium group and 843 in the placebo group), the mean (±SD) age was 69±13 years, 42.6% were women, and the mean pretreatment score on the Los Angeles Motor Scale of stroke severity (range, 0 to 10, with higher scores indicating greater motor deficits) was 3.7±1.3. The final diagnosis of the qualifying event was cerebral ischemia in 73.3% of patients, intracranial hemorrhage in 22.8%, and a stroke-mimicking condition in 3.9%. The median interval between the time the patient was last known to be free of stroke symptoms and the start of the study-drug infusion was 45 minutes (interquartile range, 35 to 62), and 74.3% of patients received the study-drug infusion within the first hour after symptom onset. There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale between patients in the magnesium group and those in the placebo group (P=0.28 by the Cochran–Mantel–Haenszel test); mean scores at 90 days did not differ between the magnesium group and the placebo group (2.7 in each group, P=1.00). No significant between-group differences were noted with respect to mortality (15.4% in the magnesium group and 15.5% in the placebo group, P=0.95) or all serious adverse events.

CONCLUSIONS

Prehospital initiation of magnesium sulfate therapy was safe and allowed the start of therapy within 2 hours after the onset of stroke symptoms, but it did not improve disability outcomes at 90 days. (Funded by the National Institute of Neurological Disorders and Stroke; FAST-MAG ClinicalTrials.gov number, NCT00059332.)

From the Comprehensive Stroke Center (J.L.S., S.S., D.S.L.) and the Departments of Neurology (J.L.S., S.S., D.S.L.) and Emergency Medicine (S.S., F.P.), David Geffen School of Medicine at the University of California, Los Angeles (UCLA), the Departments of Emergency Medicine (M.E.) and Neurology (G.S., N.S.), Keck School of Medicine of the University of Southern California, the Los Angeles Fire Department (M.E.), the Los Angeles County Fire Department (F.P.), the Department of Emergency Medicine, Presbyterian Intercommunity Hospital (I.K.), the Department of Emergency Medicine, Long Beach Memorial Medical Center (G.M.), and the Department of Emergency Medicine, Huntington Memorial Hospital (R.G.), Los Angeles, the Los Angeles County Emergency Medical Services (EMS) Agency, the Orange County EMS Agency, and the Department of Emergency Medicine, Harbor–UCLA Medical Center, Torrance (S.J.S.), and Stanford University, Palo Alto (S.H.) — all in California; and the National Institute of Neurological Disorders and Stroke, Bethesda, MD (R.C.). Address reprint requests to Dr. Saver at the UCLA Comprehensive Stroke Center, 710 Westwood Plaza, Los Angeles, CA 90095, or at jsaver@mednet.ucla.edu.

*A complete list of investigators in the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) phase 3 trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2015;372:528-36.
DOI: 10.1056/NEJMoa1408827
Copyright © 2015 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

Stroke is the second leading cause of death and a leading cause of adult disability worldwide. Unfortunately, currently available therapies for acute ischemic stroke, which are all reperfusion-based, are only moderately effective.[1,2] Treatment with tissue plasminogen activator (t-PA), the only pharmacologic treatment approved by a regulatory agency for the treatment of acute ischemic stroke, results in early reperfusion in less than half of treated patients, can be started only after neuroimaging has ruled out intracerebral hemorrhage, and is used in only 2 to 7% of patients with acute ischemic stroke in the United States.[1] Mechanical thrombectomy devices improve patient outcomes but must be deployed even later than thrombolytic agents, after substantial injury has accumulated, and they yield independent functional outcomes in only 33 to 37% of treated patients.[3,4]

Neuroprotection is a promising treatment strategy that is complementary to reperfusion. Neuroprotective agents interrupt the cellular, biochemical, and metabolic processes that mediate cerebral-tissue injury during or after ischemia. Because they are typically safe and potentially beneficial in patients with hemorrhagic stroke as well as in those with ischemic stroke, neuroprotective agents can, in principle, be given before brain imaging is performed, including in the prehospital setting, to stabilize threatened tissues until therapeutic or spontaneous reperfusion. More than 70 neuroprotective agents have been tested in randomized, controlled clinical trials involving patients with acute ischemic stroke, and no agent has been shown in definitive phase 3 trials to be unequivocally beneficial.[5] However, the crucial factor of delayed time to treatment hindered all the trials. Although neuroprotective agents were most beneficial in rodent and primate models of focal stroke when administered in the first 2 hours after onset, no prior clinical trial of a neuroprotective agent has enrolled any substantial cohort of patients during this time window.[5,6]

Initiating potentially neuroprotective therapies very soon after symptom onset appears to be critical if the dramatic benefits of neuroprotective agents that are evident in the laboratory are to be achieved in patients with stroke. Enrolling patients in the field is a promising approach to the challenge of testing neuroprotective agents in the hyperacute phase of stroke. Magnesium sulfate is reliably cerebroprotective in diverse animal models of stroke, exerting both vasodilatory and direct neuroprotective and glioprotective effects.[7-9] Moreover, magnesium is inexpensive, widely available, and simple to administer and also has a favorable adverse-event profile as a standard treatment for eclampsia and preeclampsia.[8,10] A pivotal trial of magnesium sulfate in patients with stroke showed no benefit when the agent was administered a median of 7.4 hours after onset but suggested potential efficacy in the subgroup of patients treated within the first 3 hours after onset.[11] After a pilot trial showed that prehospital initiation of magnesium sulfate was feasible and generally safe and that it accelerated the start of the study agent by 2 hours as compared with in-hospital initiation,[12] we undertook a pivotal trial of initiation of magnesium sulfate therapy within 2 hours after the onset of symptoms.

METHODS

STUDY DESIGN AND OVERSIGHT

The Field Administration of Stroke Therapy–Magnesium (FAST-MAG) phase 3 trial was a multicenter, randomized, double-blind, placebo-controlled, pivotal clinical trial. A total of 315 paramedic-staffed ambulances and 60 receiving hospital sites in Los Angeles and Orange Counties, California, participated in the study. Details of the study rationale and methods have been published previously.[13,14] Our hypothesis was that initiation of the neuroprotective agent magnesium sulfate by paramedics in the field would improve the long-term functional outcome of patients with acute stroke. A broader systems goal was to show that enrollment and treatment of patients with acute stroke in the field is a practical and feasible strategy for phase 3 trials.

The members of the executive committee and investigators at the study sites (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the trial, collected the data, and performed the data analysis. These investigators vouch for the accuracy and completeness of the data and analysis and for the fidelity of this report to the study protocol and statistical analysis plan, available at NEJM.org. The trial was funded by the National Institute of Neurological Disorders and Stroke, which appointed a data and safety monitoring board that oversaw the conduct of the trial. Safety events were adjudicated by an independent medical monitor.

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

The study protocol was approved by the institutional review board at each prehospital and hospital study site.

PATIENT SELECTION

Patients 40 to 95 years of age were eligible for inclusion if they had a suspected stroke as determined with the use of the modified Los Angeles Prehospital Stroke Screen (LAPSS)[13,15] and if treatment initiation could occur within 2 hours after the patient was last known to be free of stroke symptoms. Details of the study inclusion and exclusion criteria are provided in Table S2 in the Supplementary Appendix. The use of the modified LAPSS to assess suspected stroke ensured that all patients had motor deficits on entry. Pretreatment severity of stroke was assessed with the use of the Los Angeles Motor Scale (LAMS), on which scores range from 0 to 10, with higher scores indicating more severe motor weakness. For patients being transported to all hospital sites, written informed consent was obtained from the patients, if they were deemed competent to provide it, or from their legally authorized representatives, if they were available on scene. In addition, for transports to 36 hospital sites, when patients were not deemed competent and had no legally authorized representative present but were with an adult who knew them well, enrollment was allowed under rules for exemption from informed-consent requirements in emergency research regulations.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned, in 1:1 ratio, to receive a magnesium sulfate or a placebo infusion. Randomization was stratified according to enrolling ambulance. Each ambulance was stocked with one study kit at a time, containing the next assignment in its permuted-block sequence.

Magnesium sulfate or matching placebo was administered intravenously as a 15-minute bolus infusion followed by a 24-hour maintenance infusion. In the active-treatment group, the bolus dose contained 4 g of magnesium sulfate in 54 ml of normal saline infused over a period of 15 minutes; the maintenance infusion contained 16 g of magnesium sulfate diluted in 240 ml of 0.9% normal saline, infused at a rate of 10 ml per hour for 24 hours. Paramedics in the field initiated the bolus dose through infusion tubing with a fixed lumen size that automatically implemented rate control of gravity-driven infusion. Nurses started the maintenance infusion in the emergency department immediately after completion of the loading dose, using electronic infusion pumps.

Concomitant therapy followed national practice guidelines from the American Heart Association and American Stroke Association.[16,17] Patients with ischemic stroke could be treated with intravenous t-PA up to 4.5 hours after the last known time before the onset of stroke symptoms and with neurothrombectomy devices approved by the Food and Drug Administration.

OUTCOMES

The primary outcome was the degree of disability, as assessed with the use of the modified Rankin scale, 3 months after a stroke. Scores on the scale range from 0 to 6, with higher scores indicating greater disability. To ensure reliable scoring, raters used the Rankin Focused Assessment.[18] For the primary analysis, shifts in outcome across all seven levels of the modified Rankin scale were analyzed. Additional outcome measures that were assessed at day 90 included the level of activities of daily living, according to the Barthel Index (range, 0 to 100, with higher values indicating more independence); the degree of neurologic deficit, according to scores on the National Institutes of Health Stroke Scale (NIHSS; range, 0 to 42, with higher scores indicating more severe deficits); and overall functional outcome, according to scores on the Glasgow Outcome Scale (GOS; range, 1 to 5, with higher scores indicating worse function). Hierarchically prespecified secondary end points at day 90 included excellent recovery (modified Rankin score of 0 or 1, Barthel Index ≥95, NIHSS score of 0 or 1, and GOS score of 1, with the outcomes analyzed simultaneously with the use of the global test statistic),[19] minimal or no disability (modified Rankin score of 0 or 1), neurologic deficit (as assessed by the NIHSS score), good recovery (modified Rankin score ≤2, Barthel Index ≥60, NIHSS score ≤8, and GOS score of 1 or 2, with the outcomes analyzed simultaneously with the use of the global test statistic), functional independence (modified Rankin score ≤2), and death.

STATISTICAL ANALYSIS

In calculating the sample size, we projected that treatment would be beneficial in patients with cerebral ischemia and have a neutral effect in pa-

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

tients with intracranial hemorrhage or a stroke-mimicking condition. We made one interim adjustment to the sample size to account for a higher proportion of enrolled patients with intracerebral hemorrhage than projected, increasing the planned sample from 1298 to 1700 patients.[13] Among patients with cerebral ischemia, the shift in outcome distribution of the modified Rankin scale was projected to be approximately 70% of the effect observed in a meta-analysis of phase 2 trials of magnesium.[9] The primary efficacy evaluation tested the null hypothesis that the distribution of modified Rankin scores at day 90 would be identical in the magnesium and placebo groups, versus the one-sided alternative that the distribution of scores would shift lower in the magnesium group, with a probability of type I error of 0.05 and a probability of type II error of 0.20. Three interim efficacy analyses were performed with the use of an O'Brien and Fleming–type alpha-spending function. The primary hypothesis was assessed with the use of the Cochran–Mantel–Haenszel test, with adjustment for baseline severity of stroke (LAMS score of 0 to 3 vs. 4 or 5), age (<70 years vs. ≥70 years), the presence or absence of prestroke disability, and the geographic region of the enrolling ambulance. The P values for the primary hypothesis are one-sided; all other P values are two-sided.

RESULTS

STUDY PATIENTS

Between January 2005 and December 2012, a total of 1700 patients underwent randomization: 857 were assigned to the magnesium-sulfate group and 843 to the placebo group. Figure S1 in the Supplementary Appendix shows the screening, randomization, treatment, and follow-up of the patients.

Demographic and clinical characteristics were similar in the two study groups (Table 1). The mean (±SD) age was 69±13 years, and 42.6% of the patients were women. Final diagnoses of the qualifying event were cerebral ischemia in 73.3% of the patients, intracranial hemorrhage in 22.8%, and a stroke-mimicking condition in 3.9%. The mean pretreatment LAMS score was 3.7±1.3. The mode of consent was explicit written informed consent from the patient in the case of 1017 patients (59.8%), explicit written informed consent from a legally authorized representative in the case of 662 (38.9%), and initial exemption from explicit informed consent in the case of 21 (1.2%).

With regard to the systems goal of delivering

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Placebo (N=843)	Magnesium (N=857)
Age — yr	69±14	69±13
Female sex — no. (%)	367 (43.5)	358 (41.8)
Race — no. (%)†		
White	661 (78.4)	664 (77.5)
Black	113 (13.4)	106 (12.4)
Asian	62 (7.4)	77 (9.0)
Other	7 (0.8)	10 (1.2)
Hispanic ethnic group — no. (%)†	206 (24.4)	196 (22.9)
Medical history — no. (%)		
Hypertension	648 (76.9)	671 (78.3)
Diabetes	188 (22.3)	189 (22.1)
Hyperlipidemia	407 (48.3)	398 (46.4)
Atrial fibrillation	175 (20.8)	194 (22.6)
Myocardial infarction	82 (9.7)	94 (11.0)
Tobacco use‡	158 (18.7)	139 (16.2)
Alcohol use§	328 (38.9)	326 (38.0)
Prestroke function		
Living at home — no. (%)	823 (97.6)	834 (97.3)
Prestroke modified Rankin score — median (interquartile range)¶	0 (0–0)	0 (0–0)
Early severity of neurologic deficit		
LAMS score before treatment‖	3.7±1.3	3.7±1.3
NIHSS score in hospital**	11.2±9.8	11.5±9.0
Glucose level on arrival at hospital — mg/dl	136.5±52.0	133.7±50.5
Final diagnosis — no./total no. (%)		
Cerebral ischemia	613/842 (72.8)	632/857 (73.7)
Intracranial hemorrhage	192/842 (22.8)	195/857 (22.8)
Stroke-mimicking condition	37/842 (4.4)	30/857 (3.5)
Intravenous t-PA in patients with cerebral ischemia — no./total no. (%)	205/613 (33.4)	242/632 (38.3)

* Plus–minus values are means ±SD. There were no significant differences between the two study groups. The term t-PA denotes tissue plasminogen activator.
† Race and ethnic group were self-reported.
‡ Values reflect current use or use within the previous 12 months.
§ Values reflect current use.
¶ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating more severe disability.
‖ Scores on the Los Angeles Motor Scale (LAMS) range from 0 to 10, with higher scores indicating more severe motor weakness.
** Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

the study intervention to patients rapidly, the median time from the last known time before the onset of stroke symptoms to the start of study-drug infusion was 45 minutes (interquartile range, 35 to 62) (Table 2). Overall, 74.3% of the patients received the study drug in the first 60 minutes after symptom onset and 24.7% in the following 60 minutes.

PRIMARY OUTCOME

There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale between patients in the magnesium group and those in the placebo group (P=0.28 by the Cochran–Mantel–Haenszel test) (Fig. 1). Similarly, mean scores on the modified Rankin scale at 90 days did not differ between the magnesium group and the placebo group (2.7 in each group, P=1.00).

SECONDARY OUTCOMES

No benefit of magnesium sulfate therapy was seen with respect to the five prespecified secondary 90-day efficacy end points of excellent recovery, minimal or no disability, neurologic deficit, good recovery, and functional independence (Table 3). Analyses did not show heterogeneity of treatment effect according to baseline covariate in the prespecified subgroups defined according to type of stroke (cerebral ischemia vs. intracranial hemorrhage), concomitant therapy with t-PA (yes vs. no), time from onset of stroke symptoms to treatment (≤60 minutes vs. 61 to 120 minutes), age (<70 years vs. ≥70 years), sex, race, and pretreatment severity of stroke (LAMS score of 0 to 3 vs. 4 or 5). Homogeneity of effect was seen in the distribution of modified Rankin scores across all seven levels and was also seen when modified Rankin scores were dichotomized as 0 or 1 versus 2 to 6 (Fig. S3 in the Supplementary Appendix) and 0 to 2 versus 3 to 6.

SAFETY

In the overall cohort, the 90-day rate of death was 15.5%, the rate of symptomatic hemorrhagic transformation of initial cerebral ischemia was 2.7%, and rate of asymptomatic hemorrhagic transformation was 6.3%. These rates did not differ significantly between the two study groups.

The rate of serious adverse events did not differ significantly between the magnesium group and the placebo group, overall (51.2% vs. 50.1%,

Table 2. Time Intervals.*

Interval	Placebo (N=843)	Magnesium (N=857)	Total (N=1700)
Symptom onset to study-drug administration			
Median — min	46	45	45
Interquartile range — min	36–62	35–60	35–62
Distribution — no./total no. (%)			
0–60 min	612/836 (73.2)	641/851 (75.3)	1253/1687 (74.3)
61–120 min	215/836 (25.7)	202/851 (23.7)	417/1687 (24.7)
>120 min	9/836 (1.1)	8/851 (0.9)	17/1687 (1.0)
Initiation of 911 call to study-drug administration — min			
Median	30	30	30
Interquartile range	26–34	25–35	25–34
Paramedic on scene to study-drug administration — min			
Median	23	23	23
Interquartile range	19–28	18–27	18–27
Paramedic on scene to patient arrival at hospital — min			
Median	33	32	33
Interquartile range	27–39	27–39	27–39

* There were no significant differences between the two study groups.

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

P=0.67) (Table 3) or when assessed according to major organ groups (Table S3 in the Supplementary Appendix). Systolic blood pressure was slightly lower (by ≤3 mm Hg) in the magnesium group than in the placebo group at the end of the 15-minute infusion of the loading dose and from hour 20 to hour 32 after the start of the maintenance dose (24-hour infusion) but not from hour 1 to hour 16 after the start of the maintenance dose (Table S4 in the Supplementary Appendix).

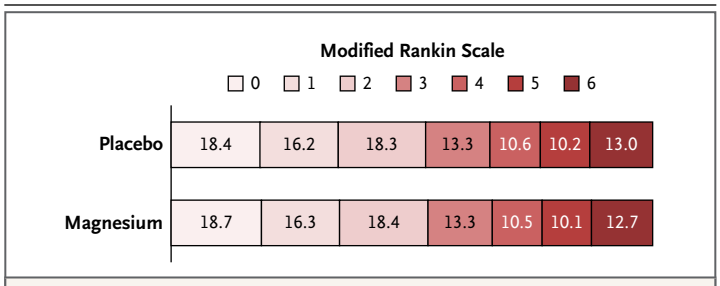

Figure 1. Functional Outcomes at 90 Days in the Magnesium and Placebo Groups, According to Score on the Modified Rankin Scale.

The primary outcome was a shift toward a more favorable distribution across the seven levels of the modified Rankin scale. Scores on the scale range from 0 to 6, with higher scores indicating increased disability. The figure shows the distribution after adjustment for pretreatment severity of stroke, age, the presence or absence of prestroke disability, and geographic region; values indicate percentage of patients. (Fig. S2 in the Supplementary Appendix shows the raw distribution of modified Rankin scores at 3 months.) There was no significant shift in the distribution of 90-day disability outcomes on the global modified Rankin scale between patients in the magnesium group and those in the placebo group (P=0.28 by the Cochran–Mantel–Haenszel test).

DISCUSSION

The FAST-MAG phase 3 trial did not confirm the primary hypothesis that prehospital initiation of magnesium sulfate in patients with a suspected stroke during the hyperacute phase would reduce the level of disability at 90 days. There was no significant difference in mortality, and the overall number of serious adverse events was similar in the magnesium group and the placebo group. The study achieved its systems aim of delivering the study agent to patients with stroke faster than in previous phase 3 trials, with nearly three quarters of the patients treated in the "golden hour," the first 60 minutes after the onset of stroke.[20]

There are several potential explanations for the neutral results with respect to magnesium sulfate. Magnesium trafficking across the blood–brain barrier is not immediate. The concentration of magnesium in the cerebrospinal fluid peaks 4 hours after parenteral administration in the presence of an intact blood–brain barrier and more quickly in regions of focal ischemia where the blood–brain barrier is disrupted.[9] Magnesium sulfate may not have accumulated in brain tissues quickly enough to yield a benefit despite rapid attainment of increased serum levels. In addition, a single neuroprotective agent may not interdict enough pathways in the molecular elaboration of ischemic injury, and combinations of agents or agents with highly pleiotropic effects may be required.[21]

In addition to testing magnesium sulfate specifically, we performed the FAST-MAG trial with the broad central aim of developing and validating methods that can be used in pivotal trials of neuroprotective treatments in the prehospital setting. To identify patients with a suspected stroke for enrollment in the study, we used a two-stage screening process. First, paramedics identified potential patients using a modified version of the LAPSS, a validated eight-item inventory that takes 1 or 2 minutes to perform.[15] Then the patient was further assessed by an enrolling physician-investigator, who reviewed the patient's condition by means of a cell-phone call with the paramedic and the patient or on-scene legally authorized representative. This approach reduced the proportion of enrolled patients with stroke-mimicking conditions to 3.9%, a proportion that is less than the 5% projected in sample-size calculations.

To maximize patient autonomy and respect for persons, whenever a competent patient or on-scene legally authorized representative was present, explicit written informed consent was obtained, elicited by a physician-investigator speaking with the consent provider by cell phone, with the use of consent forms carried in the vehicle. A simultaneous-ring, voice-over-Internet phone system connected consent providers immediately to English- or Spanish-speaking physician-consent elicitors.[22] This approach ensured knowledgeable responses to consent providers' queries and was performed in parallel with standard paramedic prehospital activities to avoid delays in care. The system succeeded in enabling informed consent without delay of care. Overall, 99% of the patients were enrolled with the use of explicit informed

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

Table 3. Secondary Efficacy and Safety Outcomes at 3 Months.*

Outcome	Placebo (N=843)	Magnesium (N=857)	Odds Ratio with Magnesium (95% CI)	P Value
Efficacy				
Minimal or no disability: modified Rankin score of 0 or 1 — no. (%)	311 (36.9)	313 (36.5)	0.98 (0.81–1.20)	0.87
Functional independence: modified Rankin score ≤2 — no. (%)	445 (52.8)	449 (52.4)	0.98 (0.81–1.19)	0.87
Neurologic deficit assessed by NIHSS score — median (interquartile range)	3 (0–42)	3 (0–19)	—	0.28
Global excellent recovery — no. (%)†			0.97 (0.82–1.15)	0.76
Modified Rankin score of 0 or 1	311 (36.9)	313 (36.5)	0.98 (0.81–1.20)	0.87
Barthel Index ≥95	435 (51.6)	427 (49.8)	0.93 (0.77–1.13)	0.47
NIHSS score of 0 or 1	353 (41.9)	349 (40.7)	0.95 (0.79–1.16)	0.66
GOS score of 1	360 (42.7)	365 (42.6)	1.00 (0.82–1.21)	1.00
Global good recovery — no. (%)‡			1.05 (0.89–1.25)	0.56
Modified Rankin score ≤2	445 (52.8)	449 (52.4)	0.98 (0.81–1.19)	0.88
Barthel Index ≥60	557 (66.1)	593 (69.2)	1.15 (0.94–1.41)	0.18
NIHSS score ≤8	537 (63.7)	569 (66.4)	1.13 (0.92–1.37)	0.26
GOS score of 1 or 2	486 (57.7)	503 (58.7)	1.04 (0.86–1.27)	0.69
Safety				
Serious adverse event — no. of patients (%)	422 (50.1)	439 (51.2)	1.05 (0.87–1.27)	0.67
Symptomatic intracranial hemorrhage — no. of patients (%)	28 (3.3)	18 (2.1)	0.62 (0.34–1.14)	0.12
Death — no. (%)	131 (15.5)	132 (15.4)	0.99 (0.76–1.29)	0.95

* Values on the Barthel Index range from 0 to 100, with higher values indicating more functional independence. Scores on the Glasgow Outcome Scale (GOS) range from 1 to 5, with higher scores indicating worse function. CI denotes confidence interval.

† Global excellent recovery was defined by four outcomes (modified Rankin score of 0 or 1, Barthel Index ≥95, NIHSS score of 0 or 1, and GOS score of 1, with outcomes analyzed simultaneously with the use of the global test statistic).

‡ Global good recovery was defined by four outcomes (modified Rankin score ≤2, Barthel Index ≥60, NIHSS score ≤8, and GOS score of 1 or 2, with outcomes analyzed simultaneously with the use of the global test statistic).

consent, and the median interval from the paramedics' arrival on the scene to the patient's arrival at the emergency department (33 minutes) was similar to that in our catchment area before the initiation of the trial (34 minutes) and in other localities during the time the study was ongoing (34 minutes).[12,23]

Additional important techniques that we used in this trial included having paramedics rate the pretreatment severity of stroke with the use of the LAMS, prestocking ambulances with the single next kit in the permuted-block randomization sequence (blinded, pre-encounter randomization), using gravity-controlled tubing to enable paramedics to administer a loading-dose infusion without the need for infusion pumps (which are complex to use) or the counting of drips (an error-prone and distracting process), and enabling administration of the maintenance dose by emergency department nurses immediately after completion of the loading dose by having ambulances carry study kits containing both field and hospital doses. In addition, diligent follow-up of patients resulted in a low dropout rate despite the rapidity with which patients and their representatives needed to make enrollment decisions. These approaches enabled the FAST-MAG trial to achieve several innovative trial-design targets, including testing prehospital pharmacologic treatment of stroke, enrolling and initiating treatment in a sub-

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

stantial number of patients in the first 60 minutes after stroke onset, and evaluating a neuroprotective study agent that was delivered in advance of recanalization therapy.

There are several limitations to this study. First, the trial was completed over an 8-year period. Although no radical changes in standard therapy for acute stroke occurred during this interval, the delivery of conventional therapy did evolve over that period of time. Second, a small proportion of patients were lost to follow-up; nonetheless, retention of patients through the final follow-up visit was very high, providing assurance that the trial findings are reliable.

Data from the trial on the characteristics of patients who were transported to the hospital in ambulances within the first 2 hours after stroke onset may aid in the design of future trials of prehospital treatment of patients with stroke. For example, the ratio of patients with hemorrhagic stroke to patients with ischemic stroke that would be expected in a prehospital trial of hyperacute stroke had not been well-delineated previously. In the United States, among patients with a focal cerebrovascular syndrome (ischemic stroke, transient ischemic attack, or intracerebral hemorrhage but not subarachnoid hemorrhage), 91 to 94% have cerebral ischemia and 6 to 9% have intracerebral hemorrhages.[24] However, because intracerebral hemorrhages are associated with headache and more severe deficits and with a younger age than is cerebral ischemia, patients with intracerebral hemorrhage are disproportionately represented among patients activating 911 systems on an early basis. For these reasons, the original power calculation projected that the trial would enroll double the population-based proportion of patients with intracerebral hemorrhage. Actual enrollment showed that the representation of patients with intracerebral hemorrhage (24%) was triple or quadruple the population-based proportion.

In conclusion, the FAST-MAG trial did not show a treatment benefit of magnesium sulfate administered in the prehospital setting among patients in whom hyperacute stroke was suspected. The trial did succeed in achieving delivery of the study agent to patients with a suspected stroke faster than in any previous pivotal trial.

Supported by the National Institute of Neurological Disorders and Stroke.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the participating paramedics of Los Angeles and Orange Counties and the leadership and staff of the Los Angeles County Emergency Medical Services (EMS) Agency, the Orange County EMS Agency, and the California EMS Authority.

REFERENCES

1. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke 2011;42:1952-5.

2. Saver JL. Improving reperfusion therapy for acute ischaemic stroke. J Thromb Haemost 2011;9:Suppl 1:333-43.

3. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. Lancet 2012;380:1241-9.

4. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med 2015;372:11-20.

5. Kidwell CS, Liebeskind DS, Starkman S, Saver JL. Trends in acute ischemic stroke trials through the 20th century. Stroke 2001;32:1349-59.

6. Ferguson KN, Kidwell CS, Starkman S, Saver JL. Hyperacute treatment initiation in neuroprotective agent stroke trials. J Stroke Cerebrovasc Dis 2004;13:109-12.

7. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 Experimental treatments in acute stroke. Ann Neurol 2006;59:467-77.

8. Saver JL, Starkman S. Magnesium in clinical stroke. In: Vink R, Nechifor M, eds. Magnesium in the central nervous system. Adelaide, Australia: University of Adelaide Press, 2011:205-16.

9. Muir KW. Magnesium for neuroprotection in ischaemic stroke: rationale for use and evidence of effectiveness. CNS Drugs 2001;15:921-30.

10. Dubé L, Granry J-C. The therapeutic use of magnesium in anesthesiology, intensive care and emergency medicine: a review. Can J Anaesth 2003;50:732-46.

11. Muir KW, Lees KR, Ford I, Davis S. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. Lancet 2004; 363:439-45.

12. Saver JL, Kidwell C, Eckstein M, Starkman S. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. Stroke 2004;35(5):e106-e108.

13. Saver JL, Starkman S, Eckstein M, et al. Methodology of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) phase 3 trial: part 1 — rationale and general methods. Int J Stroke 2014; 9:215-9.

14. Saver JL, Starkman S, Eckstein M, et al. Methodology of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) phase 3 trial: part 2 — prehospital study methods. Int J Stroke 2014; 9:220-5.

15. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles Prehospital Stroke Screen (LAPSS). Stroke 2000;31:71-6.

16. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:870-947.

17. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.

Association/American Stroke Association. Stroke 2010;41:2108-29.
18. Saver JL, Filip B, Hamilton S, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). Stroke 2010;41:992-5.
19. Tilley BC, Marler J, Geller NL, et al. Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. Stroke 1996; 27:2136-42.
20. Saver JL, Smith EE, Fonarow GC, et al. The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. Stroke 2010;41:1431-9.
21. Rogalewski A, Schneider A, Ringelstein EB, Schäbitz WR. Toward a multimodal neuroprotective treatment of stroke. Stroke 2006;37:1129-36.
22. Sanossian N, Starkman S, Liebeskind DS, et al. Simultaneous ring voice-over-Internet phone system enables rapid physician elicitation of explicit informed consent in prehospital stroke treatment trials. Cerebrovasc Dis 2009;28:539-44.
23. Ramanujam P, Castillo E, Patel E, Vilke G, Wilson MP, Dunford JV. Prehospital transport time intervals for acute stroke patients. J Emerg Med 2009;37:40-5.
24. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics — 2013 update: a report from the American Heart Association. Circulation 2013; 127(1):e6-e245. [Erratum, Circulation 2013; 127(23):e841.]
Copyright © 2015 Massachusetts Medical Society.

The New England Journal of Medicine
Downloaded from nejm.org at GLASGOW UNIVERSITY LIBRARY on January 11, 2021. For personal use only. No other uses without permission.
Copyright © 2015 Massachusetts Medical Society. All rights reserved.