

# Prehospital Neuroprotective Therapy for Acute Stroke Results of the Field Administration of Stroke Therapy–Magnesium (FAST–MAG) Pilot Trial

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**Background and Purpose**—To demonstrate that paramedic initiation of intravenous magnesium sulfate (Mg) in the field in focal stroke patients is feasible, safe, and yields significant time-savings compared with in-hospital initiation of neuroprotective therapy.

**Methods**—We performed an open-label clinical trial. Inclusion criteria were: (1) likely stroke as identified by the Los Angeles Prehospital Stroke Screen; (2) age 45 to 95; and (3) treatment initiation within 12 hours of symptom onset. Paramedics initiated 4 g Mg loading dose in the field, followed by 16 g over 24 hours in hospital.

**Results**—Twenty patients were enrolled, with mean age 74 (range 44 to 92), and 50% were male. Final diagnosis was acute cerebrovascular disease in all (ischemic 80%, hemorrhagic 20%). Study agent infusion began a median of 100 minutes after symptom onset (range 24 to 703), and 70% received study agent within 2 hours of onset. The interval from paramedic arrival on scene to study agent start was: field-initiated, 26 minutes (range 15 to 64) versus in-hospital initiated (historic controls), 139 minutes (range 66 to 300;  $P < 0.0001$ ). Paramedics rated patient status on hospital arrival as improved 20%, worsened 5%, and unchanged 75%. Median NIHSS on hospital arrival was 11 in all patients and 16 in patients unchanged since field treatment start. Good functional outcome at 3 months (Rankin  $\leq 2$ ) occurred in 60%. No serious adverse events were associated with field therapy initiation.

**Conclusions**—Field initiation of Mg sulfate in acute stroke patients is feasible and safe. Prehospital trial conduct substantially reduces on-scene to needle time and permits hyperacute delivery of neuroprotective therapy. (*Stroke*. 2004; 35:e106-e108.)

**Key Words:** stroke ■ neuroprotection ■ emergency medical services ■ clinical trials

Neuroprotective therapies interrupt the biochemical, cellular, and metabolic elaboration of injury in ischemic environments and are promising acute stroke interventions.<sup>1</sup> Delayed time to delivery of experimental therapy has hindered past human neuroprotection in clinical trials.<sup>1–6</sup> The Field Administration of Stroke Therapy–Magnesium (FAST–MAG) Pilot Trial was performed to investigate the feasibility, safety, and achievable time-savings of paramedic initiation of magnesium sulfate neuroprotective therapy for patients with acute stroke.

## Methods

This was a nonrandomized, open-label, phase 2, feasibility clinical trial. The target population was patients with acute, ambulance-transported stroke, both ischemic and hemorrhagic.

Inclusion criteria were: (1) suspected stroke identified by the Los Angeles Prehospital Stroke Screen (LAPSS); (2) age 45 to 95; and (3) last known well time  $\geq 15$  minutes and  $\leq 12$  hours of treatment initiation.

Exclusion criteria were: (1) recent trauma; (2) seizure disorder; (3) known chronic renal impairment; (4) coma; (5) respiratory distress; (6) systolic blood pressure  $< 90$  or  $> 220$ ; (7) woman of child-bearing age; (8) recent stroke within past 30 days; and (9) rapidly resolving deficit.

All patients transported by 3 UCLA-based Los Angeles Fire Department ambulances were screened. Each ambulance carried written informed consent forms and a dedicated FAST–MAG cellular phone. In nontrauma, noncomatose patients reporting symptoms of possible neurologic origin, paramedics performed the Los Angeles Prehospital Stroke Screen, an 8-item, 1- to 2-minute stroke screening inventory.<sup>7–9</sup> When patients met LAPSS screening criteria, paramedics contacted an on-call physician–investigator. By phone, the physician–investigator reviewed the patient presentation, performed final determination of study eligibility, and elicited informed consent.

All enrolled patients received active magnesium sulfate (Mg). Paramedics initiated a loading dose in the field, administering a prefilled syringe containing 2.5 g Mg in 5 mL normal saline (Abboject; Abbott Laboratories) by slow intravenous push over 10 minutes. Emergency department staff administered the remainder of

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TABLE 1. Key Time Intervals in Trial Patients (n=20)

Interval	Time±SD (min)	Range
Last known well to study infusion start	206±234	24–703
Symptoms first observed to study infusion start	89±127	23–614
911 call to study infusion start	34±9	22–66
Paramedic arrival on scene to study infusion start	26±10	15–61
Emergency department arrival to study infusion start	−11±6	(−25)–(−1)

the loading dose, an additional 1.5 g Mg, followed by a maintenance infusion of 16 g Mg over 24 hours.<sup>10</sup>

Before study infusion start, paramedics performed the Los Angeles Motor Scale (LAMS, a measure of stroke deficit severity)<sup>11</sup> and the Glasgow Coma Scale. On hospital arrival, paramedics completed a Paramedic Global Impression of Change form, a 5-point Likert scale.

Follow-up NIHSS evaluations were performed at hospital arrival, 24 hours, 48 hours, 4 days, and 90 days. Modified Rankin Scale, Barthel Index, and Glasgow Outcome Scale measures were obtained on days 4 and 90.

A key feasibility endpoint was time interval from paramedic arrival on scene to start of study agent infusion. Outcomes on this endpoint in the FAST-MAG Pilot Trial cohort were compared with a historical control group consisting of 25 consecutive patients transported to UCLA by paramedic ambulances and enrolled in standard post-arrival fashion in <6-hour neuroprotective trials not requiring pretreatment neuroimaging over the previous 4 years.

Additional feasibility endpoints included achievement of target magnesium levels of approximately twice the normal concentration by the paramedic-initiated bolus infusion, the proportion of patients completing study treatment, and the proportion of enrolled patients with final diagnoses of acute cerebrovascular disease and acute ischemic stroke.

No formal sample size calculation was performed; the sample size of 20 was selected as adequate to explore the feasibility of study procedures. The trial was Institutional Review Board-approved and monitored by an external Data Safety and Monitoring Committee (DSMC).

## Results

Twenty-eight patients met enrollment criteria; 20 were enrolled. Reasons for nonenrollment were: patient not competent and no legally authorized representative present (3); consent form not in patient's native language (2); patient/legally authorized representative declined participation (2); and study-trained paramedics not on shift (1).

Among the 20 enrolled patients, mean age was 74 (range 44 to 92) and 50% were male. Final diagnosis in all patients was acute stroke, ischemic in 16 (80%) and hemorrhagic in 4 (20%). The median pretreatment LAMS score was 4 (range 1 to 5). The median NIHSS score on emergency department arrival was 11 (range 2 to 24). In the 15 patients rated by paramedics as not changing since field treatment start, median NIHSS on emergency department arrival was 16 (range 4 to 24).

Study agent infusion began a median of 206 minutes from last known well time (range 24 to 703) (Table 1). Five patients (25% of cohort) received study agent within 1 hour, and 9 patients (45%) received study agent between 1 to 2 hours after last known well time.

Clinical features were similar between the FAST-MAG and historical control cohorts (Table 2). Intervals from paramedic arrival on-scene to study infusion start were decreased in FAST-MAG versus control patients: 26 minutes

TABLE 2. Clinical Characteristics

	FAST-MAG Pilot (n=20)	Previous Neuroprotective Trial Patients (n=25)
Age	74 (SD±14)	73 (SD±16)
Sex (male), %	50	52
Stroke type, %		
Ischemic	80	84
Hemorrhage	20	12
Nonstroke	0	4
Initial emergency department NIHSS	11 (IQR 7–18)	10 (IQR 6–14)

IQR indicates interquartile range.

(95% CI: ±4.2, range 15 to 61) versus 139 minutes (CI: ±28, range 66 to 300;  $P<0.0001$ ). In contrast, on-scene to emergency department arrival intervals did not differ: 37 minutes (95% CI: ±4) versus 34 minutes (95% CI: ±8),  $P=0.50$ .

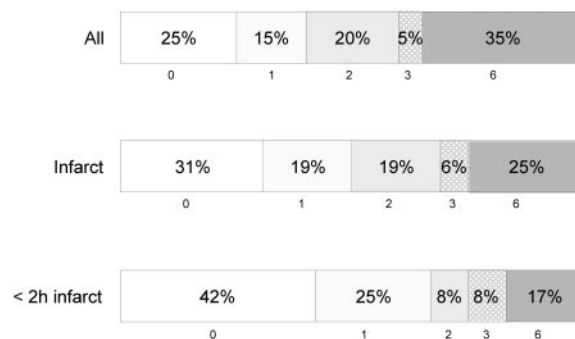
Nineteen of 20 patients completed the full prehospital Mg infusion. In 1, Mg was stopped because of skin flushing. In the 19 patients receiving the full dose, postbolus serum Mg levels were 3.6 mEq/L (mean) (range 2.4 to 5.7). No serious adverse events related to field initiation of therapy were observed.

On the Paramedic Global Impression of Change Form, 4 patients (20%) were rated as improved, 15 (75%) as unchanged, and 1 (5%) as worse. All patients who improved or worsened were infarct patients.

Dramatic early recovery<sup>12</sup> occurred in 6 of 16 infarct patients, including 5 of 12 treated within 2 hours of onset. At day 90, 40% of all patients achieved a modified Rankin Scale score ≤1 and 60% had modified Rankin Scale score ≤2 (Figure).

## Discussion

Prehospital trials for focal stroke pose several unique study design challenges, including stroke identification, stroke characterization, deficit evolution in the field, and consent elicitation. To address these issues, in addition to the usual armature of acute stroke clinical trials, the FAST-MAG Pilot trial used several novel instruments and strategies, including the Los Angeles Prehospital Stroke Screen (LAPSS) to identify patients for trial entry, the Los Angeles Motor Scale (LAMS) for pretreatment characterization of stroke severity,



Day 90 modified Rankin scores in all trial patients (n=20), infarct patients (n=16), and <2-hour infarct patients (n=12). No patient had modified Rankin Scale scores of 4 or 5 at day 90.

the Paramedic Global Impression of Change score to delineate prehospital deficit evolution, and a novel approach to eliciting consent for trial participation in the field.

In the FAST-MAG trial, the LAPSS performed well, with a final diagnosis of acute cerebrovascular disease in all patients. The previously demonstrated high sensitivity and specificity of the LAPSS when used by paramedics to identify stroke in the field was likely further reinforced by FAST-MAG trial procedures in which the enrolling physician–investigator reviewed the presentation by phone with paramedics, patients, and on-scene witnesses.

Extended neurologic deficit rating scales, such as the NIHSS, are too time-consuming and unwieldy to deploy easily in the prehospital setting. The LAMS rates severity of face, arm, and leg weakness on a 0 to 5-point scale and requires no additional time to perform, because it is derived directly from the LAPSS physical examination. The LAMS demonstrates excellent inter-rater reliability, good to excellent concurrent validity against the NIHSS, and good long-term outcome predictive validity.<sup>11,13</sup> In the FAST-MAG trial, the LAMS proved easy to implement and yielded scores well-distributed across the scoring range, indicating good discriminant validity.

Eliciting informed consent for prehospital stroke trials is challenging. Most recent prehospital treatment trials have been conducted for conditions that render patients incompetent to provide consent, such as cardiac arrest, under regulations permitting waiver of explicit consent in emergency circumstances.<sup>14</sup> In acute stroke, however, many patients retain decision-making capacity and require fully informed consent.<sup>15</sup> Having paramedics elicit consent has the drawbacks of having nonstroke experts answering subject queries and of diverting paramedic attention from prehospital duties.

The FAST-MAG Pilot Trial used a novel strategy to elicit consent in the field. Rescue vehicles carried written informed consent forms and cellular phones that permitted rapid connection to on-call physician–investigators. The physician–investigator discussed the trial with the consent provider by phone while paramedics performed prehospital care duties unimpeded. Phone consents for study participation are a commonly accepted aspect of emergency acute stroke research. Extension of this practice to the prehospital setting raises no major novel ethical issues and proved quite feasible. Trial enrollment and implementation procedures did not increase paramedic on-scene to emergency department arrival times.

Prehospital enrollment in the FAST-MAG Pilot Trial did permit accelerated start of neuroprotective therapy, decreasing the interval from paramedic arrival on scene to start of study infusion by nearly 2 hours. Three quarters of the infarct cohort were treated within 2 hours of onset, and nearly one-third within 1 hour of onset.

Clinical outcomes in this open-label pilot trial must be interpreted cautiously, but they were encouraging. Dramatic early recovery occurred in 42% of <2-hour infarct patients. Good 90-day global functional outcome (Rankin  $\leq 2$ ) was achieved by 69% of all patients and 75% of <2 hour infarct patients. No serious adverse events specifically related to field initiation of study agent were noted.

The FAST-MAG Pilot Trial demonstrates the feasibility of paramedic administration of neuroprotective agents to protect

the brain during transport and extend the time window for revascularization therapy. Field initiation of Mg sulfate in acute stroke is feasible, safe, and potentially efficacious. Based on these results, large-scale, pivotal trials of Mg sulfate and other neuroprotective agents can be planned with field initiation of study agent within 1 to 2 hours of onset, a time window not previously explored in neuroprotective studies, when the benefits of neuroprotective acute stroke therapies are likely to be greatest.

## Appendix

### FAST-MAG Trial Study Personnel

Investigators: Marc Eckstein, MD; Chelsea Kidwell, MD; Megan Leary, MD; David Liebeskind, MD; Bruce Ovbiagele, MD; Jeffrey L. Saver, MD; Sidney Starkman, MD; Margaret Tremwel, MD. Coordinators: Katrina Ferguson, Kristi Gough, Jennifer Llanes. Data Safety and Monitoring Board Members: Jose Biller, MD (Chair); Bruce Dobkin, MD; James Sayre, PhD; Samuel Stratton, MD

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