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FAST-MAG: No Benefit of Prehospital Magnesium in Stroke

Sue Hughes | February 14, 2014

SAN DIEGO, California — Giving magnesium to stroke patients in the ambulance soon after symptoms began did not reduce the severity of disability measured 3 months later in the Field Administration of Stroke Therapy–Magnesium Phase 3 Clinical Trial (FAST-MAG).

Administration of intravenous magnesium proved to be safe, resulting in no more serious adverse reactions than placebo infusions. However, there was no benefit in outcome. The primary outcome, modified Rankin scale (mRS) score at 90 days, was exactly the same in both groups at 2.7 months.

But the study did successfully demonstrate that up to 75% of stroke patients calling emergency services early can be started on treatment in the first "golden hour" after symptoms emerge, which opens the door to testing other possibly brain-saving therapies, researchers say.

The study was presented yesterday at the American Stroke Association (ASA) International Stroke Conference (ISC) 2014 by Jeffrey L. Saver, MD, professor of neurology and director of the stroke center at University of California Los Angeles.

"This is the first time a stroke therapy has been tested in a prehospital setting in a phase 3 pivotal trial," Dr. Saver told *Medscape Medical News*. "It shows it is feasible. This will help with the design and planning of studies looking at the delivery of other agents in the field."

Moderator of an ASA press conference on the study, Bruce Ovbiagele, MD, Medical University of South Carolina, Charleston, said, "This opens up a whole new arena for us to test other promising new therapies in the prehospital setting. The FAST-MAG study shows it is feasible — it can be done. This is the big message from this study."

Why Magnesium Didn't Work

Dr. Saver said that potential reasons for the neutral results in FAST-MAG could include the following: Magnesium passage across the blood–-brain barrier may be slow despite early systemic delivery, magnesium as a single agent may be insufficient to suppress the molecular ischemic cascade, or improvements over time in standard care reduced the opportunity to demonstrate benefit. The latter point is supported by observations of interim analysis point estimates being favorable for magnesium, better supportive care being implemented at primary stroke centers, and tissue plasminogen activator (tPA) being given more often and faster.

The trial involved 1700 stroke patients within 2 hours of symptom onset, who were randomly assigned to a loading dose (4 g over 15 minutes) of magnesium sulfate or matched saline placebo in the ambulance. Upon arrival in the hospital emergency department, a maintenance infusion of 16 g of magnesium sulfate or matched placebo was given over 24 hours.

The mean patient age was 69 years, 42.7% of patients were female, median

pretreatment stroke severity on the Los Angeles Motor Scale was 4.0, and median early post-treatment National Institutes of Health Stroke Scale severity on hospital arrival was 9.0. Final diagnosis of the presenting event was acute cerebral ischemia in 73.0%, acute hemorrhagic stroke in 23.2%, and a stroke mimic in 3.8%.

FAST-MAG involved collaboration among 315 ambulances, 40 emergency medical service (EMS) agencies, 60 receiving hospitals, and 2988 paramedics in Los Angeles and Orange counties in California. In the study, the median time for receiving treatment was 45 minutes after symptoms began, and 74% of patients began receiving treatment within an hour.

Dr. Saver said that it was possible that magnesium did not reach the brain in time to show benefit because it is known to have a slow penetration through the blood–brain barrier.

"We know magnesium penetrates the blood–brain barrier slowly," he said in an interview. "But in an injured area of the brain, the blood–brain barrier breaks down to some extent and we thought that would increase the uptake."

He also noted that some studies have assessed magnesium in pregnant women with preeclampsia who have had spinal taps. "So we had some understanding that it can access the CNS [central nervous system], and we were hopeful that if we gave it very early there would be sufficient concentrations in the brain. Maybe 1 lesson from FAST MAG would be that in future we need to agents that have fast penetration of the blood–brain barrier."

Despite a series of failures of studies testing potential neuroprotectant agents in stroke, experts are still hopeful that this approach will be successful in future.

"We are good at reducing stroke size in animals with these neuroprotective agents, but the agents have been given in the first few hours in these studies, and this has proved challenging to do in human patients," Dr. Saver noted.

"Until now, the studies in humans have all given the neuroprotectives many hours after stroke onset," he added. "The FAST-MAG trial is the first study where we have successfully given the agent very early. Now we have a platform to test other agents in the same time window as we have seen impressive results in animals."

Lessons Learned

Walter Koroshetz, MD, neurologist and deputy director of the National Institutes of Health's (NIH's) National Institute of Neurological Disorders and Stroke, sponsor of the FAST-MAG study, says that lessons can be learned from the trial.

"The trick is to try to stack the deck so there is a greater chance of getting a positive result before starting phase 3," Dr. Koroshetz told *Medscape Medical News*. "The NIH have a new network to do more prehospital trials, but we need phase 2 studies first that demonstrate some biological effect before going into a large costly phase 3 trials. There is an issue of whether magnesium gets in to the brain fast enough. In future we will need better preliminary studies showing that this happens and the drug involved interacts with its target before launching phase 3 studies."

Dr. Koroshetz also noted that a surrogate marker needs to be developed that gives information on whether the agent is reducing stroke size. "This would be very helpful before starting a large clinical outcome trial. We have been limited by lack of technology

in the past, but now we have new imaging devices that can look at stroke size. So this may now be possible."

He says the key is to give neuroprotectants very early, and preferably in patients who will also receive thrombolysis. "If you have a blocked vessel which stays blocked, it is hard to see how any neuroprotectant will work. Their effect is to slow down the process of brain cell death, but if the vessel stays blocked the cells will die anyway. However, if the neuroprotectant is given very early on, they could protect the brain cells somewhat until blood flow is restored with thrombolysis. Previous trials haven't done this, as they didn't get there fast enough. With the system developed for FAST-MAG, we can now test new agents in a setting where they could actually work."

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Dr. Koroshetz congratulated the FAST-MAG investigators for developing such a system. "It is a very difficult process to get all the different emergency medical services working in the same way. They have done a great job to have achieved this in Orange County for this trial."

"We had 40 different EMS providers in the study, both rural and urban," Dr. Saver commented to *Medscape Medical News*. "Some were big organizations; others were tiny."

He explained that all paramedics in this trial were trained to use the Los Angeles Pre-hospital stroke screen (LAPSS) to diagnose stroke. This 8-item inventory takes about 1 to 2 minutes and allows the recognition of stroke with high accuracy. "It is a well-known part of international training curriculum for paramedics. Most paramedics have already been trained in it. The paramedics in our trial had to undergo a 2 -hour training session in LAPSS performance and study procedures, and there were revision programs at regular intervals. This is an easily replicable program that can be exported to EMS in other places."

More Neuroprotectives in the Pipeline

He noted that other neuroprotective agents now being tested in the prehospital setting include the following:

- Glyceryl trinitrate: This inhibits the metabolism of nitric oxide. It has been tested in a pilot study in the United Kingdom and is now being tested by Dr. Saver's group in California in a phase 2 prehospital trial.
- NA1: This blocks cytotoxic damage by inhibiting downstream N-methyl-D-aspartate injury. It is now being tested in a moderate size phase 2b trial in Canada.
- Remote ischemic preconditioning: With this treatment, inflatable pads are placed on the legs, causing low blood flow. This is believed to turn on protective programs in the body to cope with low oxygen environments. Phase 2 studies have shown an encouraging signal of efficacy in a prehospital setting.

Dr. Saver explained that tPA cannot be given at present in a prehospital setting because

hemorrhagic stroke has to be ruled out with computed tomography (CT). The use of ambulances with a CT scanner on board has been studied in Germany and is now starting to be tested in the United States.

"Giving a neuroprotectant in the ambulance is much easier as we don't have to do a scan first," Dr. Saver commented. But his group is hoping to do a proof-of-concept study of prehospital tPA using ambulances equipped with CT scanners.

"It is easier in Germany as they have a system where doctors are already in ambulances routinely," he added. "That is not the case in the US but we may introduce this concept or use telemedicine for reading the CT scan."

FAST-MAG was supported by the National Institute of Neurological Disorders and Stroke.

International Stroke Conference (ISC) 2014. Abstract 214. Presented February 13, 2014.

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Cite this article: FAST-MAG: No Benefit of Prehospital Magnesium in Stroke. *Medscape*. Feb 14, 2014.