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Magnesium Sulfate and Hematoma Expansion: An Ancillary Analysis of the FAST-MAG Randomized trial

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Abstract

Background: Intracerebral hemorrhage (ICH) is the deadliest form of stroke. In observational studies, Lower serum magnesium has been linked to more hematoma expansion and intracranial hemorrhage, implying that supplemental magnesium sulfate is a potential acute treatment for patients with ICH and could reduce hematoma expansion. FAST-MAG, a clinical trial of magnesium sulfate started prehospital in patients with acute stroke within two hours of last known well enrolled, including several hundred patients with acute ICH. In this ancillary analysis, we assessed the effect of magnesium sulfate treatment upon hematoma expansion in patients with acute ICH.

Methods: We retrospectively analyzed data that were prospectively collected in the FAST-MAG study. Patients received intravenous magnesium sulfate or matched placebo within two hours of onset. We compared hematoma expansion among patients allocated to intravenous magnesium sulfate or placebo with a Mann-Whitney *U*. We used the same method to compare neurologic deficit severity (NIH Stroke Scale) and global disability (modified Rankin Scale) at 3 months.

Results: Among 268 ICH patients meeting study entry criteria, mean 65.4 +/− 13/4 years, 33% were female, and 211 (79%) had a history of hypertension. Initial deficit severities were median [interquartile range] 4 [3 – 5] on the Los Angeles Motor Scale in the field and NIH Stroke Scale 16 [9.5 – 25.5] early after hospital arrival. Follow-up brain imaging was performed a median of 17.1 [11.3 – 22.7] hours after first scan. The magnesium and placebo groups did not statistically differ in hematoma volume on arrival, 10.1 [5.6 – 28.7] vs. 12.4 [5.6 – 28.7] mL (P=0.6), or

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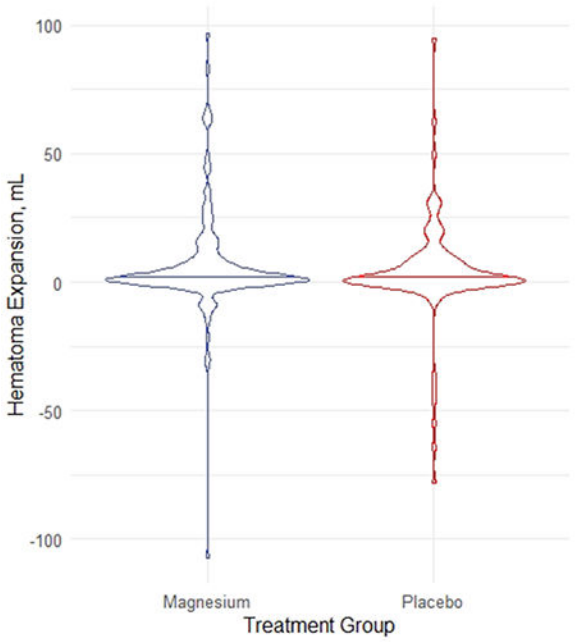
hematoma expansion, 2.0 (0.1 – 7.4) vs. 1.5 (−0.2 – 8) mL (P=0.5). There was no difference in functional outcomes (modified Rankin Scale 3-6), 59% vs. 50% (P=0.5).

Conclusions: Magnesium sulfate did not reduce hematoma expansion or improve functional outcomes at 90 days. A benefit for patients with initial hypomagnesemia was not addressed.

Clinical Trial Registration: ClinicalTrials.gov NCT00059332

Graphical Abstract



Intracerebral hemorrhage (ICH) often leads to dependence or death at follow-up. Early hematoma expansion (HE) occurs in up to one-third of ICH patients and is detected by hematoma volume growth from initial to follow-up brain imaging.[1] More HE leads to more disability and death at follow-up.[2] Reducing HE is a biologically plausible strategy to improve patient outcomes. Clinical trials intended to reduce HE have had mixed results, and several antihypertensive and hemostatic agents have had marginal effects on HE.[3–6] Additional safe and effective treatments to reduce HE are needed.

In observational studies, lower serum magnesium levels have been linked to more HE and intracranial hemorrhage.[7,8] Magnesium sulfate could reduce HE by hemostatic effects and blood pressure lowering.[7,8] Magnesium sulfate would be a potentially attractive pharmacologic treatment for ICH because it is well tolerated and inexpensive.

The FAST-MAG randomized clinical trial of magnesium versus placebo began study infusion in paramedic ambulances prehospital in patients with acute stroke symptoms. As study treatment was started prior to brain imaging, it was anticipated that both ischemic and hemorrhagic stroke patients would be enrolled. In addition to primary analysis in the overall study population, separate analyses for magnesium clinical outcome effects in patients with

ischemic stroke and intracerebral hemorrhage were pre-specified secondary analyses.[9] We tested the hypothesis that magnesium sulfate reduces HE in patients with acute ICH.

METHODS

Details of the multicenter FAST-MAG trial have been previously published.[9] In brief, patients with an acute neurological deficit suggestive of stroke were enrolled by one of 315 ambulances. Study treatment with magnesium sulfate or placebo started prehospital. Patients were randomized 1:1 by sequential assignment in permuted-block sequence to magnesium (4 gm in 54 mL normal saline, then an additional 16 gm in 240 mL normal saline) over 24 hours, or matching normal saline. For data access, contact JLS.

All patients underwent acute brain imaging upon hospital arrival (which occurred after start of study agent). In patients with ICH on initial imaging, follow-up imaging was frequently obtained per the standard clinical policies of each receiving hospital. This post-hoc study analyzed the subset of ICH patients in whom follow-up brain imaging was obtained within the first 24 hours after arrival. Hematoma volumes were calculated using the A*B*C/2 method[10] by an expert diagnostic neuroradiologist at a central imaging core lab. Our primary endpoint was HE (final minus diagnostic hematoma volume).

Normally distributed data are presented as mean ± SD, while non-normally distributed data are presented as median [Q1 – Q3]. Hematoma volumes are not normally distributed, and so were compared between groups (magnesium sulfate or placebo) using the Mann-Whitney *U*. We explored correlations between measured post-study treatment serum magnesium concentration and HE using Spearman correlation coefficient.

RESULTS

A total of 72.8% (268/383) ICH patients met study criteria of undergoing follow-up brain imaging within 24 hours after initial brain imaging (Figure S1). Baseline and workflow characteristics of the patients by treatment group are shown in Table 1. Overall age was mean 65.4 ± 13.4 years, 33% were female, 211 (79%) had history of hypertension, pretreatment deficit severity on the Los Angeles Motor Scale was median 4 [3 – 5], and the initial NIH Stroke Scale early after hospital arrival was 16 [9.5 – 25.5].

Allocation to magnesium vs placebo was not associated with statistically significant differences in initial ICH volume, hematoma expansion, or 90 day neurologic deficit and functional independence outcomes (Table 2). In the 199 patients with a serum magnesium level measured clinically after study infusion start, there was no correlation between the initial post-serum magnesium level and HE (rho = 0.004, P=0.9).

DISCUSSION

We found that treatment with magnesium sulfate was not associated with reduced initial hematoma volume, hematoma expansion volume, or functional outcomes at 3 months.

The findings of this study contrast with observational data that suggested an association of higher serum magnesium with improved HE and clinical outcomes.[8] There are several potential explanations to explain the discrepancy. One possibility is that in observational ICH studies patients with higher serum magnesium levels tend to be healthier. Unfortunately, pre-treatment magnesium levels were not available. It is also possible that HE occurs primarily in patients with abnormally low rather than normal serum magnesium levels and that fewer such patients were enrolled in FAST-MAG. It is possible that as a treatment, magnesium sulfate is not potent enough to correct any deficiencies in hemostasis compared to other treatments that have reduced HE (e.g., tranexamic acid, Factor VII).[3–5] While other biomarkers of hemostasis (platelet activity,[11] thromboelastography[12]) predict HE, these were not collected in FAST-MAG and might have been helpful to select a cohort of patients more likely to have HE. FAST-MAG was not powered to reduce hematoma volume, and may be under-powered to detect an effect. Finally, the observation may have been due to chance.

In conclusion, we found no effect of early magnesium sulfate therapy on HE and clinical outcomes at 90 days in patients with acute ICH. While observational data associated HE and serum magnesium, the administration of magnesium sulfate seems unlikely to be an effective treatment for acute ICH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-Standard Abbreviations and Acronyms:

ICH	intracerebral hemorrhage
HE	hematoma expansion

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Table 1.

Baseline and Workflow Patient Characteristics

Variable	Magnesium (N=145)	Placebo (N=123)
Age, years	65.1 ± 13.1	64.5 ± 13
Female	53 (37)	36 (29)
Hispanic or Latinx	49 (34)	40 (33)
Race, White Black Asian Pacific Islander American Indian/Alaskan Native	116 (80) 11 (8) 15 (10) 3 (2) 0	96 (78) 12 (10) 13 (11) 1 (1) 1 (1)
Historical hypertension	116 (80)	95 (77)
Historical hyperlipidemia	54 (37)	47 (38)
Historical diabetes	25 (17)	23 (19)
Previous stroke	14 (10)	4 (3)
Systolic Blood Pressure, prehospital	176 ± 25	175 ± 26
Diastolic Blood Pressure, prehospital	100 ± 20	100 ± 18
Prehospital motor deficit (LAMS score) 1 2 3 4 5 10	 2 (1) 14 (10) 25 (17) 34 (23) 69 (48) 1 (1)	 4 (3) 4 (3) 32 (26) 30 (24) 52 (42) 1 (1)
Time from last known well to study agent start (mins)	44 (35-59)	43 (36-61)
Time from last known to 1st brain imaging (mins)	82 (69-100)	83 (70-102)
Time from 1st to follow-up brain imaging (hrs)	18.0 (15.2-22.7)	18.1 (15.1-22.7)

Table 2.

Imaging and Clinical Outcomes

Variable	Magnesium (N=145)	Placebo (N=123)	P values
Initial hematoma volume, mL	10.1 (5.6 – 28.7)	12.4 (5.6 – 28.7)	0.60
Follow-up hematoma volume, mL	15.3 (8.3 – 37.7)	14.7 (6.3 – 34.4)	0.56
Hematoma Expansion, mL	2 (0.1 – 7.4)	1.5 (−0.2 – 8)	0.49
NIH Stroke Scale at 90 days	6 (2 – 24)	5 (2 – 21)	0.56
Modified Rankin Scale at 90 days 0, no symptoms 1, no motor deficit 2, mild disability 3, moderate disability, independent 4, moderate severe disability 5, bed bound 6, dead	 2 (2) 10 (7) 26 (18) 22 (22) 23 (16) 30 (21) 32 (22)	 1 (1) 6 (5) 36 (30) 16 (13) 15 (12) 21 (17) 26 (21)	0.46
Functional Independence, mRS 0 - 2	38 (26)	43 (35)	0.16