Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage

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ABSTRACT

Objective: We tested the hypothesis that admission serum magnesium levels are associated with hematoma volume, hematoma growth, and functional outcomes in patients with intracerebral hemorrhage (ICH).

Methods: Patients presenting with spontaneous ICH were enrolled in an observational cohort study that prospectively collected demographic, clinical, laboratory, radiographic, and outcome data. We performed univariate and adjusted multivariate analyses to assess for associations between serum magnesium levels and initial hematoma volume, final hematoma volume, and in-hospital hematoma growth as radiographic measures of hemostasis, and functional outcome measured by the modified Rankin Scale (mRS) at 3 months.

Results: We included 290 patients for analysis. Admission serum magnesium was 2.0 ± 0.3 mg/dL. Lower admission magnesium levels were associated with larger initial hematoma volumes on univariate ($p = 0.02$), parsimoniously adjusted ($p = 0.002$), and fully adjusted models ($p = 0.006$), as well as greater hematoma growth ($p = 0.004$, $p = 0.005$, and $p = 0.008$, respectively) and larger final hematoma volumes ($p = 0.02$, $p = 0.001$, and $p = 0.002$, respectively). Lower admission magnesium level was associated with worse functional outcomes at 3 months (i.e., higher mRS; odds ratio 0.14, 95% confidence interval 0.03–0.64, $p = 0.011$) after adjustment for age, admission Glasgow Coma Scale score, initial hematoma volume, time from symptom onset to initial CT, and hematoma growth, with evidence that the effect of magnesium is mediated through hematoma growth.

Conclusions: These data support the hypothesis that magnesium exerts a clinically meaningful influence on hemostasis in patients with ICH. *Neurology*® 2017;89:813–819

GLOSSARY

FAST-MAG = Field Administration of Stroke Therapy–Magnesium; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **IRB** = institutional review board; **mRS** = modified Rankin Scale.

Spontaneous intracerebral hemorrhage (ICH) carries the highest morbidity of any form of stroke.^{1,2} Coagulopathy and platelet dysfunction are associated with increased hematoma growth and worse functional outcomes; correction of those abnormalities is a potential means of limiting neurologic injury.^{3,4} Deficiency of calcium, a cofactor involved in coagulation and platelet activation, has been theorized to contribute to hematoma growth in patients with ICH; associations between hypocalcemia and hematoma size have recently been reported.⁵ Magnesium also plays an important role in coagulation through the tissue factor–activated factor VII pathway, factor IX, and platelet aggregation.^{6–9} In fact, magnesium may have a more potent effect on platelet aggregation than calcium.⁹ Magnesium infusion has demonstrated encouraging results for hemostasis and the treatment of coagulopathy in cirrhotic patients before liver transplantation and in models of trauma-associated coagulopathy.^{10–12} We hypothesized that magnesium's role in platelet aggregation and coagulation may have implications for patients with spontaneous ICH. We sought to test the hypothesis that low serum magnesium level at the time of hospital presentation is associated with admission hematoma

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volume, in-hospital hematoma expansion, and 3-month functional outcomes in patients with spontaneous ICH.

METHODS Patients presenting directly to Northwestern Memorial Hospital with spontaneous ICH between November 2006 and March 2016 were prospectively enrolled in an observational cohort study. All cases were diagnosed by a board-certified vascular neurologist or neurointensivist utilizing CT. Patients with ICH attributed to trauma, hemorrhagic conversion of ischemic stroke, structural lesion, or vascular malformation were excluded. All patients were admitted to a neuro/spine-intensive care unit using a standardized protocol and admission order set. The Glasgow Coma Scale (GCS) score was prospectively recorded at the time of initial evaluation by a trained neurologist or neurosurgeon. Our protocol includes at least one repeat noncontrast head CT to assess for hematoma growth, as previously reported in detail.¹³ We quantified hematoma growth by the change in hematoma volume between initial and subsequent CT scans. The last CT acquired within 48 hours of the initial CT scan was used for determination of hematoma growth and final hematoma volume. We also identified those cases with an increase in hematoma volume $\geq 26\%$, which has previously been found to be a threshold associated with functional outcomes.¹⁴

Demographic information, medical history, home medications, standardized clinical instruments (GCS, pre-ICH modified Rankin Scale [mRS]), pretreatment blood pressure, laboratory data, imaging data, medical management variables, surgical interventions, and medical complications were prospectively recorded. Hematoma volumes were measured on industry standard DICOM images using Analyze software (Mayo Clinic, Rochester, MN) by a semi-automated process. This high reliability technique has been used as an endpoint in other ICH studies.¹⁵ Because initial laboratory and clinical data were not uniformly available for patients transferred to our institution from another facility, this study included only patients with ICH who presented directly to our hospital.

After evaluating continuous variables for distribution characteristics, we determined that a log transformation was indicated to render initial and final hematoma volumes as normally distributed. We built a fully adjusted multivariate model by including clinical variables that have been associated with hematoma volume and hematoma growth in prior research. We also performed univariate testing to identify previously unrecognized associations between hematoma volume and hematoma growth and other clinical variables in our dataset. We found no additional variables with an association stronger than $p \leq 0.1$. To ensure that the resulting model did not produce a spurious association due to overfitting, we also created parsimoniously adjusted models by backward stepwise approach from the fully adjusted model with a removal criterion of probability of F to remove ≥ 0.1 . In order to evaluate for an association between admission magnesium level and functional outcomes at 3 months, we limited the analysis to patients presenting within 6 hours of symptom onset, for whom the risk of further hematoma growth is greatest and potential for therapeutic interventions may thus be most relevant. We analyzed outcomes using the 3-month mRS (a validated functional outcome scale from 0 [no symptoms] to 6 [death]) adjusted for age, admission GCS, initial hematoma volume, time from symptom onset to initial CT, and hematoma growth. The mRS scores were obtained using a structured interview format.^{16,17} Interviews were performed by a certified examiner by telephone.

Telephone acquisition of the mRS has been found to have good agreement with face-to-face acquisition.^{18,19} After determining that the data did not fulfill the proportional odds assumption for ordinal regression modeling, as assessed by the test of parallel lines, we found the data were suitable for a generalized linear model. We developed an outcome model using a generalized estimating equation with cumulative logit link function, and confirmed successful model convergence. The model was edited by sequentially removing magnesium and hematoma growth to confirm a mediation relationship of magnesium acting through hematoma growth, a standard biostatistical technique.²⁰ All models included only patients for whom complete data for each variable were available.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review board (IRB). Written informed consent was obtained from the patient or a legally authorized representative. The IRB approved a waiver of consent for patients who died during initial hospitalization and those who were incapacitated and for whom a legal representative could not be located.

RESULTS We included 290 patients (mean 65 ± 14 years old, 52.1% female) with requisite data for analysis. Presentation within 6 hours of symptom onset occurred in 175 (60%) patients. Admission mean serum magnesium level was 2.0 ± 0.3 mg/dL. There were 64 (22.1%) patients with anticoagulant use or with another form of coagulopathy (predominantly from liver dysfunction). Of these patients, 28 (9.7%) were taking warfarin, although not all of these patients had therapeutically elevated coagulation measures. An increase in hematoma volume $\geq 26\%$ occurred in 20.7% of patients. A more complete summary of the patients' demographic and clinical characteristics is shown in table 1.

Lower admission magnesium levels were associated with larger initial hematoma volumes on univariate, parsimoniously adjusted, and fully adjusted models (all $p < 0.02$; table 2). Likewise, in univariate and multivariate models (table 2), we found a significant association between lower admission magnesium levels and greater hematoma growth, and larger final hematoma volumes. Finally, among those presenting within 6 hours of symptoms onset, lower admission magnesium level was associated with worse functional outcomes at 3 months (higher mRS) after adjustment for age, admission Glasgow Coma Scale score, initial hematoma volume, time from symptom onset to initial CT, and hematoma growth ($n = 103$, adjusted odds ratio 0.14, 95% confidence interval 0.03–0.64, $p = 0.011$; table 3).

Finally, we performed analyses designed to evaluate for a relationship between magnesium and hematoma growth consistent with a pathophysiologic link. First, we found that hematoma growth became significantly associated ($p = 0.036$) with 3-month mRS in a model that excludes admission magnesium. Second, admission magnesium remained significant ($p = 0.011$)

Table 1 Patient characteristics (n = 290)

Characteristics	Values
Age, y	65.2 ± 14.4
Sex (female)	151 (52.1)
Race	
Unknown/other	1 (0.3)
American Indian/Native Alaskan	2 (0.7)
Asian	6 (2.1)
Black or African American	119 (41.0)
Native Pacific Islander	10 (3.4)
White	152 (52.4)
Hispanic ethnicity	27 (9.3)
Premorbid mRS	0 (0-0)
Admit GCS	13 (8-15)
Admit NIHSS	10 (3-19)
ICH score	1 (0-2)
Initial hematoma volume	9.8 (3.7-26.0)
Intraventricular hemorrhage on presentation	124 (42.8)
CT angiogram spot sign present (of 229 scans)	19 (8.3)
Lobar location	110 (39.1)
Warfarin	28 (9.7)
Novel oral anticoagulant	1 (0.3)
LMWH	4 (1.4)
Other coagulopathy	31 (10.7)
Aspirin use	101 (34.8)
Admission INR	1.1 (1.0-1.2)
Admission PTT, s	29.7 (27.0-33.2)
Admission HCT, %	40.2 (36.4-42.9)
Admission platelet count, K/ μ L	227 (187-282)
Admission platelet function (ARU)	558 (450-639)
First systolic BP, mm Hg	186 ± 41
First diastolic BP, mm Hg	100 ± 27
Admission serum calcium, mg/dL	9.3 ± 0.5
Admission serum magnesium, mg/dL	2.0 ± 0.3
Time from symptom onset to initial CT, h	3.3 (1.0-13.1)
Time between initial and follow-up CT, h	24.2 (10.7-36.2)
Change in hematoma volume, mL	0.1 (-0.8 to 2.1)
Hematoma growth $\geq 26\%$	20.7
Delayed intraventricular hemorrhage	8.8

Abbreviations: BP = blood pressure; GCS = Glasgow Coma Scale; HCT = hematocrit; ICH = intracerebral hemorrhage; INR = international normalized ratio; LMWH = low molecular weight heparin; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PTT = partial thromboplastin time.

Values are n (%), mean $\pm$ SD, or median (interquartile range).

with hematoma growth removed, providing statistical evidence that magnesium may mediate an effect on functional outcomes through hematoma growth.²⁰

DISCUSSION In this observational cohort of patients with ICH, we found that lower serum magnesium level at hospital admission was independently associated with larger baseline hematoma volumes, larger final hematoma volumes, and hematoma growth. In addition, we found that among those presenting within 6 hours of symptom onset, lower admission magnesium level was associated with worse functional outcome at 3 months, after adjustment for patient age and measures of disease severity. These data suggest that serum magnesium levels at the time of ICH may play a pathophysiologic role in hemostasis, with important clinical consequences and potential therapeutic implications.

While our study was not designed to elucidate the molecular mechanisms underlying the association between magnesium and hematoma characteristics, multiple prior studies support a mechanistic role for magnesium in coagulation, platelet adhesion, and hemostasis. Sekiya et al.²¹ used calcium-dependent probes to coagulation factor IX to demonstrate that the factor undergoes conformational changes in the presence of magnesium, even when excessive calcium is available. Furthermore, the activation of factor IX was shown to be enhanced by the presence of magnesium across a broad range of calcium concentrations and, at physiologic levels of ionized calcium, the full conformational change and biological activity of factor IX could only be achieved in the presence of magnesium.²¹ Compared to human plasma devoid of magnesium, physiologic concentrations of magnesium (1 mmol/L, approximately 2.4 mg/dL) in human plasma augment coagulation factor X activation, increase clotting activity of activated factor IX, and enhance clotting through the tissue factor–activated factor VII pathway.⁶ Others have demonstrated that magnesium accelerates factor X activation through both a factor IX–mediated pathway and by direct activation by tissue factor–activated factor VII complex; coagulation times are accelerated by magnesium up to a concentration of 2 mmol/L (approximately 4.8 mg/dL).⁷ In addition, magnesium contamination of commercial blood collection systems and citrate solutions has been shown to shorten coagulation times measured by prothrombin time in clinical blood samples.^{22,23}

Santoro⁹ examined the effect of divalent cations on adhesion of platelets to collagen matrix and found that physiologic levels of magnesium increased platelet adhesion to collagen nearly 6-fold compared to the absence of cations; the addition of a physiologic amount of calcium to magnesium reduced platelet adhesion to one-third of the magnesium only level. In healthy volunteers, infusions of magnesium sulfate increased adenosine diphosphate, ristocetin, and collagen-induced platelet aggregation and decreased

Table 2 Hemostasis models for intracerebral hemorrhage patients

Variables with $p < 0.1$	Unadjusted model			Fully adjusted model			Parsimonious model		
	β	SE	p	β	SE	p	β	SE	p
Initial intraparenchymal hematoma volume (log-transformed) ^a									
Admission magnesium	-0.42	0.18	0.02	-0.50	0.18	0.006	-0.54	0.18	0.002
Lobar hematoma	—	—	—	0.39	0.11	<0.001	0.36	0.10	<0.001
Age, y	—	—	—	0.009	0.004	0.01	0.010	0.003	0.004
Male sex	—	—	—	0.17	0.10	0.09	0.17	0.092	0.06
Final intraparenchymal hematoma volume (log-transformed) ^a									
Admission magnesium	-0.46	0.20	0.02	-0.61	0.20	0.002	-0.61	0.19	0.001
Lobar hematoma	—	—	—	0.35	0.12	0.004	0.39	0.11	0.001
Age, y	—	—	—	0.007	0.004	0.08	0.008	0.004	0.04
Male sex	—	—	—	—	—	—	0.20	0.10	0.06
Change in intraparenchymal hematoma volume ^b									
Admission magnesium	-6.4	2.2	0.004	-6.1	2.3	0.008	-6.3	2.2	0.005
Platelet count	—	—	—	0.020	0.008	0.01	0.023	0.007	0.002
Time between initial and final CT scans	—	—	—	-1.9	0.9	0.03	-2.0	0.83	0.02
Admission calcium	—	—	—	—	—	—	-2.3	1.1	0.04

Abbreviations: CT = computed tomography; SE = standard error.

^aFully adjusted model includes age, sex, hematoma location (lobar vs other), time from onset to initial CT scan, admission international normalized ratio, admission partial thromboplastin time, admission platelet count, admission hematocrit, admission platelet function in aspirin resistance units, admission serum calcium, admission serum magnesium, admission systolic blood pressure.

^bFully adjusted model includes age, sex, hematoma location (lobar vs other), initial hematoma volume, time between initial and repeat CT scan, admission international normalized ratio, admission partial thromboplastin time, admission platelet count, admission hematocrit, admission platelet function in aspirin resistance units, admission serum calcium, admission serum magnesium, admission systolic blood pressure.

levels of the intrinsic antithrombotics protein S and C compared to preinfusion levels, changes that favor hemostasis.⁸ Acute addition of magnesium sulfate to apheresed platelet units has been shown to reduce coagulation times measured by thromboelastography and increase platelet adhesion to collagen surfaces when exposed to shear forces.²⁴

The combination of adenosine, lidocaine, and magnesium has been investigated in animal models of acute traumatic coagulopathy and appears to normalize clotting times and reduce clot lysis from trauma-related coagulopathy and hyperfibrinolysis.^{11,12} Human studies yield similar findings. In a study of 27 cirrhotic patients awaiting liver

transplantation, infusion of magnesium sulfate shortened coagulation times and increased clot strength as measured by thromboelastography.¹⁰ In a randomized controlled study of 40 patients undergoing single-level microscopic lumbar discectomy, bolus infusion followed by continuous infusion of magnesium sulfate resulted in significantly less surgical blood loss.²⁵

Warfarin-induced coagulopathy and aspirin-induced platelet dysfunction have been associated with hematoma expansion and worse outcome in ICH.^{3,4} In light of the evidence supporting magnesium's role in hemostasis, we speculate that the effect of low magnesium on outcomes in patients with spontaneous ICH is mediated through accelerated prehospital hematoma growth, leading to larger initial hematoma volumes and in-hospital hematoma expansion. This in turn results in worse functional outcomes at 3 months. In a mediation relationship, one variable affects a second variable (the mediator) that then affects a third variable.²⁰ We were able to demonstrate this mediation relationship using established statistical methods, showing associations between (1) serum magnesium level and hematoma growth, (2) serum magnesium and patient functional outcome, (3) hematoma growth and functional outcome (when magnesium is excluded from the model), and (4) magnesium level and functional outcome

Table 3 Adjusted model for 3-month modified Rankin Scale score in patients presenting within 6 hours of symptom onset (n = 103)

Characteristics	Odds ratio (confidence interval); p
Age, y	1.01 (0.99-1.04); 0.32
Admission Glasgow Coma Scale score	0.72 (0.64-0.81); < 0.001
Admission magnesium, mg/dL	0.14 (0.03-0.64); 0.011
Initial hematoma volume, mL	1.04 (1.02-1.06); < 0.001
Time from symptom onset to initial CT, h	0.0008 (0-0.26); 0.016
Hematoma volume change, mL	1.04 (0.99-1.09); 0.11

when both magnesium and hematoma growth are included in the outcome model.²⁰ While this approach supports a hematoma growth–mediated mechanism, it is possible that mechanisms unrelated to hematoma expansion may also contribute to the association between magnesium and functional outcome.

It is noteworthy that the association between serum magnesium level and hematoma characteristics persisted when we limited the analysis to only patients presenting within 6 hours of symptom onset. This suggests that there may be an opportunity for early interventions to improve hemostasis through magnesium administration. Acute administration of magnesium has previously been investigated in aneurysmal subarachnoid hemorrhage and in 2 randomized clinical trials of acute stroke.^{26–28} These studies did not demonstrate functional outcome benefit.^{26–28} However, these studies were based on animal models suggesting vasodilatory and neuroprotective roles for magnesium in tissue at risk for ischemia and both acute stroke trials focused on ischemic stroke. Most patients in these studies would not have been expected to benefit from enhanced hemostasis. Since the acute stroke trials enrolled patients based on presentation with a stroke syndrome before identifying the cause as hemorrhagic or ischemic stroke, both trials enrolled patients with ICH.^{26,27} However, neither trial was designed to test the effect of magnesium administration in patients with ICH, and magnesium was administered without regard to baseline serum levels. In fact, the most recent trial (Field Administration of Stroke Therapy–Magnesium [FAST-MAG]) accomplished the impressive feat of administering magnesium to suspected stroke patients in the field before hospital admission laboratory studies were collected.²⁷ It is possible that the group of patients with ICH and hypomagnesemia might benefit from parenteral magnesium administration. Future work could investigate if magnesium treatment is beneficial in patients presenting acutely with ICH and lower baseline serum magnesium levels.

There are a number of limitations to our study. It was not designed to investigate potential pathophysiologic mechanisms of magnesium in ICH. While magnesium's role in coagulation and platelet function is attractive, alternative mechanisms including blood pressure effects, vasodilation, neuroprotection, and glial cell protection may have mediated magnesium's effect rather than hemostasis.^{29–32} However, we observe with interest that in the FAST-MAG trial of acute magnesium administration for stroke, the rate of symptomatic hemorrhagic transformation of ischemic stroke was lower in those receiving magnesium (reported 3.3% vs 2.1%, $p = 0.12$), suggesting the possibility of a hemostatic effect.²⁷ Our study also

represents a single center's observational experience and will need to be replicated. In another center's retrospective cohort of 128 patients with spontaneous ICH, hypomagnesemia (≤ 1.7 mg/dL) occurred in 33.6% of patients and was associated with more severe clinical presentation. In that cohort, patients with hypomagnesemia had larger mean hematoma volume, though the difference between groups was not significant (reported 43.4 ± 61.9 vs 31.1 ± 40 mL, $p = 0.9$).²⁹ That study did not present data on patient outcome after hospital discharge. In another observational study, low serum levels of the cation calcium were found to be associated with hematoma volumes and hematoma expansion in spontaneous ICH.⁵ Those authors posited a mechanism related to calcium's role in coagulation and platelet function, similar to the mechanism that may underlie our findings. While those authors did not investigate associations with serum magnesium, we were able to demonstrate an association between serum calcium level and hematoma growth consistent with their findings in our parsimoniously adjusted model. However, associations with serum calcium did not remain significant in any of our other adjusted models or our functional outcome model. Lower serum magnesium could also represent an epiphenomenon of more severe brain injury or greater baseline medical comorbidity. Alternatively, it is possible that serum magnesium consumption could result from hemostatic processes in larger hematomas. We also used total serum magnesium levels instead of ionized magnesium levels, which may represent the more biologically active form of magnesium. Ionized magnesium levels are not commonly acquired in clinical practice. We are particularly interested in the associations between magnesium, hematoma characteristics, and functional outcome in patients presenting within a time window with opportunity for intervention to limit brain injury. We chose 6 hours as the acute window for our analysis based on prior ICH clinical trials.³³ However, it is possible that 6 hours may not represent the optimal time window for studying magnesium-associated mechanisms.²⁷

Serum magnesium levels at time of hospital admission were independently and inversely associated with initial hematoma volumes, final hematoma volumes, and hematoma growth in patients with spontaneous ICH. In those presenting within 6 hours of symptom onset, lower admission magnesium level was associated with worse functional outcome at 3 months after correcting for age and other measures of disease severity. Magnesium's role in coagulation, platelet aggregation, and hemostasis is a plausible mechanism linking serum magnesium level to hematoma expansion and long-term functional outcome after spontaneous ICH and merits further study.

AUTHOR CONTRIBUTIONS

Dr. Liotta: originated the idea for the study, designed and conceptualized the study, analyzed and interpreted the data, collected study data, drafted the manuscript, revised the manuscript for important intellectual content. Dr. Prabhakaran: collected study data, revised the manuscript for important intellectual content. Dr. Sangha: collected study data, revised the manuscript for important intellectual content. Dr. Bush: revised the manuscript for important intellectual content. Dr. Long: revised the manuscript for important intellectual content. Dr. Trevick: revised the manuscript for important intellectual content. Dr. Potts: revised the manuscript for important intellectual content. Dr. Jahromi: revised the manuscript for important intellectual content. Dr. Kim: revised the manuscript for important intellectual content. Dr. Manno: revised the manuscript for important intellectual content. Dr. Sorond: revised the manuscript for important intellectual content. Dr. Naidech: designed and conceptualized the study, collected study data, revised the manuscript for important intellectual content. Dr. Maas: designed and conceptualized the study, analyzed and interpreted the data, collected study data, drafted the manuscript, revised the manuscript for important intellectual content.

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