Serum Magnesium Levels and Outcomes in Patients With Acute Spontaneous Intracerebral Hemorrhage

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Background—Magnesium (Mg) has potential hemostatic properties. We sought to investigate the potential association of serum Mg levels (at baseline and at 48 hours) with outcomes in patients with acute spontaneous intracerebral hemorrhage (ICH).

Methods and Results—We reviewed data on all patients with spontaneous ICH with available Mg levels at baseline, over a 5-year period. Clinical and radiological outcome measures included initial hematoma volume, admission National Institutes of Health Stroke Scale and ICH scores, in-hospital mortality, favorable functional outcome (modified Rankin Scale scores, 0–1), and functional independence (modified Rankin Scale scores, 0–2) at discharge. Our study population consisted of 299 patients with ICH (mean age, 61±13 years; mean admission serum Mg, 1.8±0.3 mg/dL). Increasing admission Mg levels strongly correlated with lower admission National Institutes of Health Stroke Scale score (Spearman's *r*, −0.141; *P*=0.015), lower ICH score (Spearman's *r*, −0.153; *P*=0.009), and lower initial hematoma volume (Spearman's *r*, −0.153; *P*=0.012). Higher admission Mg levels were documented in patients with favorable functional outcome (1.9±0.3 versus 1.8±0.3 mg/dL; *P*=0.025) and functional independence (1.9±0.3 versus 1.8±0.3 mg/dL; *P*=0.022) at discharge. No association between serum Mg levels at 48 hours and any of the outcome variables was detected. In multiple linear regression analyses, a 0.1-mg/dL increase in admission serum Mg was independently and negatively associated with the cubed root of hematoma volume at admission (regression coefficient, −0.020; 95% confidence interval, −0.040 to −0.000; *P*=0.049) and admission ICH score (regression coefficient, −0.053; 95% confidence interval, −0.102 to −0.005; *P*=0.032).

Conclusions—Higher admission Mg levels were independently related to lower admission hematoma volume and lower admission ICH score in patients with acute spontaneous ICH. (*J Am Heart Assoc.* 2018;7:e008698. DOI: 10.1161/JAHA.118.008698.)

Key Words: functional independence • hemostasis • intracerebral hemorrhage • magnesium • neuroprotection • outcome

Magnesium (Mg) is a cation with essential roles in normal physiological function.[1] Mg modulates vascular smooth muscle tone, peripheral vascular resistance, and blood flow dynamics.[2] Mg also plays crucial roles in hemostasis by accelerating activation of factor X via factor VII–tissue factor,[3] causing conformational changes in coagulation factor IX[4] that augment its biological activities,[5] potentiating platelet aggregation,[6] and decreasing levels of the intrinsic antithrombotics protein S and C.[6] Clinical applications for Mg on the basis of its hemostatic properties

have been proposed. Mg infusion has demonstrated encouraging results in trauma-induced coagulopathy[7,8] and has been shown to decrease surgical blood loss in patients undergoing microscopic lumbar discectomy.[9]

Spontaneous intracerebral hemorrhage (ICH) is the second most common subtype of stroke and leads to severe disability or death.[10] Platelet dysfunction and coagulopathy are major causes of hematoma expansion and mortality in patients with ICH.[10] Mg may have potential therapeutic implications on the basis of its hemostatic properties. A recent retrospective study

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Clinical Perspective

What Is New?

- Higher admission serum magnesium levels are associated with lower admission hematoma volume and lower admission intracerebral hemorrhage score in patients with acute spontaneous intracerebral hemorrhage.
- In addition, higher admission serum magnesium levels are associated with higher odds of functional independence and favorable functional outcome at discharge in univariate analyses.

What Are the Clinical Implications?

- The findings of our study are hypothesis generating and require independent confirmation by prospective multicenter studies and potentially in a randomized controlled trial provided our findings are validated by additional, prospective, and larger data sets.

hypothesized that Mg exerts a clinically meaningful influence on hemostasis in patients with ICH.[11] Another retrospective study showed that low admission Mg levels occurred in one third of patients with ICH and were associated with worse clinical presentation and intraventricular hemorrhage.[12]

The relationship between Mg levels, hematoma volume, and clinical outcome in ICH remains unclear because of limited literature. To clarify this relationship, we sought to evaluate the association of serum Mg levels at admission and at 48 hours with clinical and neuroimaging outcomes in patients with acute spontaneous ICH.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

We conducted a retrospective analysis of a prospectively collected database of consecutive patients with acute (<24 hours) spontaneous ICH in a tertiary-care stroke center from January 1, 2011 to December 31, 2015, as previously described.[13–15] Inclusion criteria were as follows: spontaneous cause for ICH, adult age (>18 years old), and available serum Mg level at admission. Exclusion criteria were as follows: nonspontaneous causes of ICH (including traumatic ICH, metastatic hemorrhagic cerebral lesions, ICH resulting from venous sinus thrombosis, and ICH resulting from underlying vascular lesions), ICH attributable to supratherapeutic international normalized ratio in the setting of prehospital anticoagulation or coagulopathy (threshold international

normalized ratio of 1.5),[16] and thrombocytopenia (platelets <50 000/mm^3).[13,14] Per hospital protocol, all patients with ICH were initially admitted to the intensive care unit. Target systolic blood pressure goal was <140 mm Hg during the first 24 hours after admission, achieved with intravenous pushes of enalapril, hydralazine, or labetalol and/or continuous nicardipine infusion. If clinically stable, systolic blood pressure parameters were relaxed to goal <160 mm Hg after 24 to 48 hours of admission, per treating physician's decision.[13,15] Institutional investigation review board approval for this study was granted on the basis of the acute ICH database. Board waived the need for patient consent.

Baseline Characteristics and Outcome Measures

We obtained demographics, medical history, premorbid modified Rankin Scale (mRS) scores, and baseline radiological and clinical parameters, as previously reported.[13,14] Baseline severity of neurological dysfunction was documented using National Institutes of Health Stroke Scale (NIHSS) score, whereas baseline severity of ICH was quantified by ICH score, as previously described.[13–15] Mg levels were obtained within 6 hours of hospitalization, similar to other laboratory values, such as international normalized ratio, glucose, platelets, and lipid levels. In addition, Mg levels were recorded at 48 hours, if available. All patients underwent computed tomography of the head (CTH) at hospital admission. Follow-up CTH was acquired within 6 to 24 hours of initial CTH, as previously described.[15]

The clinical and radiological outcome measures included admission hematoma volume (measured using ABC/2 method, as previously described),[13,17] hematoma expansion (defined as an absolute increase of >12.5 mL or a relative increase of >33% in hematoma volume at the 6- to 24-hour follow-up CTH compared with the admission CTH),[18] admission NIHSS score, admission ICH score, severe neurological dysfunction (defined as NIHSS score >10 points at admission),[19] severe ICH (defined as ICH score >2 points at admission),[18,19] large hematoma volume (defined as hematoma volume >30 cm^3),[18] favorable functional outcome (FFO) at hospital discharge (defined as mRS scores of 0–1), functional independence (FI; defined as mRS scores of 0–2) at hospital discharge, and in-hospital mortality.

Statistical Analysis

Continuous variables with normal distributions were presented as means with SD, whereas those with skewed distributions were presented as medians with interquartile range. Categorical variables were presented as percentages. Statistical comparisons between different subgroups were performed using the Pearson's χ^2 test, unpaired *t* test, and Mann-Whitney *U* test. Correlations between serum Mg levels (at baseline and

at 48 hours) and admission NIHSS score, admission ICH score, admission hematoma volume, and absolute and relative hematoma increase were evaluated using Spearman's correlation coefficient (r). Simple and multiple linear regression analyses were used to evaluate the associations between baseline characteristics and hematoma volume, square root of NIHSS score, and ICH score. Before simple and multiple linear regression analyses, admission hematoma volume was cube root transformed for each patient to satisfy statistical assumptions about normality of distribution.[20] Similarly, admission NIHSS scores were square transformed for each patient to satisfy statistical assumptions about normality of distribution.[21] In all univariable analyses, a threshold of $P<0.1$ was used to identify candidate variables for inclusion in multiple linear regression models that tested statistical significance hypothesis with an α value of 0.05.[22] Univariable and multivariable logistic regression models assessed the associations of baseline characteristics with FFO and FI at hospital discharge. In all univariable analyses, a threshold of $P<0.1$ was used to identify candidate variables for inclusion in multivariable logistic regression models that tested statistical significance hypothesis using the likelihood ratio test with an α value of 0.05. We reported all associations as linear regression coefficients in linear regression models and odds ratios (ORs) in logistic regression models, with their corresponding 95% confidence intervals (CIs). The Statistical Package for the Social Sciences, version 20 (IBM Corporation, Armonk, NY) was used for all statistical analyses.

Results

Of 672 patients with spontaneous ICH admitted to our comprehensive stroke center between January 1, 2011 and December 31, 2015, 299 met study inclusion criteria (mean age, 61±13 years; 40% women; admission serum Mg level, 1.8±0.3 mg/dL; median ICH score, 1 point [interquartile range, 0–3 points]; median admission NIHSS score, 10 points [interquartile range, 3–18 points]; median baseline ICH volume, 7.1 cm^3 [interquartile range, 2.5–17.5 cm^3]). Baseline characteristics for the study population are presented in Table 1. Severe ICH (ICH score, >2) was documented in 25% of patients, whereas large ICH volume was documented in 12% of patients. Serum Mg level at 48 hours was documented in 191 patients (mean±SD, 2.0±0.3 mg/dL). Serum Mg levels significantly ($P<0.001$ by paired t test) increased at 48 hours compared with baseline (absolute increase, 0.22 mg/dL; 95% CI, 0.16–0.28 mg/dL).

Table 2 depicts the association of serum Mg levels (at baseline and at 48 hours) with admission NIHSS score, admission ICH score, and admission hematoma volume. Higher admission Mg levels correlated with lower admission NIHSS score (Spearman's r, −0.141; $P=0.015$), lower ICH score (Spearman's r, −0.153; $P=0.009$), and lower initial hematoma volume (Spearman's r, −0.153; $P=0.012$). There was no correlation ($P>0.1$) of serum Mg levels at 48 hours with admission NIHSS score, ICH score, and initial hematoma volume. There was no significant correlation of serum Mg levels (at baseline and at 48 hours) with absolute and relative hematoma increase ($P>0.1$) (Table S1). Similarly, we did not document any significant association between serum Mg levels (at baseline and at 48 hours) with severe neurological dysfunction (NIHSS score >10), severe ICH (ICH score >2), large hematoma volume (>30 cm^3), and hematoma expansion ($P>0.1$) (Table S2). In addition, no correlation was noted between admission Mg levels and final ICH volume on follow-up CT scan (Spearman's r, −0.119; $P=0.112$).

Univariate associations of serum Mg levels (at baseline and at 48 hours) with discharge functional outcomes are depicted in Table 3. Patients with ICH with FI and FFO at discharge had higher admission Mg levels (1.9±0.3 versus 1.8±0.3 mg/dL [$P=0.022$] and 1.9±0.3 versus 1.8±0.3 mg/dL [$P=0.025$], respectively). Admission serum Mg levels did not differ between patients who died or remained alive during hospitalization (1.8±0.4 versus 1.8±0.3 mg/dL; $P=0.990$). There was no significant association of Mg levels at 48 hours with any discharge outcomes ($P>0.1$).

Because the hematoma volume had a skewed distribution (2.112; $P<0.001$ by 1-sample Kolmogorov-Smirnov test), we used the cube root transformed hematoma volume as the target variable in simple and multiple linear regression models. This transformation reduced the skew of the target variable to 0.317 ($P=0.293$ by 1-sample Kolmogorov-Smirnov test; Table S3). Associations between clinical and radiographic variables and the cubed root of hematoma volume at admission are presented in Table 4. Several demographic variables were associated with cubed root of hematoma volume on simple linear regression analysis: black race, history of hyperlipidemia, history of chronic kidney disease, lobar location for ICH, intraventricular location for ICH, and serum Mg levels at admission. Increasing admission Mg level (per 0.1-mg/dL increase) was negatively correlated with admission hematoma volumes (simple linear regression coefficient, −0.024; 95% CI, −0.044 to −0.003; $P=0.026$). Multiple linear regression analyses identified the following independent predictors of admission hematoma volume: black race, history of hyperlipidemia, lobar location for ICH, intraventricular location for ICH, and admission serum Mg levels. More specifically, a 0.1-mg/dL increase in admission serum Mg levels was independently and negatively associated with the cubed root of hematoma volume (multiple linear regression coefficient, −0.020; 95% CI, −0.040 to −0.000; $P=0.049$) after adjusting for potential confounders.

Table 1. Baseline Characteristics of the Study Population (n=299)

Variable	Value
Baseline clinical characteristics	
Age, mean±SD, y	61±13
Female sex, %	40
BMI, mean±SD, kg/m^2	29±8
Race, %	
White	19
Black	56
Asian	1
Hispanic	23
Other	1
Hypertension, %	87
Diabetes mellitus, %	34
Hyperlipidemia, %	29
Congestive heart failure, %	7
Current smoking, %	33
Coronary artery disease, %	10
Chronic kidney disease, %	14
Statin pretreatment, %	24
Moderate-to-heavy alcohol consumption, %	29
Antiplatelet pretreatment, %	27
Oral anticoagulation pretreatment, %	4
NIHSS admission score, median (IQR)	10 (3–18)
Severe stroke on admission, %*	49
SBP on admission, mean±SD, mm Hg	186±43
DBP on admission, mean±SD, mm Hg	106±28
Baseline laboratory values	
INR on admission, mean±SD	1.1±0.2
Platelet count ×10^3/μL, mean±SD	226±72
Serum magnesium on admission, mean±SD, mg/dL	1.8±0.3
Serum glucose on admission, mean±SD, mg/dL	157±83
Baseline CT findings	
Lobar hemorrhage, %	26
Intraventricular hemorrhage, %	47
Baseline ICH volume, median (IQR), cm^3	7.1 (2.5–17.5)
Large ICH volume (>30 cm^3), %	12
ICH score, median (IQR)	1 (0–3)
Severe ICH, %†	25
Follow-up laboratory values	
Serum magnesium at 48 h, mean±SD, mg/dL‡	2.0±0.3

Continued

Table 1. Continued

Variable	Value
Follow-up CT findings	
Follow-up ICH volume, median (IQR), cm^3§	7.1 (2.4–14.7)
Hematoma expansion, %§	19
Absolute hematoma volume increase, median (range), cm^3§	0 (−19 to 39)
Relative hematoma volume increase, median (IQR), %§	0 (−82 to 350)

BMI indicates body mass index; CT, computed tomography; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and SBP, systolic blood pressure.
*Severe stroke on admission was defined as NIHSS score >10 points.
†Severe ICH was defined as ICH score >2.
‡Data were available in 191 patients.
§Data were available in 180 patients.

Because the NIHSS score inherently has a skewed distribution (skewness, 0.937; *P*<0.001 by 1-sample Kolmogorov-Smirnov test), we used the square root transformed NIHSS as the target variable in multiple linear regression models. This transformation reduced the skew of the target variable to 0.055 (*P*=0.056 by 1-sample Kolmogorov-Smirnov test; Table S3).

Associations between clinical and radiographic variables and the square root of admission NIHSS score are shown in Table S4. A 0.1-mg/dL increase in admission Mg levels was negatively correlated with admission NIHSS score in simple linear regression analysis (linear regression coefficient, −0.073; 95% CI, −0.141 to −0.006; *P*=0.034); however, this association did not retain its significance in multiple linear regression model after adjustment for potential confounders (multiple linear regression coefficient, 0.040; 95% CI, −0.099 to 0.020; *P*=0.189). The following 4 variables emerged as independent (*P*<0.05) predictors of admission NIHSS score in multiple linear regression analyses: body mass index, hyperlipidemia, admission serum glucose, and intraventricular extension of ICH.

Associations between clinical and radiographic variables and admission ICH score are shown in Table 5. The following variables were associated with ICH score on simple linear regression analyses: body mass index, history of hypertension, history of hyperlipidemia, admission serum glucose, admission systolic blood pressure, admission diastolic blood pressure, and admission serum Mg. Multiple linear regression analyses identified the following independent predictors of admission ICH score: body mass index, history of hypertension, history of hyperlipidemia, admission serum glucose level, and admission serum Mg level. More specifically, a 0.1-mg/dL increase in admission serum Mg levels was independently and

Table 2. Correlations of Serum Mg Levels (at Baseline and at 48 Hours) With Admission NIHSS Score, Admission ICH Score, and Admission Hematoma Volume

Outcomes	Serum Mg Levels, mg/dL			
	Baseline	P Value	48 h	P Value
NIHSS score Spearman's correlation coefficient (r)	−0.141	0.015	−0.094	0.420
ICH score	−0.153	0.009	−0.022	0.766
Hematoma volume	−0.153	0.012	+0.048	0.518

ICH indicates intracerebral hemorrhage; Mg, magnesium; and NIHSS, National Institutes of Health Stroke Scale.

negatively associated with admission ICH score (multiple linear regression coefficient, −0.053; 95% CI, −0.102 to −0.005; P=0.032) after adjustment for potential confounders.

Univariate and multivariate associations between clinical and radiographic variables with FI at discharge are shown in Table S5. Increasing admission Mg level was related to higher odds of FI in univariable logistic regression analysis (OR per 0.1-mg/dL increase, 1.10; 95% CI, 1.01–1.20; P=0.024). However this association did not retain its significance in multivariable logistic regression models (OR, 1.00; 95% CI, 0.86–1.18; P=0.965). Increasing admission ICH score (OR per 1-point increase, 0.25; 95% CI, 0.14–0.47; P<0.001) and increasing admission hematoma volume (OR per 1-cm^3 increase, 0.96; 95% CI, 0.92–1.00; P=0.038) independently predicted lower odds of FI at discharge.

Univariate and multivariate associations between clinical and radiographic variables and FFO at hospital discharge are displayed in Table S6. Increasing admission Mg level was related to higher odds of FFO in univariable analysis (OR per 0.1-mg/dL increase, 1.11; 95% CI, 1.01–1.21; P=0.026).

Table 3. Univariable Associations of Serum Mg Levels (at Baseline and at 48 Hours) With Functional Outcomes at Hospital Discharge

Outcomes		Serum Mg Levels, mg/dL			
		Baseline*	P Value	48 h*	P Value
Favorable functional outcome (mRS scores 0–1)	Yes	1.9±0.3	0.025	2.0±0.3	0.220
	No	1.8±0.3		2.0±0.3	
Functional independence (mRS scores 0–2)	Yes	1.9±0.3	0.022	2.0±0.2	0.437
	No	1.8±0.3		2.0±0.3	
Mortality	Yes	1.8±0.4	0.990	2.1±0.4	0.421
	No	1.8±0.3		2.0±0.3	

Mg indicates magnesium; and mRS, modified Rankin Scale.
*Data are given as mean±SD.

However, this association did not retain its significance in multivariable logistic regression models (OR per 0.1-mg/dL increase, 1.01; 95% CI, 0.87–1.19; P=0.865). Increasing admission ICH score (OR per 1-point increase, 0.33; 95% CI, 0.18–0.63; P=0.001) independently predicted lower odds of FFO at discharge.

Discussion

Our study shows that higher admission serum Mg levels were independently associated with lower admission hematoma volume and lower admission ICH score in patients with acute spontaneous ICH. In addition, higher admission serum Mg levels were associated with higher odds of FI and FFO at discharge in univariate analyses. However, these associations failed to reach significance in multivariate models. It is plausible that the potential beneficial effects of admission Mg levels on functional outcomes may be mediated through an independent impact of Mg on ICH score and hematoma volume, because increasing ICH score and increasing hematoma volume emerged as independent predictors of poor functional outcomes at hospital discharge.

Our findings are partially in line with the observations of Liotta et al, who reported an independent association of lower admission Mg levels with larger initial hematoma volumes and worse functional outcomes at 3 months.[11] However, there are important methodological considerations when comparing the 2 studies. First, our study excluded ICH caused by coagulopathy. In contrast, Liotta et al evaluated a sample in which 22.1% of patients had some form of underlying coagulopathy.[11] It is likely that patients with ICH with underlying coagulopathy received some form of hemostatic treatment in their study (ie, plasma or factor concentrates), which may have confounded the potential influence of Mg on hemostasis. Second, we also evaluated follow-up serum Mg levels at 48 hours, which was not done by Liotta et al.[11] We did not detect any association between serum Mg levels at 48 hours and any of the outcome variables. This observation may indicate that the influence of Mg on hemostasis is maximal in the first few hours after ICH ictus, when the possibility of hematoma expansion and neurological injury are highest. Alternatively, a lack of observed association may simply be type II error because of limited sample size, because follow-up Mg levels were not available in the entire study population. Finally, the 2 studies differed in the duration of follow-up, because we were unable to evaluate the functional status of our patients at 3 months, whereas Liotta et al[11] assessed mRS scores at 3 months.

Another indication of the potential hemostatic property of Mg comes from the FAST-MAG (Field Administration of Stroke Therapy–Magnesium) trial, in which prehospital infusion of Mg sulfate was administered to patients with acute stroke

Table 4. Simple and Multiple Linear Regression Analyses Evaluating the Association of Baseline Characteristics With the Cube Root of Hematoma Volume on Hospital Admission

Variable	Simple Linear Regression		Multiple Linear Regression	
	Linear Regression Coefficient (95% CI)	P Value	Linear Regression Coefficient (95% CI)	P Value
Age (per 10-y increase)*	−0.013 (−0.061 to 0.036)	0.606	…	…
Female sex	−0.070 (−0.199 to 0.059)	0.287	…	…
Black race	−0.163 (−0.273 to 0.000)	0.050	−0.154 (−0.286 to −0.023)	0.021
BMI†	−0.031 (−0.113 to 0.051)	0.453	…	…
Hypertension	0.126 (−0.067 to 0.319)	0.200	…	…
Diabetes mellitus	0.031 (−0.103 to 0.166)	0.645	…	…
Hyperlipidemia	−0.129 (−0.269 to 0.011)	0.070	−0.153 (−0.285 to −0.022)	0.022
Congestive heart failure	−0.017 (−0.263 to 0.230)	0.895	…	…
Current smoking	0.048 (−0.087 to 0.183)	0.486	…	…
Coronary artery disease	0.103 (−0.113 to 0.318)	0.349	…	…
Chronic kidney disease	−0.158 (−0.340 to 0.024)	0.089	−0.075 (−0.251 to 0.101)	0.403
Moderate-to-heavy alcohol consumption	0.013 (−0.126 to 0.151)	0.857	…	…
Baseline mRS score‡	0.035 (−0.030 to 0.101)	0.290	…	…
Statin pretreatment	−0.069 (−0.217 to 0.078)	0.354	…	…
Antiplatelet pretreatment	0.037 (−0.105 to 0.180)	0.608	…	…
OAC pretreatment	0.066 (−0.254 to 0.386)	0.685	…	…
Lobar ICH	0.225 (0.083 to 0.368)	0.002	0.305 (0.163 to 0.446)	<0.001
Intraventricular ICH	0.245 (0.120 to 0.369)	<0.001	0.304 (0.180 to 0.429)	<0.001
Serum glucose§	0.003 (−0.005 to 0.011)	0.439	…	…
Serum magnesium‖	−0.024 (−0.044 to −0.003)	0.026	−0.020 (−0.040 to 0.000)	0.049
Admission SBP¶	0.009 (−0.006 to 0.023)	0.258	…	…
Admission DBP¶	0.012 (−0.010 to 0.035)	0.288	…	…

BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; OAC, oral anticoagulation treatment; and SBP, systolic blood pressure.
*Per 10-year increase.
†Per 1-kg/m² increase.
‡Per 1-point increase.
§Per 10-mg/dL increase.
‖Per 0.1-mg/dL increase.
¶Per 10–mm Hg increase.

symptoms.[23] Although this trial failed to show any improvement in outcome at 90 days, the rate of symptomatic hemorrhagic transformation after ischemic stroke tended to be nonsignificantly lower in the group that received prehospital Mg sulfate (2.1% versus 3.3%; P=0.12), indicating a possible hemostatic effect of Mg.[11,23]

The univariate association of higher Mg levels with improved functional outcomes at hospital discharge cannot be attributed to a potential decrease in hematoma expansion because serum Mg levels at admission and at 48 hours did not correlate with hematoma expansion in our cohort. This could imply that, in addition to influencing hemostasis, Mg might have possible neuroprotective effects for patients with ICH.[24] Preclinical data suggest that Mg exhibits multiple complementary neuroprotective mechanisms, including

inhibition of glutamate release,[25] restoration of blood-brain barrier integrity, decrease in brain edema,[26] and noncompetitive antagonism of N-methyl-D-aspartate receptor activation via blockage of voltage-dependent calcium channels.[24,27] Moreover, the antihypertensive effect of Mg could be protective in patients with ICH.[24]

Two randomized studies have examined the effects of short-term Mg infusion in patients experiencing acute stroke.[23,28] A total of 168 (8.3% of the total enrolled patients) patients with acute ICH were infused with Mg or placebo before brain imaging in the IMAGES (Intravenous Magnesium Efficacy in Stroke) trial.[28] The point estimate of treatment effect quantified as reduction in death or disability was favorable (OR, 0.84; 95% CI, 0.41–1.74) in this cohort, although the sample size of patients with ICH was small to

Table 5. Simple and Multiple Linear Regression Analyses Evaluating the Association of Baseline Characteristics With ICH Score on Hospital Admission

Variable	Simple Linear Regression		Multiple Linear Regression	
	Linear Regression Coefficient (95% CI)	P Value	Linear Regression Coefficient (95% CI)	P Value
Age*	0.040 (−0.080 to 0.159)	0.514	…	…
Female sex	0.151 (−0.164 to 0.467)	0.346	…	…
Black race	0.101 (−0.232 to 0.434)	0.550	…	…
BMI†	−0.263 (−0.464 to −0.063)	0.010	−0.307 (−0.498 to −0.116)	0.002
Hypertension	0.562 (0.102 to 1.023)	0.017	0.548 (0.103 to 0.994)	0.016
Diabetes mellitus	0.027 (−0.302 to 0.356)	0.873	…	…
Hyperlipidemia	−0.514 (−0.853 to −0.175)	0.003	−0.450 (−0.772 to −0.127)	0.006
Congestive heart failure	0.276 (−0.342 to 0.895)	0.380	…	…
Current smoking	−0.117 (−0.448 to 0.214)	0.488	…	…
Coronary artery disease	−0.296 (−0.818 to 0.226)	0.266	…	…
Chronic kidney disease	−0.223 (−0.677 to 0.232)	0.336	…	…
Moderate-to-heavy alcohol consumption	−0.060 (−0.401 to 0.280)	0.727	…	…
Baseline mRS score‡	0.041 (−0.058 to 0.140)	0.413	…	…
Statin pretreatment	−0.284 (−0.643 to 0.076)	0.121	…	…
Antiplatelet pretreatment	0.137 (−0.211 to 0.486)	0.439	…	…
OAC pretreatment	−0.044 (−0.833 to 0.744)	0.912	…	…
Admission serum glucose§	0.040 (0.022 to 0.058)	<0.001	0.041 (0.024 to 0.059)	<0.001
Admission serum magnesium‖	−0.055 (−0.107 to −0.004)	0.034	−0.053 (−0.102 to 0.005)	0.032
Admission SBP¶	0.051 (0.015 to 0.087)	0.006	0.029 (−0.068 to 0.106)	0.121
Admission DBP¶	0.059 (0.004 to 0.115)	0.037	0.019 (−0.002 to 0.128)	0.665

BMI indicates body mass index; CI, confidence interval; DBP, diastolic blood pressure; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; OAC, oral anticoagulation treatment; and SBP, systolic blood pressure.
*Per 10-year increase.
†Per 1-kg/m² increase.
‡Per 1-point increase.
§Per 10-mg/dL increase.
‖Per 0.1-mg/dL increase.
¶Per 10–mm Hg increase.

detect any significant difference.[24,28] Similarly, in the FAST-MAG trial, no outcome benefit was documented with prehospital Mg infusion in the subset of patients with ICH (n=195).[23] Some explanations may be considered for the observed lack of association in both trials. First, both studies were not designed to evaluate the protective effect of Mg infusion in patients with ICH.[23,28] Second, baseline Mg levels were unknown in both studies, and it is possible that the potential hemostatic and neuroprotective effects of Mg may be exerted only in patients with low serum Mg levels.[11]

Several limitations in our study should be noted. First, the modest sample size and retrospective analysis of prospectively collected data are important methodological shortcomings. Second, clinical outcomes (mRS score and mortality) were evaluated at discharge and not in a prolonged subacute time frame (3 months) that maximizes clinical recovery after ICH. However, as we reported

previously,[13,14] a subsequent 3-month follow-up evaluation would have likely improved functional outcome but would likely reflect clinical improvements made after rehabilitation and physical therapy. Third, 48-hour serum Mg levels were not available in our entire study population. In our cohort, we did not see any correlation between Mg levels at 48 hours and any of the outcome variables. Nevertheless, this lack of association may be attributed to type II error because of limited sample size (n=191). Fourth, the possibility of residual confounding factor affecting the results cannot be ruled out completely. Fifth, our data allowed us to detect only a statistical association between Mg levels and outcomes in patients with acute spontaneous ICH. The observational study design did not allow us to establish a cause-effect relationship between baseline serum Mg levels and outcome measures in patients with ICH. Sixth, we only included patients with spontaneous ICH in the present

study, considering the fact that patients with ICH with associated coagulopathy and/or trauma are frequently on anticoagulation and receive hemostatic treatment in form of factor concentrates or plasma in the emergency department. We believe that hemostatic treatment would be a major confounding factor while evaluating the potential hemostatic property of Mg in patients with ICH. Seventh, the ABC/2 score accurately estimates hematoma volume in cases of round-to-ellipsoid shape of the hematoma and overestimates volume in irregular and separated shapes.[29] However, separated and irregular hematoma shapes occur more frequently in oral anticoagulation therapy–related ICHs,[29] and we did not include ICH caused by coagulopathy in our cohort. Eighth, we included patients with acute ICH presenting within 24 hours of symptom onset in our study. However, the time between symptom onset and brain CT was not recorded, which did not allow us to account for the effect of presentation to scan time on different outcomes variables while evaluating the hemostatic properties of Mg. Ninth, the possibility of type I error attributable to multiple comparisons needs to be taken into account in the interpretation of our results. Finally, the findings of our study are hypothesis generating and require independent confirmation by prospective multicenter studies and potentially in a randomized controlled trial provided our findings are validated by additional, prospective, and larger data sets.

In conclusion, our study demonstrates that higher admission serum Mg levels may be associated with smaller initial hematoma volume and lower admission ICH score in patients with acute spontaneous ICH. Future multicenter randomized controlled clinical trials are needed to explore potential therapeutic implications of Mg infusion in patients with acute ICH with lower admission Mg levels.

Author Contributions

Goyal: Study concept and design, acquisition of data, analysis and interpretation, and critical revision of the article for important intellectual content. Tsivgoulis: Analysis and interpretation and critical revision of the article for important intellectual content. Malhotra, Inoa, Alsherbini, Alexandrov, Arthur, Elijovich, and Chang: Critical revision of the article for important intellectual content. Houck, Khorchid, and Pandhi: Acquisition of data and critical revision of the article for important intellectual content.

Disclosures

Arthur is a consultant for Codman, Medtronic, Microvention, Penumbra, Sequent, Siemens, and Stryker; and has received research support from Sequent and Siemens. Elijovich is a consultant for Codman Neurovascular, Medtronic, MicroVention, Penumbra, Sequent, and Stryker. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Correlations of serum magnesium (Mg) levels (at baseline and at 48 hours) with absolute and relative hematoma increase.

Serum Magnesium	Absolute hematoma increase		Relative hematoma increase	
	Spearman's correlation coeffiecent (r)	p	Spearman's correlation coeffiecent (r)	p
Baseline	+0.027	0.717	+0.012	0.873
48hours	-0.069	0.425	-0.070	0.420

Table S2. Univariable associations of serum magnesium (Mg) levels (at baseline and at 48 hours) with clinical and radiological early outcomes.

Serum Mg	Severe neurological dysfunction (NIHSS>10)			Severe ICH (ICH score>2)			Large hematoma volume (>30cm^3)			Hematoma exp	
	yes	no	p	yes	no	p	yes	no	p	yes	no
Baseline(mg/dL)	1.8±0.3	1.9±0.3	0.183	1.8±0.3	1.8±0.3	0.752	1.8±0.4	1.8±0.3	0.203	1.8±0.3	1.8±0
48 hrs (mg/dl)	2.0±0.4	2.0±0.3	0.649	2.0±0.4	2.0±0.3	0.863	2.0±0.3	2.0±0.3	0.504	2.0±0.2	2.0±0

Table S3. Skeweness and normality transformations of outcome variables.

Variable	Skewness	One-sample Kolmogorov-Smirnov test
Admission NIHSS-score	0.937	<0.001
Square root transformed admission NIHSS-score	0.055	0.056
Admission intracerebral hemorrhage volume	2.112	<0.001
Cube root transformed admission intracerebral hemorrhage volume	0.317	0.293

Table S4. Simple and multiple linear regression analyses evaluating the association of baseline characteristics with the square root of NIHSS-score on hospital admission.

	Simple linear regression		Multiple linear regression	
	Linear Regression Coefficient (95%CI)	P	Linear Regression Coefficient (95%CI)	p
Age*	-0.078 (-0.236, 0.081)	0.337	-	-
Female sex	0.314 (-0.108, 0.735)	0.144	-	-
African-American race	0.435 (-0.008, 0.877)	0.054	-0.009 (-0.417, 0.400)	0.967
BMI**	-0.302 (-0.568, -0.035)	0.026	-0.239 (-0.473, -0.005)	0.045
Hypertension	0.623 (0.010, 1.235)	0.046	0.208 (-0.354, 0.769)	0.474
Diabetes	0.077 (-0.360, 0.514)	0.730	-	-
Hyperlipidemia	-0.834 (-1.285, -0.384)	<0.001	-0.713 (-1.114, -0.312)	0.001
Congestive heart Failure	0.794 (-0.013, 1.601)	0.054	0.595 (-0.113, 1.300)	0.098
Current smoking	0.202 (-0.238, 0.643)	0.367	-	-
Coronary artery disease	-0.127 (-0.828, 0.574)	0.722	-	-
Chronic kidney disease	-0.139 (-0.742, 0.464)	0.651		
Moderate-to-heavy alcohol consumption	0.026 (-0.429, 0.482)	0.909		
Statin pretreatment	-0.372 (-0.854, 0.109)	0.129	-	-
Antiplatelet pretreatment	0.013 (-0.452, 0.476)	0.956		
OAC pretreatment	-0.782 (-1.835, 0.271)	0.145		
Lobar ICH	-0.729 (-1.193, -0.266)	0.002	-0.154 (-0.587, 0.279)	0.485
Intraventricular ICH	1.530 (1.152, 1.908)	<0.001	1.333 (0.967, 1.700)	<0.001
Admission serum glucose***	0.048 (0.024, 0.073)	<0.001	0.038 (0.016, 0.060)	0.001
Admission serum Magnesium#	-0.073 (-0.141, -0.006)	0.034	-0.040 (-0.099, 0.020)	0.189
Admission SBP##	0.063 (0.015, 0.112)	0.010	-0.040 (-0.112, 0.033)	0.280
Admission DBP##	0.116 (0.043, 0.189)	0.002	0.063 (-0.002, 0.128)	0.059

NIHSS: National Institutes of Health Stroke Scale Score; BMI: body mass index, OAC: Oral Anticoagulation treatment, ICH: Intracerebral hemorrhage SBP: systolic blood pressure, DBP: diastolic blood pressure, 95%CI: 95% confidence interval
*per 10 year increase **per 1 kg/m² increase, *** per 10mg/dl increase,
per 0.1 mg/dl increase, ##per 10mmHg increase

Table S5. Univariable and multivariable logistic regression analyses evaluating the association of baseline characteristics with the likelihood of discharge functional independence (mRS-scores of 0-2).

	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P	OR (95%CI)	P
Age*	0.89 (0.74, 1.08)	0.238	-	-
Female sex	0.62 (0.37, 1.03)	0.065	0.90 (0.40, 2.01)	0.801
African-American race	0.85 (0.51, 1.43)	0.546	-	-
BMI**	1.13 (0.83, 1.55)	0.445	-	-
Hypertension	0.55 (0.28, 1.09)	0.089	1.40 (0.51, 3.85)	0.514
Diabetes	0.92 (0.55, 1.53)	0.736	-	-
Hyperlipidemia	1.95 (1.15, 3.30)	0.013	1.27 (0.55, 2.89)	0.577
Congestive heart Failure	0.49 (0.16, 1.49)	0.206		
Current smoking	0.79 (0.47, 1.34)	0.378	-	-
Coronary artery disease	1.15 (0.51, 2.59)	0.730	-	-
Chronic kidney disease	1.98 (1.02, 3.85)	0.044	2.60 (0.70, 9.62)	0.152
Moderate-to-heavy alcohol consumption	0.87 (0.51, 1.50)	0.613	-	-
Statin pretreatment	0.79 (0.44, 1.41)	0.418		
Antiplatelet pretreatment	0.53 (0.29, 0.95)	0.034	0.53 (0.22, 1.25)	0.144
OAC pretreatment	1.57 (0.49, 5.09)	0.450		
Hematoma volume***	0.95 (0.92, 0.97)	<0.001	0.96 (0.92, 1.00)	0.038
Admission serum glucose$	0.94 (0.90, 0.98)	0.006	0.98 (0.93, 1.03)	0.373
Asmission serum Magnesium#	1.10 (1.01, 1.20)	0.024	1.00 (0.86, 1.18)	0.965
Admission SBP##	0.94 (0.89, 1.00)	0.050	0.97 (0.87, 1.08)	0.549
Admission DBP##	0.93 (0.85, 1.02)	0.110		
Admission ICH score###	0.19 (0.12, 0.29)	<0.001	0.25 (0.14, 0.47)	<0.001
Admission NIHSS###	0.71 (0.64, 0.78)	<0.001	0.72 (0.64, 0.80)	<0.001

BMI: body mass index, OAC: Oral Anticoagulation treatment, SBP: systolic blood pressure, DBP: diastolic blood pressure, 95%CI: 95% confidence interval; NIHSS: National Institutes of Health Stroke Scale Score; ICH: intracerebral hemorrhage
*per 10 year increase **per 1 kg/m^2 increase, ***per 1 cm^3 increase
$per 10mg/dl increase,
per 0.1 mg/dl increase, ##per 10mmHg increase, ### per 1 point increase

Table S6. Univariable and multivariable logistic regression analyses evaluating the association of baseline characteristics with the likelihood of discharge favorable functional outcome (mRS-scores of 0-1).

	Univariable analysis		Multivariable analysis	
	OR (95%CI)	P	OR (95%CI)	P
Age*	0.89 (0.72, 1.09)	0.257	-	-
Female sex	0.76 (0.44, 1.33)	0.342		
African-American race	1.03 (0.58, 1.83)	0.926	-	-
BMI**	1.13 (0.81, 1.59)	0.471	-	-
Hypertension	0.65 (0.31, 1.36)	0.253		
Diabetes	0.64 (0.35, 1.15)	0.137	-	-
Hyperlipidemia	1.95 (1.11, 3.43)	0.020	1.29 (0.55, 3.03)	0.556
Congestive heart Failure	0.52 (0.15, 1.83)	0.310		
Current smoking	0.75 (0.42, 1.36)	0.346	-	-
Coronary artery disease	1.27 (0.54, 3.01)	0.585	-	-
Chronic kidney disease	2.61 (1.31, 5.17)	0.006	3.45 (1.06, 11.27)	0.040
Moderate-to-heavy alcohol consumption	0.86 (0.47, 1.56)	0.617	-	-
Statin pretreatment	0.72 (0.37, 1.38)	0.319		
Antiplatelet pretreatment	0.47 (0.24, 0.92)	0.029	0.52 (0.21, 1.31)	0.165
OAC pretreatment	1.67 (0.49, 5.71)	0.416		
Hematoma volume***	0.91 (0.87, 0.95)	<0.001	1.00 (0.96, 1.05)	0.968
Admission serum glucose$	0.94 (0.89, 0.99)	0.011	0.97 (0.92, 1.02)	0.271
Asmission serum Magnesium#	1.11 (1.01, 1.21)	0.026	1.01 (0.87, 1.19)	0.865
Admission SBP##	0.94 (0.88, 1.00)	0.039	0.94 (0.84, 1.05)	0.252
Admission DBP##	0.92 (0.83, 1.02)	0.101		
Admission ICH score###	0.19 (0.12, 0.30)	<0.001	0.33 (0.18, 0.63)	0.001
Admission NIHSS###	0.67 (0.59, 0.76)	<0.001	0.69 (0.59, 0.80)	<0.001

BMI: body mass index, OAC: Oral Anticoagulation treatment, SBP: systolic blood pressure, DBP: diastolic blood pressure, 95%CI: 95% confidence interval; NIHSS: National Institutes of Health Stroke Scale Score; ICH: intracerebral hemorrhage
*per 10 year increase **per 1 kg/m^2 increase, ***per 1 cm^3 increase
$per 10mg/dl increase,
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Serum Magnesium Levels and Outcomes in Patients With Acute Spontaneous Intracerebral Hemorrhage

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