Magnesium: pathophysiological mechanisms and potential therapeutic roles in intracerebral hemorrhage

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Abstract

Intracerebral hemorrhage (ICH) remains the second-most common form of stroke with high morbidity and mortality. ICH can be divided into two pathophysiological stages: an acute primary phase, including hematoma volume expansion, and a subacute secondary phase consisting of blood-brain barrier disruption and perihematomal edema expansion. To date, all major trials for ICH have targeted the primary phase with therapies designed to reduce hematoma expansion through blood pressure control, surgical evacuation, and hemostasis. However, none of these trials has resulted in improved clinical outcomes. Magnesium, an ubiquitous element that also plays roles in vasodilation, hemostasis, and blood-brain barrier preservation, and hemostasis. However, none of these trials has resulted in improved clinical outcomes. Magnesium, a ubiquitous element that also plays roles in vasodilation, hemostasis, and blood-brain barrier preservation, represents another potentially novel therapy because of its roles in both primary and secondary stages of ICH. To date, recent large randomized multi-center trials have targeted this primary stage—the attenuation of hematoma volume expansion through blood pressure control (Anderson et al., 2013; Qureshi et al., 2015; Liotta et al., 2017; Goyal et al., 2018) and hemostasis (Mayer et al., 2008)—but have failed to demonstrate clinical efficacy. Although several large trials targeting this primary stage continue at this time, the evaluation and targeting of novel therapeutics for the secondary stage may hold some promise (Belur et al., 2013). Smaller trials using novel therapeutics—sulfonlurea, minocycline, and fingolimod—have already proved promising for attenuating PHE and improving ICH clinical outcome (Fu et al., 2014; Chang et al., 2017a, b). Magnesium, an essential element with wide biological functions, represents another potentially novel therapy because of its roles in both primary and secondary stages of ICH. Although the potential role of magnesium as a neuroprotectant in acute ischemic stroke has been well documented (Chang et al., 2014a) and has led to two large multi-center randomized trials to evaluate for clinical efficacy (Muir et al., 2004; Saver et al., 2015), the physiological mechanisms for magnesium therapy in ICH are poorly understood. Although the potential role of magnesium therapy in ICH can be extrapolated from these two studies, to date no trial has been designed to specifically evaluate magnesium therapy in ICH. Recently, three modest-sized retrospective studies (Behrouz et al., 2015; Liotta et al., 2017; Goyal et al., 2018) have highlighted potential therapeutic roles for magnesium in attenuating hematoma volume and improving clinical outcome in ICH. In this review, we will highlight the physio-
logical mechanisms for magnesium, its role as a therapeutic intervention in neuropathology, and its potential as a neuroprotectant in ICH.

**Physiological Roles of Magnesium**

The physiological roles of magnesium have been studied extensively through *in vitro* and *in vivo* models. In human beings, magnesium is renally excreted with physiological concentrations ranging from 0.7–1.1 mM (Westeraïer et al., 2013). Magnesium is an essential ion for various enzymatic activities that include the metabolism of carbohydrates, fat, and protein, as well as electrolyte metabolism and protein synthesis (Chakraborti et al., 2002). Its widespread properties make it particularly useful in three key physiological mechanisms: vasodilation, hemostasis, and BBB preservation.

Magnesium’s role in vasodilation likely relates to its properties as a Ca$^{2+}$ channel antagonist that inhibits Ca$^{2+}$ influx and release from the sarcoplasmic reticulum, its ability to increase prostacyclin synthesis, and its inhibition of angiotensin converting enzyme (Reinhart, 1991). Decreased intracellular Ca$^{2+}$ leads to inactivation of calmodulin-dependent myosin light chain activity and decreased vascular contraction (Altura et al., 1987). Rabbit models further specified this vasodilatory role by demonstrating the inhibitory effect of magnesium on L-type Ca$^{2+}$ channels on basilar artery smooth muscle cells (Sharma et al., 2012). Rat models have also suggested endothelin-1 inhibition as a potential mechanism for magnesium’s vasodilatory properties (Kemp et al., 1999) and highlighted that vasoconstriction of penetrating arterioles accompanies hypomagnesemia (Murata et al., 2011).

Magnesium’s role as an essential cofactor in hemostasis—particularly in tissue factor-induced coagulation—is heterogeneous and affects multiple factors in the coagulation cascade. Magnesium has been shown to enhance tissue factor-induced coagulation by augmenting the binding of Ca$^{2+}$ to factor IX, stabilizing the conformation of Ca$^{2+}$-factor IX complex, and potentiating the activation of factor IX by factor Xα (Sekiya et al., 1995). Additionally, magnesium was also shown to enhance coagulation by strengthening the interaction between tissue factor and the γ-carboxyglutamate-rich domain of factor X (Gajskiewicz et al., 2015). However, other *in vitro* studies utilizing factor IX-deficient plasma also demonstrated shorter tissue factor-induced coagulation times after magnesium infusion, suggesting that magnesium may also exert its coagulation effects independent of the traditional coagulation pathway (van den Besse-laar, 2002).

Several mechanisms help explain the role of magnesium in preserving BBB. First, magnesium is a known antagonist of N-methyl-D-aspartate receptors, which has a well-defined role in BBB disruption in rat models of traumatic brain injury (McIntosh et al., 1990; Imer et al., 2009). Second, the use of neurokinin-1 antagonists has been shown to potentiate the therapeutic effects of magnesium therapy in rat models of traumatic brain injury (Ameliorate et al., 2017). Third, rat models have shown that magnesium is a potential inhibitor of oxidized low-density lipoproteins, which facilitate BBB disruption through nicotinamide adenine dinucleotide phosphate activation (Schreurs and Cipolla, 2014). And fourth, *in vitro* studies have shown magnesium enhanced BBB properties through improved expression of low-density lipoprotein receptor-related protein and phosphatidylinositol binding clathrin assembly protein (Zhu et al., 2018).

However, the transport of magnesium into cerebrospinal fluid (CSF) spaces after neurological injury remains unclear. Although studies have not shown significant differences in magnesium CSF concentrations among controls and patients treated for neurological diseases (Kapaki et al., 1989), the validity of the patients’ neurological disease may be suspect without confirmed central nervous system lesions. Subsequent studies have not yielded definitive results. Although one study that evaluated induced hypermagnesemia after neurological injury only documented marginal increases in CSF magnesium concentrations (McKee et al., 2005), other studies have shown that magnesium CSF concentrations can vary in ischemic stroke patients with significantly lower concentrations noted in those who have higher mortality (Bayir et al., 2009). The mechanism that results in differing levels of CSF magnesium concentration in individuals remains unknown.

**Experimental and Epidemiological Studies Highlighting Potential Therapeutic Roles for Magnesium**

These three properties of magnesium demonstrated in animal and *in vitro* models—vasodilation, hemostasis, and BBB preservation—highlight potentially useful therapeutic roles for magnesium in ICH. However, with the exception of studies evaluating magnesium’s vasodilatory properties, large-scale epidemiological studies evaluating the role of magnesium in hemostasis and BBB permeability are lacking.

Rat models have shown that magnesium infusion can inhibit endothelin-1 and preferentially vasodilate coronary and cerebral vascular beds (Kemp et al., 1999). Whether this preferential vasodilation leads to concomitant reduction and injury to the kidneys and organs supplied by the mesentery is unclear. Rat models have also shown that the vasodilation induced by magnesium infusion may also apply to smaller cerebral penetrating arteries through mechanisms independent of nitric oxide, endothelin-1, and thromboxane A2 (Murata et al., 2016). A dog model of cerebral vasconstriction showed magnesium infusion into CSF spaces leading to relaxation of cerebral vessels (Mori et al., 2011). Human epidemiological studies have demonstrated that chronic magnesium deficiency can lead to prolonged hypertension through activation of the sympathetic system and increased aldosterone production and release (Quinn and Williams, 1988; Chakraborti et al., 2002).
Magnesium therapy has been shown in experimental studies to reverse coagulopathy in hemorrhagic animal models. In a rat model of hemorrhagic shock, infusion of a sodium chloride adenocaine/Mg²⁺ infusion resulted in full reversal of activated partial thromboplastin time, and prothrombin time, and improved hemodynamics. However, a synergistic effect of adenocaine and magnesium was noted as either therapies given in isolation did not have similar efficacy (Letson et al., 2012). Rat hemorrhagic models utilizing rotational thromboelastometry also further substantiated the role of adenocaine/magnesium therapy for correcting coagulopathy (Letson and Dobson, 2015).

Several studies have demonstrated magnesium’s role in preserving BBB permeability and reducing PHE. Rat models of traumatic brain injury showed that magnesium therapy significantly lowered BBB permeability and PHE when compared with controls (Esen et al., 2003; Imer et al., 2009). A rat model of placental ischemia, which mimicked pre-eclampsia, demonstrated that MgSO₄ infusion resulted in decreased cerebral edema, presumably through decreased disruption of BBB, which was extrapolated by CSF to serum albumin and protein ratios (Zhang and Warrington, 2016).

**Magnesium Use in Intracerebral Hemorrhage**

Two studies—the intracerebral magnesium efficacy in stroke trial (IMAGES) and the field administration of stroke therapy-magnesium trial (FAST-MAG)—were designed to evaluate the use of magnesium therapy in patients with acute ischemic stroke. As magnesium was administered prior to confirmation with imaging, a sub-group of patients with ICHs also received this high-dose magnesium therapy.

IMAGES was the first multi-center double-blind randomized control trial that evaluated magnesium therapy in patients with acute ischemic stroke. The study enrolled 2589 patients with a median treatment time of 7.4 hours after symptom onset. Patients received 4 g MgSO₄ bolus followed by a maintenance dose 16.15 g given over 24 hours. Although the study targeted acute ischemic stroke, 168 patients with primary ICH were also enrolled, 87 of whom received MgSO₄. Primary outcome was based on a dichotomized mRS score at hospital discharge (mRS > 2). Hypomagnesemia was associated with worse admission ICH score (OR, 2.5; 95% CI, 1.15–5.40; P = 0.03) and an increased systolic blood pressure (197.2 ± 19.5 mmHg) compared with systolic blood pressure for normomagnesemic patients (173.9 ± 23.0 mmHg) (P < 0.001). No statistical difference was noted in discharge mRS and admission hematoma volume between normal magnesium and hypomagnesemia groups (Behrouz et al., 2015).

Liotta et al. (2017) evaluated 290 patients with spontaneous ICH; however, they did not exclude patients with pre-existing coagulopathy from chronic anticoagulation use or later-onset patients (i.e., symptom-onset > 6 hours). Functional outcome was defined by mRS at 3 months. The authors found that lower admission magnesium concentrations were associated with larger admission hematoma volumes on univariate and parsimoniously adjusted models (P = 0.02), greater hematoma volume growth (P = 0.005), and worse functional outcome (OR, 0.14; 95% CI, 0.03–0.64; P = 0.011). The authors separately evaluated and found an association between hematoma growth and magnesium levels (P = 0.036) and between functional outcome and magnesium levels (P = 0.011). They postulated that these separate significant associations suggested a hemostatic role for magnesium (via attenuation of hematoma volume expansion) that improved clinical outcome after ICH (Liotta et al., 2017).

Finally, Goyal et al. (2018) evaluated magnesium con-
centrations at admission and at 48 hours post-ICH onset in 299 patients with spontaneous ICH. The authors excluded patients with ICHs attributed to coagulopathy. They found no associations between magnesium concentrations at 48 hours and clinical outcome variables. However, multilinear regression analysis showed a significant inverse association between admission serum magnesium levels and admission hematoma volumes (regression coefficient, −0.020; 95% CI, −0.040 to −0.000; P = 0.049). Multilinear regression analysis also showed a significant inverse association between admission serum magnesium levels and admission ICH scores (regression coefficient, −0.053; 95% CI, −0.102 to −0.005; P = 0.032). Magnesium levels were not associated with functional outcomes as quantified by dichotomized hospital discharge mRS (Goyal et al., 2018).

**Potential Future Roles for Magnesium Therapy in Intracerebral Hemorrhage**

Although both IMAGES and FAST-MAG did not show any improvement in clinical outcome after ICH with magnesium therapy, these studies were not designed for the pathophysiology of ICH. The duration of magnesium infusion over a 24-hour span may have potentially utilized magnesium’s vasodilatory properties to help lower blood pressure. However, although numerous studies have shown an association between higher admission blood pressures and attenuation of hematoma volume in ICH (Ohwaki et al., 2004), this has not translated into improved clinical outcomes (Anderson et al., 2013; Qureshi et al., 2016). Similarly, the hemostatic properties of magnesium may have also played a role with this limited duration of therapy. However, hemostatic intervention in ICH has also not translated into improved clinical outcome (Mayer et al., 2008).

Additionally, the short duration of magnesium therapy in these two trials may have limited any benefit for minimizing BBB disruption and reducing PHE, which is theorized to progress in the first 2–3 days and peak around day 14 (Urday et al., 2015). With several smaller ICH studies targeting the secondary stage with longer duration of treatments and yielding promising results (Fu et al., 2014; Chang et al., 2017b), it is possible that any future studies utilizing magnesium as a therapeutic agent should also similarly have longer durations of therapy. Longer duration of therapy may allow magnesium to both incorporate properties useful for primary stage hematoma volume attenuation, and more importantly, incorporate therapeutic mechanisms associated with minimizing secondary stage PHE and BBB disruption in ICH.

**Conclusion**

The physiological properties of magnesium in ICH are not as well understood as with ischemic stroke models. However, three key properties of magnesium—vasodilation, hemostasis, and reduction of PHE through BBB preservation—may make magnesium therapy a worthwhile future target for improving clinical outcome after ICH. Although two large randomized trials did not demonstrate efficacy of magnesium therapy in ICH, both trials were not designed to optimize therapeutic targets for ICH pathophysiology. In contrast, several recent large retrospective trials have demonstrated associations in ICH between low admission serum magnesium levels and clinical outcome, admission hematoma volume, and hematoma expansion. The results of these studies (Table 1) suggest that with a proper methodology focused on ICH pathophysiology, magnesium may prove to have some clinical benefit in ICH.

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**References**


Table 1 Summary of clinical studies evaluating magnesium use in intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Time magnesium administered/ dosage</th>
<th>Outcome measure</th>
<th>Results and conclusion</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goyal et al. (2018)</td>
<td>299 Patients</td>
<td>N/A</td>
<td>Hematoma volume at admission, ICH score</td>
<td>Lower admission magnesium levels associated with larger hematoma volume at admission, lower admission magnesium levels associated with worse ICH scores</td>
<td>Retrospective design</td>
</tr>
<tr>
<td>Liotta et al. (2017)</td>
<td>290 Patients</td>
<td>N/A</td>
<td>Hematoma volume at admission, Functional outcome (mRS at 3 months)</td>
<td>Lower admission magnesium levels associated with larger hematoma volume at admission, lower admission magnesium levels associated with poorer functional outcome</td>
<td>No exclusion for patients with admission coagulopathy</td>
</tr>
<tr>
<td>Behrouz et al. (2015)</td>
<td>128 Patients</td>
<td>N/A</td>
<td>ICH score, Systolic blood pressure</td>
<td>Hypomagnesemia associated with worse ICH scores, Hypomagnesemia associated with higher admission systolic blood pressures</td>
<td></td>
</tr>
<tr>
<td>Saver et al. (2015)</td>
<td>1700 Stroke patients 387 ICH patients</td>
<td>Median 45 minutes after symptom onset, 4 g bolus + 16 gram infusion over 24 hours</td>
<td>Functional outcome (dichotomized mRS, Barthel Index, NIHSS scores at 3 months)</td>
<td>No difference in functional outcome between treatment and placebo groups. Outcome analysis for magnesium and placebo groups for ICH are pending.</td>
<td>Methodology designed for acute ischemic stroke</td>
</tr>
<tr>
<td>Muir et al. (2004)</td>
<td>2589 Stroke patients 168 ICH patients</td>
<td>Median 7 hours after symptom onset, 4 g bolus + 16.15 g infusion over 24 hours</td>
<td>Death or disability at 90 days</td>
<td>No difference in death or disability between treatment and placebo groups</td>
<td>Methodology designed for acute ischemic stroke</td>
</tr>
</tbody>
</table>

ICH: Intracerebral hemorrhage; mRS: modified Rankin score; NIHSS: National Institutes of Health Stroke Scale; N/A: not available.


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