

● REVIEW

Magnesium: pathophysiological mechanisms and potential therapeutic roles in intracerebral hemorrhage

Jason J. Chang^{1,2}, Rocco Armonda³, Nitin Goyal^{4,5}, Adam S. Arthur^{5,6,*}

1 Department of Critical Care Medicine, MedStar Washington Hospital Center, Washington, DC, USA

2 Department of Neurology, Georgetown University School of Medicine, Washington, DC, USA

3 Department of Neurosurgery, Georgetown University School of Medicine, Washington, DC, USA

4 Department of Neurology, University of Tennessee Health Science Center, Memphis, TN, USA

5 Semmes Murphey Clinic, Memphis, TN, USA

6 Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA

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 is a ubiquitous element that also plays roles in vasodilation, hemostasis, and blood-brain barrier preservation. Animal models have highlighted potential therapeutic roles for magnesium in neurological diseases specifically targeting these pathophysiological mechanisms. Retrospective studies have also demonstrated inverse associations between admission magnesium levels and hematoma volume, hematoma expansion, and clinical outcome in patients with ICH. These associations, coupled with the multifactorial role of magnesium that targets both primary and secondary phases of ICH, suggest that magnesium may be a viable target of study in future ICH studies.

Key Words: intracerebral hemorrhage; stroke; magnesium; vasodilation; hemostasis; blood-brain barrier; perihematomal edema

Introduction: Intracerebral Hemorrhage

Of the 795,000 people newly-diagnosed with stroke each year, Intracerebral Hemorrhage (ICH) remains the second-most common subtype (Go et al., 2013). In contrast to the improving morbidity and mortality trends of ischemic stroke and subarachnoid hemorrhage (Naval et al., 2013; Benjamin et al., 2017), ICH remains a highly morbid disease with a one-month mortality of 40–50% (Fogelholm et al., 2005; van Asch et al., 2010) and a dismal mortality rate, which has remained unimproved over an almost 30-year span (van Asch et al., 2010).

Spontaneous ICH consists of two pathophysiological stages (Chang et al., 2014b). The first stage occurs acutely and reflects initial hematoma volume and expansion. The relationship between poor clinical outcome and initial hematoma volume (Broderick et al., 1993) and hematoma growth (Brott et al., 1997; Davis et al., 2006) is well established. The second stage occurs subacutely and consists of perihematomal edema (PHE) expansion, blood-brain barrier (BBB) disruption, inflammatory mediator upregulation, global depressed cortical excitability, and apoptosis (Qureshi et al., 2003; Mun-Bryce et al., 2004; Belur et al., 2013).

To date, recent large randomized multi-center trials have targeted this first stage—the attenuation of hematoma volume expansion through blood pressure control (Anderson et al., 2013; Qureshi et al., 2016), surgical evacuation (Men-

delow et al., 2013), 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—sulfonyleurea, 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 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-

*Correspondence to:

Adam S. Arthur, MD, MPH,
aarthur@semmes-murphey.com.

orcid:

0000-0002-1536-1613
(Adam S. Arthur)

doi: 10.4103/1673-5374.251189

Received: November 8, 2018

Accepted: January 14, 2019

logical mechanisms for magnesium, its role as a therapeutic intervention in neuropathology, and its potential as a neuro-protectant 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 (Westermaier 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 XIa (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 (Gajsiewicz 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 A_2 (Murata et al., 2016). A dog model of cerebral vasoconstriction 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 intravenous 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 composite score of death and disability (represented by modified Rankin score [mRS] > 1 and Barthel Index < 95) at 90 days. Although magnesium therapy favored reduction of death and disability in the ICH subgroup, this relationship was not statistically significant (odds ratio [OR], 0.84; 95% confidence interval [CI] 0.41–1.74; *P* = 0.90). Safety analysis for the trial revealed no significant difference in adverse events between the magnesium and placebo groups (*P* = 0.25) (Muir et al., 2004).

FAST-MAG was the second multi-center placebo-controlled randomized control trial that modified the protocol used in IMAGES by evaluating magnesium therapy for acute ischemic stroke in a prehospital setting. The study enrolled 1700 patients. Magnesium administration and dosing was identical to IMAGES; however, pre-hospital administration

resulted in an ultra-early median treatment time of 45 minutes after symptom onset (Saver et al., 2015). Of the patients enrolled, 387 patients (195 from the magnesium group vs. 192 from the placebo group) were found to have ICH. Although formal *post hoc* analysis of clinical outcome differences between magnesium and placebo groups have yet to be published, one subsequent *post hoc* study of this ICH sub-group evaluating blood pressure changes showed no difference in the percentage of patients who received MgSO₄ in the favorable and poor outcome groups (56.0% vs. 46.7%; *P* < 0.09) (Chung et al., 2018). The overall rates of adverse events did not differ between the magnesium and placebo groups (*P* = 0.67) (Saver et al., 2015).

Admission Magnesium Levels as Indicators of Neuroprotection in Intracerebral Hemorrhage

To date, three retrospective studies have evaluated associations between admission magnesium serum concentrations and outcomes in patients with ICH. The earliest study to evaluate admission magnesium levels on outcome after spontaneous ICH was Behrouz et al. (2015). They studied 128 patients, and hypomagnesemia was defined as < 1.7 mg/dL. Clinical outcomes were defined by a dichotomized ICH score (Hemphill et al., 2001) (ICH score > 3 was defined as poor admission clinical outcome), hematoma volume as based on the ABC/2 method (Kothari et al., 1996), and poor outcome was based on a dichotomized mRS score at hospital discharge (mRS, 4–6). 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.

Acknowledgments: The authors wish to thank Andrew J. Gienapp (Neuroscience Institute, Le Bonheur Children's Hospital and Department of Neurosurgery, University of Tennessee Health Science Center, Memphis, TN, USA) for copy editing, preparation of the manuscript and table for publishing, and publication assistance.

Author contributions: Manuscript conception and design: JJC and NG; writing of manuscript: JJC; critical revision of manuscript for important intellectual content: JJC, RA, NG and ASA.

Conflicts of interest: JJC, RA and NG report no disclosures or conflict of interests. ASA is a consultant for Leica, Medtronic, Microvention, Penumbra, Siemens, and Stryker, receives research support from Microvention, Penumbra, and Siemens, and is a shareholder in Bendit, Cerebrotech, Serenity, and Synchron.

Financial support: None.

Copyright license agreement: The Copyright License Agreement has been signed by all authors before publication.

Plagiarism check: Checked twice by iThenticate.

Peer review: Externally peer reviewed.

Open access statement: This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Open peer reviewer: Rong Xie, Fudan University, China.

Additional file: Open peer review report 1.

References

- Altura BM, Altura BT, Carella A, Gebrewold A, Murakawa T, Nishio A (1987) Mg^{2+} - Ca^{2+} interaction in contractility of vascular smooth muscle: Mg^{2+} versus organic calcium channel blockers on myogenic tone and agonist-induced responsiveness of blood vessels. *Can J Physiol Pharmacol* 65:729-745.
- Ameliorate JL, Ghabriel MN, Vink R (2017) Magnesium enhances the beneficial effects of NK1 antagonist administration on blood-brain barrier permeability and motor outcome after traumatic brain injury. *Magnes Res* 30:88-97.
- Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, et al. (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med* 368:2355-2365.
- Bayir A, Ak A, Kara H, Sahin TK (2009) Serum and cerebrospinal fluid magnesium levels, Glasgow Coma Scores, and in-hospital mortality in patients with acute stroke. *Biol Trace Elem Res* 130:7-12.
- Behrouz R, Hafeez S, Mutgi SA, Zakaria A, Miller CM (2015) Hypomagnesemia in intracerebral hemorrhage. *World Neurosurg* 84:1929-1932.
- Belur PK, Chang JJ, He S, Emanuel BA, Mack WJ (2013) Emerging experimental therapies for intracerebral hemorrhage: targeting mechanisms of secondary brain injury. *Neurosurg Focus* 34:E9.

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

Study	Sample size	Time magnesium administered/ dosage	Outcome measure	Results and conclusion	Limitations
Goyal et al. (2018)	299 Patients	N/A	<ul style="list-style-type: none"> Hematoma volume at admission ICH score 	<ul style="list-style-type: none"> Lower admission magnesium levels associated with larger hematoma volume at admission Lower admission magnesium levels associated with worse ICH scores 	<ul style="list-style-type: none"> Retrospective design
Liotta et al. (2017)	290 Patients	N/A	<ul style="list-style-type: none"> Hematoma volume at admission Functional outcome (mRS at 3 months) 	<ul style="list-style-type: none"> Lower admission magnesium levels associated with larger hematoma volume at admission Lower admission magnesium levels associated with poorer functional outcome 	<ul style="list-style-type: none"> Retrospective design No exclusion for patients with admission coagulopathy
Behrouz et al. (2015)	128 Patients	N/A	<ul style="list-style-type: none"> ICH score Systolic blood pressure 	<ul style="list-style-type: none"> Hypomagnesemia associated with worse ICH scores Hypomagnesemia associated with higher admission systolic blood pressures 	
Saver et al. (2015)	1700 Stroke patients 387 ICH patients	<ul style="list-style-type: none"> Median 45 minutes after symptom onset 4 g bolus + 16 gram infusion over 24 hours 	Functional outcome (dichotomized mRS, Barthel Index, NIHSS scores at 3 months)	No difference in functional outcome between treatment and placebo groups. Outcome analysis for magnesium and placebo groups for ICH are pending.	<ul style="list-style-type: none"> Methodology designed for acute ischemic stroke
Muir et al. (2004)	2589 Stroke patients 168 ICH patients	<ul style="list-style-type: none"> Median 7 hours after symptom onset 4 g bolus + 16.15 g infusion over 24 hours 	Death or disability at 90 days	No difference in death or disability between treatment and placebo groups	<ul style="list-style-type: none"> Methodology designed for acute ischemic stroke

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

Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jimenez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, et al. (2017) Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 135:e146-603.

Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G (1993) Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke* 24:987-993.

Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J (1997) Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* 28:1-5.

Chakraborti S, Chakraborti T, Mandal M, Mandal A, Das S, Ghosh S (2002) Protective role of magnesium in cardiovascular diseases: a review. *Mol Cell Biochem* 238:163-179.

Chang JJ, Mack WJ, Saver JL, Sanossian N (2014a) Magnesium: potential roles in neurovascular disease. *Front Neurol* 5:52.

Chang JJ, Emanuel BA, Mack WJ, Tsvigoulis G, Alexandrov AV (2014b) Matrix metalloproteinase-9: dual role and temporal profile in intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 23:2498-2505.

Chang JJ, Khorchid Y, Kerro A, Burgess LG, Goyal N, Alexandrov AW, Alexandrov AV, Tsvigoulis G (2017a) Sulfonylurea drug pretreatment and functional outcome in diabetic patients with acute intracerebral hemorrhage. *J Neurol Sci* 381:182-187.

Chang JJ, Kim-Tenser M, Emanuel BA, Jones GM, Chapple K, Alikhani A, Sanossian N, Mack WJ, Tsvigoulis G, Alexandrov AV, Pourmotabbed T (2017b) Minocycline and matrix metalloproteinase inhibition in acute intracerebral hemorrhage: a pilot study. *Eur J Neurol* 24:1384-1391.

Chung PW, Kim JT, Sanossian N, Starkmann S, Hamilton S, Gornbein J, Conwit R, Eckstein M, Pratt F, Stratton S, Liebeskind DS, Saver JL, Investigators FM, Coordinators (2018) Association between hyperacute stage blood pressure variability and outcome in patients with spontaneous intracerebral hemorrhage. *Stroke* 49:348-354.

Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, Begtrup K, Steiner T; Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators (2006) Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. *Neurology* 66:1175-1181.

Esen F, Erdem T, Aktan D, Kalayci R, Cakar N, Kaya M, Telci L (2003) Effects of magnesium administration on brain edema and blood-brain barrier breakdown after experimental traumatic brain injury in rats. *J Neurosurg Anesthesiol* 15:119-125.

Fogelholm R, Murros K, Rissanen A, Avikainen S (2005) Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry* 76:1534-1538.

Fu Y, Hao J, Zhang N, Ren L, Sun N, Li YJ, Yan Y, Huang D, Yu C, Shi FD (2014) Fingolimod for the treatment of intracerebral hemorrhage: a 2-arm proof-of-concept study. *JAMA Neurol* 71:1092-1101.

Gajsiewicz JM, Nuzzio KM, Rienstra CM, Morrissey JH (2015) Tissue factor residues that modulate magnesium-dependent rate enhancements of the tissue factor/factor VIIa complex. *Biochemistry* 54:4665-4671.

Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, et al. (2013) Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 127:e6-245.

Goyal N, Tsvigoulis G, Malhotra K, Houck AL, Khorchid YM, Pandhi A, Inoa V, Alsherbini K, Alexandrov AV, Arthur AS, Elijovich L, Chang JJ (2018) Serum magnesium levels and outcomes in patients with acute spontaneous intracerebral hemorrhage. *J Am Heart Assoc* 7:e008698.

Hemphill JC, 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC (2001) The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. *Stroke* 32:891-897.

- Imer M, Omay B, Uzunkol A, Erdem T, Sabanci PA, Karasu A, Albayrak SB, Sencer A, Hepgul K, Kaya M (2009) Effect of magnesium, MK-801 and combination of magnesium and MK-801 on blood-brain barrier permeability and brain edema after experimental traumatic diffuse brain injury. *Neurol Res* 31:977-981.
- Kapaki E, Segditsa J, Papageorgiou C (1989) Zinc, copper and magnesium concentration in serum and CSF of patients with neurological disorders. *Acta Neurol Scand* 79:373-378.
- Kemp PA, Gardiner SM, March JE, Rubin PC, Bennett T (1999) Assessment of the effects of endothelin-1 and magnesium sulphate on regional blood flows in conscious rats, by the coloured microsphere reference technique. *Br J Pharmacol* 126:621-626.
- Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, Khoury J (1996) The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* 27:1304-1305.
- Letson HL, Dobson GP (2015) Correction of acute traumatic coagulopathy with small-volume 7.5% NaCl adenosine, lidocaine, and Mg²⁺ occurs within 5 minutes: a ROTEM analysis. *J Trauma Acute Care Surg* 78:773-783.
- Letson HL, Pecheniuk NM, Mhango LP, Dobson GP (2012) Reversal of acute coagulopathy during hypotensive resuscitation using small-volume 7.5% NaCl adenosine and Mg²⁺ in the rat model of severe hemorrhagic shock. *Crit Care Med* 40:2417-2422.
- Liotta EM, Prabhakaran S, Sangha RS, Bush RA, Long AE, Trevick SA, Potts MB, Jahromi BS, Kim M, Manno EM, Sorond FA, Naidech AM, Maas MB (2017) Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage. *Neurology* 89:813-819.
- Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T; FAST Trial Investigators (2008) Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 358:2127-2137.
- McIntosh TK, Vink R, Soares H, Hayes R, Simon R (1990) Effect of noncompetitive blockade of N-methyl-D-aspartate receptors on the neurochemical sequelae of experimental brain injury. *J Neurochem* 55:1170-1179.
- McKee JA, Brewer RP, Macy GE, Phillips-Bute B, Campbell KA, Borel CO, Reynolds JD, Warner DS (2005) Analysis of the brain bioavailability of peripherally administered magnesium sulfate: A study in humans with acute brain injury undergoing prolonged induced hypermagnesemia. *Crit Care Med* 33:661-666.
- Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, Investigators SI (2013) Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. *Lancet* 382:397-408.
- Mori K, Miyazaki M, Hara Y, Aiko Y, Yamamoto T, Nakao Y, Esaki T (2011) Temporal profile of the effects of intracisternal injection of magnesium sulfate solution on vasodilation of spastic cerebral arteries in the canine SAH model. *Acta Neurochir Suppl* 110:39-42.
- Muir KW, Lees KR, Ford I, Davis S; Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators (2004) Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet* 363:439-445.
- Mun-Bryce S, Wilkerson A, Pacheco B, Zhang T, Rai S, Wang Y, Okada Y (2004) Depressed cortical excitability and elevated matrix metalloproteinases in remote brain regions following intracerebral hemorrhage. *Brain Res* 1026:227-234.
- Murata T, Horiuchi T, Goto T, Li Y, Hongo K (2011) Vasomotor response induced by change of extracellular potassium and magnesium in cerebral penetrating arterioles. *Neurosci Res* 70:30-34.
- Murata T, Dietrich HH, Horiuchi T, Hongo K, Dacey RG Jr (2016) Mechanisms of magnesium-induced vasodilation in cerebral penetrating arterioles. *Neurosci Res* 107:57-62.
- Naval NS, Chang T, Caserta F, Kowalski RG, Carhuapoma JR, Tamargo RJ (2013) Improved aneurysmal subarachnoid hemorrhage outcomes: a comparison of 2 decades at an academic center. *J Crit Care* 28:182-188.
- Ohwaki K, Yano E, Nagashima H, Hirata M, Nakagomi T, Tamura A (2004) Blood pressure management in acute intracerebral hemorrhage: relationship between elevated blood pressure and hematoma enlargement. *Stroke* 35:1364-1367.
- Quinn SJ, Williams GH (1988) Regulation of aldosterone secretion. *Annu Rev Physiol* 50:409-426.
- Qureshi AI, Suri MF, Ostrow PT, Kim SH, Ali Z, Shatla AA, Guterman LR, Hopkins LN (2003) Apoptosis as a form of cell death in intracerebral hemorrhage. *Neurosurgery* 52:1041-1048.
- Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JJ, Toyoda K, Wang Y, Yamamoto H, Yoon BW; ATACH-2 Trial Investigators and the Neurological Emergency Treatment Trials Network (2016) Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. *N Engl J Med* 375:1033-1043.
- Reinhart RA (1991) Clinical correlates of the molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 121:1513-1521.
- Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, Moreau G, Goldweber R, Sanossian N; FAST-MAG Investigators and Coordinators (2015) Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N Engl J Med* 372:528-536.
- Schreurs MP, Cipolla MJ (2014) Cerebrovascular dysfunction and blood-brain barrier permeability induced by oxidized LDL are prevented by apocynin and magnesium sulfate in female rats. *J Cardiovasc Pharmacol* 63:33-39.
- Sekiya F, Yamashita T, Atoda H, Komiya Y, Morita T (1995) Regulation of the tertiary structure and function of coagulation factor IX by magnesium (II) ions. *J Biol Chem* 270:14325-14331.
- Sharma N, Cho DH, Kim SY, Bhattarai JP, Hwang PH, Han SK (2012) Magnesium sulfate suppresses L-type calcium currents on the basilar artery smooth muscle cells in rabbits. *Neurol Res* 34:291-296.
- Urday S, Kimberly WT, Beslow LA, Vortmeyer AO, Selim MH, Rosand J, Simard JM, Sheth KN (2015) Targeting secondary injury in intracerebral haemorrhage--perihematomal oedema. *Nat Rev Neurol* 11:111-122.
- van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ (2010) Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol* 9:167-176.
- van den Besselaar AM (2002) Magnesium and manganese ions accelerate tissue factor-induced coagulation independently of factor IX. *Blood Coagul Fibrinolysis* 13:19-23.
- Westermaier T, Stetter C, Kunze E, Willner N, Raslan F, Vince GH, Ernestus RI (2013) Magnesium treatment for neuroprotection in ischemic diseases of the brain. *Exp Transl Stroke Med* 5:6.
- Zhang LW, Warrington JP (2016) Magnesium sulfate prevents placental ischemia-induced increases in brain water content and cerebrospinal fluid cytokines in pregnant rats. *Front Neurosci* 10:561.
- Zhu D, Su Y, Fu B, Xu H (2018) Magnesium reduces blood-brain barrier permeability and regulates amyloid-beta transcytosis. *Mol Neurobiol* 55:7118-7131.