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Review Article

Serum magnesium level and hematoma expansion in patients with intracerebral hemorrhage

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ABSTRACT

Spontaneous intracerebral hemorrhage (ICH) is a devastating subtype of stroke that results in significant rates of mortality and morbidities. The initial hematoma volume, hematoma expansion (HE), blood pressure (BP), and coagulopathy are considered strong predictors of clinical outcomes and mortality. Low serum magnesium (Mg^{++}) levels have been shown to be associated with larger initial hematoma and greater HE. Coagulopathy, platelet dysfunction, high BP, and increased inflammatory response might form the mechanistic link between low serum Mg^{++} levels, larger hematoma size and greater HE. However, randomized clinical trials administering intravenous Mg^{++} have shown no benefit over placebo in ICH patients. The confounding effect of hypocalcemia and a delay in Mg^{++} trafficking across the blood-brain barrier might explain the futile results for intravenous Mg^{++} therapy. In the current review, we will discuss the evidence regarding the possible role of low serum Mg^{++} level on HE in acute ICH.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for 10 to 30% of all acute cerebrovascular events and is the most devastating with potentially life-threatening consequences [1]. So far, no treatment has yielded conclusive benefits, and ICH still represents a major public health issue [2]. The initial hematoma volume and hematoma expansion (HE) have been shown to be independent predictors of 30-day mortality and poor functional outcome [1,3]. Several randomized controlled trials aimed at limiting HE through a variety of strategies including the administration of recombinant factor VIIa (rFVIIa) [4], platelet transfusion [5], tranexamic acid [6], and aggressive blood pressure (BP) reduction during the acute ICH stage [7] have not shown significant effects to improve the functional outcomes. Consequently, the identification and targeting of other potential risk factors for HE may be of clinical interest. Recent studies [8,9] have shown that low serum magnesium (Mg^{++}) levels have been associated with larger initial hematoma volume, HE, and unfavorable outcomes. In this regard, Mg^{++} may significantly influence HE by playing key roles in the coagulation cascade, platelet function, BP control, and inflammatory response. The aim of this review is to highlight the relationships between Mg^{++} and HE in patients with acute ICH and provide critical insights into the underlying pathophysiology (Table 1).

2. Hematoma expansion in ICH

Different criteria have been used to define HE on follow-up CT scans. Most studies have adopted a relative cut-off (*i.e.* an increase > 26% or 33%), an absolute threshold (typically an increase ≥3, 6 or 12.5 ml), or a combination of both [10]. The mechanisms involved in HE are not fully elucidated and are a matter of ongoing debate. According to the *Persistent Bleeding Model*, HE occurs through the continuous bleeding from a culprit vessel. However, no direct evidence of single persistently bleeding vessel has been obtained from

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Table 1
Summary of published studies on the role of Mg^{++} level in stroke.

Authors	Year	Study type	Sample size	Stroke subtype	Outcomes
Liotta et al. [8]	2017	Prospective cohort study	290	ICH	Lower Mg^{++} levels were associated with larger initial hematoma volumes, greater HE and worse functional outcome at 3 months.
Goyal et al. [9]	2018	Retrospective cohort study	299	ICH	Higher Mg^{++} levels were associated with lower initial hematoma volume and lower admission ICH score.
Muir et al. [58]	2004	Randomized clinical trial	2589	IS	Mg^{++} infusion within 12 h of acute IS did not reduce the chances of death or disability significantly.
Behrouz et al. [34]	2015	Retrospective cohort study	128	ICH	HMg was associated with higher admission ICH score, lower GCS score. No association was found between HMg and poor discharge outcome.
Saver et al. [20]	2015	Randomized clinical trial	1700	IS and ICH	Mg^{++} infusion within 2 h of stroke symptom onset did not improve disability outcomes at 90 days.

Abbreviations: ICH intracerebral hemorrhage, Mg magnesium, HE hematoma expansion, IS ischemic stroke, HMg hypomagnesemia, GCS Glasgow Coma Scale.

histopathology [2]. Conversely, the *Avalanche Model* considers HE as the consequence of the mechanical shear stress exercised by initial hematoma on the surrounding vessels, which results in multiple sequential ruptures maintaining bleeding [11]. This model is in line with the common finding of multiple smaller, satellite hemorrhages at the periphery of a large hematoma [12], a radiological finding also referred to as island sign [13], which is considered an acceptable predictor of HE when CTA is unavailable [14]. Furthermore, focal hypodensities within an ICH detected by non-contrast CT scans have been associated with HE, which might reflect different ongoing phases of bleeding and thus mark a hematoma with sites susceptible to further rupture and HE [15]. Additionally, early HE can occur due to re-bleeding into the necrotic tissue around the initial hematoma. Contributing factors include the increase in local tissue pressure and mechanical injury, reduction of cerebral blood flow, local fibrinolytic effect, induction of plasma proteases, and secondary inflammatory response [16]. CTA spot sign, which indicates active bleeding sites following venous contrast injection, is a putative indicator of active bleeding during ICH [17]. Furthermore, the initial insult from the hemorrhage sets off a cascade of various metabolic processes, which ultimately lead to perihematomal inflammation and edema by disruption of the blood-brain barrier (BBB). The edema leads to further mass effect, raised intracranial pressure and often causes further neurologic decline. This process commences soon after the initial ICH but may persist for several days [18].

3. Magnesium and ICH

Mg^{++} is one of the most abundant intracellular cations that is involved in several important physiologic functions. It is a cofactor for DNA and protein synthesis, neuromuscular excitability, oxidative phosphorylation, enzyme activity, regulation of parathyroid hormone (PTH) secretion, and has been recognized to have neuroprotective and glioprotective effects [19,20]. Mg^{++} is mainly stored in bone and intracellular space, whereas < 1% of total body Mg^{++} is circulating in extracellular fluids and serum [21]. Approximately 65% of serum Mg is ionized, 20% is bound to protein, and the rest is complexed with various anions such as phosphate and citrate [22]. Serum Mg^{++} levels are maintained in a narrow range with higher concentration in the brain and cerebrospinal fluid (CSF). This higher concentration is maintained through active BBB transport. The choroidal epithelium plays an active role in maintaining the level of Mg^{++} in the CSF by sensing changes in the CSF and altering the rate of active Mg^{++} secretion [23,24]. However, in pathological conditions such as head injury which damage the BBB, the Mg^{++} concentration in the CSF may decrease [25]. Several hormones including PTH, antidiuretic hormone, calcitonin, glucagon, and insulin control Mg^{++} metabolism. PTH increases reabsorption of Mg^{++} in the distal renal tubules by a cyclic AMP-mediated process [22]. In parallel, Mg^{++} has a direct effect on PTH secretion. Mg^{++} administration has been associated with an immediate rise in serum PTH concentration regardless of basal PTH levels—indicating the importance of Mg^{++} in PTH regulation and calcium (Ca^{++}) metabolism [27]. Although, PTH secretion is mainly regulated by Ca^{++} concentration, Mg^{++} can exert a similar effect. While low levels of Mg^{++} stimulate PTH secretion, severe hypomagnesemia (HMg) induces a paradoxical block that can lead to clinically relevant hypocalcemia [28]. HMg may result from one or more of the following mechanisms: redistribution between extracellular and intracellular space, reduced intake of dietary Mg^{++}, reduced intestinal absorption, increased gastrointestinal loss, and increased renal loss. As Mg^{++} deficiency is usually secondary to other pathological conditions or medications, the features of the primary disease may complicate or mask Mg^{++} deficiency [29]. Mg^{++} has been shown to have beneficial effects in animal models of stroke through both neuronal and vascular mechanisms, rendering it an attractive therapeutic agent [30]. Systemic administration of Mg^{++} has been associated with decreased infarct volume in

animal models of middle cerebral artery occlusion (MCAo) [31,32]. Furthermore, in embolic MCAo models, Mg^{++} administration significantly decreased the infarct volume; even when given 6 h after onset of ischemia [33]. Clinical studies have also suggested a relationship between Mg^{++} level and ICH severity. HMg is present in one-third of ICH patients and is associated with a more severe presentation and intraventricular hemorrhage [34]. Liotta et al. [8] in a retrospective cohort study investigated the association between admission serum Mg^{++} levels and extension of bleeding in ICH patients. Lower admission Mg^{++} levels were associated with larger initial hematoma volumes, as well as greater HE, and worse functional outcomes at 3 months. Goyal et al. [9] investigated the potential association of serum Mg^{++} levels (at baseline and 48 h) with outcomes in ICH patients. They found that higher admission Mg^{++} levels (1.9 ± 0.3 *versus* 1.8 ± 0.3 mg/dL; $p = .025$) were negatively correlated with the cubed root of hematoma volume at admission (multiple linear regression coefficient − 0.020 per 0.1 mg/dL increase, $p = .049$), were independently related to lower admission hematoma volume, lower admission ICH score, and favorable functional outcome. The authors have suggested the coagulopathy and platelet dysfunction as molecular mechanisms underlying the association between Mg^{++} and hematoma characteristics. There is also a possibility of other underlying mechanisms since Mg^{++} has been shown to be involved in BP regulation, inflammatory responses, and having neuroprotective properties. Moreover, HMg by affecting the PTH secretion and inducing hypocalcemia can compromise the coagulation cascade and platelet dysfunction [27,35]. Therefore, hypocalcemia in the context of HMg might be a major confounder in the association between Mg^{++} levels and HE, and it would be interesting to investigate whether Ca^{++} and Mg^{++} are both predictors of active bleeding in acute ICH, independently from each other. However, in the FAST-MAG (Field Administration of Stroke Therapy – MAG) trial [20], prehospital intravenous Mg^{++} (4 g of Mg in 54 ml of normal saline infused over a period of 15 min) followed by 24-h maintenance infusion (16 g of Mg diluted in 240 ml of normal saline, infused at a rate of 10 ml per hour for 24 h) showed no benefit over placebo and did not improve the functional outcomes at 90 days in ICH patients, which comprised 22.8% of the total stroke patients. In this clinical trial, plasma Mg^{++} was maintained at higher concentrations than placebo, since that under normal conditions choroidal endothelial cells actively transport Mg^{++} into CSF, it is likely that such activity was disturbed by stroke leading a failure in Mg^{++} entry in CNS [36]. In fact, in damaged CNS, it may take several days for the serum Mg^{++} to be transported to the CSF after the Mg^{++} concentration is maintained at a concentration above a certain level [25]. In addition, most studies have focused on total serum Mg^{++} levels rather than serum ionized Mg^{++} levels, which is the physiologically active component [37]. Therefore, the role of HMg in HE and outcomes after ICH remains controversial.

4. The role of hypomagnesemia in coagulation cascade

Impaired coagulation can potentially facilitate HE. There is evidence that ionized Mg^{++} has physiological roles in the coagulation cascade [38,39]. Although, Mg^{++} is not necessary for coagulation, it has been shown to play a crucial role in enhancing the formation of fibrin through both the extrinsic and intrinsic pathways. Factor IXa, in the presence of factor VIII, platelet membrane phospholipid and Ca^{++}, can activate factor X that, in turn, can facilitate the conversion of prothrombin to thrombin [40]. Thrombin plays an important role in the conversion of fibrinogen to fibrin and cross-linking fibrin strands. It has been also demonstrated that Mg^{++} stabilizes the native factor IX conformation and enhance the ability of factor IXa to activate factor X [39]. This is possible as the presence of Mg^{++} augments the affinity of factor VIII to factor IXa and, thus, increases its catalytic effect. Mg^{++} enhances the activation of FX by TF/VIIa, and at physiologic concentrations, a combination of Mg^{++} and Ca^{++} results in greater enzymatic activity of TF/VIIa than with Ca^{++} alone [38]. It can be easily rationalized that patients with HMg will have disturbed coagulation in both the extrinsic and intrinsic pathways of the coagulation system. Given the observed associations described above, further studies specifically designed to investigate the role of HMg in coagulopathy affecting initial hematoma volume or its expansion are warranted.

Nonetheless, an *in vivo* study performed by Ames et al. [41] showed that the effect of Mg^{++} sulfate on coagulation was not clinically significant. In this study, healthy volunteers were given 4 g of Mg^{++} sulfate intravenously that did not result in any significant change in thromboelastography parameters associated with coagulation. Furthermore in a prospective laboratory study using the blood samples from patients with atrial fibrillation undergoing mitral annuloplasty, Kang et al. [42] demonstrated that Mg^{++} infusion did not influence coagulation in the pre-bypass period. Indeed, activated clotting time and thromboelastographic parameters did not change significantly after Mg^{++} infusion. Nevertheless, these studies were not conducted in a population of patients with HMg or in ICH patients.

5. Magnesium and platelet dysfunction

Platelets are essential for the maintenance of hemostasis, and platelet dysfunction leads to deranged coagulation and increased bleeding time [43]. *In vitro* evidence suggests that divalent cations can modulate blood coagulation and platelet activity [44]. Mg^{++} has been shown to play a role in the inhibition of platelet aggregation in a dose-dependent manner [45–48]. Through various pathways, Mg^{++} can negatively affect the ability of platelets to change the conformation of the cytoskeleton, impact their surface properties and decrease the stability of their aggregation [48]. These effects are thought to be mediated by the altered expression of glycoproteins on the platelet surface that occurs in the presence of Mg^{++} and has detrimental impact on the ability of the platelets to adhere to collagen at the site of injury [48]. Mg^{++} also has been shown to inhibit the release of dense granules in platelets [44]. The dense granules of platelets contain ADP, ATP, serotonin, Ca^{++}, epinephrine, which all play roles in platelet activation, recruitment, and aggregation [44,49]. The role of Mg^{++} in platelet granule secretion is unclear [50]. A randomized controlled trial by Shechter et al. [51] evaluated whether oral Mg^{++} treatment inhibits platelet-dependent thrombosis in patients with coronary heart disease. Though the study did not find a significant effect of Mg^{++} treatment on platelet aggregation, they did show that Mg^{++} significantly alters platelet function resulting in inhibition of platelet-dependent thrombosis.

6. Magnesium and BP regulation

High BP levels have been associated with HE and poor neurological functional outcomes in ICH patients [52,53]. Many factors have been implicated in high BP pathogenesis including the hyperactivation of the sympathetic nervous system and renin-angiotensin-aldosterone pathway. Intracellular ions, such as K^{+}, Ca^{++}, Na^{+}, and Mg^{++} can also modulate BP levels [54]. Previous studies have shown a close inverse correlation between supplementation of Mg^{++} and BP level, indicating the potential role of Mg^{++} deficiency in the pathogenesis of high BP [55]. One of the mechanisms by which Mg^{++} lowers BP is by mimicking a natural Ca^{++} channel blocker. Mg^{++} competes with Na^{+} for binding sites on vascular smooth muscle cells, increases prostaglandin E, binds to K^{+} in a cooperative manner, induces endothelial-dependent vasodilation, improves endothelial dysfunction, and decreases intracellular Ca^{++} and Na^{+}; all these effects can translate into a reduction of BP levels [56]. Furthermore, a correlation has been reported between the renin-angiotensin system and Mg^{++}. Hypertensive patients with high renin activity have significantly lower serum Mg^{++} levels than normotensive subjects, and plasma renin activity is inversely associated with serum Mg^{++} [57]. Behrouz et al. [34] in a

retrospective cohort study reported the significance of HMg in ICH patients. The results of this study demonstrated that low admission Mg^{++} levels correlated with higher systolic BP but did not influence the outcomes at discharge [34]. In a large randomized, placebo-controlled trial in ischemic stroke patients, intravenous administration of Mg^{++} within 12 h of symptom onset significantly reduced mean BP by 3–4 mmHg. However, IV Mg++ did not improve death or disability 90 days post-stroke [58]. Further prospective cohort studies are needed to clarify the correlation between low serum Mg^{++} level and BP in ICH patients.

7. Magnesium and systemic inflammatory response

There is accruing evidence that the acute ICH-mediated inflammatory response strongly influences the risk of HE, early neurological deterioration and development of post-stroke complications [59–61]. Systemic inflammatory response syndrome (SIRS) is a systemic reaction to acute stress. SIRS signals the inability of anti-inflammatory mechanisms to downregulate a profound state of inflammation [62]. This hyperinflammatory state contributes to secondary brain injury. Among the inflammatory mediators, interleukin (IL)-6 and IL-10 are especially high in ICH patients, and positively correlate with admission GCS [63]. Audebert et al. [64] reported that inflammatory reactions after stroke result from the activation of cellular, humoral, and metabolic mechanisms, which can lead to an increase in necrotic tissue in the ischemic penumbra. Mg^{++} plays an important role in the regulation of immune systems and inflammatory response [65,66]. Experimental HMg is recognized to have a significant effect on the process of inflammation [67]. It has been shown that HMg activates the inflammatory response by increasing circulating amounts of IL-1, IL-6, and TNF-α [68]. The high level of inflammatory cytokines can cause disruptive and non-disruptive changes in the BBB and at the presence of stroke where the damaged BBB is further sensitized by the systemic inflammatory response [69]. The breakdown of BBB results in an increased capillary permeability and brain edema formation after ICH [70]. HMg can also result in increased activation of macrophages, neutrophils, and endothelial cells [71]. The initiation of the inflammatory response in the context of the HMg could be due to opening of the *N*-methyl-D-aspartate Ca^{++} channels and activation of the NFkB—a group of inducible transcription factors implicated in the regulation of crucial steps of immune responses through regulation of the gene expression of a large number of cytokines and other immune response genes (Fig. 1) [67]. Moreover, HMg can induce immune response through activation of neuroendocrinological pathways by altering the production or activity of neurotransmitters such as acetylcholine, catecholamine, and substance P [72]. In addition, oxidative stress following inflammatory response could worsen the tissue damage even further during the HMg. Previous studies have shown the elevation of the oxidative stress indices and reduced antioxidant status in Mg^{++}-deficient animals [67]. The role of Mg^{++} on the immune system has been further highlighted by the study of Thongprayoonl at al [65]. which demonstrated that patients with SIRS and HMg at the time of admission had an increased risk of developing septic shock during hospitalization. It may be hypothesized that HMg may trigger SIRS by enhancing the ongoing inflammation in the context of ICH and, thus, worsen the outcomes.

8. Hypomagnesemia in critically ill patients

In the hyperacute stage of ICH, the serum levels of catecholamine and cortisol/corticosterone increase [73]. The hypothalamic–pituitary–adrenal (HPA) axis, an important hormonal response system to stress, might be involved in this process [74]. HPA axis activation increases Mg^{++} requirement and increases cellular Mg^{++} loss. Higher levels of catecholamines increase Mg^{++} binding to free fatty acid and might be responsible for a reduction in serum Mg^{++} level [75]. Moreover, many acute illnesses (including ICH) result in hyperglycemia, glucose intolerance, and insulin resistance [76]. Insulin resistance may affect Mg^{++} metabolism and has been associated with a lower serum Mg^{++} concentration [22]. For the aforementioned possibilities, the association between Mg^{++} levels and HE might not necessarily imply causality. Low Mg^{++} levels may represent the consequence and not the cause of larger initial ICH. Mg^{++} could act as a negative stress reactant and timing of blood samples for Mg^{++} measurement may be an important confounder, with a drop in Mg^{++} level proportional to ICH severity and time from onset to Mg^{++} measurements. Nonetheless, low serum Mg^{++} level could also independently affect the coagulation cascade, platelet function, and cause increased arterial vasculature tone.

9. Conclusion

Given the association between ICH volume, HE, and outcomes,

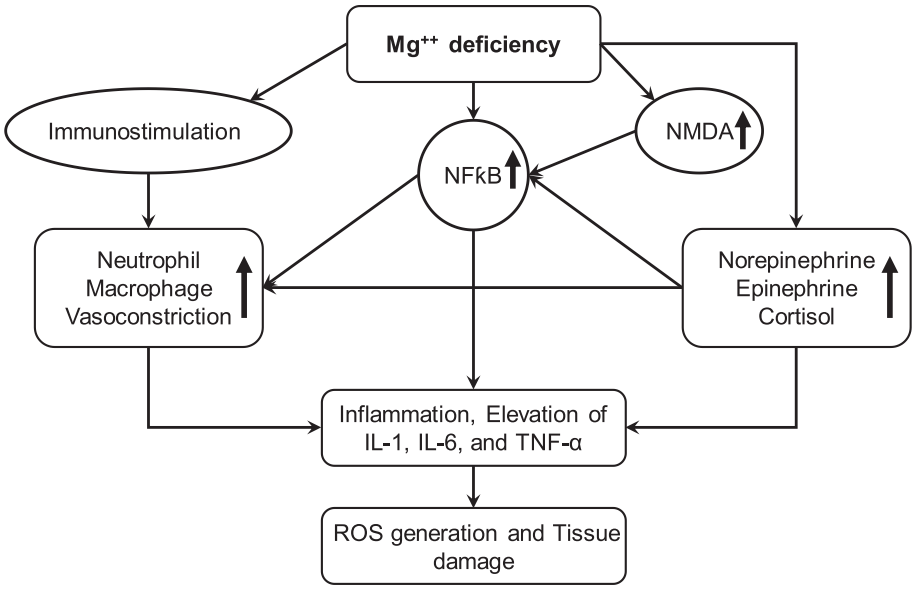

Fig. 1. Interrelationship between Mg^{++} deficiency and inflammation.
Mg^{++}: Magnesium, NFκB: nuclear factor κB, NMDA: *N*-methyl-D-aspartic acid, ROS: reactive oxygen species, TNF: tumor necrosis factor, IL: interleukin.

therapeutic interventions aimed at preventing HE could represent an effective treatment strategy. Although HMg has been associated with larger initial hematoma, early HE, and worse functional outcome, prehospital intravenous Mg^{++} followed by 24-hour maintenance showed no benefit over placebo and did not improve disability outcomes in ICH patients [20]. Potential explanations for these negative findings might include the delay in Mg^{++} trafficking across the BBB and the confounding effects of hypocalcemia in Mg^{++} deficient patients. Furthermore, hypocalcemia plays a mechanistic role in coagulation, platelet activation, and BP regulation [35]. HMg may drop the Ca^{++} levels by compromising the secretion of PTH and, in turn, worsen coagulopathy, cause platelet dysfunction, and increase BP. The neutral results of previous studies of Mg^{++} therapy in ICH might have been in part due to underlying hypocalcemia in Mg^{++} deficient patients or the altered transport of Mg^{++} into the brain after ICH reducing or eluding its neuroprotective effect. This underlines the rationale for a clinical trial of ultra-early, high-dose Mg^{++} and Ca^{++} therapy in acute ICH. Preclinical research enhances the rationale of this kind of intervention. The use of Mg^{++} has been explored in a variety of experimental stroke models [77]. Mg^{++} has shown to reduce hippocampal cell damage in models of global forebrain ischemia and decreased cerebral infarct volume after focal ischemia [77]. In experimental subarachnoid hemorrhage studies, Mg^{++} has shown to reduce cerebral vasospasm and acute brain lesion volume, protect cellular metabolism, and postpone anoxic depolarization [78]. Mg^{++} infusion has been also demonstrated to have hemostatic properties and corrected coagulopathy by improving clot kinetics, propagation, and firmness in acute hemorrhagic trauma [79,80].

Notably, Mg^{++} is inexpensive, easy to administer and widely available, yields predictable serum concentrations following intravenous infusion, and has a favorable tolerability profile. Due to its renal excretion, adverse events may substantially develop only in patients with kidney failure; heart conduction may be slowed, but the risk of symptomatic bradyarrhythmias is overall low [81]. Mg^{++} also showed synergetic effects when combined with other compounds, like radical scavengers, and this makes its use appealing within combination therapies, including neuro-protectant strategies [77].

Target for future therapy to improve the ICH outcome may also include treatment with Ca^{++}. Indeed, meaningful correlations have been recently found between admission Ca^{++} levels and hematoma volume and expansion. Although the underlying pathophysiology is still not completely understood, coagulopathy, platelet dysfunction, and high BP may play roles [35]. Acute therapy with Ca^{++} in the emergency room could represent a potential modality for hyperacute treatment in the setting of a clinical trial. Following intravenous administration, Ca^{++} levels rise immediately, with effects lasting 30 min to 2 h once dosing has finished. Attention in administering Ca^{++} should be paid towards the risk of cardiac arrhythmias and the effects on BP levels [35]. Furthermore, hypocalcemia correction should not exceed the normal range as hypercalcemia has shown to be associated with cerebral vasospasm and early neuronal damage by NMDA receptor-mediated Ca^{++} intracellular influx [82,83].

Although direct hemostatic therapy is most likely to be the biggest difference-maker in limiting HE, attention must be paid to HMg and hypocalcemia.

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Conflict of interest

The authors declare that they have no conflict of interest.

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