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REVIEW ARTICLE

The Role of Serum Calcium Level in Intracerebral Hemorrhage Hematoma Expansion: Is There Any?

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Abstract

Spontaneous intracerebral hemorrhage (ICH) is a devastating form of stroke, with a high rate of mortality and morbidity. Even with the best current medical or surgical interventions, outcomes remain poor. The location and initial hematoma volume are strong predictors of mortality. Hematoma expansion (HE) is a further marker of poor prognosis that may be at least partly preventable. Several risk factors for HE have been identified, including baseline ICH volume, anticoagulation, and computed tomography angiography spot signs. Recent studies have shown the correlation of serum calcium (Ca^{++}) levels on admission with HE. Low serum Ca^{++} level has been associated with larger hematoma volume at the time of presentation, HE, and worse outcome. Although the causal and mechanistic links between low serum Ca^{++} level and HE are not well understood, several mechanisms have been proposed including coagulopathy, platelet dysfunction, and higher blood pressure (BP) in the context of low serum Ca^{++} level. However, low serum Ca^{++} level might be only a biomarker of the adaptive response due to acute inflammatory response following acute ICH. The purpose of the current review is to discuss the evidence regarding the possible role of low serum Ca^{++} level on HE in acute ICH.

Keywords: Intracerebral hemorrhage, Serum calcium, Ionized calcium, Hematoma expansion

Introduction

Intracerebral hemorrhage (ICH) is a medical emergency with potentially life-threatening consequences. ICH represents the second most common (15%) stroke subtype, where 58% of ICH patients die within one year [1, 2]. The prognosis and pathophysiology of ICH is complex [3]. The initial hematoma volume and subsequent hematoma expansion (HE) are critical determinants of clinical outcome after ICH [4, 5]. Several large randomized controlled trials targeting HE with early aggressive blood pressure (BP) lowering or recombinant factor VII have failed to improve clinical outcomes [6, 7]. This highlights the need to identify other targets for therapeutic intervention after ICH.

Recent studies have focused on the role of serum calcium (Ca^{++}) levels in initial hematoma volume and HE. It has been suggested that a lower Ca^{++} level is associated with higher baseline hematoma volume, increased risk of HE, and worse outcome [8, 9]. In the context of ICH, Ca^{++} levels are directly involved with platelet function and in several steps of the coagulation cascade [10–12]. Therefore, patients with low Ca^{++} levels may have impaired hemostatic mechanisms [13, 14]. Serum Ca^{++} also seems to play a role in inducing arterial relaxation and secondary BP reduction through activation of perivascular receptors [15]. Therefore, lower levels of Ca^{++} may lead to HE through elevated BP [16]. In this review, we discuss the potential mechanisms that Ca^{++} may be involved with in the pathophysiology of cerebral HE.

Pathophysiology of Early HE

Understanding the pathophysiology of HE is one of the fundamental keys to developing an effective therapy for

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ICH [17]. The exact pathophysiology underlying HE is not fully elucidated. The "persistent bleeding" model suggests that the cerebral HE occurs through the continuous extravasation from the culprit vessel or vessels that initially rupture [18]. Active contrast extravasation observed in computed tomography angiography (spot sign) is reported in about one-third of patients scanned within the first three hours of presentation and has been associated with HE and increased mortality [19, 20]. The "avalanche" model proposes that the mechanical shear of surrounding vessels induced by the initial bleed results into multiple sequential ruptures that maintain bleeding [21]. There has been an association between irregular shapes of the hematoma and early HE, which might be due to multifocal bleeding sites [22]. It is also suggested that early HE occurs due to rebleeding into the necrotic tissue that forms acutely around the initial hematoma. Possible contributing factors include increased local tissue pressure and mechanical injury, diminished cerebral blood flow, local fibrinolytic effect, plasma protease induction, and secondary inflammatory response [23]. Secondary bleeding from arterioles and venules might be the result of increased intravascular hydrostatic pressure and the deposition of proinflammatory molecules with the destruction of the blood–brain barrier. Bleeding may then continue due to local coagulopathy and regional ischemic and mechanical injuries [3, 24].

Low Serum Ca^{++} Level and ICH

Ca^{++} plays a key role in many physiological functions including skeletal mineralization, muscle contraction, impulse transmission in neurons, hormone secretion, and the coagulation cascade [25]. In the blood and extracellular fluid, Ca^{++} is found in three forms. The most common Ca^{++} is the ionized or free-state (~51%) followed by protein-bound (~40%) and an anion-bound complex (~9%). Ionized Ca^{++} (iCa^{++}) is the only active form contributing to physiological processes [26]. Ca^{++} homeostasis is regulated by the action of parathyroid hormone (PTH), vitamin D metabolites, and calcitonin. PTH increases serum Ca^{++} directly by stimulating bone and renal Ca^{++} reabsorption. Also, PTH indirectly, through calcitriol (1,25-dihydroxy vitamin D3), increases gastrointestinal (GI) absorption of Ca^{++} [27]. Calcitonin by targeting the bone, kidney, and GI lowers serum Ca^{++} levels. Extracellular iCa^{++} regulates PTH secretion through interaction with calcium-sensing receptors (CaSRs) which are located at the surface of the parathyroid cells. An increase in extracellular Ca^{++} rapidly decreases PTH secretion and vice versa [28, 29]. Hypocalcemia may occur in patients of all ages with various etiologies. Differentiating acute from chronic hypocalcemia and severely symptomatic from asymptomatic is crucial for determining the appropriate treatment [30].

The incidence of low serum Ca^{++} level ranges from 24–26% in ischemic stroke [31–33] and 10–14% in ICH [8, 9]. Most studies have focused on total serum Ca^{++} levels rather than serum iCa^{++} levels, which is the physiologically active component [8, 9, 31–33]. Serum Ca^{++} has been associated with outcomes in both ischemic and hemorrhagic strokes (Table 1). Higher serum Ca^{++} on admission has been accompanied by lesser stroke severity, smaller cerebral infarct volume, and better functional outcome [31–33]. Furthermore, elevated admission serum Ca^{++} level has been associated with good outcomes at discharge and 3 months among acute ICH patients [34]. Conversely, lower serum Ca^{++} level has been significantly related to higher presence of cerebral micro-bleeds in ischemic stroke patients with atrial fibrillation and/or rheumatic heart disease [35]. Recent studies have shown that low serum Ca^{++} level at time of admission is accompanied by larger hematoma volume, HE, and worse outcomes in ICH [8, 9]. Inoue et al. [9] in a prospective study investigated the association between serum total Ca^{++} levels and hematoma volume. The results implied that low Ca^{++} levels at the time of admission were associated with larger hematoma volume and higher National Institutes of Health Stroke Scale scores among patients with ICH. Furthermore, Morotti et al. [8] carried out a retrospective cohort study on the association of serum total Ca^{++} levels and extent of bleeding in patients with ICH. In this study, lower Ca^{++} levels were independently associated with higher baseline hematoma volumes, and higher Ca^{++} levels were associated with decreased risk of HE. The observed results might be due to compromised coagulation cascade, increased BP, and platelet dysfunction as a result of low serum Ca^{++} level [8, 9]. However, hypocalcemia in critical patients might be a secondary phenomenon as a result of inflammatory responses and alterations in PTH–vitamin D axis following acute illness [36]. Low total Ca^{++} may also be a marker of chronic illness, due to low albumin or renal disease. From a clinical and therapeutic perspective, hematoma volume on admission and HE may be at least partly preventable and therefore could be an appealing target for several ICH therapeutic strategies [37]. Although optimizing Ca^{++} homeostasis could play a role in preventing HE in ICH, due to dysfunction in PTH–vitamin D axis in critical conditions such as ICH, low serum Ca^{++} level might be only a biomarker of the adaptive response or chronic illness and not a true pharmacological target.

Low Serum Ca^{++} Level and Coagulopathy in ICH

ICH complicated by coagulopathy is a medical emergency which can lead to a larger hematoma volume and increased risk of mortality. Immediate recognition

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

Authors	Year	Study type	Calcium type	Sample size	Stroke types	Outcomes	Outcomes
Morotti et al. [8]	2016	Retrospective cohort study	Serum total Ca^{++} (iCa^{++} in subgroup of patients)	2103	ICH	Baseline hematoma volume and hematoma expansion	Low Ca^{++} level was associated with higher baseline hematoma volume. Higher serum Ca^{++} level was associated with decreased risk of hematoma expansion
Inoue et al. [9]	2013	Prospective cohort study	Serum total Ca^{++}	273	ICH	Hematoma expansion and functional outcomes	Low serum Ca^{++} level at the time of admission was associated with larger hematoma volume and higher NIHSS score
You et al. [34]	2016	Prospective cohort study	Serum total Ca^{++}	365	ICH	Functional outcomes	Higher serum Ca^{++} level at the time of admission but not phosphate was positively associated with excellent outcome at discharge or 3 months after discharge
Ovbiagele et al. [31]	2008	Retrospective cohort study	Serum total Ca^{++} collected at early (< 4.5 h) and delayed (72–96 h) time	826	IS	Functional outcomes	Higher serum Ca^{++} level after 72–96 h from symptom onset predicted greater independence 3 months after ischemic stroke. Serum Ca^{++} level at early time had no prognostic significance
Liu et al. [35]	2016	Prospective cohort study	Serum total Ca^{++}	67	IS (cardioembolic)	Cerebral micro-bleeds (CMBs)	Lower serum Ca^{++} level independently associated with CMBs in stroke patients with atrial fibrillation and/or rheumatic heart disease
Guo et al. [48]	2015	Prospective cohort study	Serum total Ca^{++}	362	IS (systemic thrombolysis, IVT)	Hemorrhagic transformation after IVT	Lower serum Ca^{++} level on admission was associated with hemorrhagic transformation after IVT
Buck et al. [32]	2007	Prospective cohort study	Serum total Ca^{++}	173	IS	Initial diffusion-weighted magnetic resonance imaging (DWI) infarct volume	Elevated serum Ca^{++} level on admission was associated with smaller cerebral infarct volumes among patients with acute stroke

Ca^{++} calcium, *CMBs* cerebral micro-bleeds, *DWI* diffusion-weighted magnetic resonance imaging, *iCa^{++}* ionized calcium, *ICH* intracerebral hemorrhage, *IS* ischemic stroke, *IVT* intravenous thrombolysis, *NIHSS* National Institutes of Health Stroke Scale

of coagulopathy during ICH is crucial for correct and rapid treatment to reduce ongoing bleeding and improving survival rate [38, 39]. The interactions of the clotting factors with each other and with phospholipids require Ca^{++} at every step of the cascade. The formation of the fibrin clots, which are relatively resistant to plasma-mediated lysis, is the final stage of coagulation [14, 40, 41]. Clot stability might be affected by many factors, including local Ca^{++} concentration, blood pH, and platelet count [42]. Ca^{++} is a critical cofactor for the enzymes in the coagulation cascade and plays an integral role in the formation of fibrin, which is crucial in secondary hemostasis and the stabilization of the platelet plug [43]. Furthermore, the vitamin K-dependent clotting factors FII, FVII, FIX, and FX along with proteins C and S are negatively charged. The same is true for the membranous phospholipids. iCa^{++} acts as a bridge between these surfaces and coagulation factors at the damaged endothelium [44]. Required concentration of the Ca^{++} ions for many reactions in the coagulation cascade is far below the physiologic iCa^{++} concentration. The variation in serum Ca^{++} levels has little effect on individual factor activation. However, there is evidence that Ca^{++} concentration may have clinically relevant effects on coagulation under certain circumstances [45]. One study discovered that iCa^{++} had a concentration-dependent association effect with clot strength where decreased iCa^{++} levels were associated with reduced clot strength in thromboelastography measurements in patients with preexisting coagulopathies [46]. The results suggest that hypocalcemia may worsen an existing coagulopathy. In rodent models, hypocalcemia resulting from citrate infusion is found to be associated with prolonged blood clotting time and bleeding tendency [47]. Furthermore, previous studies [8, 48] have shown that low serum Ca^{++} on admission has been associated with hemorrhagic transformation of the ischemic stroke after intravenous thrombolysis, larger hematoma volume at presentation in ICH patients, and increased risk of HE. Even though one could postulate that a very low Ca^{++} in the local milieu would lead to coagulopathy and HE, it is unlikely that there is a significant deficiency of Ca^{++}, either acute or chronic, that might lead to impaired hemostasis. Although Ca^{++} is an integral part of various steps of the coagulation cascade, serum hypocalcemia has never been directly attributed to either a bleeding or thrombotic disorders in vivo, with the exception of massive transfusion for severe bleeding [43]. Massive blood transfusion may result in ionized hypocalcemia due to chelation of Ca^{++} by citrate-containing blood products since blood is anticoagulated with sodium citrate and citric acid. It chelates (binds to) circulating iCa^{++}, thereby reducing plasma iCa^{++} concentration [49]. Accordingly, it is difficult to explain etiologically spontaneous ICH or HE caused by mild-to-moderate low serum Ca^{++} level. Therefore, further studies specifically designed to investigate the role of low serum Ca^{++} level in coagulopathy affecting initial hematoma volume or its expansion is warranted.

Low Serum Ca^{++} Level and Platelet Dysfunction in ICH

Platelet aggregation at the sites of the disintegrated vasculature is essential for thrombosis, and reduced platelet activity has been associated with HE and worse functional outcomes at 3 months [50, 51]. Platelets have a key role in the hemostatic process, which protect the integrity of the vascular system at the site of injury. Bleeding stops as the result of a complex series of responses including contraction of the blood vessel wall, the formation of a platelet plug at the site of injury, conversion of fibrinogen to fibrin, and contraction of the clot [52, 53]. Platelets have several adhesion receptors and complex regulatory machinery allowing their response to a set of stimuli. There are several steps toward the formation of the platelet plug including adhesion, cytoskeletal reorganization, secretion, and amplification loops. These steps finally activate the fibrin receptor (GPIIb/GPIIIa). Platelet activation could be started by various agonists, including thromboxane A2 (TxA_2), sub-endothelial collagens, adenosine diphosphate released from activated platelets, and thrombin generated by the coagulation cascade. These agonists activate different platelet receptors, trigger different signaling pathways, and eventually increase the intracellular Ca^{++} concentration [54–56]. Ca^{++} is a common second messenger for most signaling pathways in platelets and plays an important role in activation and aggregation of the platelets and the thrombus formation [57]. Endogenous activation and exogenous activation of the platelet membrane receptors by the agonists lead to the influx of Ca^{++} into the platelets [58]. The increased concentration of free Ca^{++} results in structural and functional changes in the platelets. The shape of the platelet changes from a disk to a spiny sphere, the granules in the platelet are centralized, and their contents secreted during the platelet release reaction [59]. Also, the increased intracellular Ca^{++} activates phospholipase A_2, which releases arachidonic acid from membrane phospholipids. Then, cyclooxygenase 1 converts arachidonic acid to TxA_2, a potent platelet activator [60]. Formation of the platelet plug is the final step. This is mediated by activated GPIIb/GPIIIa binding to fibrin and von Willebrand factor at high affinity [61]. A decrease in cytosolic Ca^{++} concentration can compromise all platelet-related activities and the morphological change during activation. In fact, stable platelet incorporation into the developing thrombus needs intracellular

Ca^{++} mobilization [44, 62]. Nesbitt et al. [52] reported that chelating cytosolic Ca^{++} by pretreating platelets with a high-affinity Ca^{++} chelator completely eliminated Ca^{++} fluctuation in the primary adherent cells and consequently inhibited platelet aggregation and thrombus growth. This study demonstrated that the efficiency of intercellular Ca^{++} signaling plays a key role in regulating the rate and extent of thrombus growth. Therefore, low serum Ca^{++} level could be accompanied by platelet dysfunction and worse outcomes in ICH patients. Figure 1 is a cartoon representation of the role of Ca^{++} in hemostasis due to its effect on platelet activation and coagulation cascade.

Low Serum Ca^{++} Level and Higher BP in ICH

Hypertension (HTN) is the most common risk factor for ICH and is a predictor of outcome [6, 63]. HTN is associated with structural change in the vessel wall, abnormalities in blood cells, and abnormal blood flow, which may result in thrombotic and hemorrhagic events [64]. Regulation of the Ca^{++} homeostasis has a key role in HTN, and a dietary pattern rich in Ca^{++} has been shown to reduce BP [65, 66]. Ca^{++} is involved in a signaling pathway through CaSRs which is a G-protein-coupled receptor that senses the extracellular concentration of Ca^{++} [67]. The most important function of the CaSRs is to maintain systemic Ca^{++} homeostasis by regulating the levels of PTH. However, several studies suggested that the CaSRs might have a role in the regulation of vascular tone [68]. In the vasculature, CaSRs are expressed in perivascular nerves, vascular smooth muscle cells, and endothelial cells [69]. Activation of the endothelial CaSRs in the aortic segments of the mouse induces endothelium-dependent and endothelium-independent relaxations [70]. In normotensive rats, calcilytics (CaSRs antagonists) have shown to increase BP in the presence of parathyroid glands. This effect is probably not due to increased PTH since PTH, as well as the PTH-related peptide, reduces BP. However, it is probable that secretion of potent parathyroid hypertensive factors may be suppressed after activation of the CaSRs in parathyroid glands, thereby causing a reduction in BP. Furthermore, it has been reported that hypocalcemia can stimulate unidentified parathyroid hypertensive factor secretion in parathyroid gland organ cultures [71]. Activation of the CaSRs in juxtaglomerular cells can suppress the release of the renin and subsequently decrease the level of aldosterone and angiotensin II, thereby leading to a decrease in BP [72]. Correlation between serum Ca^{++} status and BP might be explained by the following mechanisms: (a) hormonal effects, including PTH, unidentified factors, and renin, (b) CaSRs-independent and CaSRs-dependent effects of the Ca^{++} on the vascular tone [71]. Therefore, low serum Ca++ level may lead to increased vascular tone and higher BP through hormonal factors, CaSRs-dependent and CaSRs-independent mechanisms.

However, in a large retrospective study by Morotti et al. [8], there were no associations between low serum Ca^{++} level at the time of admission and high BP. Furthermore, the volume of deep ICH, which is typically considered hypertensive bleed, was not related to low serum Ca^{++} level. The results of this study did not support the hypothesis that low serum Ca^{++} level affects the extent of bleeding through higher BP. Further studies are needed to clarify the correlation between low serum Ca^{++} level and BP in ICH patients.

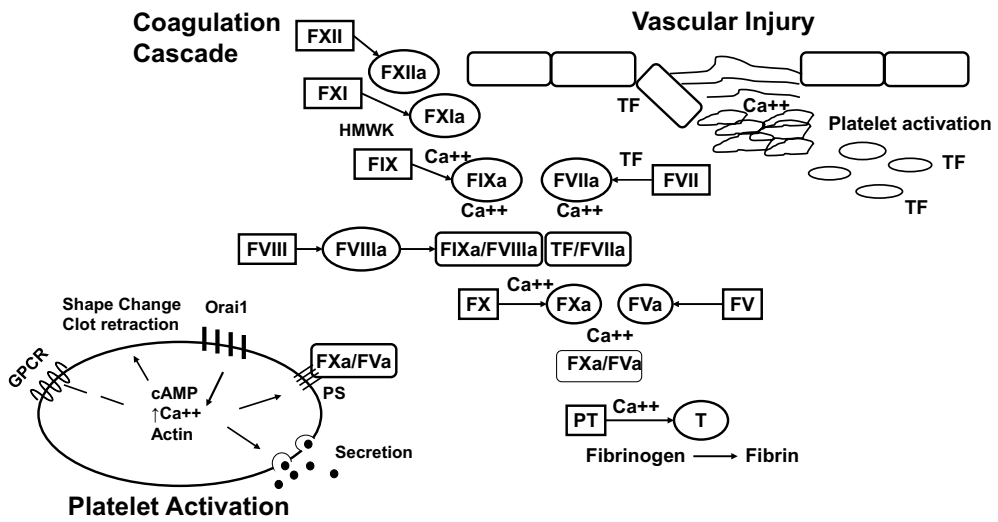

Fig. 1 Role of Ca^{++} in hemostasis

Low Serum Ca^{++} Level and Systemic Immune Response in ICH

Systemic immune response activation after ICH is manifested by increased levels of circulating cytokines, the major effector of systemic inflammation [73]. The clinical presentations of this process have been termed the systemic inflammatory response syndrome (SIRS), which is defined by the presence of 2 or more of the following criteria: leukopenia or leukocytosis, tachycardia, tachypnea, and hyperthermia or hypothermia. SIRS is a physiologic response to many acute illnesses and has been recognized as a risk factor for having poor outcomes in ICH patients, as well as ischemic stroke, subarachnoid hemorrhage, and non-neurologic illnesses [74–76]. True hypocalcemia is common in critically ill patients requiring intensive care unit admission and has been associated with SIRS and increased mortality [77–79]. In patients with acute stress disorders, the etiology of hypocalcemia is multifactorial. The proposed mechanisms are the catecholamine-mediated translocation of plasma Ca^{++} into tissues, disturbance in PTH secretion and function as well as vitamin D deficiency, transfusion of the citrated blood, alkalosis, and hypomagnesemia. However, in many other patients the etiology of hypocalcemia remains unclear; in one study, more than 50% of patients had no clear reason for hypocalcemia [36, 80–82]. Furthermore, an inflammatory process could increase the sensitivity of parathyroid cells by upregulating CaSRs expression and inducing hypocalcemia [83]. Ionized hypocalcemia triggers homeostatic responses to restore extracellular Ca^{++} by increasing secretion of PTH in the parathyroid glands to promote the release of Ca^{++} stored in bone. Also, PTH activates the renal formation of $1,25(OH)_2D_3$, which enhances Ca^{++} absorption from the gastrointestinal tract and Ca^{++} reabsorption by the kidneys. These calcitropic hormones increase L-type Ca^{++} channel activity in cell membranes leading to increased cytosolic free Ca^{++}, and subsequently, mitochondrial Ca^{++} overloading with organelle-based oxidative stress [84, 85]. Excessive cytosolic Ca^{++} leads to premature activation of intracellular enzymes, activation of ROS-generating enzymes, formation of free radicals, mitochondrial dysfunction, impaired autophagy, vacuolization, and necrosis [86, 87]. Thus, low serum Ca^{++} level could be a secondary phenomenon in acute ICH that represents the acute stress. Consequently, low serum Ca^{++} level could adversely affect the coagulation cascade, platelet function and may cause increased arterial vasculature tone and HTN.

Discussion

To date, studies that evaluated the association of the blood Ca^{++} and ICH outcome have focused on serum Ca^{++} at the time of admission without assessing the serum Ca^{++} status before hospitalization. Current studies indirectly support the hypothesis that a low Ca^{++} level in the hyperacute stage of ICH is an indicator of larger hematoma volume, HE, and more severe neurological deficit. Given the association described in the published studies and quickly modifiable nature of low serum Ca^{++} level, it could be a target for future therapy to improve the outcome after ICH. Acute therapy with Ca^{++} in the emergency room setting, or even a mobile stroke unit could be a potential modality for hyperacute therapy with Ca^{++} for a clinical trial. If there is any association between low serum Ca^{++} level with coagulopathy, BP, and platelet dysfunction, the serum Ca^{++} level can be rapidly corrected with a simple intervention to decrease the risk of the HE. However, even in this situation, there should be a limitation in administering Ca^{++}. Correcting Ca^{++} level should not exceed the normal range since previous studies have shown the association of the hypercalcemia with cerebral vasospasm and early neuronal death caused by NMDA receptor-mediated Ca^{2+} intracellular influx, which could worsen the possible perihematomal ischemia and the outcomes [88, 89]. However, we should be cautious in interpreting the outcomes of these studies since the association was established with just a one-time low serum Ca^{++} level value. There might be a more complex underlying pathophysiology, and low serum Ca^{++} level might be a secondary phenomenon and a biomarker of PTH–vitamin D axis dysfunction following acute immune response in ICH. Furthermore, while HE is present in about a 19–29% of ICH patients, low serum Ca^{++} level at admission has been reported in only 10–14% of ICH patients. Currently, serum total Ca^{++} level is measured as a routine diagnostic workup. Clinical practice regarding correction of Ca^{++} is currently heterogeneous with regards to timing, dosing, type of calcium supplementation, and monitoring. A prospective study assessing the prognostic value of iCa^{++} levels in ICH patients would be useful to provide more reliable information regarding the role of Ca^{++} in ICH expansion and outcomes. Even though low serum Ca^{++} level in ICH patients may be a primary or a secondary phenomenon, ICH patients are still likely to benefit from Ca^{++} correction if there is a true hypocalcemia, which may contribute to ICU morbidity via cardiac and neurological mechanisms.

Before implementing any change in the guidelines, these findings require more investigation into the mechanistic relationship between Ca^{++} levels and ICH that appear more complex than we realize. Since the iCa^{++} is the active physiologic component, future studies could incorporate serum iCa^{++} rather than serum total Ca^{++} into models and test for enhanced predictive power over existing models. The clinical benefit and therapeutic

time window for Ca^{++} level modification, as well as the Ca^{++} threshold level that is beneficial for ICH prevention, remain unknown, and further investigation of these issues is warranted.

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