Pakistan Journal of Neurological Sciences (PJNS)

Volume 16 | Issue 2 Article 5

6-2021

Association of Hypomagnesaemia & Hypocalcemia with Intracerebral Hemorrhage and Outcome

Muhammad Hassan
Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU) Islamabad

Naveed Ullah Khan
Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU) Islamabad

Mansoor Iqbal
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Haris Majid Rajput
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

Ehsan-Ur- Rehman
Shaheed Zulfiqar Ali Bhutto Medical University, PIMS, Islamabad, Pakistan

See next page for additional authors

Association of Hypomagnesaemia & Hypocalcemia with Intracerebral Hemorrhage and Outcome

Authors

Muhammad Hassan, Naveed Ullah Khan, Mansoor Iqbal, Haris Majid Rajput, Ehsan-Ur- Rehman, Waleed Shahzad, and Mazhar Badshah

ASSOCIATION OF HYPOMAGNESAEMIA & HYPOCALCEMIA WITH INTRACEREBRAL HEMORRHAGE AND OUTCOME

Muhammad Hassan[1,2], Naveed Ullah Khan[1,2], Mansoor Iqbal[1,3], Haris Majid Rajput[1,3], Ehsan-Ur-Rehman[1,2], Waleed Shahzad[1,2], Mazhar Badshah[1,4]

[1] Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad, Pakistan.
[2] Resident Neurologist, Department of Neurology, SZABMU.
[3]Assistant Professor, Department of Internal Medicine, SZABMU.
[4] Professor, Department of Neurology, SZABMU.

Correspondence: Dr. Muhammad Hassan *Department of Neurology, Shaheed Zulfiqar Ali Bhutto Medical University (SZABMU), Islamabad Email ID: drhassaanshafqat2011@gmail.com*

Date of submission; *January 22, 2021 April 06, 2021 April 13, 2021*

Abstract

OBJECTIVE: Determine if hypomagnesemia & hypocalcemia on admission was associated with ICH and outcome.

BACKGROUND: Magnesium is a vascular smooth muscle relaxant and appears to provide protection against cellular injury in experimental stroke models. The implication of low serum magnesium in primary ICH is not well defined.

DESIGN/METHODS: All patients with a primary ICH presented to PIMS, Islamabad prospectively analyzed in a pilot study. Demographics, initial lab values, ICH location, Mg+2 level, NIHSS & MRS at presentation were recorded. All patients with INR <= 1.5 were included in this study. We took normal serum magnesium in our study was 1.8 - 2.5 mEq/dL. Statistical significance was determined using linear regression adjusting for admission systolic blood pressure (SBP).

RESULTS: We identified 66 patients who met the inclusion criteria. The mean age was 52.76 years with minimum and maximum age was 25 and 80 years respectively. Total male and female patients were 40 (61%) and 26 (39.4%). The total number of patients with hypomagnesemia was 23 (30%) and with hypocalcemia was 54 (65%). All patients having hypomagnesemia (30%) also had subsequent hypocalcemia. Mean systolic Blood pressure (SBP) was 156.65 mmHg and 55patients (84.62%) presented with high SBP. All patients with hypomagnesemia presented with high SBP (p=0.001). Hypomagnesemia and hypocalcemia both were showed statically significant association with poor MRS & NIHSS score (p=0.013 and p=0.001). Hypomagnesemia was not showed statistically significant relation with the outcome (p=0.11) while hypocalcemia showed a remarkable association with outcome (p=0.001).

CONCLUSIONS: Hypomagnesemia and hypocalcemia were associated with higher admission ICH in patients with lower ICH severity. While the study was limited by small numbers so future studies are needed to determine if correction improves functional outcome in any targeted group of patients with ICH.
Keywords: Intracranial Hemorrhage (ICH); Magnesium (Mg+2); Calcium (Ca+2).

INTRODUCTION:

Spontaneous intracerebral hemorrhage (ICH) is one of the most catastrophic type of stroke, associated with high morbidity and mortality[(1)]. Magnesium is a vascular smooth muscle relaxant and appears to provide protection against cellular injury in experimental stroke models. The implication of low serum magnesium in primary ICH is not well defined. Magnesium plays a central role by the involving in cascade of coagulation of tissue factor VII, factor IX, and aggregation of platelets. In fact, magnesium may have a more potent effect on platelet aggregation than calcium. It was speculated that magnesium may have

implications for individuals with spontaneous ICH in platelets aggregation and coagulation. We were aiming to test the hypothesis that in spontaneous ICH patients, decreased plasma magnesium levels are related with ICH & functional outcomes.

In the recent past, along with hypomagnesemia, hypocalcemia also has been significantly associated with extent of bleeding in patients with intracerebral hemorrhage[(2-3)]. Low serum calcium, a cofactor

involved in coagulation and platelet activation, has been said to contribute to growth of hematoma in patients with ICH; there has been reports of association between low calcium level and hematoma size. As platelets function & coagulation cascade involves both elements, impaired hemostasis caused by hypocalcemia and hypomagnesemia may explain this association[4]. In addition, there has also been an association between the severity of aneurysmal subarachnoid hemorrhage with low serum magnesium and its related complications such as delayed cerebral ischemia[5], although conflicting results have been reported[6]. However, studies investigating this association in the context of intracranial hemorrhage and functional outcomes are limited.

MATERIAL AND METHODS:

A single-center, prospective, descriptive study, which was conducted at the Department of Neurology, PIMS hospital, Islamabad for period of 6 months (February 2018 to July 2018). A total of 66 patients were included in the study using consecutive, non-purposeful sampling technique. Patient's age was between 20 and 80 years and both genders were included. All the patients had a documented arterial hemorrhage on non-contrast CT scan which is documented by consultant radiologist and only those with an INR of ≤ 1.5 were selected for the study. All those patients who had an inconclusive neuroimaging, traumatic head injury, subarachnoid hemorrhage, venous hemorrhage, space occupying lesions, metabolic encephalopathy or those who were unwilling were excluded from the study. Normal Calcium (free serum calcium) & magnesium values were defined as 8.9 – 10.1mg/dl & 1.5 – 2.0 mg/dl respectively. Blood pressure in ER was recorded from previous mentioned BP on referral slip especially in those after 24 hours of onset of stroke. Data was analyzed with a statistical software SPSS version 24 (SPSS Inc. Chicago, IL USA). Discrete variables were listed as counts or percentages and continuous variables were listed as means ± SD. Chi-square test was used for univariate analysis of categorical variables. Significance was set at $p<0.05$.

RESULTS:

We studied a total of 66 patients with mean age of 52.76±14.5 ranging from 25 to 80 years presenting in Pakistan Institute of Medical Sciences, a tertiary care hospital in the heart of Pakistan: Islamabad. 60.6% (n=40) of the patients were male while 39.4% (n=26) were females. 23 patients (34.8%) with intracerebral hemorrhage at presentation were found to have low serum magnesium levels while 2 patients (3.03%) had a high serum magnesium level at presentation in ICH. The rest of the 41 patients (62.12%) had a normal serum magnesium level at the time of presentation with intracerebral hemorrhage as shown in figure no.1. All the patients with low serum magnesium levels at presentation had a high systolic blood pressure >140mmHg (p=<0.001). Among the 66 patients with ICH, 54 patients (81.8%) had a low serum calcium level, 2 patients (3.03%) had hypercalcemia while the rest of the 10 patients (15.15%) had normal serum calcium level as shown in figure no.2. Mean systolic blood pressure in our study was 156.65mm of Hg with 55 patients (83.33%) in the high blood pressure range, 9 patients (13.63%) in the normal range and 2 patients (3.03%) had a systolic blood pressure in the lower range. Higher and lower systolic blood pressure were defined as ≥140mm of Hg and ≤ 90mm of Hg.

All the patients presented to the Emergency department in no more than 7 days after the event: with 34 patients (51.52%) presenting within 24 hours of the event and the rest of the 16 patients (24.24%), 10 patients (15.15%) and 6 patients (9.09%) presenting within 36 hours, 72 hours, and 7 days respectively. Among our patients 48 patients (72.72%) were hypertensive, 28 patients (42.42%) were diabetic, and 6 patients (9.09%) were on anti-coagulation therapy previously because of associated comorbid like atrial fibrillation, metallic valve replacement or deep vein thrombosis. 15 patients (22.73%) had more than 2 risk factors i-e DM and HTN while 4 patients (6.06%) were diabetic, hypertensive and were on anti-coagulation. Intraparenchymal bleed was seen in 56 of our patients (84.85%), 4 patients (6.06%) had subarachnoid hemorrhage while 6 of our patients (9.09%) had brain stem bleed. 18 out of our 66 patients developed hydrocephalus amount which 16 had intraparenchymal bleed and 2 patients had brain stem bleed. Mortality was 39.39% (26 patients) among our 66 patients with in the first 7 days. MRS score at presentation among our patients is shows in figure no.4. Hypomagnesemia and hypocalcemia both showed statistically significant association with poor MRS (p=0.013). MRS and level of magnesium was showed in figure no.5. Hypomagnesemia did not show statistically significant relation with outcome i.e., death (p=0.11) while hypocalcemia showed a remarkable association with outcome (p=0.001).

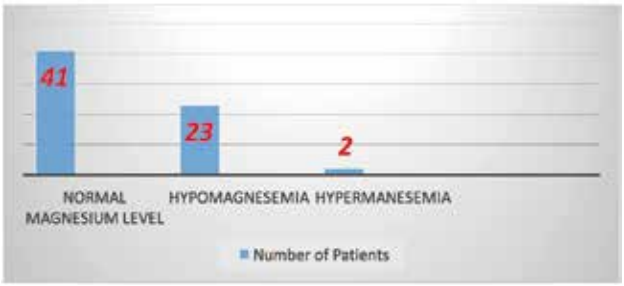

Figure No.1: ICH patients with level of magnesium

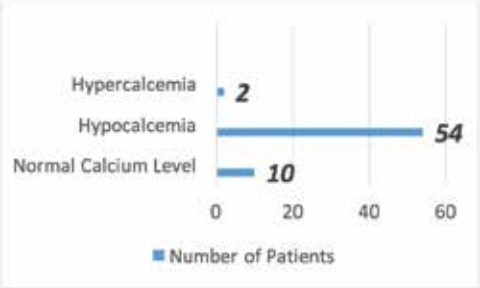

Figure No.2: ICH patients with Calcium Level

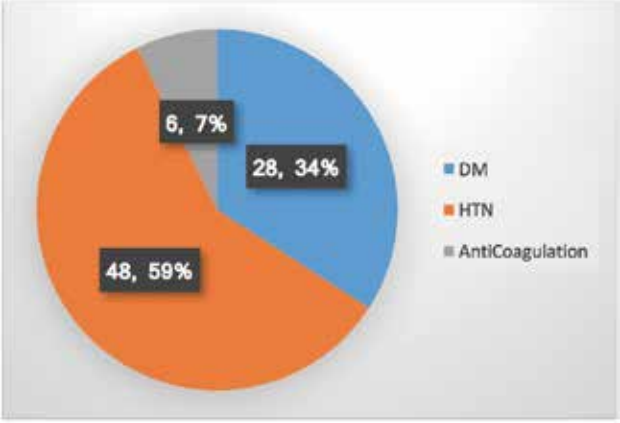

Figure No. 3: Patients Risk Factor

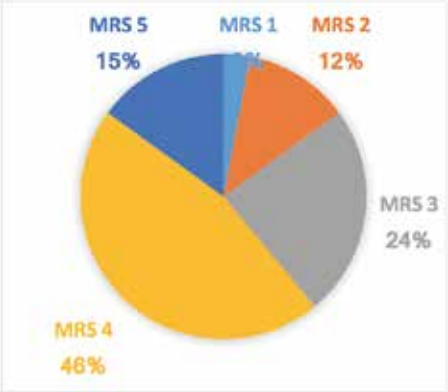

Figure no.4: Modified Rankin Score (MRS) at presentation in ICH patients

Magnesium Level with MRS

		MRS				
		1.00	2.00	3.00	4.00	Total
Magnesium Level	Normal	2	4	10	24	40
	Hypomagnesemia	0	4	2	14	20
	Hypermagnesemia	0	0	0	2	2
Total		2	8	12	40	62

Figure no.5: Modified Rankin Score (MRS) at presentation and magnesium level.

DISCUSSION:

Evidence exists in the literature showing an association between serum magnesium and calcium levels with new onset intracerebral hemorrhage or hematoma expansion[2]. Mechanisms through which this could be the possible cause is direct relation of calcium and magnesium with coagulation cascade and its effect on vascular smooth muscles, where hypocalcemia can cause vasoconstriction and elevated blood pressure[7]. There is a relationship between low admission serum calcium levels and larger hematoma volume among patients with acute intracerebral hemorrhage[8]. Similar findings were derived from another cohort study where low serum calcium levels were associated with intra cerebral hematoma expansion[2]. In this subgroup, patients with hypocalcemia (albumin-corrected calcium <8.4 mg/dL) had higher international normalized ratio values than non-hypo calcemic patients. Although the difference was not significant, the trend suggests that hypocalcemia-induced subtle alterations of the coagulation pathway may predispose aneurysms to increased risk of rupture. In our study we also found that a significant number of patients (81.8%; N=54 patients) had hypocalcemia at presentation.

In a randomized controlled trail, there was no improvement in the functional status of acute stroke patients after administration of magnesium, but in a recent observational study Liotta et. al.[3] found that lower magnesium serum levels at admission were associated with larger intracerebral hemorrhage volume, hematoma expansion and worse functional outcomes. As stated earlier that magnesium also plays a crucial role in the coagulation cascade, platelets activation and hemostasis, this may possibly support the hypothesis that magnesium may also have a pathophysiological role in intracranial aneurysmal rupture and intracerebral hemorrhage. Villa et al[7] also showed that magnesium is a crucial constituent of the blood coagulation cascade, and it potentiates coagulant activities of factor IX and rule of calcium.

In our study we concluded that lower serum magnesium and calcium were statistically significantly associated with poor MRS (P = 0.013). Our study also showed that serum magnesium levels at time of hospital admission were independently and inversely associated with patients presented with spontaneous ICH. Hypocalcemia is strongly statistically associated with ICH (p=0.001). Hypomagnesemia and Hypocalcemia both showed remarkable relation with the outcome of the patients. Furthermore, Hypocalcemia was also associated with worst

outcomes i.e., death (P=0.001). However, hypomagnesemia did not show any such significant association (P=0.11). It is requested for further research the need to extend this study into new phase as serum magnesium level and serum calcium level associated with initial hematoma volumes, final hematoma volumes, and hematoma growth on large cohort.

The main limitation on our study is that it was not designed to investigate potential pathophysiologic mechanisms of serum magnesium and calcium levels in ICH. We don't calculate relationship of electrolyte with volume expansion. Our study also represents a single center's observational experience and will need to be replicated. We didn`t find association between hypomagnesemia and volume expansion because of limited resources.

References

1. Qureshi AI, Mendelow AD, Hanley DF. Intracerebral hemorrhage. Lancet. 2009;373(9675):1632–1644.
2. Morotti A, Charidimou A, Phuah CL, Jessel MJ, Schwab K, Ayres AM et al. Association between serum calcium level and extent of bleeding in patients with intracerebral hemorrhage. JAMA Neurol. 2016; 73:1285–1290.
3. Liotta EM, Prabhakaran S, Sangha RS, Bush RA, Long AE, Trevick SA et al. Magnesium, hemostasis, and outcomes in patients with intracerebral hemorrhage. Neurology. 2017;89:813-819.
4. Vadivel K, Agah S, Messer AS, Cascio D, Bajaj MS, Krishnaswamy S, and et. al. Structural and functional studies of γ-carboxyglutamic acid domains of factor VIIa and activated protein C: role of magnesium at physiological calcium. J Mol Biol. 2013;425(11):1961-81.
5. Can A, Du R. Calcium, magnesium, and subarachnoid hemorrhage. Aging. 2018;10(9):2212.
6. Koide M, Nystoriak MA, Krishnamoorthy G, O'connor KP, Bonev AD, and et. al. Reduced Ca2+ spark activity after subarachnoid hemorrhage disables BK channel control of cerebral artery tone. J Cereb Blood Flow Metab. 2011;31(1):3-16.
7. Villa-Etchegoyen C, Lombarte M, Matamoros N, Belizán JM, Cormick G. Mechanisms involved in the relationship between low calcium intake and high blood pressure. Nutrients. 2019;11(5):1112.
8. Inoue Y, Miyashita F, Toyoda K, Minematsu K. Low serum calcium levels contribute to larger hematoma volume in acute intracerebral hemorrhage. Stroke. 2013;44:2004–6.

Conflict of interest: Author declares no conflict of interest.
Funding disclosure: Nil

Author's contribution:

Muhammad Hassan; Concept, data collection, manuscript writing, Data analysis, manuscript review
Naveed Ullah Khan; manuscript writing, manuscript review
Mansoor Iqbal Chaudhary; manuscript writing, manuscript review
Haris Majid Rajput; Manuscript writing, manuscript writing
Ehsan-Ur- Rehman; data collection, manuscript review
Waleed Shahzad; Data collection, manuscript review
Mazhar Badshah; Concept, manuscript review