IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 24, Issue 2 Ser. 6 (February. 2025), PP 22-25
www.iosrjournals.org

Association Of Hypocalcemia With Mortality And Morbidity In Patients With Moderate To Severe Traumatic Brain Injury

Author

Dr. Mahesh Kumar Agarwal Senior Resident MCh.Neurosurgery ,
Dr.Prateek Malpani, Dr.Yash Madnani , Dr.Rakesh Gupta , Dr.Zafar Sheikh ,
Dr.Paresh Sodhiya , Dr.Mukesh Sharma

Corresponding Author : Dr.Mahesh Kumar Agarwal
(maheshagarwal175@gmail.com)

Abstract

Background: *The present study has been conducted to assess whether hypocalcemia can be used as a prognostic factor in the outcome of traumatic brain injury.*

Materials and Methods: *This prospective study was done on 100 patients with moderate to severe traumatic brain injury. Serum calcium levels of patients had a Glasgow coma scale of 3–13 points following traumatic brain injury, with demonstrable intracranial lesions in cranial computed tomography were included. Student's t test, chi square test and Fisher's exact test were used for comparative analysis. Logistic regression and receiving operative curves analysis analysis were also done to assess the risk factors.*

Results: *Statistically significant difference were found in the Ca2+levels on the 3rd day of admission between the patients with GOS ≤3 and the patients with GOS>3 (P=0.029). The best level of higher sensitivity (86.27%) and specificity (68.66%) of hypocalcaemia on 3rd 2+ day was the Ca2+ value of 1.14 mmol/L.*

Conclusion: *The serum Ca levels on day 3 could be useful for the prediction of mortality and disability in patients with moderate to severe traumatic brain injury.*

Date of Submission: 21-02-2025 Date of Acceptance: 01-03-2025

I. Introduction

Traumatic brain injury (TBI), sometimes referred to as acquired brain injury, significantly increases death and lifetime impairment. Traumatic brain injury accounts for 25% to 30% of all accidental deaths and 27% of trauma-related hospital deaths (TBI). Each year, 1.5 to 2 million people are [1] injured and over a million people die in India. RTAs (60%) are the most common cause of TBIs, followed by falls (20%–25%) and violence (10%).Alcohol usage is recognised to be a confounding factor in 15%–20% of TBIs at the time of [2,3] injury. Around the world, 3.2 million people are thought to [4] be living with long-term disability brought on by TBI. Although there have been significant advancements in the field of TBI research, the number of outcome predictors are not huge in number. We still have to rely on the MRI findings to [5-7] evaluate the long term prognosis. Recent focus on various blood biomarkers in TBI has generated tremendous results. The present study has been conducted to assess whether hypocalcemia can be used as a prognostic factor in the outcome of traumatic brain injury.

II. Materials And Methods

Sampling This prospective study was done in a tertiary care hospital in north India. The ethical approval was obtained from the institutional ethical committee. A total of 100 patients who were 18-75 years old and had a Glasgow Coma Scale score of 3-13 following the TBI with demonstrable intracranial lesions in cranial computed tomography were include in the study. Patients with the following characteristics were excluded:TBI older as 3 days,intake of medications, conditions or diseases affecting calcium metabolism (such as hyperparathyroidism, acute pancreatitis, massive blood transfusion, and treatment with hydrochlorothiazide), multisystem trauma, exposed fracture,lacerated spleen,liver,great vessels or hypovolemic shock III–IV, lesions in the brainstem as an isolated finding, previous treatment in another clinic, pregnancy, hyperphosphatemia (>1.32 mmol/L), hypomagnesemia (<0.61 mmol/L), alcoholism, hypoalbuminemia at the hospitalary admittance and prior disability to TBI.

Methodology

The patients admitted to the emergency room were managed according to the Advanced Trauma Life Support guidelines. After stabilization, tests were conducted to measure hematic biometry, blood chemistry and serum electrolytes (sodium, potassium, calcium, and ionized calcium). Additionally, arterial blood gases were taken. To provide further care for the patients, a crystalloid solution, gastric protector, analgesic, and sedative (if needed) were administered. For intubation, propofol and rocuronium were used. At hospital admittance, the clinical variables included age, sex and pupillary reaction noted. Additionally, respiratory rate and heart rate, along with systolic blood pressure,diastolic blood pressure, and mean arterial pressure were measured. All the parameters were evaluated.

Statistical Analysis

The data was tabulated in Microsoft excel and analysed with SPSS v.24 software. The continuous variables are presented with mean and standard deviation.The categorical variables are presented with frequency and percentage.Student's t-test was used for the comparison of the continuous variables and Chi-squared test or Fisher's exact test were used for the comparison of the categorical variables. Logistic regression was used to identify the potential risk factors.Receiving operative curves (ROC) were also used to evaluatesensitivity, specificity, predicted positive value and negative predicted negative value for different points of clinical interest. The p value ≤ 0.05 is considered as statistically significant.

III. Results

Among the 100 patients, 54 had Glasgow Outcome Score (GOS) ≤3 and 46 had GOS>3. There were 64 males and 36 females with age ranging from 18-75 years. The demographic and clinical variables are presented in Table 1. There were statistically significant difference between the GOS≤3 and GOS>3 groups in terms of GCS at admission, GCS at discharge, mean arterial tension (mmHg), presence of anisocoria and pupillary reactivity ($p<0.05$) which can be noted as risk factors.

Table 1: Demographic And Clinical Variables

Parameters	GOS≤3 (n=54)	GOS>3 (n=46)	p value
Gender (male/female)	31/23	33/13	0.136
Age (years)	38.2 (18-72)	42.7 (20-75)	0.144
GCS at admittance	10.08±3.64	8.64±3.71	0.039
GCS at discharge	9.08±1.02	13.65±5.02	0.006
ICU days	24.02±14.21	21.25±13.07	0.377
Mean arterial tension (mmHg)	109.50±21.10	115.82±17.20	0.031
Cardiac frequency	110.46±31.33	109.30±31.37	0.914
Respiratory frequency	17.71±2.03	18.28±2.15	0.223
pH	7.40±0.07	7.37±0.05	0.183
pH day 3	7.45±0.08	7.42±0.09	0.207
Isocoria (%) Yes No	38/54 (70.4%) 16/54 (29.6%)	41/46 (89.1%) 5/46 (10.9%)	0.010
Pupillary reactivity (%) Yes No	29/54 (70.4%) 25/54 (29.6%)	37/46 (80.4%) 9/46 (19.6%)	0.004

Table 2 shows the difference in the blood parameters between the GOS≤3 and GOS>3 groups on three intervals which were day 0, day 3 and day 7. On the day 0, patients with GOS≤3 had higher total leukocytes count, potassium level and lower hematocrit, hemoglobin, sodium, calcium and glucose levels in comparison to the patients with GOS>3 but there were no statistically significant differences. On the day 3, patients with GOS≤3 had highertotal leukocytes count, haematocrit, haemoglobin and lower sodium, potassium, calcium and glucose levelsin comparison to the patients with GOS>3 and only the difference in the calcium level between the groups was statistically significant ($p<0.05$). On the day 7, patients with GOS≤3 had highertotal leukocytes count, haematocrit, haemoglobin, glucose and lower sodium, potassium, calcium levels in comparison to the patients with GOS>3 but there were no statistically significant differences.

Table 2: Blood parameters at day 0, day 3 and day 7

Days	Parameters	GOS≤3 (n=54)	GOS>3 (n=46)	p value
Day 0	Total leukocytes (×10^{3}/µL)	16.21±7.19	14.00±6.65	0.142
	Hematocrit (%)	40.99±8.54	45.58±10.12	0.660
	Hemoglobin (g/dL)	14.26±2.32	16.08±8.42	0.715
	Sodium (mmol/L)	140.45±6.40	141.46±5.17	0.508
	Potassium (mmol/L)	4.55±0.59	4.45±0.55	0.893
	Ca^{2+}ion (mmol/L)	1.30±0.30	1.34±0.14	0.544
	Glucose (mg/dL)	133.22±39.48	135.62±51.95	0.815
Day 3	Total leukocytes (×10^{3}/µL)	12.71±6.53	12.36±5.04	0.928
	Hematocrit (%)	37.34±6.68	34.64±7.69	0.278
	Hemoglobin (g/dL)	12.50±2.30	11.48±2.70	0.156
	Sodium (mmol/L)	141.46±7.87	142.62±8.33	0.319
	Potassium (mmol/L)	4.70±0.44	4.72±0.66	0.951
	Ca^{2+}ion (mmol/L)	1.07±0.14	1.13±0.08	0.029
	Glucose (mg/dL)	131.04±42.73	132.26±50.98	0.773
Day 7	Total leukocytes (×10^{3}/µL)	13.22±5.08	11.77±3.66	0.181
	Hematocrit (%)	36.84±6.79	33.86±8.16	0.392
	Hemoglobin (g/dL)	12.58±2.87	12.11±3.22	0.593
	Sodium (mmol/L)	138.80±9.02	140.41±6.91	0.664
	Potassium (mmol/L)	4.74±0.61	4.86±0.47	0.426
	Ca^{2+}ion (mmol/L)	1.36±0.07	1.40±0.23	0.514
	Glucose (mg/dL)	142.44±59.18	145.70±50.21	0.572

Table 3: Logistic Regression Model For The Patients With GOS ≤3

Parameters	Odds ratio	Lower 95%	Upper 95%	p value
Pupillary reactivity	8.2	2.07	46.11	<0.001
Hypocalcaemia (Ca^{2+}<1.14 mmol/L) on 3rd day	4.21	1.97	10.32	0.016

Logistic regression analysis for the GOS≤3 group showed that, pupillary reactivity and hypocalcemia or Ca2 <1.1 mmol/L on day 3 were the significantly potential risk factors with odds ratio of 8.2 (95%CI: 2.07-46.11) and 4.21 (95% CI:1.97-10.32) respectively (Table 3)

Table 4: Levels of Ca on 3 Day Of Clinical Importance

Serum ionized calcium on 3rd day (mmol/L)	Sensitivity (%)	Specificity (%)	Predicted Positive Value	Predicted Negative Value
1.32	0.02	100.00	1.00	0.43
1.14	86.27	68.66	0.74	0.73
1.09	97.43	26.71	0.70	0.79
0.98	100.00	16.28	0.63	1.00

The ROC analysis showed that, the best level of higher 2+ sensitivity (86.27%) and specificity (68.66%) of Ca on 3rd day was the value of 1.14 mmol/L. Other levels of clinical importance can also be seen in Table 4.

IV. Discussion

The results of the study found that the Ca values in serum on the third post traumatic day to be a prognostic factor for mortality and morbidity in moderate/severe TBI, with a level of significance (p=0.012).A similar result was seen the study done by Vinas-Rios et al demonstrating a significant difference for serum hypocalcemia at day 3 after TBI between [8] survivors and non survivors. Neuronal death leads to hypocalcemia that results in the development of cerebral edema. Patients with poor outcome had an impaired pupillary reactivity which was an indirect sign. Impaired pupillary reactivity is an important clinical sign for raised intracranial pressure with imminent risk of cerebral herniation/cerebral ischemia [9,10] correlating with bad prognosis. In the present study there was an association of hypocalcemia rd at 3 day in ionized calcium after moderate/severe TBI with bad outcome (GOS ≤3).A variety of mechanisms have been postulated to be involved in TBI such as neuroinflammation, neuronal hypoxia, loss of cerebral vessel autoregulation, and [11-14] brain edema with MRI as a reliable prognostic marker. Based on the level of hypocalcemia, there is significant

variation in the risk for the patient to die or suffer moderate/severe disability. A worst or poor outcome, defined as death or moderate/severe disability respectively, was 2+ evident in all patients with a level of Ca of 0.98 mmol/L or lower. In addition, our results demonstrated that 86.27% of patients had an unfavorable outcome, consisting of death or moderate/severe disability when the serum hypocalcemia level was lower than 1.14 mmol/L. The relationship of hypocalcemia with morbidity and mortality after TBI could be the diminution of Ca due tothe 2 + sudden influx of intracellular Ca . This can lead topostischemic neuronal damage.Rise of intracellular 2+ Ca plays a role in apoptotic processes due to inhibition of m it o c h o ndr i a l e n z y m a ti cpro c e s s e s a nd l ipa s e [15] activation. The proinflammatory proteins/molecules to 2+ which the Ca binds,are also elevated following trauma due to tissue hypo-oxygenation and increase of the catabolic and [1 1 , 1 6] pro inflammatory processes. The reason for the hypo-oxygenation can be the loss of cerebrovascular autoregulation, as a consequence of hypoxia and neuroinflammation. Various researched reported that that TBI c o m b i n e d w i t h h y p o x i a e n h a n c e s c e r e b r a l [14-16] cytokine production. Although the comparative analysis did not show significant difference in pupillary reactivity between the patients with GOS ≤3 and the patients with GOS >3,the logistic regression analysis found it to be a significant risk factor and established it as an important prognostic factor for mortality.

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