ORIGINAL ARTICLE

Hypocalcemia as a prognostic factor in mortality and morbidity in moderate and severe traumatic brain injury

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ABSTRACT

Objectives: Our main objective was to evaluate whether serum hypocalcaemia (defined as <2.1 mmol/L [8.5 mg/dL]) and ionized serum calcium (defined as <1.10 mmol/L [4.5 mg/dL]) is a prognostic factor for mortality and morbidity (defined as Glasgow outcome score [GOS] ≤3) in early moderate and severe traumatic brain injury (TBI).

Materials and Methods: We developed a retrospective study and evaluated clinical profiles from included patients from January 2004 to December 2012. Patients were between 16 and 87 years old and had a Glasgow coma scale of 3–13 points following TBI, with demonstrable intracranial lesions in cranial computed tomography.

Results: We found a significant statistical difference ($P < 0.008$) in the ionized serum calcium levels on the 3rd day of admission between the groups: GOS ≤3 and >3 (disability/death). According with the receiving operative curves analysis, we found that the best level of higher sensitivity (83.76%) and specificity (66.66%) of hypocalcaemia of serum ionized calcium on 3rd day was the value of 1.11 mmol/L, with an odds ratio value of 6.45 (confidence intervals 95%: 2.02–20.55).

Conclusions: The serum levels of ionized calcium on day 3 could be useful for the prediction of mortality and disability in patients with moderate and severe TBI.

Key words: Glasgow outcome score, hypocalcemia, ionized serum calcium, prognostic factor, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the most common disorders within the vast neurological field. The incidence of TBI in Germany is approximately 332 per 100,000, in comparison to 182 per 100,000 for strokes.[1] The effects from TBI can result in severe disability or death[2,3] and have an important social and economic impact.[4] Despite of advances in technology and increasing knowledge about its pathophysiology, there are few predictors for outcome after TBI, with magnetic resonance imaging (MRI) findings being the most important.[4,5]

Recent adoption of high throughput technologies and a change in focus from the identification of markers has fostered new optimism in this direction.[6]

Different markers have been studied, particularly bivalent cations as magnesium Mg (2^+) and calcium.[6-8]

Objective

Our objective was to evaluate whether serum hypocalcemia (defined as <2.1 mmol/L [8.5 mg/dL]) and hypocalcemia of ionized serum calcium (defined as <1.10 mmol/L [4.5 mg/dL]) is a prognostic factor for mortality and morbidity (defined as Glasgow outcome score [GOS] ≤3) in early moderate and severe TBI.

Materials and Methods

We developed a retrospective study evaluating clinical profiles from included patients from January 2004 to December 2012. Patients were between 16 and 87 years old and had

Access this article online

Quick Response Code:

Website: www.asianjns.org

DOI: 10.4103/1793-5482.161171

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a Glasgow coma scale (GCS) of 3–13 points following TBI, with demonstrable intracranial lesions in cranial computed tomography. The retrospective evaluated patients were included from the registries from the University Clinic Evangelisches Krankenhaus, Oldenburg, Germany.

Patients with the following characteristics were excluded:

- TBI older as 3 days
- Intake of medicaments, 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
- Prior disability to TBI.

Management and intervention

The patients were admitted to the emergency room and handled according to the guidelines of Advanced Trauma Life Support. Once the patients were stabilized, blood samples for hematic biometry, blood chemistry and serum electrolytes (sodium, potassium, calcium, ionized calcium), and arterial blood gases were taken.

The routine treatment included a crystalloid solution, gastric protector, analgesic and sedative in case of agitation. For intubation purposes, we used propofol plus rocuronium.

Clinical variables at hospital admittance consisted of age, sex, seizures, and pupillary reaction assessment. We measured respiratory and cardiac frequency, as well as, arterial systolic, diastolic, and mean arterial pressures.

Statistical analysis

We utilized the program JMP.[7-9] We completed an analysis of descriptive statistics, obtaining the measures of central tendency and dispersion of all the variables. For the comparative analysis, we used the Student's *t*-test for continuous variables with normal distribution and the Wilcoxon/Kruskal–Wallis test for continuous variables without normal distribution. For categorical variables, the Chi-squared test was applied and for tables with boxes <5, the Fisher's exact test was utilized. Statistical significance was considered with a value of $P < 0.05$. We calculated the odds ratio (OR) with of confidence intervals (CI) of 95%. We made an analysis of logistic regression with the variables that showed a significant difference ($P < 0.05$) in the bivariate analysis. In the final model, they were expressed with OR (CI 95%), as well as with multiple coefficient correlation R^2. We also made an analysis of receiving operative curves (ROC) in order to determine the level of higher sensitivity and specificity. There were calculated sensitivity, specificity, predicted positive value, and predicted negative value for different points of clinical interest.

Results

We compiled data from 99 patients with moderate and severe TBI that fulfilled the inclusion criteria with a median age of 42 years old (range: 16–87). From the studied patients, 67 (67.67%) were of male gender and 32 (32.32%) of female gender. Fifty-two (52.52%) patients had a GOS ≤3 and 47 (47.47%) had a GOS >3. The demographic and clinical variables, basal pH levels, and number of days in the intensive care unit are shown in Table 1.

After evaluation of the hospitalization variables, it could be seen that most of them did not show a significant difference, with the exception of GCS at the admittance (0.041), mean arterial pressure at admittance (0.018) and GCS at discharge (<0.001) known to be risk factors associated with poor prognosis. In our study, there were no differences in the demographic variables, basal pH levels, and number of days in the intensive care unit and days of intubation [Table 1], as well as in the blood cellularity measures and serum electrolyte levels at hospital admittance [Table 2]. Therefore, we consider the variables at the beginning of our study as nonhomogenous especially regarding GCS upon arrival. The GCS at the admittance was analyzed in each group separately due to the marked difference between the groups in order to avoid a statistical bias, mean arterial pressure, and Hemoglobin at day 3 was considered in the analysis of logistic regression as a potential confounding factor [Table 3].

Table 1: Demographic and clinical variables, basal pH levels, intubation days, and number of admittance days in the ICU

	GOS≤3 (*n*=52)	GOS>3 (*n*=47)	*P*
Gender (male/female)	32/20	35/12	0.167§
Age (years)†	36.5 (16-80)	45 (16-87)	0.079‡
GCS at admittance*	8.40±3.03	7.2±3.09	0.041‖
GCS at discharge*	10.07±0.85	14.71±4.17	<0.001
ICU days*	20.02±11.84	17.71±10.89	0.314‖
Mean arterial tension (mmHg)*	103.75±17.58	111.52±14.33	0.018‖
Cardiac frequency*	92.05±26.11	91.08±26.14	0.845‖
Respiratory frequency*	14.76±1.69	15.23±1.79	0.186‖
pH*	7.36±0.08	7.39±0.83	0.193‖
pH day 3*	7.39±0.06	7.41±0.05	0.159‖
Isocoria (%)			
Yes	47/52 (90.3)	35/46 (76.08)	
No	5/52 (9.6)	11/46 (26.9)	0.054¶
Pupillary reactivity (%)			
Yes	40/52 (76.9)	30/47 (63.8)	
No	12/52 (23.1)	17/47 (46.2)	0.152¶

§Fisher's exact test, †Median (ranges), ‡Wilcoxon ranges, *Mean±SD, ‖Student's *t*-test, ¶Chi-squared test. ICU – Intensive care unit; GOS – Glasgow outcome score; GCS – Glasgow coma scale; SD – Standard deviation

The comparison in the GCS at the discharge between groups is statistical significant ($P < 0.001$) this is explained because of the bad prognosis of the second group [Table 1].

We found a significant statistical difference ($P < 0.008$) in the ionized serum calcium levels on the 3rd day of admission between the groups: GOS ≤3 and >3 (disability/death) [Table 2]. In the serum sodium levels on the 7th day, we also found a statistical difference ($P < 0.047$) between groups [Table 2].

We calculated an OR of 6.6 (95% CI: 2.28–40.36) ($P < 0.009$) for the association of hypocalcemia of ionized serum calcium (<1.10 mmol/L) on 3rd day and the disability/death group.

The best logistic regression model included: Absent pupillary reactivity, hypocalcemia of ionized serum calcium (<1.10 mmol/L) on day 3, and serum sodium dysregulation on day 7. These variables substantiated poor GOSs in 28.08% ($R^2 = 0.2808$, $P < 0.002$) [Table 3].

In our model, we have attempted to analyze the studied variables in order to establish which of them influence the dependent variable, GOS.

It appears that in the included cases, pupillary reactivity, hypocalcemia of ionized serum calcium on day 3 and serum sodium dysregulation on day 7 following trauma were significant factors in our study. However, in comparison to our initial results, GCS at admittance (analyzed separately in each group in order to avoid a statistical bias as mentioned before), mean arterial pressure at admittance and hemoglobin at day 3 was nonsignificant and thereby potential confusing factors.

According with the ROC analysis, we found that the best level of higher sensitivity (83.76%) and specificity (66.66%) of ionized serum calcium on 3rd day was the value of 1.11 mmol/L), with an OR value of 6.45 (CI 95%: 2.02–20.55). Other levels of clinical importance can also be seen in Table 4.

Discussion

We found ionized calcium values in serum on the third posttraumatic day to be a prognostic factor for mortality and morbidity in moderate/severe TBI, with a level of significance of $P < 0.008$ in our study. A similar result was seen in our previous study demonstrating a significant difference for serum hypocalcemia at day 3 after TBI between survivors and nonsurvivors.[7]

The role of hypocalcemia in moderate/severe TBI still remains unclear. However, based on the initially proposed pathophysiological mechanism hypocalcemia could interfere with the development of cerebral edema due to neuronal death [Figure 1]. As an indirect sign patients with bad outcome had an impaired pupillary reactivity. The latter is a crucial clinical sign for intracranial elevated pressure with imminent risk of cerebral herniation/cerebral ischemia correlating with bad prognosis.[10,11]

Although the role of hypocalcemia is poorly understood, in our study there was an association of hypocalcemia at

Table 2: Chemistry variables and blood cellularity at 0 and 3 days

	GOS≤3 (*n*=52)	GOS>3 (*n*=47)	*P*
Day 0			
Total leukocytes (×10³/μL)*	13.51±5.99	11.67±5.54	0.118‖
Hematocrit (%)*	34.16±7.12	37.98±8.43	0.550‖
Hemoglobin (g/dL)*	11.88±1.93	13.40±7.02	0.596‖
Sodium (mmol/L)*	139.54±5.33	140.38±4.31	0.399‖
Potassium (mmol/L)*	3.79±0.49	3.71±0.46	0.90‖
Calcium (mmol/L)*	1.97±0.48	2.00±0.36	0.823‖
Ca⁺⁺ion (mmol/L)*	1.08±0.25	1.12±0.12	0.453‖
Glucose (mg/dL)*	136.02±32.90	138.02±43.29	0.880‖
Day 3			
Total leukocytes (×10³/μL)*	10.59±5.44	10.30±4.17	0.773‖
Hematocrit (%)*	31.12±5.57	28.87±6.41	0.065‖
Hemoglobin (g/dL)*	10.42±1.92	9.57±2.25	0.047‖
Sodium (mmol/L)*	142.05±6.56	143.85±6.94	0.189‖
Potassium (mmol/L)*	3.92±0.37	3.92±0.55	0.943‖
Calcium (mmol/L)*	2.03±0.22	1.92±0.12	0.069‖
Ca⁺⁺ion (mmol/L)*	1.09±0.12	1.15±0.06	0.008‖
Glucose (mg/dL)*	130.87±35.61	141.88±42.48	0.213‖
Day 7			
Total leukocytes (×10³/μL)*	11.02±4.23	9.81±3.05	0.151‖
Hematocrit (%)*	30.70±5.66	28.22±6.80	0.077‖
Hemoglobin (g/dL)*	10.48±2.39	10.09±2.68	0.494‖
Sodium (mmol/L)*	139.83±7.52	142.84±5.76	0.047‖
Potassium (mmol/L)*	3.95±0.51	4.05±0.39	0.355‖
Calcium (mmol/L)*	1.74±0.71	1.97±0.15	0.263‖
Ca⁺⁺ion (mmol/L)*	1.13±0.06	1.17±0.19	0.428‖
Glucose (mg/dL)*	143.70±49.32	140.58±41.84	0.790‖

*Mean±SD, ‖Student's *t*-test. SD – Standard deviation; GOS – Glasgow outcome score

Table 3: Logistic regression model: GOS≤3

Parameter	OR	Lower 95%	Upper 95%	*P*
Pupillary reactivity	7.1	1.34	51.4	0.01
Hypocalcaemia of serum ionized calcium (<1.10 mmol/L) on 3rd day	3.03	1.32	9.14	0.004
7th day serum sodium	1,18	1.05	1.35	0.002

OR – Odds ratio; GOS – Glasgow outcome score

Table 4: Levels of ionized serum calcium on 3rd day of clinical importance

Serum ionized calcium on 3rd day (mmol/L)	Sensitivity (%)	Specificity (%)	PPV*	PNV†
1.28	0.02	100	1	0.42
1.11	83.76	66.66	0.72	0.71
1.06	94.59	25.93	0.68	0.77
0.95	100	15.81	0.61	1

*PPV – predicted positive value; †PNV – predicted negative value; OR – Odds ratio

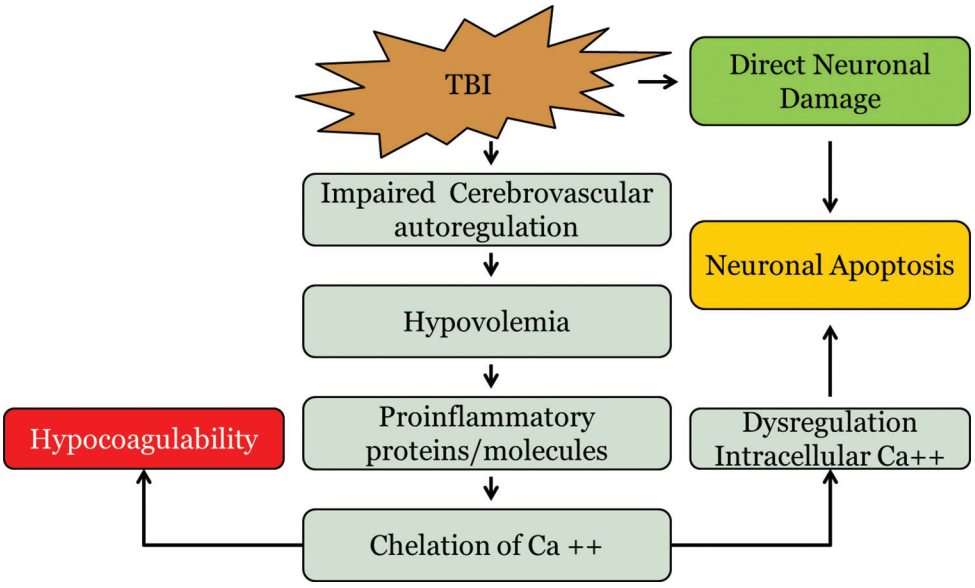

Figure 1: Proposed pathophysiological mechanism

3rd 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 brain edema with MRI as a reliable prognostic marker.[12-15] In the following their role in hypocalcemia following TBI will be discussed.

We described that depending on the level of hypocalcemia, the risk for the patient to die or suffer moderate/severe disability varies significantly. A worst or poor outcome, defined as death or moderate/severe disability respectively, was evident in all patients with a level of hypocalcemia of 0.95 mmol/L or lower. In addition, our results demonstrated that 83.76% of patients had an unfavorable outcome, consisting of death or moderate/severe disability when the serum hypocalcemia level was lower than 1.11 mmol/L.

The association of hypocalcemia with morbidity and mortality after TBI could be the diminution of ionized calcium due to the sudden influx of intracellular ionized calcium. This could induce neuronal postischemic damage.[16] As mentioned above an increase of intracellular calcium plays a role in apoptotic processes due to inhibition of mitochondrial enzymatic processes and lipase activation.[16]

Moreover, the chemical binding of ionized calcium to proinflammatory proteins/molecules might play a role. These are elevated following trauma due to tissue hypo-oxygenation and increase of the catabolic and proinflammatory processes.[12,17]

Secondary hypoxia after TBI promotes adverse outcomes in patients with TBI. One cause might be the loss of cerebrovascular autoregulation, as a consequence of hypoxia and neuroinflammation.[15,17] Different study groups discovered that TBI combined with hypoxia enhances cerebral cytokine production.[15-17]

At the beginning of our analysis, the GCS values at admittance demonstrated a significant difference between the groups of patients. Later according to the logistic regression analysis, the GCS at admittance was not significant in explain the difference between the group of patients in ionized serum calcium on day 3, becoming a confounding bias. Herewith GCS at admittance cannot be considered a significant determinator in our study.

The pupillary reactivity was not significant in the comparative analysis between patients with a GOS ≤3 and those with a GOS >3. Considering the fact that pupillary reactivity is a well-known and important clinical sign for highly elevated intracranial pressure and, therefore, a prognostic factor for outcome, we included it into our calculations.

We found pupillary reactivity to be significant in the final regression model, confirming its role as a crucial prognostic factor for mortality.

Retrospective data collection could limit the validity of our findings because of possible inherent bias. In our study, this possibly can be attributed to diverse primary clinical documentation or inconsistencies in data registration and the fact that data were collected by the first Author only (JMVR).

It is necessary to perform additional prospective and controlled studies with a larger population and a longer follow-up period in order to improve the statistical significance of the obtained data avoiding the possible source of bias such as missing information or discrepancies in patient's data.

Conclusion

As seen in our study, the serum levels of ionized calcium on day 3 as well as impaired pupillary reactivity are significantly associated with higher mortality and disability rates in patients with moderate and severe TBI. We believe that the value of ionized serum calcium of 1.11 mmol/L can be utilized as a reliable cut-off point.

Therefore, hypocalcemia should alert the treating physician and make him aware of the severity of the on-going pathophysiological process.

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How to cite this article: Manuel VRJ, Martin SA, Juan SRJ, Fernando MAL, Frerk M, Thomas K, *et al*. Hypocalcemia as a prognos! tic factor in mortality and morbidity in moderate and severe traumatic brain injury. Asian J Neurosurg 2015;10:190-4.

Source of Support: Nil, **Conflict of Interest:** None declared.