Relationship between Magnesium Concentration and Severity of Patients's Traumatic Brain Injury

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Abstract

Neuronal damage in traumatic brain injury is caused by primary injury at the time of the event and also delayed processes following the injury. Alterations in ion homeostasis have been implicated for the occurrence of this progressive secondary injury cascade. Magnesium is one of the most important ions that affect many metabolism in the CNS. Magnesium (Mg^{2+}) levels in the blood have been shown to be depressed for hours to days following head injury. The objective of this study is to define the relationship between levels of ionized magnesium concentration and severity of traumatic brain injury. Analysis of data was carried out through a retrospective review of medical records and based on a systematized database pertaining to patients with head injury treated in Neurosurgery ward Hasan Sadikin Hospital Bandung in March 2011– August 2011. A GCS score was assigned and blood sample was obtained within 24 h upon presentation. Patients were grouped into three categories: Group 1 (GCS 14-15), Group 2 (9-13) and Group 3(GCS<9), consisting of 18 patients each. There were 40 males and 14 females with average age of 32 years. Average levels of ionized Mg^{2+}in Group 1 were 2.12 mg/dL, p=0.0, CI=0.27 (0.14–0.40), Group 2=1.84 mg/dL, p=0.0, CI=0.47 (0.34–0.60) and Group 3=1.65 mg/dL, p=0.0, CI=0.19 (0.06–0.32). The conclusion of this study is that decrease in the serum magnesium (Mg^{2+}) concentration is considered to be related to the severity of the injury.

Keywords: magnesium, traumatic brain injury

Abbreviations used in this paper: CT = computerized tomography; TBI = traumatic brain injury; GCS = Glasgow Coma Scale; Mg^{2+}= magnesium; NMDA = n-methyl-D aspartate

Hubungan antara Konsentrasi Magnesium dengan Tingkat Keparahan Cedera Otak Traumatik pada Pasien dengan Cedera Kepala

Abstrak

Kerusakan neuron pada cedera otak traumatik disebabkan oleh cedera primer pada saat kejadian dan juga proses kerusakan yang timbul setelah kejadian trauma. Perubahan dalam hemostasis ion akan menyebabkan progresivitas dari kaskade mekanisme cedera sekunder. Magnesium adalah salah satu ion yang berperan penting mempengaruhi berbagai metabolisme dalam susunan sistem saraf pusat. Kadar magnesium (Mg^{2+}) dalam darah terbukti menurun beberapa jam sampai dengan hari sesudah terjadinya cedera otak traumatik. Tujuan penelitian ini adalah menentukan hubungan antara kadar ion magnesium dengan tingkat keparahan cedera otak traumatik. Analisis data retrospektif dilakukan berdasarkan rekam media pasien dengan diagnosis cedera kepala di bagian Bedah Saraf Rumah Sakit Hasan Sadikin Bandung selama 1 Maret–30 Agustus 2011. Pencatatan GCS dan pengambilan darah dalam 24 jam pertama. Pasien dikategorikan ke dalam tiga kelompok; Kelompok 1 (GCS 14-15), Kelompok 2 (9-13,) dan Kelompok 3 (GCS <9), yang masing – masing terdiri atas 18 pasien. Pasien terdiri atas 40 pria dan 14 wanita dengan umur rata–rata 32 tahun. Rata-rata kadar ion Mg^{2+} dalam kelompok 1 adalah 2,12 mg/dL, p=0,0, CI=0,27 (0,14–0,40), Kelompok 2= 1,84 mg/dL, p=0,0, CI = 0,47 (0,3–0,60,) dan Kelompok 3 = 1,65 mg/dL, p=0,0, CI = 0,19 (0,06–0,32). Kesimpulan penelitian adalah bahwa penurunan kadar magnesium (Mg^{2+}) serum mempunyai korelasi yang signifikan dengan tingkat keparahan cedera otak traumatik.

Kata kunci: *magnesium, cedera otak traumatik*

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Introduction

Traumatic brain injury (TBI) occurs when a sudden trauma causes damage to the brain. TBI affects people of all ages and manifests itself with high morbidity and mortality. Despite many studies on traumatic brain injury, few markers have been applicable to diagnose trauma at tissue concentration. Some of the neuronal damage in TBI is caused by primary or mechanical injury occurring at the time of the traumatic event. However, much of the damage also appears to involve secondary or delayed processes that are activated in the hours, days, or weeks following the injury. Several factors have been implicated in the occurrence of this progressive secondary injury cascade, including alterations in ion homeostasis.[1-,4]

Magnesium ion is gaining increasing recognition as a critical factor in neuronal cell function. The finding that magnesium ions mediate the gate n-methyl-D aspartate class of glutamate and the mitochondrial permeability transition pore has rekindled earlier enthusiasm for magnesium as an important regulator of central nervous system function.[2-5] A number of studies have supported a role for the level of

free magnesium in the brain as an important factor in the development of secondary traumatic and ischemic brain injury. The administration of magnesium after experimental TBI is neuroprotective and attenuates neuromotor dysfunction and cell death in the injured cortex.[2-5]

This study was undertaken to help address the significancy of magnesium in head injured patients. The study population consisted of 54 patients divided into three groups: mild, moderate and severe head injured patients.

Material and Methods

Patient Population

From March to August 2011, all head injured patients admitted to our institution, either diagnosed as mild, moderate or severe head injury caused by closed head injury, were examined and identified, and their medical records were retrospectively reviewed.

This study examined 1) whether serum ionized Mg^{2+} concentrations are reduced by traumatic brain injury (TBI); 2) whether the extent of reduction correlates with severity of trauma assessed by the Glasgow Coma Scale (GSC) score.

Data Collection

Inclusion criteria included patients between age 14 to 70 years with diagnosis of closed TBI treated in our department, whereas exclusion criteria were multiple trauma patients with AIS ≥ 3, GCS 3 after resuscitation and without head CT scan.

Patients' demographic, clinical, and neuroimaging data, including age, sex, admission GCS score, severity of head injury, and concentration of serum ionized Mg^{2+} were collected. Colorimetric method using COBAS INTEGRA 400 PLUS was used to measure serum ionized Mg^{2+}.

Statistical Analysis

Data were processed on a personal computer by using commercially available statistic software. The ANOVA test was used to compare severity of head injury and concentration of Magnesium in the blood. A probability value of less than 0.05 was considered statistically significant.

Result and Discussion

Result

The average age of the 54 patients was 32 years (ranging from 15 to 69 years old) and 22.49% of these patients were female. Figure 1 shows the average Mg^{2+} value of each of these groups. The mild head injury group had average 2.12 mg/dL, moderate head injury 1.84 mg/dL and severe head injury 1.65 mg/dL. Normal Mg^{2+} concentration is regarded about 1.8–3.0 mg/dL.

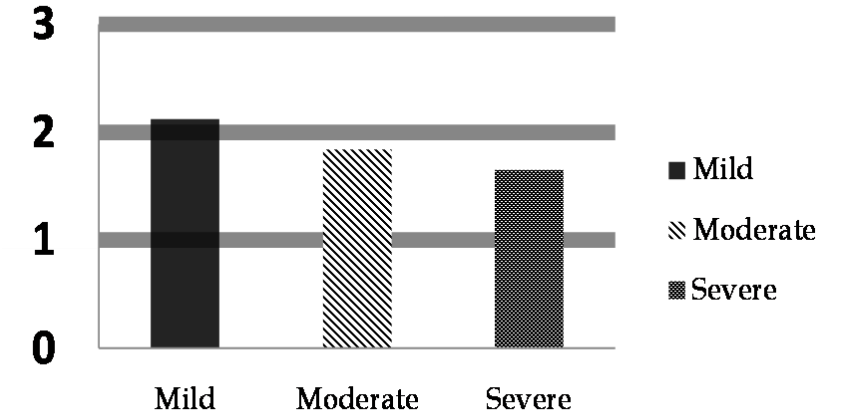

Figure 1. Average of Mg^{2+} Value in Each Group according to the Severity of Head Injury

Table 1. Statistical Analysis of Severity of Head Injury and Mg^{2+} Value between All Three Groups

ANOVA

Magnesium_Level

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2.035	2	1.018	26.510	.000
Within Groups	1.958	51	.038		
Total	3.993	53			

After processing data using commercial software, we found that the p value and confidence interval in each group consisted of Group 1 p=0.0, CI =0.27 (0.14–0.40), Group 2 p=0.0, CI =0.47 (0.34–0.60) and Group 3 p=0.0, CI = 0.19 (0.06–0.32). This shows a strong correlation between severity of head injury and Mg^{2+} value as shown on Table 1 and Table 2.

Table 2. Statistical Analysis of Severity of Head Injury and Mg^{2+} Value between All Three Groups

Multiple Comparisons

Magnesium Level

LSD

Head Injury	Head Injury	Mean Difference	Std. Error	Sig.	95% Confidence Interval Lower Bound	95% Confidence Interval Upper Bound
Mild	Moderate	.27611*	.06531	.000	.1450	.4072
	Severe	.47333*	.06531	.000	.3422	.6044
Moderate	Mild	-.27611*	.06531	.000	-.4072	-.1450
	Severe	.19722*	.06531	.004	.0661	.3283
Severe	Mild	-.47333*	.06531	.000	-.6044	-.3422
	Moderate	-.19722*	.06531	.004	-.3283	-.0661

*. The mean difference is significant at the 0.05 level.

Discussion

Magnesium is the major intracellular divalent cation. The concentration of magnesium in serum is closely regulated within the range of 1.8–3.0 Mg^{2+}/dL, of which 30% is protein-bound and another 15% is loosely attached to phosphate and other anions. Half of the 25 g (1.000 mmol) of total body magnesium is located in bone, only half of which is insoluble in the mineral phase.[3,5,6]

Magnesium is one of the most important ions in the CNS as it is a cofactor for approximately 325 enzymes in cells and is required for all ATP-consuming and producing reactions, including glycolysis, Krebs cycle activity and oxidative phosphorylation. Although this ion is localized primarily in the intracellular compartment, its presence in the extracellular compartment is also critical for its physiologic function and homeostatic functions, including regulation of neuromuscular and vascular tone, protein synthesis, DNA and RNA aggregation, maintenance of plasma membrane integrity and the noncompetitive blockade of the NMDA-receptor channel, thereby acting as a calcium antagonist. Because of its involvement in a number of bioenergetics and biochemical activities, magnesium appears to play an important role in normal neuronal activity. Furthermore, magnesium also seems to block the activation of NO-synthetase after cerebral injury and also acts as a potent antioxidant.[2,4,6,7]

The pathophysiology of TBI occurs in two phases, a primary phase and a

secondary phase. During the primary phase, there is localized neuronal death at the site of impact as a direct consequence of the biomechanical injury. During this phase, there is a decrease in cerebral blood flow, resulting in hypoxia and ischemia with an increase of brain oxidative metabolism. A shortage of glucose and an acute increase in energy demand results in anaerobic metabolism of glucose (hyper-glycolysis) and release of lactate. These exacerbate the effects of the primary physical insult. The primary phase activates the subsequent and irreversible secondary phase, with long-term effects. During this secondary phase, several imbalances in the biochemical homeostatic pathways and factors contribute to the cascade of events resulting in irreversible neuronal degeneration and death, distal to the injured site. As shown on Figure 2, excitotoxicity with excessive release of glutamate occurs and causes an overstimulation of the postsynaptic NMDA receptors that control the ionic channels. There is a failure of calcium homeostasis and a massive influx of sodium, calcium, and water, with delayed calcium deregulation. Ischemia due to increased ICP in the primary phase also adversely affects the secondary phase.[1,2,4,5,6,8]

Magnesium has an important role in homeostatic regulation of the pathways involved in the delayed secondary phase of brain injury. During normal physiological processes, magnesium is a non-competitive inhibitor of the NMDA receptors and it thereby regulates calcium influx. [5,8,9]

Divalent ion metabolism (calcium, phosphorus, and magnesium) following injury has not been studied as extensively as that of the monovalent ions (sodium, potassium and chloride). Difficulty in demonstrating a role for magnesium in secondary injury after trauma has been that, unlike calcium, measurement of magnesium concentration has been technically difficult and the available techniques largely inadequate.[2,4,5,12]

Several studies have also stated that experimental TBI causes an immediate substantial decline in brain intracellular free and total Mg^{2+} concentration that lasts for up to four days following TBI. Ionized and total Mg^{2+} has also been shown to be significantly lowered following TBI. In summary, studies have demonstrated that brain total and free magnesium concentration declines after trauma, with the intracellular free magnesium concentration falling by as much as 60 percent. Although the exact mechanism of action by which magnesium improves posttraumatic outcome is unknown, the fact that magnesium is a critical regulatory cation in such a large number of cellular functions dictates that any alteration in free ion concentration may have wide ranging consequences.[2]

Vink et al demonstrated 70% decline of intracellular free Mg^{2+} in the cortex of brain-injured rats within the first hour of injury, and non-recovery of the same over the next 3 hours.

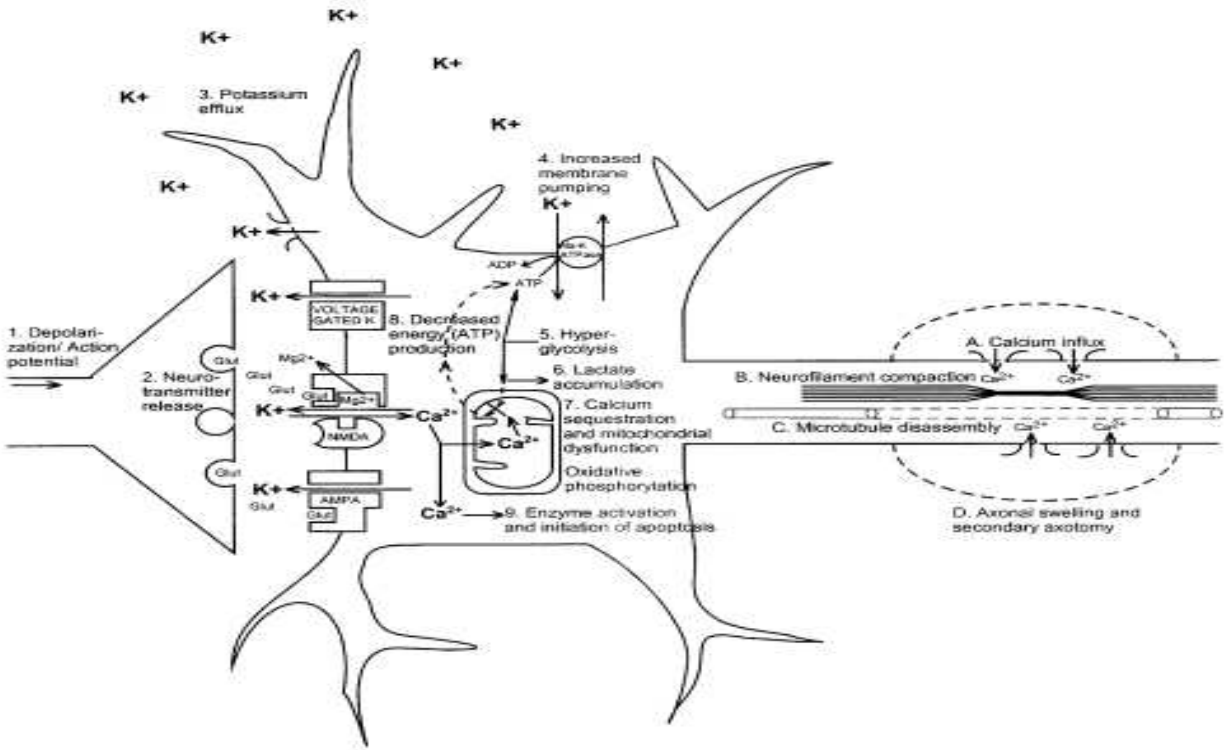

Figure 2. Magnesium Cascade after TBI.

(1) Intracellular magnesium levels fall after injury, resulting in loss of the voltage block on the NMDA receptor channel, allowing calcium influx. (2) Magnesium is a necessary cofactor for glycolitic and oxidative enzymes, and a decrease in the available Mg^{2+} inhibits both gycolisis and (3) oxidative phophorylation. (4) In turn, there is a decrease in the production of ATP and an overall reduction in the cell's bioenergetic state.[8]

They later demonstrated its correlation with functional outcome.[7,11] From our study we found that serum Mg^{2+}level correlated significantly with severity of head injury as compared in each group ($p < 0,05$). Mg^{2+}value was also significantly much lower in severe head injury group than in the rest. This finding is consistently the same as many of the studies mentioned above.

Trauma-induced decreases in brain magnesium have been associated with neurological motor dysfunction and restoration of magnesium homeostasis has therefore become a target for therapeutic interventions. Many studies have demonstrated that pre- or posttraumatic administration of magnesium chloride ($Mg^{2+}Cl2$) or magnesium sulfate ($Mg^{2+}SO4$) could restore brain free magnesium levels, attenuate brain edema, and improve both neurological and cognitive outcome in various models of experimental TBI.[2,9,10]

In addition to its impact on the bioenergetic state, it has been proposed that Mg^{2+} plays a pivotal role in determining the extent of excitotoxic damage following TBI. This has been shown consistently in many studies before.

Conclusion

Decrease in the serum Mg^{2+} concentration is considered to be related to the severity of the injury. We recommend that Mg^{2+} levels can be used to represent biochemical changes in head trauma to represent the extent of the injury. Further studies are needed to prove the efficacy of magnesium and also its vital role for therapy.

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