Original Article

Indian Journal of Neurotrauma (IJNT)
2005, Vol. 2, No. 2, pp. 103-106

Serum ionic magnesium in traumatic brain injury

SS Dhandapani MBBS, **Aditya Gupta** M Ch, **S Vivekanandhan***
AK Mahapatra M Ch, **VS Mehta** M Ch
Departments of Neurosurgery and Neuro-biochemistry*, Neurosciences centre,
All India Institute of Medical Sciences, New Delhi.

Abstract: Magnesium is an important ion in the body milieu, being a component of several enzymatic processes in the intra- and extracellular compartments. We have compared serum ionic magnesium levels between patients of severe closed traumatic brain injury and normal volunteers, so as to correlate the magnesium levels to severity of head injury. The study was carried out on fifty four patients of closed head injury with GCS 5-8. Biochemical analysis of serum for ionic magnesium was done at admission. The test was also performed on 20 normal volunteers and the results were studied for significant differences. Magnesium levels were compared between various subgroups defined by age, sex, admission interval, alcohol dependence, GCS, CT findings and appropriate statistical analyses done. Serum ionic magnesium levels in patients of severe head injury were in the range 0.15 to 0.45 mmol/ L (Mean 0.37 mmol/ L) as compared with control range 0.4 to 0.6 mmol/ L (Mean 0.44 mmol/ L) which was statistically significant. Additionally it was found that patients presenting earlier than 6 hrs had significantly lower serum ionic magnesium levels compared with those presenting later. Other subgroup differences were not statistically significant. Admission serum ionic magnesium levels of patients with severe closed TBI appear to be significantly lower than those of normal controls, more so within the first 6 hours after injury.

Keywords: brain injury, Glasgow Coma Scale, head injury, serum magnesium,

INTRODUCTION

Traumatic brain injury (TBI) remains the biggest killer of individuals under 50 yrs of age[1]. In the last two decades, it has become clear that the effects of the traumatic event are not all instantaneous, but a substantial component of neuronal cell death resulting from the primary injury may begin hours later, with the primary injury initiating a secondary injury cascade made up of deleterious pathophysiological and biochemical reactions[2]. The delayed development of secondary injury creates an opportunity for therapeutic intervention and considerable effort is being directed toward identifying the secondary injury factors and developing interventions that may potentially prevent their actions. Despite many research studies on TBI, few markers have been applicable to diagnose trauma at tissue concentration. Serum magnesium alterations in TBI have been scarcely studied, but may have important implications related to the cytotoxic and reperfusion injury pathway of secondary brain damage[1,2]. We carried this study to compare serum ionic magnesium levels in patients of severe closed TBI at admission and normal volunteers and to identify factors that may be associated with altered serum magnesium levels.

Address for correspondence: Dr. Aditya Gupta M Ch, Assistant Professor, Dept. of Neurosurgery, AIIMS, New Delhi -110029.
Ph: (011) 26588700 Extn. 4914
Email: adityagupta71@gmail.com
Awarded Best paper award at the 14th National Neurotrauma Conference, Kolkata : 20 Aug 2005.

METHODS

Fifty four patients of severe head injury admitted under the Neurosurgical department of All India Institute of Medical Sciences, from Jan to Dec, 2004, fulfilling the following criteria were taken up for the study.

Inclusion criteria:

1. Closed TBI
2. Glasgow coma scale (GCS) 5,6,7 and 8
3. Age 18 to 60
4. Admitted within 12 hours of injury

Exclusion criteria:

1. Hypotension [Systolic BP 90 mmHg] for 10 min
2. Bilateral absent pupillary light reflex
3. Blood urea more than 50 mg/ dL
4. Significant multiorgan injury

The serum samples were analyzed for ionic magnesium (Mg^{2+}) on critical care analyzer (Nova biomedical corps, USA) using Mg^{2+} ion selective electrode with neutral carrier ionophores. Other routine biochemical parameters were also analyzed. The test was also performed on 20 normal

volunteers to arrive at a control range. The clinical and radiological data of patients were collected prospectively. Magnesium levels were compared between control population and head injury patients. Comparisons were also done among various subgroups defined by age, sex, admission interval, alcohol dependence, GCS, and Computed tomography (CT) findings.

Statistical analysis

SPSS software (version 10) was used for statistical analysis. The mean magnesium levels were compared among various groups using the independent-samples T test. Numeric variables were analyzed using the Pearson correlation coefficient. Categorical data was analyzed with Chi-square test. Two sided significance tests were used throughout and the significance level was kept at $P< 0.05$.

RESULTS

Admission serum ionic magnesium levels in patients of severe closed head injury were in the range 0.15 to 0.45 mmol/ L (Mean 0.37, SD +0.04 mmol/ L) as compared with the control range 0.4 to 0.6 mmol/ L (Mean 0.44, SD +0.05 mmol/ L). The difference was found to be statistically significant ($p< 0.001$).

The Pearson correlation coefficient between age and serum ionic magnesium levels in the TBI group was -0.17 and it was not statistically significant (P=0.22).

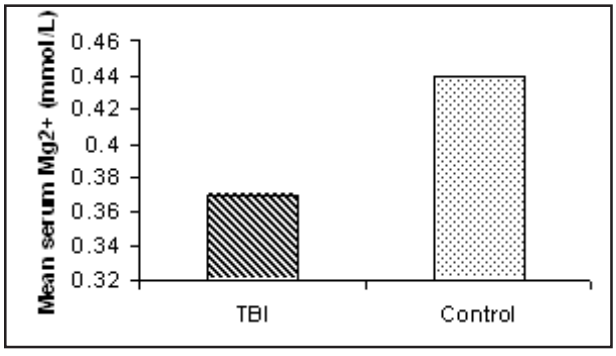

FIGURE 1: Magnesium in TBI and control

Female head injury patients had significantly lower serum ionic magnesium levels (Mean 0.32 mmol/ L) as compared to male head injury patients (Mean 0.38 mmol/ L) ($p=0.004$).

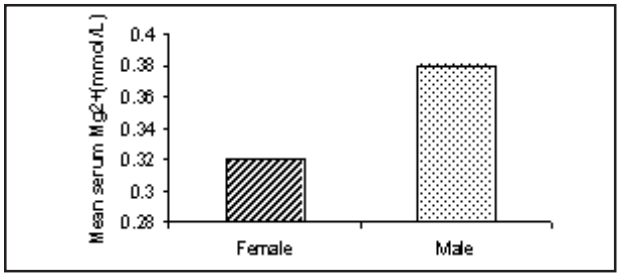

FIGURE 2: Sex difference

Hypomagnesaemia (Ionic $Mg^{2+} < 0.4$ mmol/ L) was noted in 28 out of 34 patients (82.4%) who had presented earlier (< 6 hrs), but only in 9 out of 20 (45%) who had presented later ($p=0.004$).

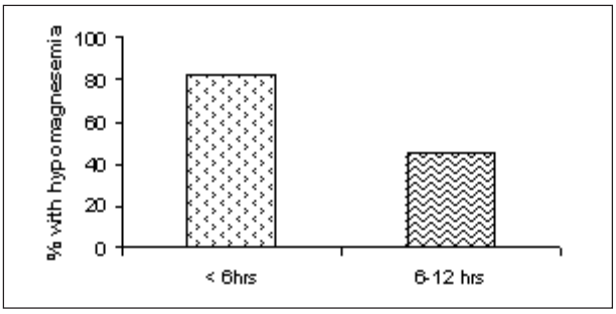

FIGURE 3: Admission interval and hypomagnesaemia

Table 1. Alcohol dependence and Mg^{2+}

Alcohol dependence	Mean serum Mg^{2+} mmol/ L	N
No	.37	41
Yes	.38	13

Table 2. GCS and Mg^{2+}

GCS	Mean serum Mg^{2+} mmol/ L	N
5	.39	11
6	.39	9
7	.37	18
8	.37	16

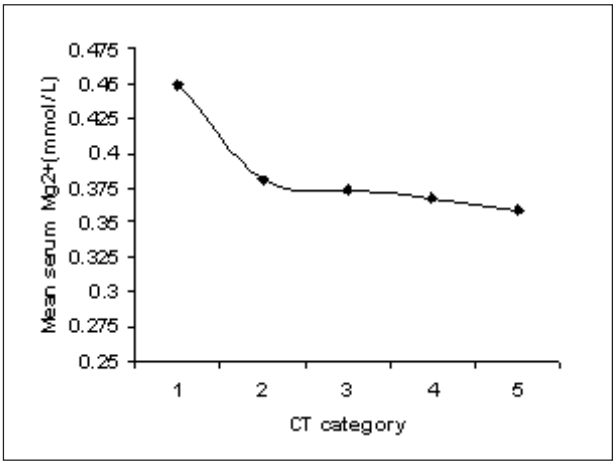

FIGURE 4 : CT category and Mg^{2+}

The relationship between ionic magnesium levels and alcohol dependence, GCS, CT category (TCDB)[3] are as follows, none of which were statistically significant.

Discussion

Magnesium is the second most abundant intracellular cation[4] and the fourth most abundant cation in the body and is present in more than 300 enzymatic systems[5], crucial for ATP metabolism and protein synthesis and is also an essential transmembrane and intracellular modulator of electrical activity. Magnesium concentration affects a number of secondary injury factors including neurotransmitter release, ion changes, oxidative stress, protein synthesis, and energy metabolism[6].

Vink *et al* demonstrated 70% decline of intracellular free magnesium in the cortex of brain-injured rats, using ^{31}P MRS, within the first hour of injury and non-recovery of the same over the next three hours[7]. They later demonstrated its correlation with functional outcome[8]. In a small group of patients with severe TBI, plasma total magnesium was found to be low[9]. Parallel reduction in free ionized magnesium has been found in animal[10] and human[11] studies which correlated with the outcome[10] and severity[11]. This is most likely due to enhanced glucose metabolism[12,13] and can also be due to urinary losses[9]. Supporting experimental studies have also demonstrated that inducing a brain magnesium deficiency prior to injury exacerbates the functional deficits and that attenuating the post-traumatic decline attenuates the functional deficits after TBI[14].

Mendez *et al* in their study of children with head injury found sustained decrease of total magnesium levels in all subgroups of head injury, whereas ionic magnesium levels were low only in patients of severe TBI which got normalized by 24 hours, thereby suggesting ionic magnesium as a biochemical marker of severe TBI and mechanisms in restoring their blood levels[15].

The key role of magnesium in TBI is due to NMDA receptor noncompetitive blockade as described in detail in animal experiments by Johnson *et al*[16]. Though NMDA blockade is the most plausible mechanism of its action in TBI, other possible mechanisms are calcium channel antagonism[17], inhibition of glutamate release[18], maintenance of CBF[19], suppression of apoptosis[1], and âAPP upregulation[2]. They act together or in isolation to attenuate excitotoxic secondary axotomy[2], inhibit traumatic vasospasm[19], suppress vasogenic and cytotoxic edema[20] and as the ultimate result probably provide neuroprotection.

Our study shows significant reduction of serum ionic magnesium in severe TBI (0.37 mmol/ L) as compared with control (0.44 mmol/ L), which was more so within the first 6 hours after trauma. We could not detect any other significant correlation possibly due to small number of patients and narrow inclusion criteria.

Further studies are required to confirm the findings of the present study and to elucidate causes of hypomagnesaemia in TBI and mechanisms involved in maintaining their blood levels. Considering the crucial role of magnesium, its fall in TBI patients and its low cost, it could be a candidate for trial as a neuroprotective agent in the unsolved mystery of TBI for years to come.

CONCLUSION

Admission serum ionic magnesium levels of patients with severe closed TBI appear to be significantly lower than those of normal controls, more so within the first 6 hours after injury.

REFERENCES

1. Vink R, Nimmo AJ, Cernak I. An overview of new and novel pharmacotherapies for use in Traumatic Brain Injury. *J Exp Pharm Phy* 2001; 28:919-21.
2. Reilly PL. Brain injury: the pathophysiology of the first hours. 'Talk and Die revisited'. *J Clin Neurosci* 2001; 8:398-403.
3. Marshall LF, Marshall SB, Klauber MR: A new classification of head injury based on computerized tomography. *J Neurosurg* 1991:75 (Suppl):S14-S20
4. Kaye P, O'Sullivan I .The role of magnesium in the emergency department. *Emerg Med J* 2002; 19: 288-91.
5. Fox C, Ramsoomair D, Carter C. Magnesium: Its proven and potential clinical significance. *South Med J* 2001; 94:1195-201.
6. Ozgurtas T, Kahraman S. State of the art of new data on the role of magnesium in brain injury: clinical interest of measurements of total and ionized magnesium. *Magnes Res.* 2004; 17:327-34.
7. Vink R, McIntosh TK, Demediuk P, Faden AI. Decrease in total and free magnesium concentration following traumatic brain injury in rats. *Biochem Bioph Res Comm* 1987; 149: 594-9.
8. Vink R, McIntosh TK, Demediuk P, Weiner MW. Decline in intracellular free magnesium is associated with irreversible brain injury following brain trauma. *J Biol Chem* 1988; 263:757-61.
9. Polderman KH, Bloemers FW, Peerdeman SM, Girbes AR. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med* 2000; 28:2022-5.
10. Bareyre FM, Saatman KE, Helfaer MA, Sinson G, Weisser JD, Brown AL, McIntosh TK. Alterations in ionized and total blood magnesium after experimental traumatic brain injury: relationship to neurobehavioral outcome and neuroprotective efficacy of magnesium chloride. *J Neurochem* 1999; 73:271-80.

11. Memon ZI, Altura BT, Benjamin JL, Cracco RQ, Altura BM. Predictive value of serum ionized but not total magnesium levels in head injuries.
Scand J Clin Lab Invest 1995; 55: 671-7.

12. Andersen BJ, Marmarou A. Post-traumatic selective stimulation of glycolysis.
Brain Res 1992; 585:184-9.

13. Kuroda Y, Inglis FM, Miller JD, McCulloch J, Graham DI, Bullock R. Transient glucose hypermetabolism after acute subdural hematoma in the rat.
J Neurosurg 1992; 76:471-7.

14. McIntosh TK, Faden AI, Yamakami I, Vink R. Magnesium deficiency exacerbates and pretreatment improves outcome following traumatic brain injury in rats: ^{31}P magnetic resonance spectroscopy and other studies.
J Neurotrauma 1988; 5:17-31.

15. Mendez DR, Corbett R, Macias C, Laptook A. Total and ionized plasma magnesium concentrations in children after traumatic brain injury.
Pediatr Res 2005; 57:347-52.

16. Johnson JW, Ascher P. Voltage-dependent block by intracellular Mg2+ of N-methyl-D-aspartate-activated channels.
Biophys J 1990; 57:1085–90.

17. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker.
Am Heart J 1984; 108:188 –93.

18. Smith DAS, Connick JH, Stone TW. Effect of changing extracellular levels of magnesium on spontaneous activity and glutamate release in the mouse neocortical slice. *Br J Pharmacol* 1989; 97: 475– 82.

19. Chi OZ, Pollak P, Weiss HR. Effects of magnesium sulfate and nifedipine on regional cerebral blood flow during middle cerebral artery ligation in the rat.
Arch Int Pharmacodyn Ther 1990; 304:196 –205.

20. Okiyama K, Smith DH, Gennarelli TA, Simon RP, Leach M, McIntosh TK. The Sodium channel blocker and glutamate release inhibitor BW1003C87 and Magnesium attenuate regional cerebral edema following experimental brain injury in the rat.
J Neurochem 1995; 64:802-9.