



The role of serum magnesium level and RBC magnesium level in migraine: a case-control study

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ABSTRACT

Magnesium has a crucial contribution in the pathogenesis of migraine. Low magnesium level has been detected in patients with migraine. The RBC magnesium assay is a good method to assess for deficiency. Aim of the present study is to find the role of magnesium in patients with migraine and to study the correlation between serum and RBC magnesium levels in case and control group. It is a prospective case control study done in 20 healthy volunteers and in 20 patients with migraine diagnosed on the basis of International Headache Society (IHS) criteria. The mean serum and RBC magnesium levels in patients with migraine was found to be significantly lower than that of the control group. The RBC magnesium levels were lower even when the serum magnesium levels were near normal in patients with migraine. Magnesium deficiency is a precipitating factor for migraine and prophylactic administration of magnesium will be an effective option to reduce the frequency of migraine attacks.

Keywords: Migraine, Serum Magnesium level, RBC Magnesium level, headache

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INTRODUCTION

Magnesium is an important intracellular cation, playing a critical role in various physiologic processes. Magnesium has a crucial contribution in the pathogenesis of migraine by causing variations in neurotransmitter release, increasing cortical spreading depression and platelet hyperaggregation. Magnesium is a key factor for the functioning of sodium potassium ATPase, glucose metabolism and cellular cytoskeleton contraction[1].

Magnesium metabolism is closely linked with that of calcium. Calcium magnesium sensing receptor located in the parathyroid hormone secreting cells of the parathyroid gland acts by sensing the levels of ionized calcium and magnesium, thereby controlling the release of parathyroid hormone[2][3].

Serum levels of magnesium do not accurately reflect total body stores of magnesium [4]. Therefore patients who actually have low ionized or free magnesium levels may have normal serum levels. Urinary fractional excretion of magnesium and the magnesium load test are more better tests to assess total body magnesium levels. The RBC Magnesium levels are more specific and an early indicator of magnesium deficiency compared to serum magnesium levels. When serum magnesium levels are low, the intracellular magnesium is released into the blood to maintain the serum levels. Hence the serum magnesium levels will be normal but the RBC magnesium will give a more accurate result. Therefore, given its commercial availability, the RBC magnesium assay may be a good way of assessing for deficiency [5][6].

The currently accepted theory explaining the pathogenesis of migraine is based on the hyperexcitable ‘trigeminovascular complex’ in patients who are genetically predisposed to migraine. Calcitonin gene-related peptide (CGRP) and substance P are released by this complex when migraine is triggered leading to vasodilation, mast cell degranulation, increased vascular permeability and blood vessel oedema and meningeal neurogenic inflammation. This stimulates the trigeminal nerve which transmits the signals to brainstem trigeminal nucleus caudalis and then to thalamic nuclei and the cortex, where migraine pain is perceived[7][8].

Decreased serum and RBC magnesium levels in the periphery indicated reduced cerebral levels of magnesium which lowers the threshold for migraine.

Hence oral or intravenous magnesium supplements will help to reduce the neurogenic inflammation by preventing vasospasm[9], inhibiting platelet aggregation[10], stabilization of cell membranes and reducing the formation of inflammatory mediators.

MATERIALS AND METHODS

A prospective case control study was conducted to assess the role of magnesium in migraine and to study the correlation between serum and RBC magnesium levels in 20 healthy volunteers and in 20 patients with migraine. Approval from the ethical committee was obtained before conducting the study.

The inclusion criteria for cases were

- 1) Patients, in the age group of 20-50 years, with definite migraine diagnosis on the basis of International Headache Society (HIS) criteria, attending the headache clinic of Justice KS Hegde Charitable Hospital between August –September 2016.
- 2) No history of magnesium supplements consumption.

For control:

Healthy age and sex matched individuals between the age group of 20-50 years, without migraine coming to Justice KS Hegde Charitable Hospital between August 2016- September 2016.

Exclusion criteria:

- 1) Patients below the age of 20 years and above 50 years.
- 2) Non- consenting patients.
- 3) Patients with associated hypothyroidism and Kidney diseases, Diabetes Mellitus, history intake of diuretics, as these factors can alter the magnesium levels in the body.

After obtaining an informed consent from all patients, a detailed history regarding the type and location of headache and family history of migraine was obtained. Blood samples were collected from all patients and levels of serum and RBC magnesium was estimated by using magnesium assay kit. The magnesium level of patients with migraine was compared to that of the control population. The collected information was summarized by using frequency and percentage. To compare the difference between the groups, unpaired T test was used. P value less than 0.05 was considered significant. Statistical analysis was performed using SPSS 17 software.

THE MAGNESIUM ASSAY KIT:

The Magnesium Assay kit provides a simple and direct procedure for measuring magnesium levels in a variety of samples. The magnesium concentration is determined by a coupled enzyme assay that takes advantage of the specific requirement of glycerol kinase for Mg^{2+} , resulting in a colorimetric (450 nm) product proportional to the magnesium present. This assay gives a linear range of 3-15 nanomoles of magnesium and exhibits no detectable interference with Fe^{2+} , Cu^{2+} , Ni^{2+} , Zn^{2+} , Co^{2+} , Ca^{2+} , and Mn^{2+} . The Magnesium reference range for this kit was: Serum magnesium level-: 1.6-2.6mg/dl and RBC magnesium level-: 4.2-6.8mg/dl.

RESULTS

In our study, on estimating the serum magnesium level, the mean serum magnesium level of 20 patients with migraine was found to 1.6 mg/dl which was within the lower limit according to the reference range provided by the kit, where as that of the 20 healthy volunteers in the control group was 2.1 mg/dl which was within normal limits. The estimated P Value was 0.0001(<0.05) and was found to be significant.

On estimating the RBC magnesium levels, the mean RBC magnesium level of the 20 patients with migraine was found to be 4.32 mg/dl, which was again in the lower limit considering the reference range provided by the kit used, whereas that of the 20 healthy volunteers in the control group was 6.38mg/dl ,which was in the normal range. The estimated P value was <0.0001(<0.05) and was found to be significant.

Hence as per our results of the study, both the serum and RBC Magnesium levels were found to be significantly lower in patients with migraine compared to a healthy control group. It was also found that the RBC magnesium levels when compared to its reference range was lower even when the serum magnesium levels were near normal in patients with migraine, indicating that RBC magnesium level is a more accurate and early indicator of magnesium deficiency when compared to serum magnesium levels.

DISCUSSION

Magnesium deficiency plays a major role in the pathogenesis of migraine. In our study, the results obtained correlate significantly to this theory.

On reviewing the literature, the study done by Gonullu H et al reported reduced levels of magnesium, zinc and copper in patients with migraine when compared to a healthy control group. The results of our study are similar to it with

the estimated mean value of serum and RBC magnesium being significantly lower in patients with migraine when compared with that of healthy volunteers [11].

The study done by Samaie A et al analysed serum magnesium levels in migraineurs within and between headache attacks. They found that there was no significant difference in the serum total Mg levels within and between migraine headache attacks. They also noted that, the serum total Mg level was notably lower in the group with these migraineurs compared to the control group. We obtained similar results in our study [12].

The study conducted by Talebi M et al included 140 patients with migraine and 140 healthy volunteers. There was no significant difference between the mean level of serum magnesium in patients with migraine with aura and without aura, however, there was a significant linear relationship between the amount of serum magnesium and the frequency of headache. This again signifies the effect of magnesium deficiency leading to more frequent attacks of migraine [13].

Roudbari SA evaluated serum ionised magnesium and calcium level in migraineurs during interictal period and control group. Their study showed lower magnesium and higher calcium level in migraineurs compared with control group especially in subjects of migraine without aura and women with menstrually aggravated migraine. The results are comparable with that of our study obtaining significantly lower levels of magnesium in patients with migraine [14].

On the contrary, a study done by Assarzagdegan F et al recorded the serum levels of ionized magnesium in patients with migraine. Ninety-six patients were included in the study, 48 for each of case and control groups. Significant difference was not seen in the groups [15].

A double blind, randomised, placebo controlled study done by Koseoglu E et al concluded that magnesium is a beneficial agent in prophylaxis of migraine without aura. Hence simple oral supplements of magnesium can act as an effective prophylactic agent to prevent and reduce the frequency of migraine attacks [16].

CONCLUSION

Migraine has been associated with low levels of magnesium in the brain, CSF and serum and RBCs. True magnesium levels are best assessed with red-blood cell (RBC) magnesium, the magnesium load test or ionized magnesium (Mg^{2+}) levels. Magnesium prophylaxis will be a simple, safe and

effective option to reduce the distress of patients with migraine by preventing attacks of headache. However a study with a larger sample size will be required to confirm the inference of our study.

Compliance with Ethical Standards:

Funding: This study was funded by Nitte university under their postgraduate research programme.

Conflict of Interest: The Authors declare that there is no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

TABLE NO :1 – SERUM AND RBC MAGNESIUM LEVELS IN THE CASE AND CONTROL GROUP

SERUM MAGNESIUM LEVEL	CASE (MEAN VALUE) 1.6 mg/dl	CONTROL (MEAN VALUE) 2.1 mg/dl	P VALUE 0.0001
RBC MAGNESIUM LEVEL	CASE (MEAN VALUE) 4.32 mg/dl	CONTROL (MEAN VALUE) 6.38 mg/dl	P VALUE < 0.0001

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