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Low Magnesium Concentration in Erythrocytes of Children with Acute Asthma

Mostafa Sedighi^{1,2}, Zahra Pourpak¹, Behrouz Bavarian², Reza Safar Alizadeh¹, Ahad Zare¹, and Mostafa Moin¹

¹ Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran ² Emergency Department of Children Hospital Medical Center, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Magnesium (Mg) is the second most abundant intracellular cation and is involved in numerous physiological functions, including protein folding, intracellular signaling and enzyme catalysis. It has been shown that magnesium deficiency exacerbates pulmonary airways hyperreactivity. Several studies suggest that magnesium level has no effect on asthma but others had shown a contributory effect. Because of its intracellular abundance, the aim of this study was to determine if there was any difference in plasma and intracellular Mg concentrations of children with acute asthma compared to non asthmatic children.

Twenty nine patients with acute asthma aged 2 to11 years admitted to the emergency department of hospital and 37 non asthmatic children with the same age were included in our study. 0.5 mL of heparinized whole blood samples of patients who were meeting inclusion criteria at the onset of admission with bronchoconstriction and before using any medication was drawn and it was immediately sent to the laboratory. Plasma and erythrocytes were separated and stored at -20C and later their Mg levels were quantified with atomic absorption spectrophotometry method.

The average plasma and intracellular magnesium levels in patients were $(0.79 \pm 0.098 \text{ mmol/L})$ and $(1.17 \pm 0.27 \text{ mmol/L})$ respectively. Results of 37 non asthmatic persons [plasma (0.85 ± 0.1 mmol/L) and erythrocytes $(1.33 \pm 0.21 \text{ mmol/L})$] showed that there was no significant difference between plasma Mg levels in two groups (p 0.06) but intracellular magnesium level was significantly lower (p 0.03) in patients group.

These results indicate that intracellular Mg level may be a more accurate method to assess Mg level in patients with asthma. Hence, determination of Mg concentration in erythrocytes may be used in evaluation of asthma pathophysiology. There are recommendations for using intravenous Mg sulfate in acute asthma, and this study supports the rational for using it in emergency departments for acute severe asthma.

Key words: Asthma; Children; Magnesium

INTRODUCTION

Asthma is an important health care problem worldwide. It is the most common inflammatory chronic disease in childhood. Magnesium (Mg) is the

Corresponding Author: Zahra Pourpak, MD, PhD; Immunology, Asthma and Allergy Research Institute, Children Medical Center, No. 62, Dr. Gharib St, Keshavarz Blvd, Tehran 14194, Iran. Tel: (+98 21) 6693 8545, Fax: (+98 21) 6642 8995, Email: zpourpak@hbi.ir

second most abundant intracellular cation, and it is involved in numerous physiological functions, including protein folding, intracellular signaling, enzymatic reactions involving protein and nucleic acid metabolisms and enzyme catalysis (Mg is cofactor for > 300 cellular enzymes).¹ Serum Mg contributes less than 1% of the total amount of the body.¹ Therefore, an increasing interest can be noted in the measurement of its intracellular concentration.^{2,3} Many clinical studies linked reduced Mg concentrations to many disease states, especially coronary heart disease, hypertension, pediatric pulmonary disorders and many others.^{2,4}

Mg is involved in pathophysiological reactions related to asthma. Mg has been shown to relax bronchial smooth muscle in vitro and to bronchodilate asthmatic airways in vivo;5, 6 inhibition of release of acetylcholine from cholinergic nerve terminals and of histamine from mast cells, promotion of nitric oxide synthesis and prostacycline generation are all changes in intracellular Mg associated with concentrations.^{7, 8} On the basis of the critical role of Mg in the regulation of bronchial smooth muscle cell contractility via its effects on calcium transport activation and phosphorylation/dephosphorylation of intracellular reactions, it has been proposed that the intracellular Mg content may determine the excitability of these cells.^{1, 5} Several studies have shown that intravenous application or inhalation of Mg could alleviate symptoms in acute and stable asthma.⁴ In asthma, basophil and mast cells release chemical mediators upon appropriate antigen stimulus.^{8,9} The primary trigger for the release of mediators from basophil and mast cells is a rise in cellular calcium concentration.¹⁰ Mg is a natural calcium channel blocker.11, 12

Recent studies in acute and chronic asthma have shown no significant difference of plasma Mg concentrations in asthmatic and non asthmatic control groups.^{11, 13} Previously low intracellular Mg content in patients with stable asthma has been found, but not all studies have confirmed this finding.^{11, 13} There are a number of reports concerning cellular Mg concentration in samples of healthy adult persons but data on cellular Mg concentration in children population are rather scarce. The aim of this study was to compare total Mg concentration in plasma and in erythrocytes of children suffering from acute bronchoconstriction, at the onset of attack and before taking any medication.

MATERIALS AND METHODS

Experimental Group Patients

Twenty nine patients (23 boys and 6 girls aged between 2-11years) were examined. All patients were outpatients suffering from acute asthma attack and `admitted to emergency department with acute asthma. They had positive history of asthma and were under as thma controller drugs such as β agonists and steroids. Clinical diagnosis of acute severe asthma was based on the all signs such as tachypnea, nasal flaring, wheezing, intercostals, sub costal, and suprasternal muscle retraction; and use of accessory muscles. They were not dehydrated or feverish. Patients with localized wheezing, fever, symptoms of pneumonias, or those who had any history of cardiac, renal, or hepatic dysfunction, were excluded from this study. Also patients with family history of diabetes mellitus, or receiving any Mg-wasting drugs such as diuretics and those without past history of asthma were not included in this study. Samples of patients were taken at the onset of bronchoconstriction, before using any medication.

After taking written consent from parents of patients who were meeting inclusion criteria, samples were taken at the onset of admission and before using any medication. None of them received any aggressive treatment such as admission to PICU or the need for mechanical ventilation

The protocol was approved by Ethics Committee of the Tehran University of Medical Sciences and conducted according to the guidelines of the Helsinki Declaration.

Control Group

Thirty seven healthy non asthmatic children aged between 2 to 11 years referring for screening programs to laboratory entered in this study and 0.5 ml of their excess heparinized whole blood samples were obtained. Their personal and family medical history and clinical presentation excluded any atopic or allergic diseases.

Sample Preparation and Biochemical Analysis Method

0.5 mL of aspirated whole blood was drawn into a metal-free syringe containing sodium heparin and immediately sent to laboratory. Samples were centrifuged and plasma and erythrocytes were

separated; erythrocytes were then washed with normal saline and lysed using hypotonic solution of NaCl. Samples were stored at -20c. Intracellular and plasma Mg levels were analyzed with atomic absorption spectrophotometry method.

Statistical Analysis

Statistical analysis was performed by using the NCSS for windows software. Mean, standard deviation and p values of two groups were obtained for comparison.

RESULTS

The results are summarized in the table 1. The mean and standard deviation values of total Mg concentrations in plasma and erythrocytes of patients were ($0.79 \pm 0.098 \text{ mmol/L}$) and ($1.17 \pm 0.27 \text{ mmol/L}$) respectively.

The results of this study in the group of 37 healthy children (aged 2-11) showed more plasma Mg concentration $(0.85 \pm 0.1 \text{ mmol/L})$ compared to literature data.

The mean and standard deviation values of total Mg concentration in plasma and erythrocytes of control group were ($0.85 \pm 0.1 \text{ mmol/L}$) and ($1.33 \pm 0.21 \text{ mmol/L}$) respectively. At the onset of asthma attack, Mg concentration in erythrocytes was significantly lower (p=0.03) in patients compared to control children and plasma Mg concentration, in all samples showed insignificant (p=0.06) difference within the control and patients group.

 Table 1. Mean and standard deviation of Mg levels in

 Plasma and erythrocytes of patients and control groups.

		Plasma	Erythrocytes
		(mmol/L)	(mmol/L)
Patients	Mean	0.79	1.17
	S.D	± 0.098	± 0.27
Controls	Mean	0.85	1.33
	S.D	± 0.10	± 0.21
P-value		0.06	0.03

DISCUSSION

This study has shown that in acute asthma there is low plasma and significantly lower erythrocyte Mg content (p= 0.03) in patients with acute asthma. It is known that magnesium (Mg) is involved in smooth muscle relaxation.^{14, 15} Many studies have been conducted to show the Mg status in asthmatic patients with conflicting results.^{16, 17}

In the majority of them, no difference was found in erythrocyte Mg content between patients with stable asthma and healthy subjects.^{2, 15}

Magnesium status of patients is usually determined by measuring serum or plasma Mg concentrations. Many studies demonstrated the superiority of measuring the intracellular content of Mg over measuring serum concentrations in determining the Mg status of patients.^{18, 19} Serum Mg measurements tend to reflect short-term variations in intake, but not total body Mg stores. Normal serum Mg value does not exclude Mg deficiency in cells.

This study also indicated that Mg ions have a role in the pathogenesis of asthma, especially during a bronchoconstriction attack. Some studies have shown that during bronchial challenge with histamine, when "experimental" bronchoconstriction occurs. an intracellular Mg content show a significant fall.²⁰ Presence of either experimental or exacerbation induced bronchoconstriction leads to a significant fall in erythrocyte Mg content.²¹ Redistribution of Mg in the organism occurs during the acute asthmatic attack (cellular depletion, lower elimination and increased observed).²² Increased plasma Mg are Mg concentration in plasma could be a result of Mg release from leukocytes with subsequent increase in target cells of the attack.²² At the same time, organism saves Mg through its renal mechanism.²²

All the above-mentioned data could possibly lead to the hypothesis that the reduced Mg levels in erythrocytes -- and possibly in intracellular space in general- is the result and not the cause of bronchoconstriction in an asthmatic exacerbation. It is speculated that when bronchoconstriction occurs, Mg is forced out of intracellular space and works as a natural calcium-channel blocker in order to relax airway smooth muscle. One plausible explanation for the above-mentioned theory might be that products of oxidative stress produced in asthma exacerbation, like hydrogen peroxide (H2O2), can possibly act as indirect triggers destroying Na/Mg adenosine triphosphatase antiport to pour Mg out of erythrocytes. Other inflammatory chemokines, such as interleukins, might take part to this process, through cyclic adenosine monophosphatase regulation.^{23, 24}

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