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Research Article

Magnesium Status and Therapeutic Effects in Asthmatic Children

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Abstract

The study aimed at outlining the possible role of magnesium (Mg) in the pathogenesis and treatment of bronchial asthma. Twenty seven asthmatic children (mean age 9.07 ± 3.79 years) were studied during wheezy episodes : 8 with mild persistent asthma, 8 with moderate persistent asthma and 11 with severe persistent asthma. Fifteen age and sex matched healthy children were included as a control group. Measurement of Mg concentration was carried out in serum (SMg), 24 hours urine sample (UMg) and intracellularly in mononuclear cells (MMg) and erythrocytes (EMg) by atomic absorption spectrophotometry.

Asthmatic children had significantly lower Mg whether extracellular (SMg: 0.7 ± 0.18 mmol/L, UMg: 2.68 ± 8 mmol/L) or intracellular (MMg: 1.7 ± 1.22 fmol/cell, EMg: 0.09 ± 0.03 fmol/cell)compared to controls (SMg: 0.85 ± 0.12 mmol/L, UMg:3.9 ± 0.73 mmol/L, MMg:3.75 ± 2.03 fmol/cell and EMg: 0.198 ± 0.026 fmol/cell with $p < 0.001$ in all except EMg where $p < 0.05$).

Patients with severe asthma had significant deficiency of SMg as well as intracellular Mg when compared to controls with significant decrease in UMg excretion. In moderate asthma, there was a deficiency in intracellular Mg but SMg was comparable to controls possibly maintained by decreased renal excretion as evident from the decreased UMg concentration. Patients with mild asthma had significant deficiency only in EMg. The degree of Mg deficiency whether intra or extracellular, closely followed the grade of asthma severity with significant lower SMg, UMg, MMg and EMg in severe as compared to mild asthma and significantly lower MMg and EMg in severe as compared to moderate asthma. SMg and MMg also correlated negatively with respiratory rate and positively with peak expiratory flow rate (PEFR) in severely asthmatic children.

Intravenous infusion of $MgSO_4$ (50 mg/kg), given to severely asthmatic children who did not respond to 3 doses of nebulized B_2 - agonist, resulted in clinical improvement and significant increase in PEFR, SMg, MMg and EMg with further increase in MMg and EMg at follow up (after 2 - 4 wks).

It is concluded that asthmatic children suffer Mg deficiency, the degree of which increase with increasing severity of asthma. Urinary and intracellular Mg proved to be more reliable than SMg as indices of magnesium status. UMg being less invasive and easily assayed is recommended for monitoring magnesium status in asthmatics. Lastly, $MgSO_4$ infusion proved efficacious and is recommended as a bronchodilator in acute episodes.

Keywords: *Magnesium; Asthmatic Children*

Introduction

Magnesium (Mg) is a cation that has a modulatory effect on the contractile state of smooth muscle cells in various tissues. Hypomagnesemia leads to contraction while hypermagnesemia leads to relaxation [1]. The relationship between hypomagnesemia and increased contractile state may be explained by the inhibitory effect of Mg on the secretion of acetyl choline from presynaptic neurons and by the

antagonism between Mg and calcium (Ca) in the cell [2]. Mg can block the triggering effect of Ca on chemical mediator release from basophils and mast cells [3]. It can also inhibit the synthesis of prostanoids enhanced by Ca ion influx [4].

As asthma is characterised by widely varying degrees of contraction of bronchial smooth muscles, Mg deficiency could perpetuate the contractile state of bronchial smooth muscles [1]. Furthermore, Mg therapy might be an appropriate approach to the problem. However, the results of clinical studies of Mg therapy in asthma have been conflicting [5,6].

Aim of the Study

This study aimed at evaluation of intra- and extra-cellular Mg concentration in asthmatic children with different grading of severity as well as studying the possible therapeutic effect of Mg in acute severe asthma.

Subjects and Methods

The study comprised 27 asthmatic children (as a stratified random sample) followed up at the Pediatric Allergy and Immunology Unit of Ain-Shams University. They were 14 males and 13 females with a mean age of 9.07 ± 3.7 years. They were classified according to the Expert Panel Report II Guidelines for diagnosis and management of asthma, [7], into: 8 with mild persistent asthma (mean age 8.12 ± 3.27 years), 8 with moderate persistent asthma (mean age 9.0 ± 3.85 years) and 11 with severe persistent asthma (mean age 9.8 ± 4.26 years). Their mean duration of illness was 6.5 ± 1.06 years. Fifteen healthy children, 10 males and 5 females, were included in the study as a control group. Their ages ranged from 4 to 14 years with a mean value of 8.6 ± 2.9 years. They were studied for the sake of comparison of Mg concentration.

Exclusion criteria were: presence of any allergic problems or even family history of atopy (for controls) and any illness that could affect the Mg levels such as malnutrition, diarrhea, chronic renal failure, rickets, renal tubular acidosis, hypercalcemia and epilepsy (Reinhart, 1988).

Study design: All patients were studied during an acute exacerbation as follows:

Clinical evaluation of the patients was carried out with recording of respiratory rate (R.R.), heart rate, blood pressure, weight and height centiles [8] and chest auscultatory findings as well as recording their current medicinal treatment.

Peak expiratory flow rate (PEFR) measurement was done using a MiniWright peak flow meter[A].

[A]Clement Clarke Int. Ltd. Armed House Edinburgh way Harlow Essex CM26 England. Cat. No. 3103001.

Laboratory investigations included:

1. Routine investigations:
    a. Complete blood counts carried out by Coulter Counter T660[A].
    b. Serum total IgE assayed by ELISA technique using a kit supplied by Genzyme
    c. Corporation[B]. To overcome the age related differences in IgE levels, IgE was calculated as a percentage of the high normal for age.
2. Determination of serum calcium (Ca) carried out on the Synchron CX5 autoanalyzer using Beckman reagents[B].
3. Determination of magnesium concentration in serum (SMg), 24 hours urine sample (UMg), mononuclear cells (MMg) and erythrocytes (EMg). This was done according to the method described by Archer., *et al* [9].

[A]Coulter Corporation, Miami, Florida 33196, USA.

[B]Beckman Instrument Inc., Fullerton, California 96234-3100.

Magnesium Sulphate ($MgSO_4$) Therapy

Patients with severe asthma, who failed to respond to 3 doses of nebulized β_2-agonist, were treated with $MgSO_4$ at a dose of 50 mg/Kg as i.v. infusion over 20 minutes.

They were monitored for heart rate, respiratory rate, blood pressure, signs of respiratory distress and chest auscultation.

After baseline evaluation, these patients were followed up for PEFR, SMg, MMg and EMg at the end of the infusion and 2 - 4 weeks later during steady state asthma.

Magnesium Sulphate ($MgSO_4$) Therapy

Sample preparation

Blood sample: Ten ml venous blood were collected (2 ml clotted and 8 ml heparinized). Serum was separated from clotted samples and stored at –20^{o}C until assayed.

Each heparinized sample was split into 4 aliquots 2 ml each, diluted 1:1 with phosphate buffered saline (PBS) at pH 7.4, then layered on 2 ml Ficoll-Hypaque and centrifuged (500 x g, 20 minutes) at room temperature. Mononuclear cells and erythrocytes were harvested and pooled.

Preparation of erythrocyte lysate: pooled erythrocytes were washed thrice with 6 ml choline chloride (150 mmol/L), centrifuged (150 x g, 10 minutes) and 200 µl of the packed erythrocytes were resuspended in 1.8 ml of the same solution. Cells were counted, then lysed osmotically by Triton X-100 1% and the lysate was stored at –20^{o}C.

Preparation of Mononuclear cell lysate

Pooled cells were washed twice with buffered glucose saline and centrifuged (270 x g, 15 minutes 1st wash, 10 minutes 2nd wash). The cell pellet was resuspended in PBS (up to 1 ml) and their number was adjusted at the range of 10^5 to 10^6 cell/ml. Cells were lysed by sonication using ultrasonic homogenizer[A] (50 W at 20 KHz for 20 sec)and the lysate was stored at –20^{o}C.

Urine sample: Twenty-four hr urine was collected in clean containers containing 20 ml 6 M HCl. An aliquot of 5 ml was stored at –20^{o}C.

Analytical method: Mg concentration was measured by atomic absorption spectrophotometry[B] using acetylene and air mixture at a wave length of 285.2 nm. For MMg, standards of 0.08 to 0.4 mmol/L Mg^{+2} concentration were used to construct a calibration curve, while standards of 0.42 to 2.4 mmol/L Mg were used for SMg, UMg and EMg. Knowing the count of erythrocytes and mononuclear cells per ml, the concentration of intracellular Mg was calculated and expressed as fmol/cell. N.B. Ficoll-Hypaque, choline chloride, PBS and Triton X 100 were purchased from Sigma[C].

[A]CP – 50 Ultrasonic homogenizer, Colepanmer Instrument Co. Chicago, Illinois 60648, USA.

[B]SP9 Pye Unicam, England.

[C]Sigma Chemicals Co, P.O.Box 4508, St. Louis, MG 63178, USA.

Statistical Methods

Descriptive and analytical statistics were carried out with the aid of a computer program (Statview 4 for Apple Macintosh). Student's 't' test for paired and unpaired observations was used to compare different groups. Mann Whitney 'U' test was applied for non-parametric data. Correlation matrix was used to correlate quantitative data. A probability of less than 0.05 was taken as significant.

Results

The studied patients had a mean absolute eosinophilic count of 321.8 ± 439.21 cell/mm^3 and a mean IgE% of 156.19 ± 234.05. Their mean serum Ca was 9.12 ± 0.75 mg/dl which was insignificantly different from that of the control group.

Magnesium Status in asthmatics versus controls

The mean SMg was significantly lower in the whole group of asthmatic children (0.70 ± 0.18 mmol/L) as compared to controls (0.85 ± 0.12 mmol/L, $p < 0.001$) (Figure 1). This was obvious in the subgroup of severe asthma (0.59 ± 0.09 mmol/L, $p < 0.001$). However, SMg in moderate and mild asthma (0.75 ± 0.23 and 0.8 ± 0.15 mmol/L respectively) was insignificantly lower than controls (Table 1).

UMg was significantly lower in asthmatic patients as compared to controls (2.69 ± 0.81 mmol/L versus and 3.9 ± 0.73 mmol/L, $p < 0.001$) (Figure 1). This was encountered in severe and moderate –but not mild- grades of asthma. Intracellular Mg deficiency was a prominent finding in asthmatic children since the MMg and EMg (1.70 ± 1.22 and 0.09 ± 0.03 fmol/cell respectively) were significantly lower than the corresponding values in controls (3.75 ± 2.03 and 0.198 ± 0.026 fmol/cell respectively) (Figure 1). This applied to all grades of asthma except the mild grade where MMg was insignificantly lower than in controls.

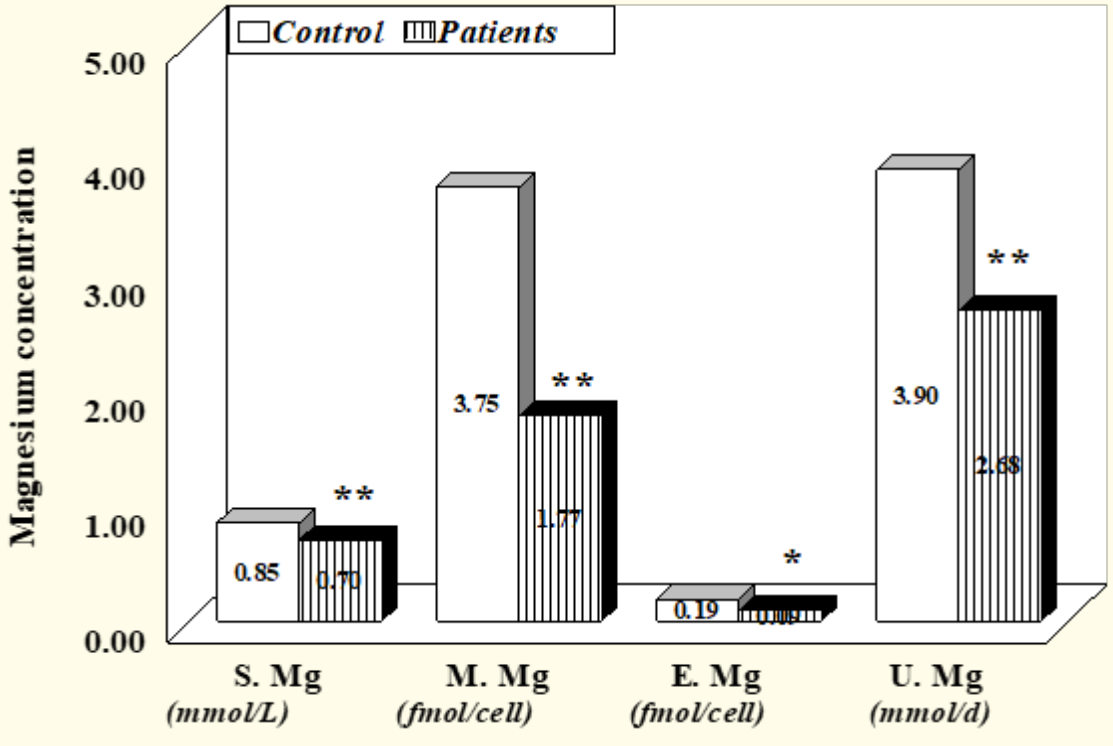

Figure 1: *Magnesium status in all studied patients versus that of the control group.*
**Significant ($p < 0.05$), ** Highly significant ($p < 0.001$).*

Relation of Mg status to the degree of asthma severity

A graded increase in Mg deficiency was observed with increasing severity of asthma. There were significant differences in SMg between severe and mild asthma, and in UMg between each of severe and moderate asthma on one hand and mild asthma on the other. The relation of Mg deficiency to asthma severity was also reflected by the significantly lower intracellular Mg -whether MMg or EMg- in severe asthma as compared to the moderate and mild degrees (Table 1).

Parameter	Controls (n = 15) X ± SD	Mild BA (n=8) X ± SD	Moderate BA (n = 8) X ± SD	Severe BA (n = 11) X ± SD
SMg (mmol/L)	0.85 ± 0.12	0.8 ± 0.14	0.75 ± 0.22	0.59 ± 0.09
t vs controls		0.9	1.48	5.9***
t vs mild			0.54	3.86***
t vs moderate				2.1
UMg (mmol/d)	3.9 ± 0.7	3.5 ± 0.5	2.4 ± 0.45	2.22 ± 0.66
t vs controls		1.27	5.2***	6.1***
t vs mild			4.8***	4.7***
t vs moderate				0.72
MMg (fmol/cell)	3.75 ± 2.03	2.9 ± 1.4	1.88 ± 0.72	0.87 ± 0.49
z vs controls		1.04	2.4*	4.5***
z vs mild			1.84	4.4***
z vs moderate				3.6***
EMg (fmol/cell)	0.19 ± 0.02	0.16 ± 0.02	0.13 ± 0.02	0.09 ± 0.03
t vs controls		2.8**	5.6*	8.27***
t vs mild			2.14	4.41**
t vs moderate				2.4*

Table 1: *Extracellular and intracellular magnesium concentration in all studied groups.*

X: Mean, SD: Standard deviation, n: Number, BA: Bronchial asthma, t: Student's t test, vs.: Versus

**: Significant (p < 0.05), **: p < 0.01, ***: p < 0.001.*

Furthermore, significant negative correlation existed between each of SMg, UMg and MMg and the respiratory rate of severe asthma patients (r = -0.45, -0.55 and –0.41 with p < 0.05 in all cases). Also, significant positive correlations existed between PEFR and each of UMg (Figure 2), SMg and MMg (r = 0.48, 0.54, 0.64 respectively with p < 0.05 in all cases).

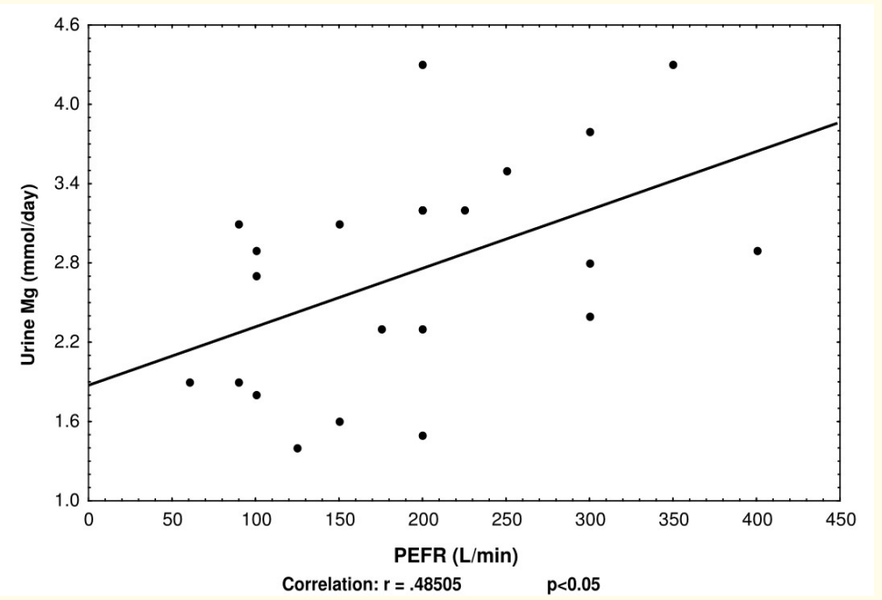

Figure 2: *Correlation between PEFR and UMg.*

Therapeutic effects of $MgSO_4$ infusion

$MgSO_4$ infusion resulted in clinical improvement in the manifestations of respiratory distress and in respiratory rate. Paired observations showed a significant increase in PEFR, SMg, MMg and EMg from pretreatment values. Follow up after 2 - 4 wks revealed a further rise in MMg and Emg (Figure 3).

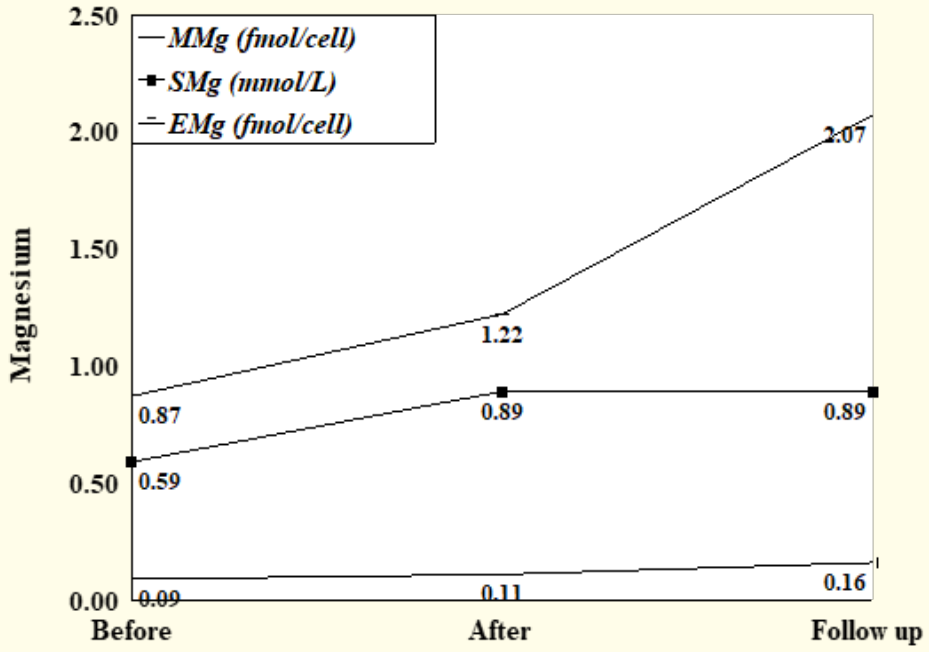

Figure 3: *Magnesium concentrations in severely asthmatic patients before and after magnesium infusion and at follow up (after 4 weeks).*

Factors affecting Mg status

Theophylline and steroids did not seem to influence magnesium status with comparable levels in patients receiving and those not receiving these drugs.

Intracellular Mg, namely MMg and EMg correlated positively and significantly with the height centiles of the studied asthmatic children ($r = 0.43$ and 0.53 respectively, $p < 0.05$). No significant correlations were observed between SMg and any of S. calcium, serum total IgE (% of normal) or eosinophil count.

Significant positive correlations were found among the parameters of Mg in the various body compartments in the whole group of asthmatic children as follows:

- SMg with UMg: $r = 0.54$ $p < 0.05$
- SMg with MMg: $r = 0.50$ $p < 0.05$
- SMg with EMg: $r = 0.64$ $p < 0.05$
- MMg with EMg: $r = 0.80$ $p < 0.05$
- UMg with EMg : $r = 0.61$ $p < 0.05$

Discussion and Conclusion

Magnesium deficiency whether absolute or relative, may lead to increased excitability of bronchial smooth muscles with consequent bronchoconstriction [10]. The possible role of magnesium in the pathogenesis of bronchial asthma as well as its treatment has regained considerable attention, particularly because of several reports confirming positive results of magnesium administration in acute airway constriction [11].

The present study was prompted by the possibility of the presence of magnesium deficiency in patients with asthma that might contribute to the increased contractile state of bronchial smooth muscle or could be the reason behind the decreased degree of reversibility of their airway obstruction. The results of the present study indicated the presence of Mg deficiency among asthmatic children as evident from the significantly lower mean SMg in the whole group of asthmatic patients compared to controls. Such a finding applied only to patients with severe asthma. However, this was not the case with mild and moderate degrees of asthma. Similar results were obtained by Dominiguez., *et al*. [12] in their study on adults with mild to moderate asthma.

Interestingly, ultrafiltration and diffusion experiments indicated that 70 - 85% of SMg is in a diffusible state. So SMg can be affected by the intracellular Mg concentration [10]. This hypothesis was supported by the finding, in the present work, of significant positive correlations between SMg on one hand and intracellular Mg, namely MMg and EMg, on the other. Mononuclear cells and erythrocytes were chosen as they have been shown to provide a feasible less invasive experimental model allowing accurate measurement of intracellular Mg [13].

The results revealed a significant deficiency of MMg in patients with moderate and in those with severe persistent asthma but was more prominent in the latter group. Furthermore, erythrocytes which are reported to conserve Mg at a concentration 3 times that in plasma [14], were found to be deficient in Mg in all grades of asthma. These findings were in agreement with those of Fantidis., *et al*. [3] and Dominguez., *et al.* [12]. However, Devalk., *et al*. [1], failed to demonstrate such a deficiency in intracellular Mg probably because their study comprised only adult asthmatic patients of the mild degree.

The observed intracellular Mg deficiency among our patients is believed to be responsible for Mg influx from the extracellular compartment with the resultant decrease in SMg as seen in patients with severe asthma. Deficiency of intracellular Mg has been shown to play a role in pathogenesis of asthma [15]. As a natural calcium antagonist, Mg can modulate smooth muscle contraction [16]. Moreover, Mg deficiency potentiates the action of calcium, reducing the intracellular level of cyclic adenosine monophosphate, and increasing the synthesis of leukotrienes and prostaglandins, all of which are important mediators of asthma [3].

A significant decrease in UMg excretion was found in moderate and severe asthmatic children of the present work. It appears that the excellent renal Mg conservation mechanism described by Adelman and Solbung [17], was successful in maintaining SMg in patients with moderate asthma. However, in severely asthmatic patients, this conservation was not enough to maintain normal level of SMg and so frank hypomagnesemia prevailed. Worth mentioning is that the UMg changes paralleled those of intracellular Mg and hence the measurement of UMg can provide an easy, non invasive and cheap alternative for the prediction of intracellular Mg changes among asthmatics.

The degree of Mg deficiency observed among asthmatic children went hand in hand with the degree of severity of asthma. In addition, MMg correlated negatively with the respiratory rate and with the frequency of asthma attacks. These together with the positive correlation observed with PEFR provide evidence incriminating Mg deficiency in the causation of bronchospasm and relating it to the severity of asthma in the pediatric age group.

The exact mechanism of this Mg deficiency among asthmatics remains to be identified. The consideration of a deficient Mg intake as a cause for hypomagnesemia seems worthwhile. This is based on the findings of a significant positive relationship between height centiles and each of MMg and EMg. It is quite understandable that asthmatic children especially of the severe degree, experience periods of limited

food intake during exacerbations and infections as a result of anorexia and respiratory difficulty superadded to the dietary restrictions that some of them suffer because of their atopic background. Moreover, epidemiological evidence exist correlating a low dietary intake of magnesium with impaired lung function, bronchial hyperreactivity and wheezing [18].

In the present study a trial was made to assess the effects of parenteral Mg therapy in acute severe asthma. There was significant elevation of the mononuclear Mg content immediately after completion of the infusion. This was in contrast to what had been reported by Okayama., *et al*. [19] that SMg ions tended to be transferred to the intracellular compartment within 24 hours. The marked intracellular Mg depletion observed in severe asthma patients in the current study might explain the rapid shift of Mg ions from the extra-to the intracellular compartment. The rapid correction of both serum and intracellular Mg deficiency was associated, in the studied patients, with obvious clinical improvement and significant increase in PEFR. Similarly, Ciarrolo., *et al.* [6] recorded significant improvement in PEFR in moderately severe asthmatic children after infusion of $MgSO_4$ at a dose of 25 mg/kg over 20 minutes that was not immediate contrary to the situation in the present study in which the dose used was 50 mg/kg. This improvement was not attainable by three successive doses of a beta-2 sympathomimetic by nebulization that preceded the Mg therapy. This indicated that Mg therapy was superior to β_2 agonists, as a bronchodilator in patients with acute severe asthma compared to β_2 agonists. Devi., *et al.* [20] demonstrated that Mg therapy had an additive effect to beta 2 sympathomimetics and seemed even to be more powerful. The fact that sulphate ion has a negligible effect on cell function, suggests that the bronchodilator effect of intravenous $MgSO_4$ comes from the magnesium ions [21].

It is to be noted that no side effects were observed with this form of therapy. This aforementioned successful role of $MgSO_4$ infusion as a bronchodilator ranks this drug among the first line rescue therapy in acute severe asthma to attain rapid relief of the symptoms and improvement in respiratory function. This facilitates the control of the condition which can further be handled easily with the traditional treatment.

In spite of the significant rise that was observed in MMg and EMg after 2 - 4 weeks during steady state asthma, the levels of MMg and EMg remained significantly lower than the control levels. This signifies that the good control of the inflammatory process in asthma can cause a significant -albeit an incomplete- improvement in Mg status. This raises the question of whether the need exists for continued Mg supplementation to children with asthma of the severe degree.

The relation between the degree of asthma severity and different intra and extra cellular parameters of Mg could be clearly demonstrated by the strong positive correlations with the PEFR and the negative ones with the respiratory rate. In other words, Mg deficiency was associated with low PEFR and high respiratory rates and vice versa. This result could prove the importance of correction Mg deficiency in the management of asthmatic patients.

To conclude, intracellular magnesium deficiency is a prominent finding in moderate and severe persistent bronchial asthma in childhood and it is intimately related to asthma severity in these patients. Also, urinary and intracellular magnesium are more reliable indices of magnesium status than serum magnesium which might be normal in spite of the presence of intracellular magnesium deficiency. However, being less invasive and technically less tedious, urinary magnesium assay is recommended for monitoring magnesium status.

The relationship of magnesium deficiency to bronchospasm is possibly a causal one and it probably results from deficient magnesium intake.

Magnesium sulphate, as an initial therapy in acute severe asthma, can result in rapid relief of the clinical symptoms as well as the respiratory functions. Moreover, good control of asthma inflammatory process can maintain and even improve the intracellular, and consequently, the total body magnesium content which appears to be strongly correlated to the control of the asthma symptoms and the respiratory functions.

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