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The Effect of Oral Magnesium Sulfate on Moderate and Severe Asthma Exacerbation in Children Referred to Pediatrics Emergency Department: The Moderating Role of Asthma Severity

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Abstract

Background: Asthma is the most common chronic disease in childhood and a cause of hospitalization. Intravenous magnesium sulfate is recommended as a complementary therapy for asthma exacerbation. This study investigates the effect of oral magnesium sulfate on moderate and severe asthma exacerbation in children.

Methods: This double-blind clinical trial was performed on 40 children, aged 5-12 years old with asthma exacerbation, who referred to Pediatric Emergency Department of Quaem Hospital in Mashhad, Iran. Patients were randomly assigned into two groups, who received magnesium sulfate (300 mg every 12 hours) or placebo capsules for 5 days. Asthma severity score based on Siriraj Clinical Asthma Score (SCAS) contained in the questionnaire was recorded for each patient at 0, 2, 6, and 24 hours after the first visit, and then daily up to 5 days. Based on their ACAS, the patients were divided into three groups by the researcher: A (Mild): 0-8, B (Moderate): 8-16, C (Severe):16-24.

Results: The mean age of subjects was 8.20 ± 2.49 years, and their mean weight was 26.32 ± 8.65 kg. Based on the asthma severity, in the magnesium group, 5 patients were classified in group A, 14 in group B, and 1 in group C; and in the placebo group 8 patients were classified in group A, 8 in group B and 4 in group C .The present study, controlling the effect of weight as a covariate, didn't show a significant effect of oral magnesium sulfate on asthma symptoms in 5-12-year-old children (P=0.15); however, after considering the severity variable as moderator, a minor effect on symptom improvements in B score was revealed.

Conclusion: Administration of oral magnesium sulfate within 5 days, didn't improve asthma exacerbation in 5-12-year-old children. So, more studies with different doses and durations are needed to determine the efficacy of oral magnesium sulfate in asthma exacerbation.

Key Words: Asthma Attacks, Child, Magnesium Sulfate.

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1- INTRODUCTION

Asthma is a chronic-inflammatory condition of the lung airways resulting in episodic airflow obstruction through airways hyper-responsiveness, bronchospasm, inflammation, mucosal edema, and mucosal plaque formation (1-5). Childhood asthma is among the most common causes of childhood emergency department visits, hospitalizations, and missed school days . In 2011, more than 10 million children (14% of U.S. children) had been diagnosed with asthma in U.S. (3, 6). In 2018, around 7.9 percent of the population of the United States had asthma (7). The prevalence of asthma in Iranian children varies from 1.26% to 11.6%, which is due to differences in sex, race and socioeconomic status in the Iranian population. Worldwide, childhood asthma appears to be increasing in prevalence, despite considerable improvements in management and pharmacopeia to treat asthma (1, 3, 6, 8). Although the cause of childhood asthma has not been determined, a combination of environmental exposures and inherent biologic and genetic susceptibilities has been implicated (1-5). The severity of asthma exacerbation in the emergency department is divided into mild, moderate and severe types. For patients with moderate to severe that do not adequately improve within 1-2 h of intensive treatment, observation or admission to the hospital is likely to be needed. Standard asthma treatments include oxygen, bronchodilators, steroids and anticholinergics, which are usually used for most patients. In addition to the standard treatment, some asthmatic children are severely ill and at risk for respiratory failure. So, they undergo intubation and mechanical ventilation, which increases the complications associated with asthma exacerbation (1, 3, 9, 11). Intravenous magnesium sulfate injection is considered as an adjunct treatment for severe asthma, when not responding to standard treatment (12-16). The major mechanism for beneficial effects of magnesium sulfate on the asthmas severity is unknown, but a few theories are mentioned. Magnesium sulfate, by activating adenylate cyclase in smooth muscle cells, leads to inhibition of calcium-dependent smooth muscle contraction and facilitates bronchodilation. Furthermore, it can inhibit mast cell degranulation and reduce acetylcholine secretion from motor neurons, stimulate the secretion of nitric oxide and prostacyclin, and reduce the release of histamine (1, 17, 19). Some epidemiological studies indicate that low magnesium intake is associated with airway hyperactivity and wheezing (17, 19). Recently, in some studies, the use of nebulized magnesium sulfate as an adjunctive treatment in addition to the standard treatment for asthma exacerbations has been mentioned (20, 21). Complications of magnesium sulfate are rare and are more common in high doses and in the injection form. Among its side effects are loss of tendon reflexes, nausea, vomiting, hypotension, dizziness, diplopia, coma cardiac arrhythmias, and respiratory failure. In administration of the injectable form, the serum magnesium level should be monitored regularly. Hyper-magnesia is unusual after administration of magnesium salts, except in patients with renal failure (22-25). So far, some studies have been published on the effects of oral magnesium sulfate in Asthma Patients. In a study, taking 450 mg/day magnesium in children with chronic asthma did not lead to any beneficial clinical effects adjunctive to standard asthma treatment (26). In contrast, two other studies, using 300 mg/day for 2 months in children and 340 mg/day for 6.5 months in adults showed improvements in asthma control and quality of life (17-18).

Since intravenous magnesium sulfate administration requires special care and attention to its possible side effects, it

seems reasonable to evaluate other ways of administration such as oral and Nebulized administration. On the other hand, due to ease of use, low cost and side effects of oral magnesium and lack of studies on children aged 5-12 years with moderate and severe asthma, this study was performed. We aimed to investigate the effect of magnesium sulfate on moderate and severe asthma exacerbation in children.

2- MATERIALS AND METHODS

2-1. Study design and population

This clinical trial was a double-blind, placebo-controlled, single-centered study, performed on 40 asthmatic children. These 40 patients were selected, based on the inclusion criteria, from among 85 children aged 5-12 years, who referred to Pediatric Emergency Department of Quaem Hospital in Mashhad in 2017 with moderate and severe asthma. The minimum sample size in the pilot studies is almost 15 persons for each group, but in this study, 20 persons were selected for each group (25). The patients were randomly assigned into two groups of magnesium (20 patients) and placebo (20 patients).

2-2. Methods

At the beginning of the visit, the demographic information and patient history regarding to the study's variables were obtained and recorded in the questionnaire. They included age, sex, weight, past medical history, family history of asthma and allergies, and clinical examination to determine the asthma severity based on Siriraj Clinical Asthma Score (SCAS) (27, 28).

2-3. Measuring tools: validity, reliability, and laboratory measurements

Asthma severity scores based on SCAS were recorded in the questionnaire. The validity and reliability of SCAS were evaluated by Saejong, et al. (Cronbach's alpha > 0.7) (27). 12 items in the questionnaire were determined for each patient at regular intervals (0, 2, 6 and 24 hours after the first visit and then it was recorded daily up to 5 days). These twelve items include respiratory rate, wheezing, retraction of intercostal or suprasternal muscle, dyspnea, cyanosis, use of accessory muscle, breath sound quality, and degree of air entry, oxygen saturation, inspiratory-expiratory ratio and cerebral function (27-29).

Each of the two groups of magnesium and placebo based on Asthma severity score was divided into three sub-groups: A (mild) = 0-8 points, B (moderate) = 8-16 points, C (severe) = 16-24 points based on clinical asthma score (CAS) in the questionnaire.

2-4. Intervention

Patients were randomly selected to receive magnesium sulfate capsules (at a dose of 300 mg every 12 hours) or placebo (in the same shape and color). Starch was used as a placebo. Random assignment of sample was considered, so that each child who referred to the emergency department with an asthma attack (if they met the inclusion criteria) was randomly placed in one of the two control or magnesium groups. The medication (oral magnesium sulfate) and placebo capsules were prepared by the pharmacist (Zojaj D. Tos Pharmaseutical Company) and the drug was packed with the symbol A and placebo with the symbol B in packages containing 10 capsules. They were given to the patients for 5 days. Patients were examined daily from the time of admission and if discharged from the hospital, followed up daily by telephone (in terms of accurate medication and side effects).

2-5. Ethical consideration

This study was carried out after obtaining permission from the Ethics Committee in medical research of Mashhad University of

Medical Sciences, as well as the written consent of the patients. At the beginning of the visit and during the study, patients were trained for possible unwanted adverse effects of drugs and for the regular use of capsules. The drug and placebo were provided at no charge for patients. This study is part of the PHD thesis of Dr. Melika Zarei Sani and was financially supported by deputy of research, Mashhad University of Medical Sciences (grant number: T4797). The study data were registered in Iranian Registry of Clinical Trials (IRCT20170915036192N2).

2-6. Inclusion and exclusion criteria

Inclusion Criteria included acute asthma diagnosis based on history and clinical examination, moderate and severe asthma exacerbation in 5-12 year-old-children with asthma, and the consent of the child and his legal guardian to enter the study.

exclusion criteria are as follows: Mild asthma exacerbation that were curable in an outpatient setting, the use of drugs that affect the absorption and secretion mechanism of magnesium including diuretics, digoxin and calcium supplements, the presence of chronic underlying diseases other than asthma, such as heart, kidney or lung disease, negligence in drug use and inappropriate follow-up by parents, children with non-Iranian nationality, and ages less than 5 years and more than 12 years.

2-7. Data Analyses

Descriptive data and mean and standard deviation were reported to describe the data. Tests of Inferential statistics including Mix ANOVA with Repeated Measure & Multiple ANOVA analyses were then applied. All analyzes were measured at a significance level of 0.05. SPSS software version 22.0 was used for data analysis. All data analyses were performed under the supervision of supervisors and advisors.

3- RESULTS

A total of 40 subjects, including 8 girls and 32 boys, were divided into two groups of 20 patients in placebo and magnesium groups. 3 girls and 17 boys were in magnesium group and 5 girls and 15 boys were in the placebo group. Twenty-two patients had family history of asthma and 18 patients did not have it. 37 patients had past medical history of asthma and 3 patients did not have it. There was no significant difference between the placebo and magnesium groups in terms of gender, family history and past medical history of asthma ($P > 0.05$).

The mean age of total subjects was 8.20 ± 2.49 years, (in the magnesium group = 8.62 ± 2.65 and in the placebo group = 8.37 ± 2.38). The mean of total weight was 26.32 ± 8.65 kg (in the magnesium group = 26.15 ± 10.01 and in the placebo group = 26.50 ± 7.31).

Classification of asthma severity in the magnesium group included 5 patients in severity A, 14 in B, 1 in C, and in placebo group 8 patients in severity A, 8 in B, and 4 in C.

According to the aim of the study, i.e., comparing the symptom improvement between the magnesium and placebo groups, for each patients, the difference in score of each test step with the score of the next step was calculated as a decrease variable (decrease in the severity of asthma symptoms between two steps), and was recorded in the data table **(Table.1)**.

Measurements were taken once at the beginning of the visit, then at 2, 6, and 24 hours after first visit, and then once a day until the 5th day, which received 8 measurements (scores). The description in brackets represents the day and hour**.** T1_0 represents the measurement of the first day, at the beginning of the visit; T1_2, the measurement of the first day, the second hour; T1_6, the measurement of the first day, the sixth hour; T1_24, the

measurement of the first day, twenty-fourth hour; T2, the second day; T3, the third day; T4, the fourth day; and T5 is representative of the fifth day.

Table-1: Mean of decrease scores in magnesium and placebo groups

Variables	Magnesium group	Placebo group
Decrease 1 (T1_0 – T1_2)	1.65 ± 1.13	1.20 ± 0.89
Decrease 2 (T1_2 – T1_6)	2.40 ± 1.78	2.45 ± 2.16
Decrease 3 (T1_6 – T1_24)	2.85 ± 2.66	4.30 ± 3.13
Decrease 4 (T1_24 – T2)	1.20 ± 1.19	1.10 ± 1.07
Decrease 5 (T2 – T3)	1.05 ± 1.31	1.25 ± 0.78
Decrease 6 (T3 – T4)	0.55 ± 1.66	0.75 ± 0.78
Decrease 7 (T4 – T5)	0.75 ± 1.16	0.50 ± 0.60

To evaluate the effect of the drug on patient's improvement, with the assumption of the normal and uniformity of variances, ANOVA analysis was carried out with repeated measurements in which, the weight effect was controlled as a covariant variable.

The Mauchly's Test of Sphericity was considered as another default of the ANOVA test. So it could not be applied for the data of the present study. Thus, the Greenhouse-Gyser test was used. **Table.2** shows the results of Test of Within-Subjects Effects (comparing the decrease of symptoms severity within one group).

According to the results of **Table 2**, the main effect of Within-Subjects decrease variable is significant (P = 0.000), which is expected, because asthma symptoms decrease over time of treatment. Furthermore, the results showed that there is no significant difference between the decrease group and other variables (P = 0.43). This means that there is no significant difference in decrease rate (symptoms improvement) between the magnesium and placebo groups. However, when the severity variable, as a moderating variable, is included in the study, the results are significant in all of the tests (P = 0.006). This means that the drug had different effects on patients with different asthma severities in the magnesium and placebo groups in one of the decrease intervals.

Table-2: Test of within-subjects effects of mixed ANOVA with repeated measure

Variables	Source	Degrees of freedom	Mean Square	F	P-value
Decrease	Sphere is assumed	6	53.71	24.6	0.000
	Greenhouse-Gyser	3.70	86.90	24.6	0.000
Decrease *group	Sphere is assumed	6	2.19	0.98	0.43
	Greenhouse-Gyser	3.7	3.54	0.98	0.41
Decrease * Severity	Sphere is assumed	12	11.21	5.02	0.000
	Greenhouse-Gyser	7.41	18.14	5.02	0.000
Decrees *group * severity	Sphere is assumed	12	6.51	2.91	0.001
	Greenhouse-Gyser	7.41	10.54	2.91	0.006
Error		204	2.32		

* The sign represents the interact effect.

The results of Test of Between-Subjects Effects (comparison the decrease of symptoms severity between the placebo and magnesium groups) shows that the drug did not show any significant improvement between the magnesium and placebo group (P = 0.15), while there was a significant difference in the rate of symptoms decrease in patients with different asthma severities (P = 0.000); however, it does not indicate that how much medicine has affected the improvement process. For this reason, the comparison between group and severity variables was also performed, which was not significant (P = 0.20). That is, if the average of all the decrease variables, for each possible interaction, is considered between the Between-Subjects variables of group and severity, there is no significant difference between them. But according to **Table 2**, the interaction between within subjects' variables of group and severity is significant; this means that there is a difference in the decrease in one of the decrease variables between the group and the specific severity. Hence, it is necessary to perform a post hoc test to find the desired decrease variable in the desired group and severity; but since this is not possible as an output in SPSS for interacts, first, all possible interactions were formed as a new variable and then the interaction of decrease with the interaction of group in severity were studied (**Table 3).**

Table-3: The composition of interaction between Group and Severity variables

Variable	Group Variable	Severity Variable
Interact 1	magnesium (1)	Severity A (0)
Interact 2	magnesium (1)	Severity B (1)
Interact 3	magnesium (1)	Severity C (2)
Interact 4	placebo (2)	Severity A (0)
Interact 5	placebo (2)	Severity B (1)
Interact 6	placebo (2)	Severity C (2)

A (mild) = 0-8 points, B (moderate) = 8-16 points, C (severe) = 16-24 points

In Order to examine the mentioned cases using the interact variable, the multivariate analysis of variance (MANOVA) was used as an independent variable and decrease variables as a dependent variables for the analysis of the data (**Table 4**). Based on **Table 4**, only the difference between the levels of interact variable is significant with decrease 3, that means the largest difference in symptom improvement has shown between interact levels, at 6 to 24 hours after the first visit. Post-Hoc tests were also applied to determine where (between which levels of interact variable) this difference is placed.

As shown by the Post-Hoc results for the dependent variable (Decrease 3), the different levels of interact variable are significantly different in symptoms improvement. Since the aim of this study is to examine the difference in symptoms improvement in placebo and magnesium groups, the difference between the interacts 1, 2 and 3 which are related to the magnesium group and interacts 4, 5 and 6 were investigated. Furthermore, to control the effect of severity on the treatment, each severity was compared with its corresponding severity from the opposite group, that is, interact 1 with 4 (severity A), 2 with 5 (severity B) and 3 with 6 (severity C). Post-Hoc results for the dependent variable (decrease 3) show that the only difference between interact 2 with 5, that is related to severity B, was significant (P = 0.007). The effect of drug

on patients with B severity score was between the magnesium and placebo groups, as symptoms decrease in magnesium group was 3.03 units greater than that of the placebo group. Regarding the significant difference in symptoms improvement among different severities in a group (magnesium or placebo), it is revealed that severity has a moderating role in treatment. For example, the difference between interact 3 with 1 (P = 0.003) and 2 (P = 0.004), reflects this role showing that the drug was more effective on symptom improvement when symptoms were more severe. Since B severity score are including 14 patients in magnesium group and 8 patients in placebo group, we can say that this result applies to most of the patients in the group. It can be concluded that the drug used in this study had an accelerating effect on symptoms improvement during 6 to 24 hours after taking the drug among subjects with B severity score, having reduced the symptoms for 3.03 units more than those who did not take the drug.

Table-4: The results of Multivariate ANOVA (MANOVA) for Decrease (dependent variable) with Interact as independent variable

Independent Variable	Dependent Variable	Degrees of freedom	Mean Square	F	Sig
Interact	Decrease 1	5	1.17	1.10	0.37
	Decrease 2	5	5.18	1.42	0.42
	Decrease 3	5	30.94	5.62	0.00
	Decrease 4	5	1.23	0.97	0.44
	Decrease 5	5	1.47	1.32	0.27
	Decrease 6	5	1.13	0.65	0.66
	Decrease 7	5	0.47	0.51	0.76
Error	Decrease 1	34	1.05		
	Decrease 2	34	3.64		
	Decrease 3	34	5.50		
	Decrease 4	34	1.26		
	Decrease 5	34	1.11		
	Decrease 6	34	1.74		
	Decrease 7	34	0.91		

4- DISCUSSION

The purpose of our study was to evaluate the effect of magnesium sulfate on moderate and severe asthma exacerbation in children. According to the results, the effect of oral magnesium sulfate on symptoms improvement of asthma exacerbation in 5-12-year-old children was not significantly influenced by weight as a variable. The results of the further findings, after considering the severity as a moderator variable, showed minor effect of oral magnesium sulfate on symptom improvement in patients with asthma exacerbation with B severity score. Despite numerous studies on asthma and its treatments, no study has previously investigated the effect of oral magnesium sulfate on acute asthma symptoms in children. Therefore, the obtained results are compared with similar studies with the same methodology. Fogarty et al. (2003) found that using 450 mg/day oral magnesium during 16 weeks in 18-60-year-old patients with chronic asthma did not show any beneficial clinical effects, in addition to the standard asthma treatment

(26), while this study showed some minor effects of oral magnesium sulfate on symptom improvement in patients. The results of Gontijo-Amaral et al. (2007), among 7-19-year-old patients with chronic asthma, showed that taking 300 mg/day oral magnesium by 2 months, decreased the bronchial responsiveness to methacholine, decreased allergen-induced skin response and provided better control of moderate persistent asthma in children (17). kazakz et al. (2010), showed that taking 340 mg/day oral magnesium in four months in 21-55-year-old patients with mild to moderate asthma resulted in the improvement of bronchial responsiveness to methacholine, peak expiratory flow rate (PEFR), as well as improvements in asthma control and quality of life (18). Fathi et al (2013), showed that taking 340 mg/d of oral Mg for two months in 19-55-year-old patients resulted in improvement of lung function in patients with mild and moderate asthma (30).

The results of these three studies showed the beneficial effects of oral magnesium sulfate in chronic asthma. Their results are not consistent with that of our study, in which only minor effects of magnesium sulfate in B severity group were confirmed. This inconsistency could be due to differences in dose, duration of drug intake and target groups. Furthermore, two of these studies were carried out among patients with chronic asthma, whereas the present study was performed among patients with asthma exacerbation. In another study by Irazuzta et al. (2017), the effect of intravenous magnesium sulfate in treatment of acute asthma was investigated among children, and the role of intravenous magnesium sulfate (infusion) as a complementary therapy was emphasized (31). Sarhan et al. (2016) investigated the nebulized magnesium sulfate in acute asthma in 11-70-year-old patients. Their results indicated clinical improvement, increased PEFR, decreased pulse rate and respiratory rate (21). However, these studies have been carried out among children with acute asthma; the inconsistency between the results of these studies and those of our study can be due to the difference between the forms of magnesium sulfate and their pharmacokinetics in the body.

5- STUDY LIMITATIONS

The limitations of the study include exclusively enrolling children 5-12 years from mashhad, Iran, Who were referred to the emergency department with an asthma attack and the samples were not previously hospitalized. Other limitations of this study were unknown peak plasma time of the oral magnesium sulfate, not enough confidence about accurate use of the drug due to the lack of immediate access to the patient, bioavailability and its absorption.

6- CONCLUSION

Generally, it was found that the oral use of magnesium sulfate has no significant effect on improvement of asthma symptoms; however it has a minor effect on symptom improvements in subjects with B severity score. Due to the limitations of this study and the small sample size, the generalization of the results should be done with caution, and generally, more research is needed to conclude about the use of magnesium sulfate in people with asthma attack.

7-CONFLICT OF INTEREST

None.

Oral magnesium sulfate on asthma exacerbation

First and Last Names: Age:

Family history of asthma and allergies: Asthma severity:

Address: Telephone number:

History of previous asthma attacks:

Items	Severity scale		
	0	1	2
1. Respiratory rate (breath/min)	< 40	40-60	>60
2. Wheezing	None	Expiration	Expiration/ inspiration
3. Expiratory wheezing - degree	None	Moderate	Marked
4. Retractions	None	1 site	>1 sites
5. Dyspnea	None	Mild	Marked
6. Degree of air entry	Normal	Decreased	Absent
7. Breath sound quality	Normal	Unequal	Decreased
8. O_2 saturation	>95%	92-94%	<91%
9. Presence of cyanosis	None	In room air	In 40%O_2
10. Use of accessory muscles	None	Moderate	Marked
11. Inspiratory:expiratory ratio (I:E ratio)	I>E	I=E	I<E
12. Cerebral function	Normal	Depressed	Coma

Asthma attack score:
At the first visit:
After 2 hours:
After 6 hours:
After 24 hours:
The time of temporary admission:
The time of Permanent admission:

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