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Efficacy of Magnesium Sulfate Treatment in Children with Acute Asthma

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Significance of the Study

- This study investigates the efficacy of systemic magnesium sulfate treatment in asthmatic children with a considerable number of patients.
- It appears to have a beneficial bronchodilator response by providing sufficient bronchodilator effect on pulmonary function parameters in children with acute asthma.
- Systemic magnesium sulfate may be considered for patients with acute asthma attack.

Keywords
Asthma · Children · Magnesium sulfate · Spirometry

Abstract

Objective: Systemic administration of magnesium sulfate ($MgSO_4$) has been proposed as a treatment for pediatric patients with acute asthma. However, previous trials show mixed results and uncertain evidence of benefit. The aim of the study was to ascertain whether intravenous (IV) $MgSO_4$ improves lung function parameters in children with acute asthma. ***Methods:*** This was a prospective clinical trial. All patients with acute asthma received 40–50 mg/kg or maximum 1,500 mg (>30 kg) of single dose IV $MgSO_4$, administered over 60 min. Spirometry was conducted before and 15 min after $MgSO_4$ infusion. ***Results:*** One hundred and fifteen children aged 6 to 17 years presenting with acute asthma and FEV_1 between 40% and 75% of predicted were included. Then, the patients were classified into 2 groups; mild asthma attack (FEV_1 ranged from 60% to 75%; $n = 50$) or moderate asthma attack (FEV_1 ranged from 40% to 59%; $n = 65$). The baseline characteristics were similar in both groups. The mean percent predicted pre and post values for FEV_1/FVC ratio (mild group: 82.59 ± 9.46 vs. 85.06 ± 8.95; moderate group: 77.31 ± 11.17 vs. 79.99 ± 11.77), FEV_1 (mild group: 67.14 ± 4.99 vs. 72.29 ± 8.05; moderate group: 48.50 ± 6.81 vs. 53.78 ± 9.81), PEF (mild group: 65.49 ± 12.32 vs. 71.37 ± 12.96; moderate group: 47.56 ± 11.78 vs. 51.97 ± 13.98), and $FEF_{25–75}$ (mild group: 58.20 ± 12.24 vs. 66.57 ± 16.95; moderate group: 37.77 ± 11.37 vs. 43.41 ± 14.19) showed a statistically significant ($p < 0.05$ for all) bronchodilator effect after $MgSO_4$ infusion in both groups with few side effects. ***Conclusion:*** Administration of IV $MgSO_4$ was associated with improved pulmonary function in children with acute asthma.

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Introduction

Asthma is the most common chronic lung disease occurring in all age groups frequently beginning in childhood. The prevalence of asthma has increased in developed countries over the last 4 decades. The disease is associated with airway inflammation and characterized by hyper-responsiveness of the airways with reversible airway obstruction. Asthma symptoms can be triggered by respiratory viruses, allergens, tobacco smoking, air pollutants, and cold or dry air. In spite of the availability of good preventive treatment, respiratory symptoms and acute attacks related to asthma in children still occur and are responsible for a considerable number of clinic or emergency visits, hospital admissions, and missed school days [1].

The main goal of treatment in acute asthma attack is to relax airway smooth muscles, decrease vascular permeability, increase mucociliary clearance, decrease mucus secretion, and most importantly, downregulate airway inflammation. The most indispensable initial treatment for asthma attack is short-acting β_2 agonists such as salbutamol/albuterol or terbutaline to relieve airway obstruction. Safe and effective inhalation of these drugs leads to bronchodilatation. Alternative additive therapies in the treatment of acute asthma attack may include inhaled ipratropium bromide, subcutaneous or inhaled epinephrine/adrenaline, intravenous (IV) or inhaled magnesium sulfate ($MgSO_4$), and IV aminophylline [2].

Among these additive therapies, $MgSO_4$ may offer a clinically useful option in treating acute asthma exacerbations in children. Although the precise mechanism by which $MgSO_4$ produces bronchodilatation of smooth muscles is not well understood, it is thought to act by enhancing calcium uptake in the sarcoplasmic reticulum and/or as a calcium antagonist. Additionally, magnesium is a cofactor regulating a number of enzymatic and cellular activities in the body, including adenyl cyclase and sodium-potassium ATP-ase, potentially enhancing the effects of β_2 agonists. Other potential beneficial mechanisms in asthma include inhibition of acetylcholine release from cholinergic nerves and reduction in the release of histamine release from mast cells [3]. About 40% of magnesium is bound to plasma proteins and requires distribution into smooth muscle tissue for activity. A retrospective study using covariate analysis investigated serum magnesium disposition by clearance and volume distribution in pediatric population, and stated that only body weight was significantly correlated with serum magnesium concentrations. The authors also reported that magnesium had a short half-life of 2.7 h serum concentration in children [4].

Though systemic $MgSO_4$ treatment in children with acute asthma may be helpful, results of published trials are conflicting regarding the impact of the treatment on respiratory distress. [5, 6]. Therefore, we hypothesized that $MgSO_4$ infusion would result in significant improvement in spirometric measures of lung function in children with acute exacerbations for asthma.

Material and Methods

This was an open intervention study conducted in the Pediatric Pulmonology Section, Mersin City Training and Research Hospital between February and June 2019. Our hospital is a tertiary pediatric hospital with the only pediatric pulmonology clinic in the region serving a population of 1,793,000. The study included a convenience sample of (1) children aged 6–17 years with MD-diagnosed asthma; (2) presenting with respiratory complaints due to asthma; (3) no history of using short-acting β_2 agonist in the past 3 h (in order to examine only systemic $MgSO_4$ response); (4) no history of oral/IV steroid use in the past 12 h; (5) respiratory stable outpatient with an oxygen saturation (SpO_2) >92% on room air; (6) spirometry with a forced expiratory volume in 1 s (FEV_1) 40% to 75% of predicted measured at the time of the clinic visit. Children who were unable to perform spirometry or who showed unstable clinical status during the study period were excluded.

Patients were given one dose of $MgSO_4$ ranging from 40 to 50 mg/kg or a maximum 1,500 mg for patients >30 kg in 100 mL of normal saline, administered over approximately 60 min at the discretion of the nurse caring for the patient. Spirometry (MIR® Spirolab model 2014, Rome, Italy) was performed before and 15 min after completion of $MgSO_4$ infusion by an experienced technician. The spirometry procedure was conducted with the children seated upright with at least 3 appropriate expiratory maneuvers. In order to examine the degree of airway obstruction, forced vital capacity (FVC), FEV_1, peak expiratory flow (PEF), and forced expiratory flow between 25 and 75% of the FVC ($FEF_{25–75}$) were included as spirometric values, and expressed as percent of predicted based on height and gender of the child. Normal values were defined using the data of the European Respiratory Society Global Lung Function Initiative [7].

All patients were continually monitored (B40® monitore, model 2016, Freiburg, Germany) for blood pressure, SpO_2, respiratory depression, and arrhythmia for the safety of magnesium infusion. Then, the patients immediately received standard care for asthma with inhalation of short-acting β_2 agonist and systemic steroid if needed as part of their management. Patients showing clinical or laboratory signs of deterioration were excluded from the study. Efficacy of $MgSO_4$ treatment was assessed as the change of FEV_1/FVC, FEV_1, PEF, and $FEF_{25–75}$ parameters before and after $MgSO_4$ infusion.

The study protocol was approved by the University of Cukurova and written informed consent was obtained from parents of the study participants. Additionally, all children were verbally informed about the study procedure.

Statistical Analysis

Statistical analyses were performed using an IBM SPSS Statistics Version 20.0 software package. Categorical variables were ex-

Table 1. Demographic characteristics of children with acute asthma

	Mild asthma (n = 50)	Moderate asthma (n = 65)	p value
Age			
Mean	10.30±2.91	10.54±3.11	0.676
Median	10 (6–17)	10 (6–17)	
Male sex	33 (66%)	41 (63.1%)	0.845
Parental asthma	11 (22%)	14 (21.5%)	1.00
First asthma symptom			
Mean	3.02±2.59	3.20±3.09	0.740
Median	2.25 (0.6–13)	2 (0.3–14)	
IgE levels, IU			
Mean	265.47±171.93	313.40±266.74	0.271
Median	205 (34–702)	267 (17–1,410)	
Inhaled allergen positivity	35 (70%)	42 (64.6%)	0.557
Allergic rhinitis	23 (46%)	31 (47.7%)	1.00
Atopic dermatitis	4 (8%)	2 (3.1%)	0.401
Indoor smoking	18 (36%)	18 (27.7%)	0.418
Current treatment			1.00
None	20 (40%)	27 (41.5%)	
Asthma prophylaxis			
Montelukast	8 (16%)	18 (27.7%)	
Inhaled steroid	16 (32%)	6 (9.2%)	
Inhaled steroid and LABA	6 (12%)	14 (21.5%)	

pressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation when the data was equally distributed or as median and minimum-maximum when non-equally distributed. The chi-square test was used to analyze categorical variables. For comparison of continuous variables between two groups, the Student's t test was used. For comparison of two related (paired) continuous variables, paired samples t test was used. A p value <0.05 was considered statistically significant.

Results

One hundred thirty-six children with asthma exacerbation were enrolled in this study. A total of 21 were excluded for insufficiently performed pulmonary function test (n = 12), nausea/vomiting (n = 4), decrease in SpO_2 level (n = 4), and hypotension (n = 1) during $MgSO_4$ infusion, resulting in a final sample size of 115 patients. Then, the patients were categorized into 2 groups according to their initial FEV_1 results (Fig. 1).

Group 1 consisted of children with a mild attack (FEV_1 between 60 and 75% of predicted) and group 2 of children with moderate attack (FEV_1 between 40 and 59% of predicted). The demographic characteristics of children are detailed in Table 1. Baseline characteristics were similar

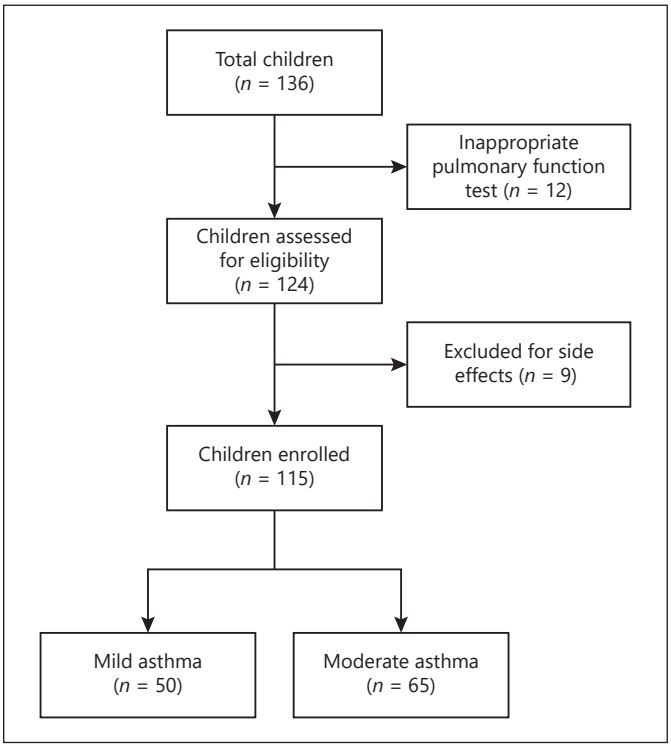

Fig. 1. Enrollment flow diagram.

Table 2. Oxygen saturation, heart rate, and blood pressure of children with acute asthma

	Pre-treatment	Post-treatment	*p* value
Oxygen saturation, %			
Mild attack	96.10±1.79	96.20±2.55	0.760
Moderate attack	95.20±2.59	95.31±2.65	0.693
Heart rate, beats per min			
Mild attack	104.48±16.40	105.16±15.58	0.712
Moderate attack	116.03±15.63	117.54±17.04	0.391
Blood pressure (systolic), mm Hg			
Mild attack	115.86±10.28	114.60±10.91	0.359
Moderate attack	117.89±12.85	115.97±12.01	0.240
Blood pressure (diastolic), mm Hg			
Mild attack	73.58±7.83	71.40±7.91	0.155
Moderate attack	72.88±10.00	72.28±9.21	0.659

Results are expressed as mean ± SD.

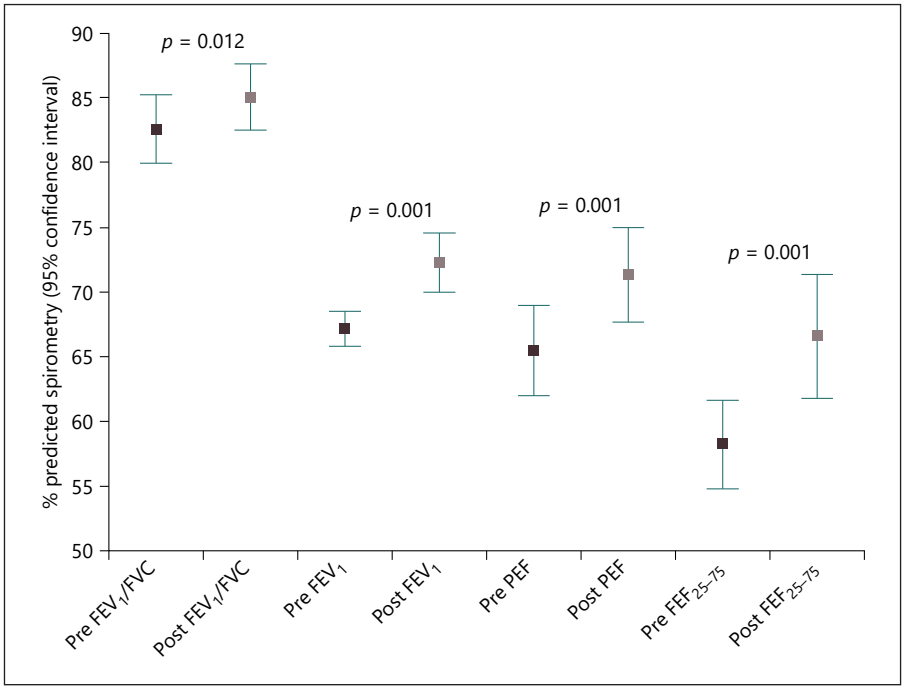

Fig. 2. Lung function parameters in children with acute asthma in the mild group.

for age at participation, sex, history of parental asthma, age of first asthma symptom, atopic status (allergic rhinitis, atopic dermatitis, allergy skin test positivity, and IgE levels), indoor smoking exposure, and current asthma medication among the 2 groups ($p > 0.05$). Additionally, there were no statistically significant differences in SpO_2, heart rate, and systolic and diastolic blood pressure changes during pre and post $MgSO_4$ infusion in either group (Table 2).

When the mean pre and post FEV_1/FVC ratio (82.59 ± 9.46 vs. 85.06 ± 8.95), FEV_1 (67.14 ± 4.99 vs. 72.29 ± 8.05), PEF (65.49 ± 12.32 vs. 71.37 ± 12.96), and $FEF_{25–75}$ (58.20 ± 12.24 vs. 66.57 ± 16.95) percent predicted values were compared, all lung function parameters showed significant improvement with $MgSO_4$ infusion in children with acute asthma in the mild group (Fig. 2). Similarly, when the mean pre and post FEV_1/FVC ratio (77.31 ± 11.17 vs. 79.99 ± 11.77), FEV_1 (48.50 ± 6.81 vs. 53.78 ±

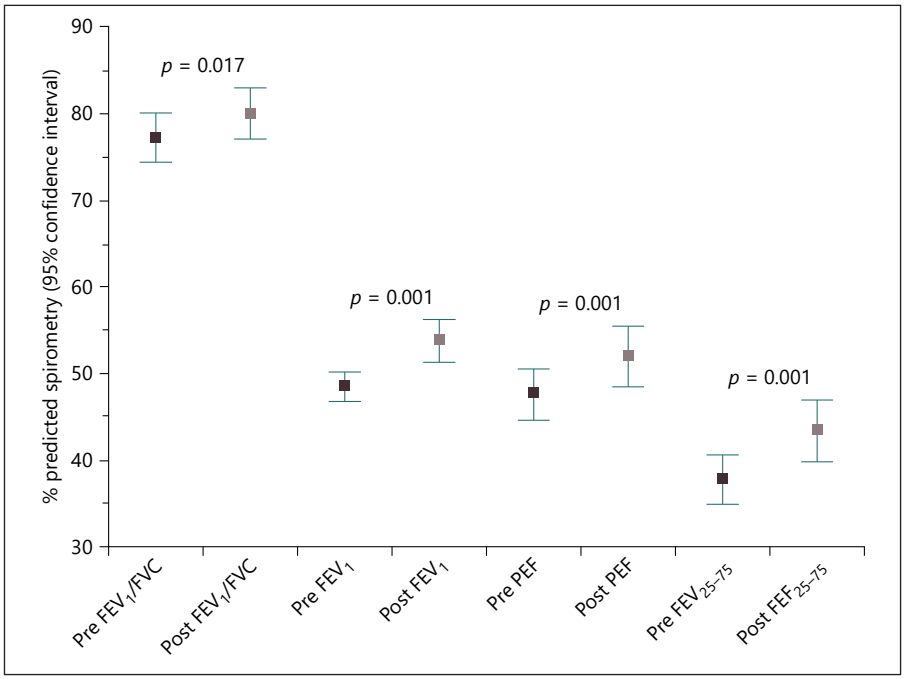

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Fig. 3. Lung function parameters in children with acute asthma in the moderate group.

9.81), PEF (47.56 ± 11.78 vs. 51.97 ± 13.98), and $FEF_{25–75}$ (37.77 ± 11.37 vs. 43.41 ± 14.19) percent predicted values were compared, all parameters again improved significantly with $MgSO_4$ treatment in children with acute asthma in the moderate group (Fig. 3).

The mean change in FEV_1 and $FEF_{25–75}$ with $MgSO_4$ infusion was 7.7 and 14.2% in the mild group, and 10.9 and 14.9% in the moderate group.

Discussion

Several studies have reported that systemic administration of $MgSO_4$ in adults with moderate to severe acute asthma resulted in significantly improved short-term pulmonary function [8, 9]. Although most studies examining the potential clinical role of $MgSO_4$ treatment in children with acute asthma have shown beneficial effect, its precise role has still not been fully elucidated [10–15]. In this regard, two meta-analyses examined the role of IV $MgSO_4$ for acute severe asthma as part of the co-therapies with inhaled β_2 agonists and systemic steroids mainly conducted in the pediatric emergency department [16, 17]. After pooling the results, IV $MgSO_4$ was found to be effective as an adjunctive therapy in avoiding hospitalization (odds ratio: 0.290, 95% confidence interval: 0.143 to 0.589). In addition, the pooled result on asthma symptom scores showed consistent improvement in the analysis. The use of IV $MgSO_4$ in the emergency room was well tolerated with only minor side effects. Both meta-analyses concluded that IV magnesium sulfate is an effective additional treatment for children with acute severe asthma who had not responded to initial standard treatment. Moreover, a recent study reported IV infusion of $MgSO_4$ during the first hour of hospitalization in patients with acute severe asthma was associated with significantly reduced percentage of children who required mechanical ventilation support [18].

In a study conducted by Singhi et al. [19] comparing the efficacy of IV $MgSO_4$, terbutaline, and aminophylline for children with acute, severe asthma poorly responsive to standard initial treatment, adding a single dose of IV $MgSO_4$ to inhaled β_2 agonists and corticosteroids was found to be more effective, and safer than using terbutaline or aminophylline when treating children with acute severe asthma poorly responsive to initial treatment.

A few studies have investigated the effect of $MgSO_4$ treatment on pulmonary function. Children treated with IV magnesium infusion in addition to nebulized salbutamol for acute asthma had significantly greater immediate improvement in PEFR compared to placebo group [10, 12]. Additionally, this effect was sustained for hours in the treatment group. A single double-blind placebo-controlled trial conducted on a limited number of children with acute asthma examined the effect of $MgSO_4$ infusion on detailed pulmonary function; the treatment

group showed greater percentage of improvement in FVC, FEV_1, and PEFR measurements, and were more likely to be discharged to their homes than the placebo group [11].

A recent Cochrane review analyzed studies on systemic $MgSO_4$ in the treatment of children with acute asthma [20]. The review emphasized that treatment with IV $MgSO_4$ reduced the odds of admission to hospital by 68% (odds ratio: 0.32, 95% confidence interval: 0.14 to 0.74). But the estimated reduction in true population in admission had a wide confidence interval between 86 and 26%. There was reduced length of hospital admission by 5.3 h with IV $MgSO_4$ treatment. The review also concluded that there was an additive benefit of $MgSO_4$ treatment on other parameters such as reduction in intensive care admissions, vital signs, spirometry, or scores on symptom scales, or the likelihood of returning to the emergency department within 48 h with generally mild and infrequent reported side effects. However, the authors concluded that it was difficult to know whether this was either evidence of safety or was sufficient to recommend such a therapy in the presence of weak effect size and small sample size in the trials in the literature.

The current prospective study has demonstrated that in children aged between 6 and 17 years with mild or moderate acute asthma, systemic infusion of $MgSO_4$ treatment resulted in a beneficial bronchodilator effect as determined by spirometry parameters. Moreover, it could be speculated that $MgSO_4$ treatment would also be beneficial in children with severe asthma based on the study results. Unlike most studies reported in children with acute asthma, the present study on a reasonable sample size has shown beneficial bronchodilator response in the absence of inhaled β_2 agonists. It should be noted that although IV $MgSO_4$ provided statistically significant bronchodilator effect in lung function parameters, its benefit appears not as potent as inhaled β_2 agonists (i.e., expected change in FEV_1 >12% and $FEF_{25–75}$ >%24) [21]. In contrast, we did not observe any improvement in SpO_2 levels with $MgSO_4$ infusion in both treatment groups. This could be related to the initially selected patients with SpO_2 levels >92% or SpO_2 might not change even in the presence of sufficient bronchodilation [22]. Because the study was aimed only at investigating the effect of $MgSO_4$ infusion on pulmonary function parameters, other outcomes (e.g., improvement in asthma symptom scores, emergency department visit, hospital admission, etc.) were not assessed. Our findings must be supported by additional studies including other parameters mentioned above.

One of the major limitations of this study is the lack of a control group. Therefore, we do not know if the children would have simply improved on their own without the magnesium sulfate treatment. The main reason for not adding a control group was ethical concerns.

Systemic use of $MgSO_4$ appears to be safe; minor side effects such as headache, muscle tightness or contraction, flushing, heart disturbances, confusion, dry mouth, malaise, and hypotension have been reported in the literature [23]. Approximately 7% of children with side effects attributed to $MgSO_4$ infusion were excluded from our study. Another limitation of this study is that magnesium levels of the study participants were not routinely measured prior to and after the treatment in order to determine a therapeutic level. However, the dose of $MgSO_4$ used suggests that it did achieve sufficient beneficial effect in the study population.

Conclusion

Systemic use of $MgSO_4$ appears to have a beneficial effect on bronchodilator response in spirometric parameters in children with acute asthma with few side effects. Thus, it may be considered for the management of children with asthma suffering from acute airway obstruction.

Acknowledgement

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Statement of Ethics

The study protocol was approved by the University of Cukurova and written informed consent was obtained from parents of the study participants. Additionally, all children were verbally informed about the study procedure.

Disclosure Statement

There is no competing interest.

Funding Sources

None.

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