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Brief Report

The effect of nebulized magnesium sulfate in the treatment of moderate to severe asthma attacks: a randomized clinical trial

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ABSTRACT

Objective: Thirty percent of people with asthma do not respond to standard treatment, and complementary therapies are needed. The objective of this study was to investigate the impact of inhaled magnesium sulfate on the treatment response in emergency department (ED) patients with moderate to severe attacks of asthma.
Methods: This study is a randomized controlled trial, enrolling patients with moderate to severe asthma in the ED. Subjects allocated to the study group were treated with the standard, plus 3 ml of 260 mmol/L solution of magnesium sulfate every 20 to 60 minutes. The control group was treated with nebulized saline as a placebo in addition to standard protocol. The study results included admission rate and changes in peak expiratory flow rate (PEFR) (primary outcomes) as well as dyspnea severity score, respiratory rate and peripheral oxygen saturation.
Results: A total of 50 patients were enrolled (25 allocated to the study group and 25 to the control group). The study group as compared to the control group had significantly more improvement in the intensity of dyspnea, PEFR and Spo_2 20, 40 and 60 minutes after intervention. In the control group, 11 patients (44%) required admission as compared to 18 (72%) in the control group ($P = .02$).
Conclusion: Adding nebulized magnesium sulfate to standard therapy in patients with moderate to severe asthma attacks leads to greater and faster improvement in PEFR, respiratory rate, oxygen saturation and respiratory rate. It also reduces hospitalization rates in this patient population.

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Introduction

Over the past few decades, the main therapeutic approach in the emergency management of asthmatic patients had consisted of inhaled $\beta 2$ agonists. Despite the effectiveness of this regimen, up to 30% of emergency department (ED) patients fail to improve and require administration of adjunct medications or hospitalization for continuous treatment [1].

Systemic or inhaled corticosteroids are very effective in treating asthma attacks. However, their full effect may take several hours [1]. Methyl xanthines such as intravenous aminophyline are rarely used in clinical practice because of their low therapeutic index and high risk of serious side effects [2]. Repeated doses of inhaled anticholinergics in combination with $\beta 2$ agonists have been shown to be beneficial in reducing the severity of asthma attack [3].

Intravenous magnesiumsulfate has been recommended as an adjunct treatment in the treatment of severe asthma [4]. Studies examining the effectiveness of inhaled magnesium sulfate are rather limited and frequently contradictory [5].

This clinical trial was designed to evaluate the clinical benefits of inhaled magnesium sulfate in the treatment of ED patients with moderate to severe asthma.

Materials and methods

This study is a randomized, double-blind, placebo-controlled clinical trial, which was conducted from January to May 2013 in 2 academic urban EDs in Tehran, Iran. The study was registered on Clinical Trials Registry (trial #IRCT2013022412588N1) and approved by the ethics committee of Iran University of Medical Sciences. Informed written consent was obtained from all participants before the enrollment.

ED patients older than 16 years presenting with moderate (dyspnea severe enough to limit usual activity or peak expiratory flow rate [PEFR], 40%-69% of expected) to severe (dyspnea interfering with speech or PEFR < 40%) asthma attack were enrolled. Exclusion criteria were as follows: the need for immediate intubation, significant impairment of heart function, kidney or liver disease, fever greater than 38.3°C, chronic lung disease (such as COPD), pregnancy or lactation, and pneumonia.

On admission, all patients underwent clinical examination. A detailed medical history was also obtained from all the patients. At baseline, the dyspnea severity score was documented by questioning the patient (a score from zero indicating no shortness of breath to 10, indicating maximum dyspnea; a score of 1-3 is considered as mild

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dyspnea, 4-6 as moderate, and 7-10 as severe dyspnea). Dyspnea score was calculated throughout the ED visit and upon admission (if applicable) as a measure of treatment and net response.

All the patients underwent pulse oximetry and peak flow measurement upon presentation and their eligibility for enrollment was assessed. If enrollment criteria were met, patients were assigned to routine care plus inhaled placebo (control group) or routine care plus inhaled magnesium sulfate, using a computer-generated randomization software. A random table was prepared by the computer, and patients were divided into 2 groups of case and control (25 patients in each group). Both patients and investigators were blinded to the content of the vials. The study vials were prepared by a research pharmacist in identical containers.

The control group received standard treatment for asthma including 2.5 mg of nebulized salbutamol, 0.5 of nebulized atrovent and 50 mg of oral prednisolone plus 3 mL of saline as placebo every 20 to 60 minutes. Subjects assigned to the study group received standard treatment plus 3 ml of 260 mmol/L solution of magnesium sulfate which was administered via a nebulizer by face mask every 20 minutes to 1hsimultaneously with the first line therapy.

Patients were under continuous pulse oximetry. PEFR was measured upon admission and every 20 to60 minutes after the beginning of treatment which was determined by a hand held mini peak flow meter. PEFR and vital signs including oxygen saturation were documented every 20 to 60 minutes. Dyspnea severity index was also documented and recorded every 20 to 60 minutes.

Both groups were monitored for the occurrence of side effects related to magnesium sulfate (hypotension, cardiac dysrhythmia and respiratory arrest). The investigators planned to stop the treatment and break the blinding code if any of these side effects occurred.

The need for admission was determined at the end of the 60 minutes by the ED physician caring for the patient who was blinded to the study allocation. The decision was made based on clinical examination (lung auscultation and the degree of respiratory muscle retraction), vital signs, as well as the dyspnea severity score.

Primary outcome measures in this study were the improvement of PEFR and the admission rate. The secondary outcomes were dyspnea severity index, respiratory rate (RR) and oxygen saturation.

Statistical analysis

Continuous variables were examined for normal distribution before analysis. Kolmogorov–Smirnov test was used for this purpose. Variables that were found to be distributed normally were compared using Student *t* test. Non-normally distributed variables were compared using Mann-Whitney *U* test. Categorical variables were reported as percentages with 95% confidence intervals. Comparison of categorical variables was performed with Fisher's exact test. α was set as .05. SPSS version 18 (SPSS, Chicago, IL) was used to perform the statistical analyses.

Results

A total of 50 patients (25 patients in the control group and 25 patients in the magnesium sulfate group) were enrolled in the present study. Baseline characteristics of the 2 groups upon presentation are shown in Table 1. As presented, groups were comparable at baseline.

Comparison of groups for response to treatment at 20 minutes is shown in Table 2. PEFR and Spo_2 were significantly higher than the control group ($P = .002$).

Eleven patients in the intervention group (44%) versus 18 patients in the control group (72%) required hospitalization. The need for hospitalization in magnesium sulfate group was lower than that in the control group ($P = .02$).

Severity of dyspnea was significantly less in the magnesium sulfate group than in the control group after 20 minutes ($P = .004$). At this time point, no patient in the study group had severe symptoms, whereas 7 patients in the control group (28%) still had severe respiratory symptoms (Figure).

Table 1
Comparison of baseline characteristics and disease severity between the 2 groups on admission

	Case group (n = 25)	Control group(n = 25)	*P*
Age	52.4 ± 16.9	53.9 ± 16.2	.754
Sex			.396
Female	14(56%)	11(44%)	
Male	11(44%)	14(56%)	
Dyspnea severity			.6
Mild	0(0%)	1(4%)	
Moderate	3(12%)	3(12%)	
Severe	22(88%)	21(84%)	
RR	35.5 ± 6.9	32.3 ± 4.8	.063
Spo_2(%)	84.1 ± 4.1	82.1 ± 5.0	.064
PEFR (% predicted)	15.1 ± 4.7	14.7 ± 6.4	.31

Similar pattern of improvement in treatment response was seen 40 and 60 minutes after enrollment in the inhaled magnesium sulfate group (Tables 2 and 3).

Treatment-related complications were not seen in any of the studied groups.

Discussion

Magnesium is the second intracellular cation in terms of concentration and is an essential cofactor in over 300 enzymatic reactions. The rationale for using magnesium sulfate in the treatment of acute exacerbations of asthma is multi-factorial. In recent years, calcium ion has been named as a factor in pathogenesis of asthma. Using magnesium to antagonize the uptake and physiological effects of calcium on smooth muscle contraction promoted the idea of using intravenous magnesium in severe asthma attacks. Furthermore, it is shown that magnesium inhibits the release of acetylcholine from cholinergic nerve terminals and therefore leads to a decrease in membrane excitability of muscle fibers and consequently the relaxation of bronchial smooth muscle. Magnesium can also reduce histamine release from mast cells (anti-inflammatory role) and stimulate the production of prostacyclin synthesis [1].

The results of using intravenous magnesium sulfate for severe asthma were encouraging. A systematic review of 13 studies involving 965 adult patients and children using intravenous magnesium sulfate therapy showed significant reduction in admission rate. However, when the analysis was limited to adults, these reductions in need for hospitalization were not observed. In the subgroup of patients with severe asthma attacks, intravenous magnesium reduced the need for hospitalization in addition to improvements in pulmonary function [6]. The promising results of administering intravenous magnesium sulfate in severe asthmatic patients and the fear of side effects of intravenous magnesium sulfate, made trying the nebulized magnesium sulfate the next logical step.

In the literature search 2 types of experimental studies were encountered in this field. First are the trials that compare the combination of salbutamol and magnesium sulfate with salbutamol and placebo (nebulized normal saline). The second types of trials are those that compare salbutamol and magnesium sulfate directly.

Table 2
Comparison of response to treatment in both groups 20 minutes after treatment

	Case group	Control group	*P*
Dyspnea severity			.004
No dyspnea	2	2	
Mild	17	6	
Moderate	6	10	
Severe	0	7	
RR	6 ± 27.2	5.7 ± 27.0	.924
Spo_2(%)	2.4 ± 94.1	4.8 ± 90.8	.002
PEFR (% predicted)	9.6 ± 24	9.4 ± 17.1	.002

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