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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:30% 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 min. 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 60min after intervention. In the control group, 11 patients (44%) required admission as compared to 18 (72%) in the control group (P = 0.02).

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.

Key words: Nebulized magnesium sulfate, asthma, respiratory rate, treatment.

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 effectivenessof inhaled magnesium sulfateare 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 two 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. Score of 1-3 is considered as mild 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 two 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 min. 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 min to 1hsimultaneously with the first line therapy.

Patients were under continuous pulse oximetry. PEFR was measured upon admission and every 20 to60 min 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 min. Dyspnea severity index was also documented and recorded every 20 to60 min.

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 min 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 (O_2 Sat).

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. Alpha was set as 0.05. SPSS version 18 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 two groups upon presentation are shown in Table 1. As presented, groups were comparable at baseline.

Comparison of groups for response to treatment at 20 min is shown in Table 2.PEFR and SPO2 were significantly higher than the control group (P = 0.002).

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 = 0.02).

Severity of dyspnea was significantly less in the magnesium sulfate group than in the control group after 20 min (P = 0.004). 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.

Similar pattern of improvement in treatment response was seen 40 and 60 min 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 [7]. 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 two 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.

In a clinical trial in 2002, Bessmertny and colleagues studied 74 patients with mild to moderate acute asthma. The study group was treated with nebulized albuterol plus magnesium sulfate and the control group was treated with nebulized albuterol plus normal saline as placebo. 30% of the control group and 19% of the case group showed more than 15% improvement in FEV1 as compared to before treatment. It showed more improvement in the control group and there was no difference in improvement in FEV1 between the two groups. The researchers concluded that nebulized magnesium sulfate in combination with albuterol had no additional benefit as compared to standard

treatment with nebulized albuterol. The important point of this study is that patients with severe asthma attacks (PEFR< 40% predicted) were excluded from the study and only mild to moderate attacks were studied; so, the results could not be generated.

In a clinical trial conducted by Hughes et al. in 2003 at two centers in New Zealand, 52 patients with severe attack of asthma were enrolled (FEV1 <50% predicted). This study showed that those treated with a combination of salbutamol and magnesium sulfate had more improvement in their FEV1at 90 min and a lower hospitalization rate as compared to salbutamol alone group.

The different responses to treatment in people with life-threatening asthma at presentation (FEV1 <30% predicted) were higher than those who had FEV1> 30% on admission. In another clinical trial, Nannini and his colleagues [5] reported similar results.

Results of trials directly comparing magnesium sulfate and salbutamol are also inconsistent. In a clinical trial on 33 patients in 1998 by Mangat et al., improvement in PEF in the magnesium sulfate group was 35% and in the salbutamol group, it was 42%, with no significant difference. The final PEF in two groups and improvement in PEF rate was also similar in both groups. The researchers concluded that nebulized magnesium sulfate has a similar bronchodilator effects with that of nebulized salbutamol and had no advantage over it [2].

In contrast, Meral and colleagues [8] in a clinical trial of 40 children with a mean age of 10.5 years showed that nebulized beta-2 agonist caused more improvement in clinical parameters (Davis-Leffert-Dabbous clinical respiratory distress score) and lung function (PEFR) than nebulized magnesium sulfate.

According to the Cochrane Review by Blitz et al. [4]:1 –Nebulized magnesium sulfate with or without beta-2 agonist is safe and can be administered to patients with moderate to severe asthma. Due to the availability and cost of its use, it is worth careful scrutiny and review in moderate to severe asthma.2 - The use of magnesium sulfate alone, competing against known and inexpensive beta-2 agonist has little advantage in

improving lung function and reducing the need for hospitalization. Evidence of application of magnesium sulfate in combination with beta-2 agonist is more convincing, and considering the advantages of combination therapy to improve lung function, especially in patients with severe asthma, is more acceptable. The advantage of combination therapy in reducing the need for hospitalization is not shown, but because of the observed tendency towards reducing the need for hospitalization, further study to answer these questions seems logical.3 - Inhaled magnesium sulfate alone has no superiority over beta -2 agonist standard therapy. This lack of preference is seen both in the spirometric response rates and need for hospitalization.

The study was design to examine the effect of adding magnesium sulfate to standard treatment in moderate to severe asthma attacks. The results showed that adding magnesium sulfate to standard therapy leads to significant improvements in both subjective and objective parameters in response to treatment, and it reduces the admission rate.

The results of the present study are similar to those obtained by Hughes and colleagues [5]. Although, Bessmertny [1] showed no additional benefit of adding magnesium sulfate, in contrast to the present study population and Hughes's study, he only enrolled subjects with mild to moderate asthma and individuals with severe asthma were excluded from his study.

In summary, the present study findings confirm the conclusions of the Cochrane review [4], and prove the benefits of adding magnesium sulfate to beta-2 agonists in treating severe asthma attacks. Similar to previous studies, the present study did not identify any serious side effect from using nebulized magnesium sulfate.

Magnesium sulfate dosage should be adjusted so that the resulting solution for nebulize should be iso-osmolar with pleural fluid (260 mmol/L). This should be done to avoid possible irritation of the bronchioles which is not iso-osmolar. For this osmolarity, a solution of 64 mg/ml of magnesium sulfate in distilled waterisprepared. Therefore, each cc of 500mg/dl of magnesium sulfate vial should be diluted with 6 cc of distilled water which makes the solution suitable for nebulizer and is similar to pleural fluid.

Some believe that if there is no limited capacity of nebulizers and if certain density of magnesium sulfate is made, maybe more and better therapeutic effects of nebulized magnesium sulfate would be seen. Studies that showed effectiveness of IV magnesium sulfate in severe asthma attacks have used 1.2-2 g of sulfate. While in most studies on nebulized magnesium sulfate, the cumulative dose was less than one gram. In this study, the cumulative dose of nebulized magnesium sulfate was 1.5 g. It is possible that the reason for better improvement seen in the present study was the higher dose of magnesium sulfate as compared to others [9,10,11].

In the present study, in addition to objective measures, a subjective measure which was severity of dyspnea according to patients' feeling upon presentation and during treatmentwas used.

Mangat and his colleagues [2] used Fischl index which included 7 parameters such as dyspnea, use of accessory muscles of respiration, wheezing on auscultation of the lungs, PR, PEFR, PP and RR for a more comprehensive assessment of treatment response. In other studies, objective criteria were mostly used to assess response to treatment.

Small sample size and the dependency of PEFR on patient's effort are limitations of the present study. This study is not generalized to patients with mild asthma attack. Clinical trial with large sample size and more variant population such as patients with COPD exacerbations is recommended.

Conclusion

Adding nebulized magnesium sulfate to standard treatment in ED patients with moderate to severe asthma attack will reduce admission rate and will result in more improvement in PEFR and dyspnea score as compared to those treated with standard treatment alone.

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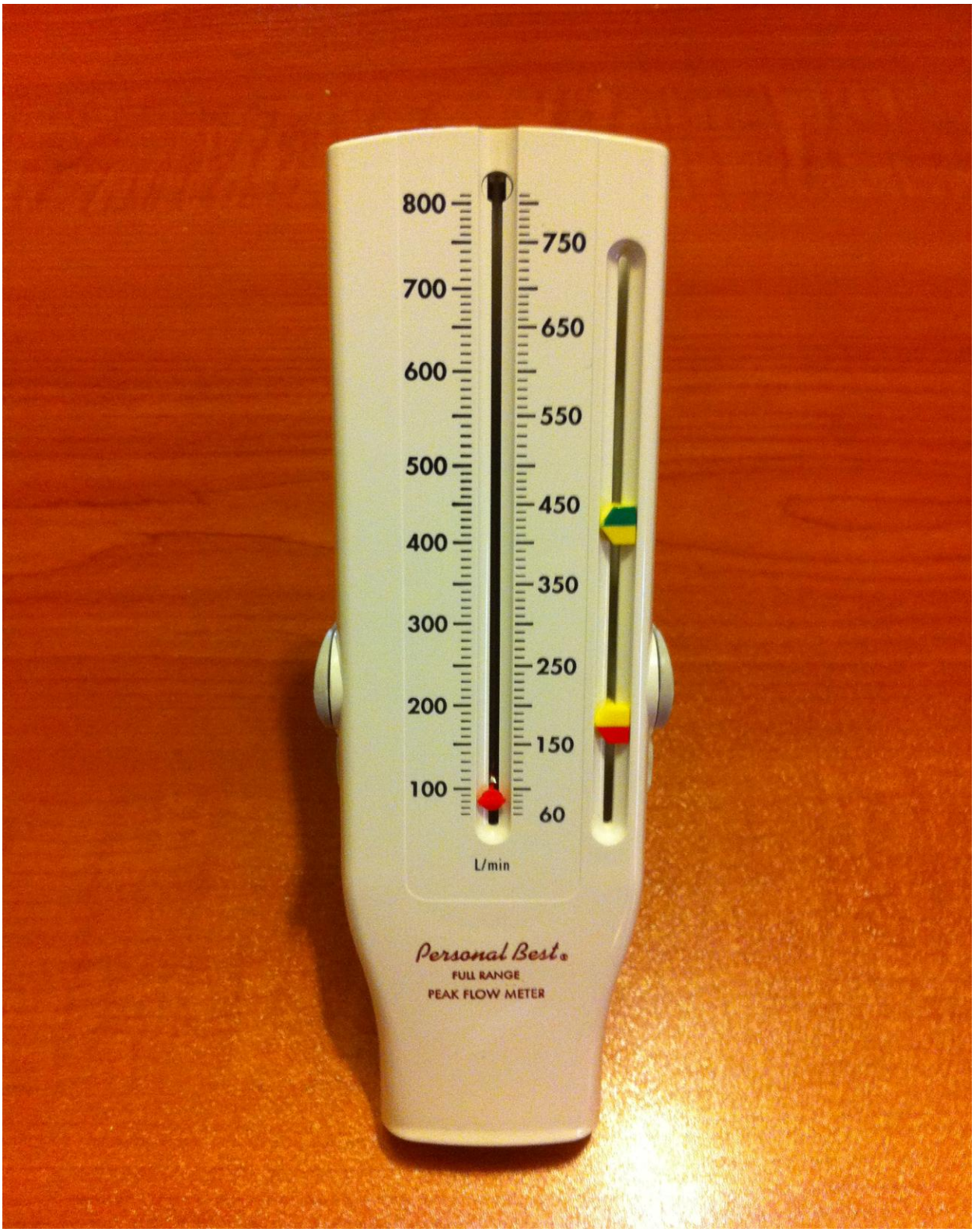

Fig. 1

	Case group (n= 25)	Control group(n = 25)	P value
Age	52.4±16.9	53.9±16.2	0.754
Sex **Female** **Male**	 14(56%) 11(44%)	 11(44%) 14(56%)	0.396
Dyspnea severity **Mild** **Moderate** **Severe**	 0(0%) 3(12%) 22(88%)	 1(4%) 3(12%) 21(84%)	0.6
Respiratory Rate(RR)	35.5±6.9	32.3±4.8	0.063
SPO2(%)	84.1±4.1	82.1±5.0	0.064
PEFR (% predicted)	15.1±4.7	14.7±6.4	0.31

PEFR(Peak Expiratory Flow rate)

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

	Case group	Control group	P value
Dyspnea severity			0.004
No dyspnea	2	2	
Mild	17	6	
Moderate	6	10	
Severe	0	7	
Respiratory Rate(RR)	27.2 ±6	27.0 ±5.7	0.924
SPO2(%)	94.1 ±2.4	90.8 ±4.8	0.002
PEFR (% predicted)	24 ±9.6	17.1 ±9.4	0.002

PEFR(Peak Expiratory Flow Rate)

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

	Case group	Control group	P value
Dyspnea severity **No dyspnea** **Mild** **Moderate** **Severe**	17(68%) 6 2 0	7(28%) 13 5 0	0.018
Respiratory Rate(RR)	20.5±4.8	21.4±4.1	0.229
SPO2(%)	97.2±2.9	94.3±3.3	<0.001
PEFR (% predicted)	48.7±23.4	36±28.7	0.002

PEFR(Peak Expiratory Flow rate)

Table 3: Comparison of response to treatment in both groups 60 minutes after the start of treatment (end of study)