Inhaled magnesium sulphate in the treatment of bronchial hyperresponsiveness

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Abstract. Magnesium sulphate (MgSO₄) is one of numerous treatment options available during acute asthma exacerbation. A significant, bronchodilating effect of intravenous MgSO₄ has been demonstrated in previous studies, but its inhaled use is less well-defined. Objective: To investigate the effects of inhaled MgSO₄ alone and in association with a β₂-agonist in the treatment of bronchial hyperresponsiveness. Methods. We conducted a placebo-controlled, double-blind clinical trial with seventy six adult patients with bronchial hyperresponsiveness. Subjects were randomized into four groups receiving four inhaled products at the end of methacholine (Mech) challenge: NaCl 0.9%, MgSO₄ alone, β₂-agonist alone, and the combination of MgSO₄ + β₂-agonist. Repeated measures of the forced expiratory volume at 1s (FEV₁) were performed at 0, 5, 10, and 20 minutes after the end of the inhalations. In the MgSO₄ and MgSO₄ + β₂-agonist groups, a blood sample was taken before and after inhalation to determine serum magnesium levels. Results. (1) Inhaled MgSO₄ led to a significant improvement of the FEV₁ from the 15th minute after its inhalation. (2) β₂-agonist significantly increased FEV₁ from the 5th minute (3) inhaled MgSO₄ + β₂-agonist led to a significantly greater FEV₁ from the 5th minute than inhaled MgSO₄ alone or inhaled β₂-agonist alone (p<0.05) (4) There is a correlation between low serum magnesium level and the increase in FEV₁ after inhalation of MgSO₄ + β₂-agonist (p<0.001). Conclusion. Inhaled MgSO₄, in combination with β₂-agonist, appears to have benefits in the treatment of bronchial hyperresponsiveness, especially when associated with hypomagnesemia.

Key words: inhaled magnesium sulphate, β₂-agonist, asthma, FEV₁

MgSO₄ is an effective bronchodilating agent in patients with severe, acute asthma when delivered parentally [1]. The use of intravenous MgSO₄ is one of numerous options available during exacerbations of asthma. MgSO₄ is thought to be effective in acute asthma attacks as a consequence of magnesium’s ability to relax smooth muscle and inhibit its contraction [2]. Magnesium is also involved in cellular homeostasis through its role as an enzymatic cofactor [2]. It is involved in acetylcholine and histamine release from cholinergic nerve terminals and mast cells, respectively. Investigators have suggested that the effect of MgSO₄ is related to its ability to block the calcium ion influx into smooth muscles of the respiratory system [2]. Finally, the role of MgSO₄...
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as an anti-inflammatory factor has been identified in adults with asthma [3]. Most previous studies have shown a significant bronchodilating effect of intravenous MgSO\textsubscript{4} in case of acute asthma [4, 5]. The potential clinical benefit of inhaled MgSO\textsubscript{4} has been studied, but research publications have produced mixed results [6, 7]. Nevertheless, the Global Initiative in National Asthma (GINA) recommendations approve the use of inhaled MgSO\textsubscript{4} during severe, acute asthma [8]. The objective of this study was to investigate the effects of inhaled MgSO\textsubscript{4} alone and in association with β\textsubscript{2}-agonist in the treatment of bronchial hyperresponsiveness.

Methods and materials

Study design

This is a prospective, double-blind, randomized, placebo-controlled trial conducted between September 2011 and March 2012. It was conducted in the Department of Physiology and Functional Explorations in the Farhat Hached Hospital in Sousse (Tunisia) (altitude <100 m). The research protocol was approved by the institutional ethics committee of Farhat Hached hospital and was in accordance with international agreements (Helsinki Declaration of 2000).

The study design consisted of a sample of patients with a known history of mild to moderate, controlled asthma (Arab ethnic group), between the ages of 28 and 42 years. Subjects were recruited from the Pulmonology Department and each of them received letters clarifying the aims of the study. When a subject was interested, an appointment for medical questionnaires and exploration was scheduled. Data from each volunteer patient included: sex, age, height, weight, smoking history, medication use, medical history, physical examination, and spirometry data. Both the researcher and the technician were blinded to the medication.

Treatment allocation

A random numbers table was used to produce the randomization sequence and this was performed by a senior researcher. A total of 76 patients took part in the study and were randomized into four groups, (G1, n = 18; G2, n = 24; G3, n = 22 and G4, n = 12) receiving respectively the four different products to reverse provoked bronchial obstruction: G1: inhaled NaCl 0.9%, G2: received MgSO\textsubscript{4}, G3: received four puffs of β\textsubscript{2}-agonist (400 μg) and G4: received MgSO\textsubscript{4} + four puffs of β\textsubscript{2}-agonist (400 μg). Both the researcher and the technician were blinded to the medication. The study medications were provided in identical nebulizers.

Subjects

Volunteer subjects aged from 28 to 42 years were included. The following inclusion criteria were applied: controlled, asthmatic adults (men or women). Patients were considered asthmatics if they had intermittent dyspnoea and wheezing that responded to β\textsubscript{2}-agonist inhalations (respiratory symptoms and airway obstruction were totally reversible to β\textsubscript{2}-agonist). If they had a normal functional test, bronchial asthma was confirmed by a positive hyperresponsiveness challenge, with a history of allergic status [8]. Thus, the diagnosis of asthma was confirmed by the presence of any of the following: i. previous documentation of spirometric evidence of asthma, ii. spirometric evidence of asthma at the time of presentation.

The following, non-inclusion criteria were applied: age less than 20 years, active cigarette smoking, pregnancy, alcohol abuse, renal failure, heart and coronary disease and current desensitization treatment. Patients having received β-agonists, oral or inhaled corticosteroids, anti-histamines, anticholinergics, calcium, magnesium and beta-blockers over the previous 72 hours were also excluded, inadequate performance of required respiratory maneuvers or inability to comply with the study procedure. The bronchial challenge was performed after the non-inclusion criteria had been verified.

Methacholine challenge test (MCT):

After randomization and group allocation, patients in all groups were invited to undergo an MCT. For this test, there was a request to abstain from bronchodilator inhalers for six hours, and anti-histamines for 24 hours before the bronchial challenge test. After the test procedure was
explained and the medical questionnaire was completed (5-10 min) by the researcher, baseline forced vital capacity (FVC, l) and 1st second forced expiratory volume (FEV$_1$, l) were measured with a daily-calibrated, portable spirometer (Pal Minato, Mediprom, Osaka, Japan). Each test was conducted by the same qualified technician. The patient was asked to perform at least three consecutive maneuvers with two of the best FEV$_1$ measurements differing by less than 5%. The challenge test was not performed in subjects whose baseline FEV$_1$ was predicted to be less than 60%, in subjects who had a recent serious illness.

After baseline spirometric measurements, subjects inhaled normal saline followed by increasing doses of Mech. FEV$_1$ was measured one minute after each inhalation. The test was stopped if the FEV$_1$ fell by 20% or more, or when the patient received the maximum, cumulative dose of Mech (3,100 μg).

An aerosol of Mech (Allerbio, Lavarenne, France) was generated by a calibrated jet nebulizer (Mediprom FDC88, Paris, France) connected to a DeVilbiss nebulizer (Ref 123016 Marquette Medical products, Englewood, CO, USA). The provocative dose of Mech (PD20) producing a 20% fall in FEV$_1$ from the post-saline value was determined (ATS guidelines) [10].

**Test of bronchodilator-induced reversibility of airway obstruction**

Patients (G1, G2, G3 and G4) received the four different products to reverse provoked bronchial obstruction: G1: inhaled NaCl 0.9%, G2: received MgSO$_4$ which was administered in inhaled form and was iso-osmolar with the pleural fluid (260 mmol/L: 1 mL of MgSO$_4$ at 10% (0.83 mol/L) + 1.3 mL saline). This was done to prevent any potential bronchiolar irritation that may be associated with solutions that are not iso-osmolar [11, 12]. G3: received four puffs of β$_2$-agonist (400 μg) and G4: received MgSO$_4$ + four puffs of β$_2$-agonist (400 μg). The solution was filtered with a single-use filter unit (Millipore MF membrane for sterilization of aqueous solution, 0.22 μm). The tidal breathing method was used for aerosol inhalation.

Reversibility of the bronchoconstriction was considered significant when FEV$_1$ increased by 12% and 200 mL, according to the criteria of (ATS guidelines) [10]. Repeated measures of the FEV$_1$ were performed at 0, 5, 10, and 20 minutes after the end of the inhalations, and before leaving the laboratory. If there was no improvement after 20 minutes of the nebulized NaCl 0.9% and MgSO$_4$, an inhaled β$_2$-agonist was given. Delta FEV$_1$ (Δ FEV$_1$) was calculated as the difference between the post- and pre-bronchodilator change in FEV$_1$.

In the MgSO$_4$ group and MgSO$_4$ + β$_2$-agonist group, a blood sample was taken before and after inhalation to determine magnesium serum levels. The magnesemia was quantified by Atomic Absorption Spectrophotometry (Beckman Coulter, Synchron CX9 Clinical System, CA, USA). The rationale for the cut-off point of low versus a normal magnesium level was estimated according to the international standards values [13].

**Statistical analysis**

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows software Package (Version 11). Ninety five percent confidence intervals (CIs) were used to express the precision of data. The results were expressed as a percentage of the reference value of FEV$_1$. The percentage predicted values of FEV$_1$ were analyzed using a general linear model for analysis of variance (ANOVA) for repeated measures. FEV$_1$ values were adjusted for sex, age, height and weight.

Non-parametric statistical tests were used to compare different groups (G1, G2, G3, and G4) with a two-sample Kolmogorov-Smirnov test and Kruskal-Wallis ANOVA by ranks test. A Wilcoxon matched pairs test was used for comparing two dependent samples. FEV$_1$ values of the same group of patients were compared at different times: 0, 5, 10, 15 and 20 minutes. Statistical significance was set at a p value ≤0.05.

**Sample size**

The sample size was calculated according to the following predictive equation: $n = (Z^2 \times p \times q) / \Delta^2$

where “n” was the number of patients required, “Z” was the 95% confidence level (= 1.96), q was equal to “1-p”, “Δ” was the precision (= 10%) and “p” was the estimation of the bronchodilating effect of MgSO$_4$ [9].
Results

At baseline, all groups were similar in terms of anthropometric characteristics (e.g., age, sex, weight and height). When comparing baseline characteristics (table 1) no differences among the groups were identified. Furthermore, all patients had similar asthma severity and bronchial hyperresponsiveness.

Twenty four patients were included in the MgSO\textsubscript{4} group. They were classified into two groups: reversible and non-reversible with MgSO\textsubscript{4}. Both groups were comparable at baseline, before inhalation of MgSO\textsubscript{4}. All patients had moderate bronchial hyperresponsiveness. Reversibility of the bronchial obstruction by MgSO\textsubscript{4} was seen in 12/24 patients, 15 minute after inhalation of MgSO\textsubscript{4}. Patients with reversible obstruction had different serum levels of magnesium. Eight patients demonstrated hypomagnesemia; four patients had normal magnesium levels.

The ΔFEV\textsubscript{1}% for patients of MgSO\textsubscript{4} group suffering from hypomagnesemia and patients with normal magnesemia was 15.0 ± 3.0%, 5.5 ± 1.2%, respectively. The inhaled MgSO\textsubscript{4} did not significantly alter magnesemia levels in the MgSO\textsubscript{4} and MgSO\textsubscript{4} + β\textsubscript{2}-agonist groups. There was no reversibility of the bronchial obstruction with NaCl 0.9%, but a significant reversibility was seen with β\textsubscript{2}-agonist five minutes after its administration. The difference between the FEV\textsubscript{1} of MgSO\textsubscript{4} and NaCl 0.9% groups was significant from the 15th minute (figure 1).

Inhaled MgSO\textsubscript{4} + β\textsubscript{2}-agonist resulted in larger improvements in FEV\textsubscript{1} than with MgSO\textsubscript{4} or β\textsubscript{2}-agonist alone (figure 1). All patients left the laboratory with a normal value for FEV\textsubscript{1} (greater than 80% of the initial value).

In the MgSO\textsubscript{4} group, the increase in FEV\textsubscript{1} did not correlate with magnesium levels (figure 2). The ΔFEV\textsubscript{1}% of 41% for patients in the MgSO\textsubscript{4} + β\textsubscript{2}-agonist group suffering from hypomagnesemia was significantly better than those of normal magnesium patients (ΔFEV\textsubscript{1}% 41.0 ± 8.6% versus 29.0 ± 6.1%, respectively; p<0.05).

In the MgSO\textsubscript{4} + β\textsubscript{2}-agonist group, the improvement of FEV\textsubscript{1} correlated significantly with magnesium (p<0.05). A correlation between low magnesium serum levels and the increase in FEV\textsubscript{1} after inhalation of MgSO\textsubscript{4} + β\textsubscript{2}-agonist was found (p<0.001). Patients with low serum Mg levels (<0.74 mmol/L) demonstrated a significant improvement in FEV\textsubscript{1} (p<0.001; figure 3).

Discussion

This study examined the bronchodilating efficacy of MgSO\textsubscript{4} following Mech challenge tests in patients with known asthma. The main findings of this study were: (1) Inhaled MgSO\textsubscript{4} resulted in significant bronchodilation within 15 minutes of inhalation. (2) Inhaled MgSO\textsubscript{4} combined with β\textsubscript{2}-agonist enhanced the bronchodilator response (3) There is a correlation between low serum magnesium level and the increase in FEV\textsubscript{1} after inhalation of MgSO\textsubscript{4} + β\textsubscript{2}-agonist (p<0.001).

Table 1. Profile of the study population.

<table>
<thead>
<tr>
<th></th>
<th>NaCl 0.9% group</th>
<th>MgSO\textsubscript{4} group</th>
<th>β\textsubscript{2}-agonist group</th>
<th>MgSO\textsubscript{4} + β\textsubscript{2}-agonist group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
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<td>24</td>
<td>22</td>
<td>12</td>
<td></td>
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<tr>
<td>Sex (M/F)</td>
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<td>12/12</td>
<td>16/6</td>
<td>5/7</td>
<td>NS</td>
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<td>Age (years)</td>
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<td>32 ± 10</td>
<td>28 ± 5.8</td>
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</tr>
<tr>
<td>Weight (Kg)</td>
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<td>69 ± 15</td>
<td>70 ± 10</td>
<td>69 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>166 ± 8</td>
<td>160 ± 8</td>
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<td>1030</td>
<td>NS</td>
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<td>FEV\textsubscript{1} (%)</td>
<td>69.7 ± 0.8</td>
<td>74.6 ± 0.7</td>
<td>73 ± 0.7</td>
<td>70 ± 0.8</td>
<td>NS</td>
</tr>
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<td>FEV\textsubscript{1}/FVC (%)</td>
<td>80</td>
<td>85</td>
<td>83</td>
<td>87</td>
<td>NS</td>
</tr>
</tbody>
</table>

M: male; F: female, FEV\textsubscript{1}: forced expiratory volume at 1 second, FVC: forced vital capacity, NS: non-significant p value > 0.05 by Kruskal-Wallis ANOVA by ranks, PD\textsubscript{20}: dose of methacholine that induced 20% of decrease of FEV\textsubscript{1}; mean values are expressed as mean ± SD
Figure 1. FEV₁, after administration of NaCl 0.9%, β₂-agonist, MgSO₄ alone and MgSO₄ + β₂-agonist.

*: MgSO₄ + β₂-agonist group showed a significant improvement in FEV₁ from the 5th minute (p<0.05) (ANOVA Friedman).

**: β₂-agonist group showed a significant increase in FEV₁ from the 5th minute (p<0.05) (ANOVA Friedman).

**: MgSO₄ group showed a significant improvement in FEV₁ from the 15th minute after inhalation of MgSO₄ (p<0.05) (ANOVA Friedman).

Mean values are expressed as mean ± SD.

Figure 2. Differences between groups with hypo- and normal magnesemia according to bronchodilator response to inhaled MgSO₄ alone.

The variation of FEV₁ was no different between hypo-and normal magnesemia groups (15.0 ± 3.0%, 5 5 ± 1.2%, respectively; p>0.05). Differences in the post-BD response between groups were not significant (8% at 20 min, p>0.05).

FEV₁: forced expiratory volume at 1s, pre-BD: pre-bronchodilator, post-BD: post-bronchodilator, mean values are expressed as mean ± SD.
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Figure 3. Differences between groups (hypo- and normal magnesemia) in the bronchodilator response to inhaled MgSO₄ in combination with β₂ agonist. The variation of FEV₁ was better in the hypomagnesemia group than in normal magnesemia group (41.0 ± 8.6% versus 29.0 ± 6.1%, p<0.05). Differences in the post-BD response between groups were significant (14% at 20 min, p<0.05).

FEV₁: forced expiratory volume at 1s, pre-BD: pre-bronchodilator, post-BD: post-bronchodilator, mean values are expressed as mean ± SD.

Magnesium’s role in asthma was first suggested in anecdotal reports of the favorable effects of MgSO₄ administration in acute exacerbations of asthma over 70 years ago [14]. Later, Durlach [15] reported a reduction in serum magnesium levels during acute asthma attacks. More recently, the possible role of magnesium in the pathogenesis of bronchial constriction, as well as in its treatment has attracted considerable attention again, particularly because of several reports confirming positive results for magnesium administration in acute airway constriction [4, 16], although some studies have reported negative results [17].

While much of the previous research examined MgSO₄ administered intravenously in acute asthma, several systematic reviews have described the effect of inhaled MgSO₄ in acute asthma. In the present study, MgSO₄ was administered in the inhaled form because this method of administration did not require careful monitoring. The aerosol route offers the advantage of a quick onset of action and lower incidence of side effects. Its disadvantages include a smaller quantity of drugs being delivered to the site of action and the patient requiring some respiratory effort to maximize its effectiveness [18].

While the bronchodilating effect of MgSO₄ administered intravenously has been confirmed by several studies [4, 5], its effect through inhalation is controversial and poorly documented. Studies addressing this subject differ methodologically and were heterogeneous, non-comparable, and used different therapeutic strategies. A meta-analysis of six trials with inhaled MgSO₄, suggests that this treatment of patients with severe asthma may have some benefits, such as lung function improvement, but it does not reduce hospital admission rates [19]. In a 2005, Cochrane review of inhaled MgSO₄ in acute asthma, nebulized magnesium in combination with β₂-agonist were shown to improve pulmonary function and trended toward benefit as regards fewer hospital admissions. Blitz et al. reported that it was difficult to draw conclusions about treatment with nebulized MgSO₄ alone as studies in this area were sparse [20]. The 2009 Cochrane review update failed to change its conclusions [21]. In a recent systematic literature review, Song and Chang affirmed that evidence for a beneficial effect of nebulized magnesium was insufficient and larger trials are required to draw confirmative conclusions on its efficacy [22].
conflicting and heterogeneous results found in the literature, and confusion exists. Some authors demonstrate that inhaled MgSO$_4$ led to a reduction in bronchial reactivity [12, 23]. However, Hill et al. and Aggarwal et al. have shown opposite effect [24, 25]. We therefore undertook this study to try to clarify the controversy. Magnesium was administered as MgSO$_4$ at a concentration isomolar to pleural fluid. At high concentrations, this cation produces significant toxicity. In fact, hypermagnesemia induces paralysis of skeletal muscles, reduces lung capacity and sometimes even induces coma and death. For these reasons, its plasma concentration was monitored before and after its inhalation. At this osmolarity, Bessmerty et al. found no significant serum magnesium changes [12]. The results of this study were in agreement with previous studies of Rouatbi et al. and Rolla et al. [6, 23] that confirmed the bronchorelaxant effect of inhaled MgSO$_4$. MgSO$_4$ inhaled by hyperreactive asthmatic patients during Mech, had bronchodilating effects. In our study, inhaled MgSO$_4$ caused an inconsistent bronchorelaxation that depended on the magnesium levels. There was a correlation between serum magnesium concentrations and the response to inhaled magnesium for a given degree of airway obstruction. This result is in agreement with those found by Alamoudi et al. and Durlach et al. [26, 27]. They confirmed that hypomagnesemia is common in chronic asthmatics. Chronic asthmatics with low Mg tend to have more hospitalizations than chronic asthmatic with normal Mg. Hypomagnesemia was also associated with more severe asthma [26]. The serum ionic Mg level was measured in this study because; it is a better indicator of Mg status in acute disease states, especially in the case of asthma, and it is independent of ethnicity [28]. In our study, serum Mg concentrations influenced the increase in FEV$_1$. Measurement of serum Mg concentrations before and after inhaled MgSO$_4$ alone or inhaled MgSO$_4$ + $\beta_2$-agonist in our patients showed the presence of a significant correlation between plasma levels of Mg and the increase in FEV$_1$ ($P<0.001$) in the MgSO$_4$ + $\beta_2$-agonist group only. In this group, patients with low serum Mg levels ($<0.74$ mmol/L) demonstrated a significant improvement in FEV$_1$ ($P<0.001$). In the MgSO$_4$ group, the increase in FEV$_1$ did not correlate with serum Mg concentrations (figure 2). Possible mechanisms by which Mg enhanced the bronchodilator response to $\beta_2$-agonist include direct relaxation of bronchial smooth muscle. Mg decreases intracellular calcium by blocking its entry and its release from the endoplasmic reticulum and by activating sodium-calcium pumps. Furthermore, inhibition of calcium’s interaction with myosin results in muscle cell relaxation [29]. Mg’s pharmacological action is based upon its ability to inhibit the release of calcium from vesicles in the sarcoplasmic reticulum, resulting in bronchial smooth muscle relaxation [30]. MgSO$_4$ has been reported in many research studies to inhibit Ca$^{2+}$ influx by blocking the voltage-dependent calcium channels, and to modulate vaso-activity by affecting the influx of extracellular Ca$^{2+}$ through dihydropyridine-sensitive, voltage-dependent channels, which accounts for much of its relaxant action on airways [31, 32]. In vitro studies show that the Mg ion (Mg$^{2+}$) modulates smooth muscle contractility and mediates release by antagonism of the action of calcium [31, 32]. By this action, Mg may determine the sensitivity of the bronchial smooth muscle to acetylcholine. An excess of Mg may decrease the depolarizing action of acetylcholine, resulting in depressed excitability of the bronchial smooth muscle cells.

The results of this study suggest that MgSO$_4$ inhibits the intra-cellular influx of calcium; however, this effect is not constant. In fact, functional improvements with inhaled MgSO$_4$ alone were inconsistent. This inconsistency might be related to selection bias in patients or variations in particular biological parameters between one individual and another. Our results also indicated that administration of inhaled MgSO$_4$ combined with $\beta_2$-agonist resulted in a significantly greater improvement in FEV$_1$, compared to inhaled MgSO$_4$ alone or $\beta_2$-agonist alone (figure 1). The poor response with inhaled MgSO$_4$ alone, suggests that it might play a role as an adjunct to $\beta_2$-agonists in acute asthma, which was also suggested by Blitz et al. and Hughes et al. [20, 33]. Our study has some limitations. The size of each randomized group is relatively small, especially the MgSO$_4$ + $\beta_2$-agonist group. In fact, during the study period, the number of patients selected exceeded 120; however, only 76 patients fulfilled the inclusion criteria. On the other hand, compared to similar published studies [12,33-36], this number is acceptable. Our study is unable to answer whether repeated doses of MgSO$_4$ alone or combined with $\beta_2$-agonist would be able to sustain the improvement in FEV$_1$. We limited our
study to seeing if a single dose of nebulized Mg offered any therapeutic benefit in terms of providing bronchodilator-induced reversibility of airway obstruction.

Conclusions

This study indicated that inhaled MgSO₄ alone had a significant, albeit weak bronchodilatory effect compared to inhaled β₂ agonist alone or in combination with a β₂ agonist. This suggests that inhaled MgSO₄, in combination with β₂ agonist, could be used as a treatment for bronchospasm. Several questions remain unanswered, including the optimum dose-response relationship. In addition, further research in this area should be encouraged to determine the mechanism by which the association of inhaled MgSO₄ and β₂ agonist enhanced bronchospasm.

Disclosure

**Financial support:** none. **Conflict of interest:** none.

References


