

Role of Magnesium Sulphate in Exacerbations of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Magnesium sulphate (MS) is a molecule with bronchodilatory properties that has been successfully used for the treatment of asthma exacerbations. The use of MS has also been evaluated for the treatment of exacerbations of chronic obstructive pulmonary disease (COPD). There are conflicting results of studies evaluating the efficiency of MS in COPD. The aim of this review is to summarize the findings of those studies and to answer the question if there is any rationale for use of MS in acute exacerbations of COPD.

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Key words: Chronic Obstructive Pulmonary Disease; Exacerbation; Magnesium Sulphate

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an important source of morbidity and mortality as the third leading cause of death around the world. The exacerbations which can occur during the clinical progression of the disease lead to an impairment in quality of

life of patients, have negative impacts on symptoms and pulmonary functions that can last for weeks, lead to an acceleration of loss of lung function, increase health expenditures and cause significant mortality^[1].

The exacerbations of COPD are associated with increased inflammatory activity in the airways and worsening airway obstruction^[2]. The primary aims of treatment of COPD exacerbations are to minimize the effects of the present exacerbation and decrease the risk for future exacerbations. For today the standart therapy for COPD exacerbations include short acting bronchodilators, systemic corticosteroids and antibiotics^[1]. However the need for the development of new therapeutic modalities for better handling COPD exacerbations continue.

Magnesium is a cation which exerts bronchodilatory effects by inhibiting the calcium mediated bronchial smooth muscle contraction^[3]. Magnesium also inhibits the release of acetyl-choline from cholinergic nerve endings and histamine from mast cells^[4]. It has beneficial effects on respiratory muscle function^[5]. In the international guidelines, intravenous MS has been denoted as an effective additional treatment option in severe asthma exacerbations which do not respond well to the standart treatment^[6]. However MS is not recommended as an add-on treatment option for the treatment of COPD exacerbations yet^[1].

CLINICAL TRIALS OF MS IN COPD EXACERBATIONS

To our knowledge, only five placebo controlled studies evaluating the efficiency of MS in COPD exacerbations exist in the literature and those studies have given rise to some conflicting results. The first clinical trial evaluated the efficiency of 1.2 gr intravenous MS used in combination with 2.5 mg albuterol. Seventy-two patients with an exacerbation of COPD were randomized into two treatment groups to receive either MS in addition to albuterol or placebo. The change in the peak expiratory flow rate (PEFR) from initiation of infusion to 30 and 45 minutes later (calculated as means of the 30- and 45- minute

values) was significantly different for two groups. However, there was no difference between the two groups with regard to the change in dyspnea scores or hospitalization rates^[7].

The second study was a randomized, double-blind, placebo controlled study with a crossover design. Twenty-four patients with a diagnosis of COPD exacerbation were randomized to two groups. Patients received either 1.5 gr intravenous MS or placebo in an intravenous solution for 20 minutes. Those who received MS the first day were given placebo the second day, and vice versa. After the infusion, 400 µg salbutamol was administered to each patient. All patients also received their standart medical treatment consisting of corticosteroids, intravenous antibiotics, oxygen, and salbutamol+ipratropium bromide every 6 hours. There were no significant differences in the absolute or percentage increases in forced expiratory volume in 1 second (FEV1) values of patients at 15, 30, and 45 minutes after the application of MS and placebo. However the absolute and percentage increases in FEV1 after administering salbutamol were significantly greater after MS treatment. The authors concluded that intravenous administration of MS has no bronchodilating effect in patients with COPD exacerbations. However it can enhance the bronchodilating effect of inhaled beta 2-agonists^[8]. They related the discrepancy between their results and results of Skorodin et al^[7], to the difference of the technique used to measure the degree of bronchial obstruction.

Potential of bronchodilatory effects of beta 2-agonists by MS were also observed in other studies^[9]. It is believed that MS exerts this effect by increasing the receptor affinity for the agonist or by externalization of the receptor on the surface of the cellular membranes of the target organ^[10].

The third clinical study evaluated the efficiency of nebulised MS. This was a randomized double blind placebo controlled trial which included 161 patients with an exacerbation of COPD. The patients received standart bronchodilatory treatment with combined salbutamol and ipratropium bromide nebulised solution, systemic corticosteroids, oxygen and either 2.5 ml isotonic MS (151 mg per dose) mixed with 2.5 mg salbutamol or placebo with nebulisation on three occasions at 30 minutes intervals. There was no significant difference between the two groups with regard to the primary outcome measure of the study which was FEV1 measured at 90 minutes. There was also no significant difference in hospitalization rates of the two groups. The authors argued that pre-dosing with bronchodilators could have led to the patients reach their maximum bronchodilatory response without further increase after administration of MS^[11].

In our own clinical experience, we treated 20 patients with an exacerbation of COPD with four daily doses of ipratropium bromide 500 mcg mixed with either 2.5 ml isotonic nebulised MS (151 mg/dose) or placebo. All patients were treated with O₂, antibiotics and oral corticosteroids. The patients were followed-up with FEV1 and visual analogue scale (VAS) dyspnea scores for 48 hours. The FEV1 values measured at 24 and 48 hours did not show significant changes compared to baseline in both groups. Dyspnea scores in both groups decreased significantly in the first day, and in only MS group in the second day. The % change in the dyspnea score at the end of first day was significantly more in the MS group compared with the placebo group (unpublished data). We believe that this significant change in the dyspnea scores without any significant change in FEV1 could have been due to the beneficial effects of MS on respiratory muscle function^[5].

One important point related with the use of nebulised form of MS is formulation of MS as an isotonic solution. Because, both hypotonic

and hypertonic nebuliser solutions can induce bronchoconstriction in patients with bronchial hyper-responsiveness^[12].

Another study evaluated the efficiency of combined use of intravenous and nebulised MS and was unable to show any superiority of MS compared with ipratropium bromide. One hundred and twenty-four patients were randomised into two groups to receive either 1.5 gr intravenous MS and nebulised MS mixed with terbutalin or intravenous placebo and nebulised ipratropium bromide mixed with terbutalin. The nebule solutions were administered at 30 intervals for four times. All patients received the standart medical treatment with systemic corticosteroids, terbutalin nebulised, antibiotics and oxygen. All patients were also treated with non-invasive mechanical ventilation. The VAS dyspnea scores of the two groups measured at 180 minutes were found comparable. There were no significant differences between the two groups with regard to hospitalization and intubation rates or death. However the improvements in PEFr and pCO₂ values of patients in the group receiving ipratropium bromide was significantly greater than the group receiving MS at 180 minutes^[13].

The last study compared the efficiency of 2 gr intravenous MS with placebo administered over 3 days in a total of 30 patients which were also receiving standart medical treatment with combined salbutamol and ipratropium bromide nebulised solution, systemic corticosteroids and antibiotics. There were no significant differences between the two groups with regard to the hospitalization rates and change in FEV1 and PEFr at 45 minutes and at third day of treatment^[14].

DISCUSSION

In three out of five published placebo controlled randomised clinical trials of MS in exacerbations of COPD, no additional benefit measured by means of improvement in pulmonary functions such as PEFr and/or FEV1 was detected^[11,13,14]. In only two of these published clinical trials the change in the dyspnea scores of patients was evaluated^[7,13]. In one of these studies, the change in dyspnea scores of patients receiving MS was not different from patients receiving placebo^[7], and in the other it was comparable to the patients receiving ipratropium bromide^[13].

In a previous review article evaluating the findings of four randomised clinical trials performed on the efficiency of MS in COPD exacerbations, the authors concluded that the place of intravenous MS in the treatment of acute exacerbation of COPD currently remains unclear and there is no trial evidence to support the use of inhalational MS^[15]. However, the results of the clinical study performed in our centre previously have shown that significant improvements in the dyspnea scores of the patients with COPD exacerbations treated with nebulised MS could be achieved. This result can give rise to the need for better selection of tools for evaluation of efficiency of MS.

It has been previously reported that bronchodilators cannot provide significant improvements in pulmonary functions, especially in FEV1 values, in COPD exacerbations as compared to their effects in asthma exacerbations^[16]. However, it is well known that they can improve dyspnea and correct arterial blood gas changes^[17]. These beneficial effects of bronchodilators are due to the correction of hyperinflation by reduction of functional residual capacity and correction of dynamic hyperinflation beside their effects on the bronchial smooth muscle^[18,19]. Additionally the roles of parameters measuring limitation of expiratory flow such as PEFr and FEV1 are well defined for the arrangement of management strategies in asthma exacerbations, however the change in spirometric values show variability in COPD exacerbations. The change in these physiological parameters do not

always show correlation with improvement in symptoms^[2]. Therefore when evaluating the efficiency of new treatment options for COPD such as MS, evaluating the changes in lung volumes and parameters of respiratory muscle function such as maximum inspiratory and expiratory pressures would be more meaningful. In only one of the previous clinical trials the maximum inspiratory and expiratory pressures were evaluated and no significant improvements in these parameters were detected with the use of MS^[7]. However the mean basal serum magnesium levels of patients in that study was beyond the normal limits which can be an explanation of lack of improvement in the respiratory muscle function by use of additional MS. These topics need to be better evaluated in future studies.

The clinical trials performed on the use of MS appear to be heterogenous in their designs. Different doses and different routes of administration of MS are used in different studies. The clinical characteristics of the patients differ from each other, since there is no standard criteria to start MS treatment in a patient with COPD exacerbation for today. Most importantly, the tools used for the evaluation of efficiency of MS treatment are different. For these reasons, making direct comparisons among published clinical trials of MS in COPD exacerbations and drawing firm conclusions on its efficiency seem to be difficult. However the use of MS in patients with COPD exacerbations appears to be safe as no important adverse effects related with the use of MS were reported in the clinical trials^[7,8,11,13,14]. Future randomized clinical studies should evaluate the use of MS as an add-on treatment in well selected and large populations of patients with COPD exacerbations. They should utilize measures of dyspnea and respiratory muscle strength in addition to the measures of airflow obstruction as tools for measuring efficiency.

CONCLUSION

MS is a cheap, practical and safe treatment option that can give promise for the treatment of COPD exacerbations. However, for today the accumulated data is not enough to make precise decisions. The efficiency and mechanisms of action of MS in exacerbations of COPD remain to be elucidated in future well designed controlled clinical trials.

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