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RESEARCH ARTICLE

ROLE OF INTRAVENOUS MAGNESIUM SULPHATE AS AN ADJUVANT THERAPY IN ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN EMERGENCY DEPARTMENT

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ABSTRACT

Magnesium sulphate (MS) is molecule with bronchodilatory properties and has been successfully used for treatment of acute exacerbation of asthma .The use of magnesium sulphate has also been evaluated for treatment of acute exacerbation of chronic obstructive pulmonary disease (copd).There is conflicting results of different studies evaluating the efficiency of Magnesium sulphate .The aim of this study is to review the findings of those studies and to answer the question if there is any rationale for use of magnesium sulphate as an adjuvant therapy in acute exacerbation of copd

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible (As per WHO). The exacerbations of COPD are associated with increased inflammatory activity in the airways and worsening airway obstruction. The primary aims of treatment of COPD exacerbations are to minimize the effects of the present exacerbation and decrease the risk for future exacerbations (1). For today the standard therapy for COPD exacerbations include short acting bronchodilators through nebulization, systemic corticosteroids and antibiotics.[1] Chronic obstructive pulmonary disease (COPD) is an important source of morbidity and mortality. Chronic obstructive pulmonary disease (COPD) is an important source of morbidity and mortality as the third leading cause of death around the world.(2) 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 in health expenditures and cause significant mortality. [2]

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. The global prevalence of physiologically defined chronic obstructive pulmonary disease (COPD) in adults aged >40 yr. is approximately 9-10 per cent. It is a major cause of morbidity and mortality worldwide. Besides the lung abnormalities, COPD is now recognized to be a condition that has an impact on other organs, the so-called systemic effects and comorbidities of COPD [2]. COPD is now well known to be a risk factor for the development of atherosclerosis and consequent cardiovascular complications [3-4]. Cardiovascular disease is undoubtedly the most significant non respiratory contributor to both morbidity and mortality in COPD. Moreover, in patients with relatively mild COPD, cardiovascular disease accounted for 42% of the first hospitalization and 44% of the second hospitalization. The

prevalence of coronary artery disease was unsurprisingly highest at 30.2%, with congestive heart failure (HF) and dysrhythmias making up another 15.7% and 13% of the cases, respectively and correlated strongly with the association for increased risk of death (P<0.05) Some studies throw a light on the role of magnesium in chronic respiratory illness. Magnesium is the second most abundant cation in the intracellular fluid. Magnesium is involved in some important functions of the respiratory system like dilatation of bronchus and bronchioles, stabilization of mast cells and clearance of debris from mucociliary system and neuroharmonal mediator release. Hypomagnesemia is associated with increased airway hyperactivity and impaired pulmonary function. It is said that due to its bronchodilating effect, a decreased level of magnesium may increase COPD exacerbations. Research is going on regarding magnesium deficiency through reduced intake in diet is associated with frequent exacerbations of COPD. [5] Magnesium is a cation which exerts bronchodilator effects by inhibiting the calcium mediated bronchial smooth muscle contraction. Magnesium also inhibits the release of acetyl-choline from cholinergic nerve endings and histamine from mast cells, it has beneficial effects on respiratory muscle function. In the international guidelines, intravenous Magnesium sulphate has been denoted as an effective additional treatment option in acute exacerbation of copd

Primary Objective:

To see the effectiveness of IV Magnesium in Emergency department treatment of patients with acute exacerbation of COPD as an adjuvant to standard treatment.

Secondary Objective: To evaluate whether Magnesium sulphate as an adjuvant can give rapid relief to patient and make him fit for discharge from Emergency department

METHODOLOGY

In this comparative prospective, unicentric study, data will be collected over a period of 1 year from the patient presenting to Emergency Department with acute exacerbation of COPD. All patients who meet the inclusion criteria and none of the exclusion criteria will be enrolled in the study after taking their voluntary consent for participating in the study. One group of patient will be given only standard initial treatment of COPD and other group of patient will be given 2gm intravenous magnesium sulphate in addition to initial standard treatment of acute exacerbation of copd. Following variables will be observed initially and after 2 hours in both groups of patients.

- HEART RATE
- RESPIRATORY RATE
- SPO2
- ABG
- PEFR

Inclusion Criteria: ▪ All patient presenting to the ED with acute exacerbation of COPD

Exclusion Criteria

- Age <18
- Pregnant lady
- And those who are immunosuppressant drugs
- Oncology patients
- CHF

Sample size: 75 patients in each group

Sample Size For Comparing Two Means

Input Data

Confidence Interval (2-sided)	95%		
Power	80%		
Ratio of sample size (Group 2/Group 1)	1		
	Group 1	**Group 2**	**Difference***
Mean	32	41	-9
Standard deviation	17	22	
Variance	289	484	
Sample size of Group 1	75		
Sample size of Group 2	75		
Total sample size	150		

*Difference between the means

Analysis: Data will be entered in Microsoft excel and will be analyzed using SPSS Version 16. Discrete variables are reported as frequency, proportions and continuous variables as mean ± SD. The qualitative data will be compared applying Chi-square test or fisher exact test.Our study both the groups are similar with respect to age. The association is not statistically significant.(P>0.05).The mean age of standard treatment group is 44.28.The mean age of Mgso4 group is 46.03. The No of Males in standard treatment group is 40 and in Mgso4 group is 37. The no of Females in standard treatment group is 35 and Mgso4group is 38.The two groups are similar with respect to sex. The association is not statistically significant (P >0.05). The two groups are similar with respect to height. (P>0.05). The mean weight in standard treatment group is 61.59. The Mean weight in Mgso4 group is 61.71.The two groups are similar with respect to weight. The association is not statistically significant (P>0.05). The mean BMI in Standard treatment group is 25.16 and in Mgso4 group is 24.85. The two groups are similar with respect to Body mass index. The association is not statistically significant (P>0.05) the two groups are similar in their baseline heart rate. (P>0.05).The two groups are different with respect to their heart rate (P=0.002).

At the baseline two groups are similar with respect to their Mean arterial pressure. (P>0.05).After 2 hours the two groups are similar with respect to their Mean arterial pressure.(P=0.71) .The two groups are similar in their SPO2 levels both at the baseline and after 2hrs(P>0.05) The two groups are similar with respect to respiratory rate both at the baseline and after 2 hours. P>0.05. The two groups are similar with respect to peak expiratory flow rate. There is statistically no significant association between the two groups (P>0.05)

RESULTS

Our results were in line with González *et al*. 2006 placebo controlled randomized trial from Spain which did not show intravenous magnesium sulfate to have significant bronchodilating effect in COPD exacerbations. However these

results are in contrast with Skorodin *et al.* study which reported bronchodilating effect of magnesium sulfate administration in these patients. This effect was more prominent than inhaled β*2*- agonists alone. In another study Amaral *et al.* in 2008 which reported IV magnesium sulfate administration in stable COPD patients could decrease lung hyperinflation and improve respiratory muscle strength. The difference between our results and Skorodin and Amaral studies was possibly due to differences in methodologies where they measured the level of bronchial obstruction using either PEFR or FEV1 as it might have underestimated the extent of bronchial obstruction compared to our study where we measured both PEFR and FEV1 by conventional spirometry. Nannini *et al*., in another study, claimed that administration of inhaled isotonic magnesium sulfate simultaneous with salbutamol had better bronchodilating effect. Similarly González hypothesized that intravenous magnesium sulfate in patients with exacerbations of COPD improved the bronchodilating effect of inhaled β*2*-agonists. We cannot compare our results with these findings as we did not evaluate bronchodilating effect of magnesium sulfate along with other bronchodilators agents. The factors such as relatively small sample size, short duration of follow-up, absence of respiratory and general symptoms questionnaire are some of the limitations of this study. Larger investigations with longer follow up time are required to address the role of magnesium sulfate in COPD exacerbation.

In three out of five published placebos controlled randomized clinical trials of Magnesium sulphate in exacerbations of COPD, no additional benefit measured by means of improvement in pulmonary functions such as PEFR and/or FEV1 was detected. In only two of these published clinical trials the change in the dyspnea scores of patients was evaluated. In one of these studies, the change in dyspnea scores of patients receiving Magnesium sulphate was not different from patients receiving placebo, and in the other it was comparable to the patients receiving ipratropium bromide. In a previous review article evaluating the findings of four randomized 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. However, the results of the clinical study performed in our center previously have shown that significant improvements in the dyspnea scores of the patients with COPD exacerbations treated with nebulized Magnesium sulphate could be achieved. This result can give rise to the need for better selection of tools for evaluation of efficiency of Magnesium sulphate

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. However, it is well known that they can improve dyspnea and correct arterial blood gas changes. 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. 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 does not always show correlation with improvement in symptoms. 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. 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 heterogeneous 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 are 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 Magnesium sulphate 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. 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

Magnesium sulphate 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 Magnesium sulphate in exacerbations of COPD remain to be elucidated in future well designed controlled clinical trial

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