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ORIGINAL ARTICLE

Effectiveness of Oral Magnesium in improving in-Hospital Outcome in patients presenting with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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ABSTRACT

Aim: To study effectiveness of oral magnesium in improving in-hospital outcome in patients presenting with COPD exacerbation.
Study Setting: It was conducted at Department of Medicine, Mayo Hospital, Lahore.
Duration of study: Six month following approval of synopsis
Study design: Comparative Cross-Sectional
Methods: Total 160 patients who fulfilled the inclusion criteria were selected . All patients regardless of the group were given conventional management in the form of oxygen inhalation, anti-cholinergic and beta-2 agonist nebulization, intravenous steroids as well as steroid nebulization and intravenous antibiotics. In addition, Group-A was given magnesium in the form of 400 mg of magnesium oxide twice daily. Both groups were followed over their time of stay in the hospital to assess effect of oral magnesium. Data were entered and analyzed by SPSS v26.0. Means were compared by applying students t-test. Two groups were compared using Chi-square test. A p-value ≤0.05 was taken as statistically significant.
Results: According to outcome distribution between groups, in group-A, 44(55%) patients were discharged, while 24(30%) needed assisted ventilation and 12(15%) expired. In group-B, 58(72.5%) patients were discharged, while 6(7.5%) needed assisted ventilation and 16(20%) expired with a p-value 0.178 (for discharge), which is not statistically significant
Conclusion: Oral magnesium does not effectively improve in-hospital outcome in those who presented with COPD exacerbation in comparison to those not receiving oral magnesium.
Keywords: Chronic Obstructive Pulmonary Disease, Acute Exacerbation, Magnesium Sulphate.

INTRODUCTION

COPD is characterized by chronic and progressive breathlessness, cough, sputum & airflow obstruction which leads to restricted activity and impaired quality of life. Exacerbation of COPD is characterized by increased dyspnea, cough, sputum and/or change in its color[1]. There is proven role of magnesium in providing enhanced bronchodilator effect in acute severe bronchial asthma however, fewer data and conflicting results are seen regarding its use in acute exacerbation of COPD. Magnesium seems a promising new modality on account of its low cost, bronchodilator properties, easy to administer and low side effects.[1]. It imposes significant economic burden on its morbidity[2]. This is accompanied by various comorbid factors that attribute to increase in morbidity & mortality[3]. Exacerbations drastically impairs quality of life, puts a burden on expenditure & are associated with increase in mortality. While smoking is a major risk factor in etiology of COPD, infections mainly account for recurrent episodes of exacerbation. Also with advancing industrialization environmental factors in form of increasing air pollution contribute to COPD exacerbation.[1-2] Effective treatment slows disease progression, improve health condition and lessen the impact on healthcare services.[6] Pulmonary rehabilitation, oxygen inhalation, inhaled & systemic corticosteroids, bronchodilators (β2-agonists and anticholinergic agents), and if required mechanical ventilation constitutes standard treatment regimen in COPD. There is compelling interest in devising increased new strategies to effectively manage and decrease severity & frequency of exacerbations.[4] Magnesium acts as bronchodilator by causing calcium channel antagonism and it depresses excitability of muscle fibers by preventing release of acetylcholine from cholinergic nerve endings. It also improves respiratory muscle function and reduces inflammatory response by stabilizing T cells and preventing degranulation of mast cells[5,7].

So far 6 studies have investigated bronchodilator effects of magnesium in COPD. Previous literature shows a randomized, double-blind, cross over analysis controlled with placebo showed that acute IV Mg loading in stable COPD patients resulted in decreased lung hyperinflation and increased function of respiratory musculature[8]. No previous studies have studied effect of oral Mg so far and our study is about oral Mg as it seems to be a promising new modality in providing better management COPD exacerbation[9].

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Operational definitions

COPD Exacerbation: It is the sudden worsening of COPD symptoms I in the form of increase in quantity of sputum or change in its color. Dyspnea scale 4 or 5 according to MRC dyspnea scale Peaked Expiratory Flow Rate < 200 L/min at presentation

Oral Magnesium : Magnesium given twice daily in the form 400mg of magnesium oxide at the time of standard treatment, adding up to a daily of 480 mg of elemental magnesium, as long as our in-hospital outcome is achieved.

In-hospital outcome: It was in the form of either: discharge of the patient, requirement for assisted ventilation either in the form of BIPAP or mechanical ventilation or death of the patient

Conventional Treatment: Pulmonary rehabilitation, Oxygen inhalation, short acting bronchodilators either in the form of anti-cholinergic or beta-2 agonist, systemic steroid and antibiotics.

Hypothesis: Oral magnesium effectively improves in-hospital outcome in patients presenting with COPD exacerbation in comparison to patients not receiving oral magnesium.

MATERIALS AND METHODS

It was a randomized control trial. The study was done at department of medicine, Mayo Hospital, Lahore. Six months after synopsis approval with random sampling. Sample size of 160 patients (each with 80 patients) has been estimated at 95% with 10% absolute precision and an predicted magnesium level of 17,11% and 7,06% with placebo.[8]

n= $Z_{1-\alpha/2}$ = confidence level 95% = 1.96

$$\frac{Z^2_{1-\alpha/2}[P_1(1-P_1)+P_2(1-P_2)]}{d^2}$$

P_1 = population proportion I = 17.11%
P_2 = population proportion II = 7.06%
d = absolute precision = 10%

Inclusion Criteria: Both female and male of 18-70 years, less than 10 years of COPD (based on history or investigations either in the form of previous chest x-rays and/or spirometric studies,. bronchial asthma was excluded on basis of history such as cough, wheeze and shortness of breath brought on by characteristic triggers like exercise, cold air or aeroallergens as well as work related exposure and symptoms; episodic symptoms, night time or early morning worsening of symptoms; personal or family history of atopy and personal history of asthma as a child. Presented with acute exacerbation requiring hospital admission and having any one of the following symptoms: Increase in purulence of sputum (based on history of any recent change in color of sputum) Increase in the quantity of sputum Dyspnea grade 3, 4 or 5 according to MRC scale. Peaked Expiratory Flow Rate < 200ml at presentation

Exclusion Criteria: Patients with complaint of chronic diarrhea , known cases of any chronic debilitating disease like chronic kidney disease, ischemic heart disease (patients who were known to have ischemic heart disease on basis of their previous suggestive history and any available record as well as clinical evaluation indicating any evidence of cardiomegaly or heart failure etc), chronic liver disease, or cerebrovascular accident, with pulmonary parenchymal disease like pulmonary fibrosis, asthma ,tuberculosis on history, examination and CXR-PA view, with bronchogenic carcinoma, Pulmonary edema diagnosed utilizing history, physical examination and investigations like chest x-ray (echo was not done) will be excluded

Data collection procedure: From ER and OPD of Mayo Hospital, Lahore 160 patients who fulfilled inclusion criteria were enrolled after taking informed consent. They were randomly allocated two groups A or B. All patients regardless of two group received conventional treatment in the form of oxygen inhalation, anti-cholinergic and beta-2 agonist nebulization, intravenous steroids as well as steroid nebulization and intravenous antibiotics. In addition, Group-A was taken as case group and was given magnesium oxide 400mg twice daily which was equivalent to 480 mg of elemental Mg. PEFR and dyspnea scoring was done on daily basis. ABGs were done in all .Group B was control which didn't receive Magnesium Oxide but was given rest of the same treatment. Both groups were followed over their stay in the hospital to assess the effect of oral magnesium in improving in-hospital outcome in form of early discharge of the patient, improvement in peak expiratory flow rate >200L/min, need for assisted ventilation or death.

Data analysis: Data were entered and analyzed by SPSS v26.0. Quantitative variables like age, PEFR volume, duration of hospital stay and duration of COPD in years were presented as mean and SD. Means were compared by applying t-test. Qualitative variables like gender and in-hospital outcome were presented as frequency and percentages. Comparison of two groups, group-A receiving oral magnesium supplementation with the group-B not receiving oral magnesium supplementation was done using Chi-square test. Statistically important was a p-value 0.05.

RESULTS

Total 160 patients were enrolled in this study. In group-A, 68(85%) patients were male and 12(15%) were female, while in group-B, 58(72.5%) were male and 22(27.5%) were female. Mean age in group-A patients was 56.57±8.163 year and 56.78±8.080 year among patients of group-B **(p=0.291)**. In group-A, 22% were in <50 years age group, while 34(42.5%) and 24(30%) were in 51-60 years and >60 years age groups respectively. In group-B, 28(35%) patients were in <50 years age group, while 26(32.5%) and 26(32.5%) were in 51-60 years and >60 years age groups respectively **(p=0.291)**.According to smoking status, 76(95%) were smokers in group-A and 70(87.5%) in group-B **(p=0.444)**. According to dyspnea grading at first day, in group-A, 38(47.5%) had grade-III, while 42(52.5%) had grade-IV and none had grade-V respectively. In group-B, 56(70%) had grade-III, while 22(27.5%) and 2(2.5%) had grade-IV and grade-V respectively **(p=0.000006)**. According to dyspnea grading at last day, in group-A, 64(80%) had grade-II, while 12(15%) and 4(5%) had grade-IV and grade-V respectively. In group-B, 62(77.5%) had grade-II, while 16(20%) and 2(2.5%) had grade-IV and grade-V respectively **(p=0.000002)**. In group-A, mean PEFR volume at day first was 201.50±53.037 and 376.25±123.382 at day-5 **(p=0.011)**, while in group-B, mean PEFR volume at day-1 was 220±52.77 and 389.75±27.83 at last day **(p=0.012)**, with a t test value of 33.37 for first day and 27.07 for last day. Mean hospital stay in group-A patients was 3.22±4.77 days and 2.95±0.5 days among patients of group-B **(p=0.607).** Comparison of means by t test showed value of 0.674. Mean duration of COPD in group-A patients was 5.6±2.03 year and 5.33±2.47 year among patients of group-B **(p=0.236)**. Comparison of means via t test gave t value of 3.745 According to outcome distribution between groups, in group-A, 44(55%) patients were discharged, while 24(30%) needed assisted ventilation and 12(15%) expired. In group-B, 58(72.5%) patients were discharged, while 6(7.5%) needed assisted ventilation and 16(20%) expired with a **p-value 0.178**, which is not statistically significant. Patients enrolled in our study wither showed improvement or deterioration in their dyspnea grading from grade III dyspnea score by the time of their last day of stay in the hospital and none of our enrolled patients were found to be in grade III. Case group did not show any significant improvement in outcome when compared to control group. Less patients were discharged in the case group who was given Magnesium Oxide as compared to control group and more patients in case group needed assisted ventilation or reached death (statistics given in the table). **In Group B - control** 72.5% of the patients were discharged while 27.5% needed assisted ventilation or died (7.5% and 20% respectively)

DISCUSSION

The global growth in COPD prevalence makes disease exacerbation an expanding phenomenon .[10] Thus, there is an increasing interest not only in planning optimal COPD treatment strategies but also in decreasing its exacerbations. These realities emphasize the need to improve treatment modalities for COPD exacerbations[10-12]. But new ways of alleviating symptoms more effectively and reducing the frequency and severity of exacerbations are often needed[13-14]. No additional benefit was detected by improving in pulmonary function, such as PEFR and/or FEV1, in the three published placebo controlled randomized magnesium clinical trials in COPD exacerbations[15-15]. The change in dyspnea scores has been measured in only two studies[16,18].

In one study, a shift in magnesium dyspnea scores was not different from the shift in placebo-receiving patients,[18] compared to ipratropium bromide , in the second study[16]. In addition, there are no trials to endorse the use of inhalational Mg in an earlier study. The authors stated that the role of Mg in treatment of acute exacerbation COPD is uncertain[19]. The clinical results at our center showed that considerable improvements could not be achieved in magnesium treated patients. More data and research is required on this. In three out of total six trails no significant benefit was shown in improvement of PEFR or dyspnea score[21]. Among rest of three trials dyspnea score was found to be significantly better in Mg group but hospital outcome was comparable in those studies[22-23].

Overall on the basis of previously studies worldwide we conclude that role of intravenous or nebulized Magnesium is debatable because of conflicting results. More research is needed on the matter as available data is not enough for a definitive approach. Our study is novel in this regard that we used oral Mg in the form of MgO. Mg is a cheap and safe drug and it's oral form has good bioavailability. We used magnesium oxide for oral use as opposed as to magnesium sulphate used in the previous clinical

trials because of its tendency to cause diarrhea when given via oral route.

Moreover, our future objective was to establish role of oral Mg in acute exacerbation of COPD so it may become as treatment to be used as long term therapy in patients of COPD if found beneficial. We took 160 patients who fulfilled inclusion criteria, and randomly assigned them to two groups. Group A was given MgO 400 mg twice daily which was equivalent to 480mg of elemental Mg. Both groups were given standard treatment for acute exacerbation in the form of intravenous steroids, intravenous antibiotics, oxygen, inhaled beta agonist and/or anticholinergics, inhaled steroids if needed like was done in most of the previous trials. Both groups were followed over the course of their stay in the hospital and ABGs were done daily to see 0_2 and $C0_2$ levels along with measurement of PEFR daily. Dyspnea score was assessed daily as well. No significant difference in PEFR between two groups was observed. Dyspnea score was also comparable among both groups and there was no significantly better outcome in terms of discharge or duration of hospital stay in the group receiving oral MgO. Clinical trials evaluating Magnesium role were heterogeneous in their designs. Various doses and routes of magnesium were employed in various studies with different formulations. It is therefore difficult to directly compare and draw firm conclusions on its efficacy with published clinical studies. For patients with COPD exacerbation, however, the use of Mg seems safe due to no major adverse effects for clinical trials[22].

A randomized, crossover study showed that acute IV Mg loading in COPD who were stable resulted in decreased lung hyperinflation and increased respiratory muscle function. Thus, magnesium in COPD should be investigated further. Oral magnesium seemed a promising new modality in providing better management but our study did not support this.[23] It was cheaper and easier to administer but it did not show any significant improvement via its bronchodilatory properties in our study, it will need further studies to support or nullify its role completely. Use of Mg as an add on treatment in COPD-exacerbations should be evaluated in future by further randomized clinical studies of well-defined and large populations. In addition to airflow obstruction as instruments for measuring performance, measures of dyspnea and breathing muscle strength should also be measured [24].

CONCLUSION

Oral magnesium does not improve in-hospital outcome in patients presenting with COPD exacerbation in comparison to patients not receiving oral magnesium supplementation. However, trails are relatively few, the possible bronchodilator effect of Mg warrants that further trials establish role of Mg as an add-on therapy in acute exacerbation of COPD.

Conflict of interest: Nothing to declare

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