

Nebulized Magnesium Sulphate Versus Saline as an Adjuvant in Acute Exacerbation of Chronic Obstructive Pulmonary Disease in a Tertiary Centre of Nepal: A Randomized Control Study

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ABSTRACT

Introduction

Magnesium has been shown to have bronchodilator properties in asthma and chronic obstructive pulmonary disease (COPD). Therapeutic benefits of nebulized magnesium in asthma has been seen. The purpose of this study was to compare therapeutic benefits of nebulised magnesium sulphate as an adjuvant with normal saline in patients with COPD exacerbation.

Methods

It was a randomized single blind interventional study of 172 cases of acute exacerbation of COPD presenting (AECOPD) with a peak expiratory flow rate (PEFR) <300 L/min measured 20 min after initial management. Patients received 5 mg salbutamol mixed with 3 ml isotonic magnesium sulphate or 3 ml normal saline on three occasions at 30 min intervals via nebulizer. The primary outcome measured was PEFR at 90 min and hospital admission, noninvasive or invasive ventilation and mortality were taken as secondary outcomes.

Results

The mean PEFR were 86.3±11.9 l/min, 97.6±19.1 l/min and 99.6±15.2 l/min after nebulization with magnesium sulphate and 79.17±14.11 l/min, 90.17±18.27 l/min and 93.17±20.63 l/min at 30, 60 and 90 minutes respectively in normal saline group which were statistically significant differences. Total 91.9% were admitted in ward and 8.1% got admitted in Medical and intermediate intensive care units from magnesium group and 81.7% were admitted in ward and 18.3% required ICU admissions in saline group. Differences in ventilation and mortality were insignificant.

Conclusion

Nebulized magnesium sulphate as an adjuvant to salbutamol treatment in the setting of AECOPD has therapeutic benefit on PEFR but no effect in terms of hospital admission, requirement of invasive or non-invasive ventilation and mortality.

Keywords

Chronic obstructive pulmonary disease, magnesium sulphate, peak expiratory flow rate

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease characterized by airflow limitation due to infiltration of small airways with inflammatory cells causing narrowing and destruction of the elastic recoil of lung parenchyma resulting in hyperinflation.¹ Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the commonest encountered disease condition by any doctor at an Emergency Room.² Globally an estimated 10-20% of the population are COPD patients resulting in more than 3 million deaths per year.³ More than 90% of COPD deaths occur in low and middle-income countries. In context of Nepal, it has been estimated that COPD accounts for more than 43% of the non-communicable disease burden and 2.56% of hospitalization.³

The management of AECOPD is mainly focused at arresting the pathogenesis and reversing potential precipitating factors, especially infection with use of antibiotics, steroids, anti-cholinergics and beta-2 agonist.^{4,5} Antibiotics and steroids have played a significant role in controlling infection and inflammation thereby facilitating airway and preventing exacerbation.⁶ Beta-2 agonist along with anti-cholinergic facilitate bronchodilation and thus relieve dyspnea and improve respiratory parameters.^{4,7} Magnesium sulphate is thought to act by inhibiting smooth muscle contraction by facilitating calcium uptake into the sarcoplasmic reticulum. It inhibits the slow inward calcium current and calcium induced calcium release.⁸ It has also been suggested to inhibit histamine release from mast cells and Acetylcholine release from cholinergic nerve terminal to act via central sedative action.⁹ Magnesium sulphate has proven to be beneficial in acute severe asthma when administered via intravenous and nebulized route.¹ Though not proven, citing the similarity in pathophysiology of acute severe asthma and AECOPD (e.g.: bronchial hyper-responsiveness), the use of nebulized magnesium sulphate is as attractive as a therapeutic option because it is can be easily administered, economically sound and with minimal side effects.¹⁰ The aim of this study was to compare the efficacy of salbutamol and magnesium sulphate nebulization versus salbutamol and normal saline nebulization in terms of PEFr in acute exacerbation of COPD patients. The secondary objective was to compare outcomes in both groups in terms of hospital admission, requirement of invasive or non-invasive ventilation and mortality.

METHODS

This was a single blinded randomized control trial conducted in 172 patients of Emergency Room of Tribhuvan University Teaching Hospital from

December 2016 to March 2017. On presentation to the Emergency Department with a provisional diagnosis of an AECOPD, potential subjects were clinically assessed and received standard initial treatment (i.e. 5 mg salbutamol and 250 mcg ipratropium bromide by nebulization and 200 mg hydrocortisone), oxygen (2 l/min nasal prongs) was given if oxygen saturations on room air were <90%. Only subjects more than 40 years^{11,12} with a peak expiratory flow rate (PEFR) <300 l/min, measured 20 min after commencement of the initial salbutamol/ipratropium nebulization were enrolled in the trial. Referred case from other hospitals with prior management, patients who received premedication with bronchodilator 6 hours prior and steroid 12 hours prior to trial and contraindications to magnesium sulphate (hypersensitivity, diabetic coma, heart block, myocardial damage, hypomagnesaemia, hypercalcemia), patients unable to perform spirometry and with systolic blood pressure less than 100 mmHg, evidence of pneumothorax, chronic kidney disease patients and pregnant women and those with motor neuron diseases were excluded from the study.

During this 20 min period informed consent was obtained and a brief questionnaire administered, obtaining information with regard to duration and severity of symptoms, medication use and smoking status. Routine blood tests creatinine, sodium, potassium, full blood count, ABG were done. The patients were randomized by drawing lots to receive one of two sequences of treatment. The medications was prepared by the investigator and were labeled as A (combination of magnesium sulphate and salbutamol) or B (salbutamol and normal saline). Thus the patients were blinded to the nature of the treatment given to a patient. Any side effects noted by the patient or physicians were recorded.

The patients received by nebulization 5 mg salbutamol mixed with A) 3 ml isotonic magnesium sulphate : 50% solution, 8.30 mosm/ml, 500 mg/ml made isotonic by dilution in sterile water at ratio 1:14 (1ml magnesium sulphate and 14 ml sterile water for injection) Or B) 3 ml normal saline on three occasions at 30 min intervals. PEFr using a hand-held spirometer on first referral ('presentation'), before the first study ('baseline' PEFr), before each subsequently and then 30 min after the last nebulization. Three measurements were made at each time point and the highest recording used for analysis. Vital monitoring was done as part of routine clinical observations and otherwise as clinically indicated. After the final recordings the decision to admit the patients was made at the discretion of the clinical team. The patient was followed up for one week after admission in ward and ICU, outcome was noted in terms of requirement of ventilatory support and mortality.

IBM SPSS software version 20 was used to enter data and analyze the data. Mean and standard deviation were calculated for each quantitative variable. Z-test for was used for mean difference for PEFR and vital signs comparison and chi square test for the other variables to establish the level of significance between the variables. P-value of <0.05 was considered to be statistically significant. Study was conducted after getting approval from Institutional Review Comimtee (IRC) of Institute of Medicine. Written consent was taken from the partipants for their enrollment in the study.

RESULTS

Total numbers of 200 patients were assessed for the study, among them 172 were included and 28 patients excluded. Recruited 172 patients were randomized, nebulized with the corresponding drugs and evaluated for the response and followed till discharge or mortality if any.

According to inclusion criteria, patients >40 years were only included in the study. Out of which mean age was 70.01 ± 10.39 years in magnesium and 68.58 ± 14.71 years in normal saline group. A total of

Table 1. Sex distribution (n=172)

Sex	Magnesium sulphate group	Normal saline group	Total	p-value
Male	43 (50.0%)	37 (43.02%)	80	0.11
Female	43 (50.0%)	49 (56.98%)	92	
Total	86 (100.0%)	86 (100.0%)	172	

17(9.9%) were 41-50 years of age, 27(15.7%) in 51-60 years age group, 55(32.0%) in 61-70 years age group, 39(22.7%) in 71-80 years group, 26(15.1%) in 81-90 years group and total 8 (4.6%)patients more than 90 years of age. Most common prevalence was seen in age group 61-70 years.

The mean PEFR at 0 min was 60 l/min in both groups. The mean PEFR was 86.3 ± 119 l/min at 30 minutes, 97.6 ± 19.1 l/min at 60 min and 99.6 ± 15.2 l/min at 90 min after nebulization with salbutamol and magnesium sulphate. The mean PEFR were 79.17 ± 14.11 l/min, 90.17 ± 18.27 l/min and 93.17 ± 20.63 l/min at 30, 60 and 90 minutes respectively in salbutamol and saline group which were statistically significant. Heart rate and

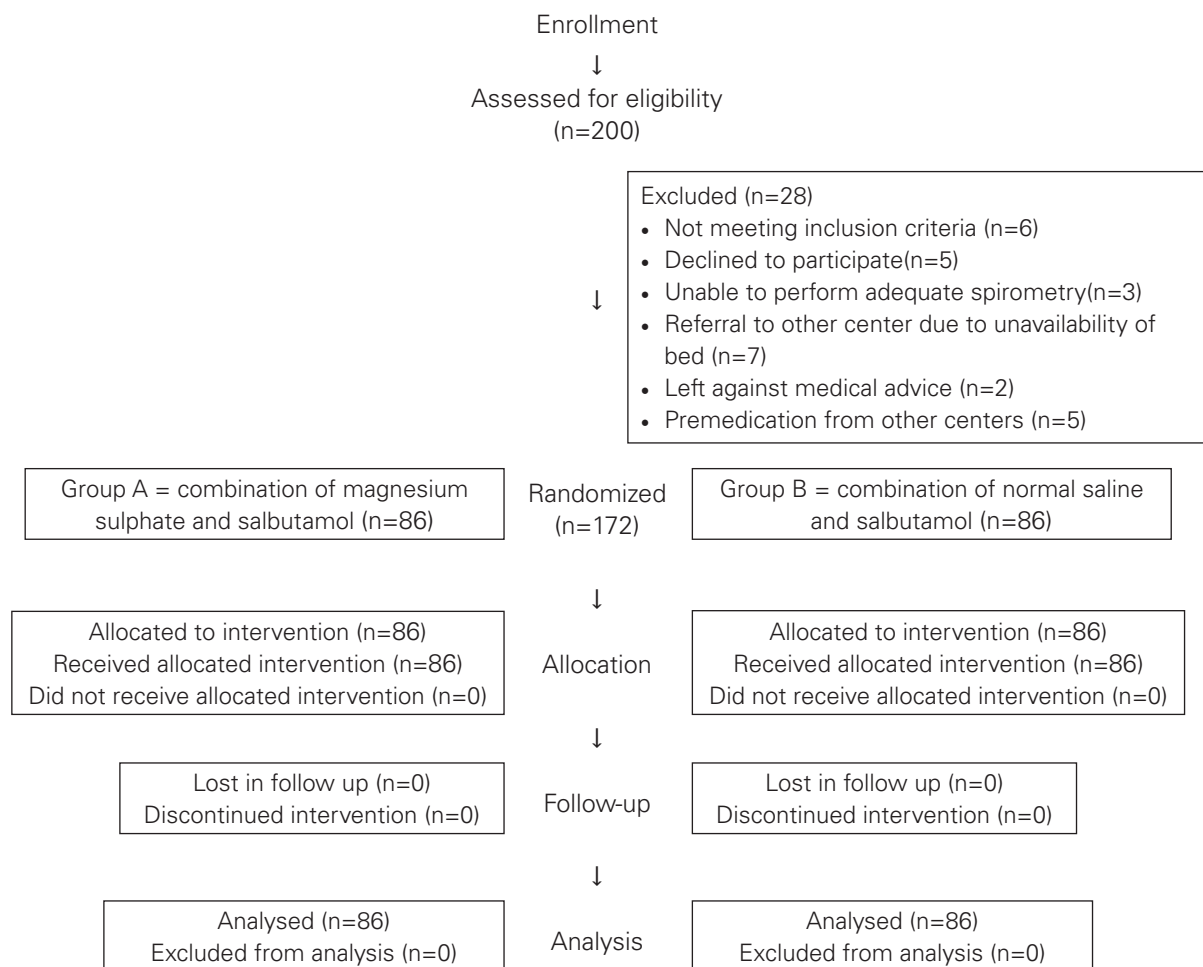


Fig 1. CONSORT flow diagram

Table 2. PEFR change at baseline and 90 min in response to nebulization (n=172)

PEFR (in L/min) at	Magnesium sulphate group	Normal saline group	p-value
0 min	60	60	
30 min	86.3±11.9	79.17±14.11	0.009
60 min	97.6±19.1	90.17±18.27	0.22
90 min	99.6±15.2	93.06±20.63	0.08

Table 3. Disposition of patients (n=172)

Admission area	Magnesium sulphate group	Normal saline group	Total	p-value
Ward	79 (92%)	70 (81%)	149	0.11
ICU	7 (8%)	16 (19%)	23	0.12

Table 4. Requirement of ventilator support (NIV/IV) in relation to treatment (n=172)

NIV/IV support	Magnesium sulphate group	Normal saline group	p-value
Yes	0	1 (1.7%)	0.08
No	86 (100%)	85 (98.3%)	

Table 5. Treatment relation with mortality (n=172)

Mortality	Magnesium sulphate group	Normal saline group	p-value
Yes	0	1 (1.7%)	0.08
No	86 (100%)	85 (98.3%)	

blood pressure change in between two groups was statistically insignificant. Z-test was used to calculate mean difference.

A total of 8% of patients got admitted in intensive care units and 92% got admitted in ward in magnesium group. In saline group, 19% got admitted in intensive care while 81% got admitted in ward. In saline group, 1.7 % of the patients underwent ventilatory support which was statistically insignificant. Chi-square test was used to compare differences between these variables. In terms of mortality, 1.7% of patients expired in normal saline group which was also statistically insignificant.

DISCUSSION

The present study was conducted to investigate the role of nebulized magnesium sulphate combined with salbutamol versus salbutamol alone in patients with acute exacerbation of COPD. Our study showed

that nebulization of combination of magnesium sulphate and salbutamol had beneficial effect in bronchodilation compared with plain salbutamol nebulization in patients with acute exacerbation of COPD. However, there were no significant differences between the two groups with regard to side effects and rates of hospitalization, ventilator support or mortality.

Several methodological issues were considered in the design of the study that is relevant to its interpretation. The primary reason for including only subjects with an PEFR<300 l/min predicted (measured 20 min after commencement of initial salbutamol and ipratropium) was that, in groups with asthma, an effect with intravenous magnesium has been found in those with more severe disease.¹³ A good correlation between forced expiratory volume in 1 second (FEV₁) and PEFR has been reported in COPD, further validating the possible use of home PEFR as a surrogate for office-based or laboratory spirometric monitoring.¹⁵

The reason for the initial bronchodilator administration of salbutamol/ipratropium nebulizers at presentation was safety as well as ensuring some standardization of bronchodilator treatment in the 20 min prior to randomization. Bronchodilators are considered first-line treatment as per guidelines for managing AECOPD but may not recommend a specific dose.¹⁶ In stable COPD it has been shown that 88% of patients achieved 90% of maximal bronchodilator with doses of inhaled salbutamol ≤1.2 mg.¹⁷ However, this pre-dosing with bronchodilators could have already led to their maximum bronchodilator response before administration of magnesium.

The magnesium used was formulated as an isotonic solution. This was important because both hypotonic and hypertonic nebulizer solutions can induce bronchoconstriction in patients with bronchial hyper-responsiveness.¹⁸ Skorodin et al reported a significant increase in peak expiratory flow from initiation to 30 and 45 min later and a statistically non-significant trend towards a reduced need for hospitalization with intravenous magnesium which support results of our study.¹⁹ This study by Gonzalez et al and Amaral et al with intravenous magnesium vs placebo also supports the bronchodilator effects of magnesium as an adjunct rather than sole bronchodilator and an increase in respiratory muscle strength measured as maximum inspiratory pressure.²⁰ Together these studies indicate that a single intravenous dose of magnesium has clinical efficacy in both stable and acute exacerbations of COPD.

More recent study on multiple nebulization of terbutaline plus ipratropium or terbutaline plus a once-only bolus of intravenous magnesium followed by repeated nebulized terbutaline and nebulized

magnesium showed no significant difference between the two groups in their primary outcome variable (which included hospital admission, intubation and hospital death rates) similar to our study result.²¹ In a similar study by, Edwards et al. the primary outcome variable of FEV₁ measured at 90 min showed no statistically significant difference between the placebo group and the magnesium sulphate group after adjustment for baseline FEV₁. Differences in the need for hospital admission did not show significance either which was similar to our study.²²

The relevance of our study to the studies done in asthma is equally comparable because the reported efficacy of magnesium in asthma exacerbations is the pretext for its use in COPD. In asthma, magnesium has been administered both intravenously and via the nebulized route. The recent Cochrane review and meta-analysis of intravenous magnesium reported an improvement only in the severe subgroup in whom peak expiratory flow and FEV₁ has shown to improve²³ However, the Cochrane review of nebulized magnesium as an adjunct in acute asthma reported a non-significant improvement in pulmonary function in the nebulized magnesium group, but significant heterogeneity between trials precluded a definitive conclusion.

Furthermore, the benefits of repeated administration of nebulized magnesium include ease of administration with no need for an intravenous line. With regard to the dose of magnesium, this was based on the work in asthma.²⁴ Most of our patients did show a significant response to nebulized therapy. We did not continue nebulization of magnesium sulphate beyond three doses although further doses of salbutamol are recommended if a patient shows only partial response to initial dose. Therefore, a possible difference between the two groups could have been masked by the small sample size. Longer follow up period for the patients would have been better for seeking any long term benefits or side effects. Since this was a single centre based study, further multicentred studies are recommended before generalization of the study is done.

CONCLUSION

This randomized single blinded study indicated that the administration of nebulized magnesium sulphate along with salbutamol in patients with COPD exacerbation demonstrate therapeutic benefit in bronchodilation in terms of improvement in PEFr however there was no evidence of significant alteration in the vital signs, hospital admission, or any form of ventilation and mortality.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Aggarwal P, Sharad S, Handa R, et al. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. *Emerg Med J* 2006; 23: 358–62.
2. Welniak TJ, Panzenbeck A, Koyfman A, et al. Chronic obstructive pulmonary disease: Emergency care in acute exacerbation. *African J Emerg Med* 2015; 5: 75–84.
3. Longmore M, Wilkinson I, Baldwin A, et al. *Oxford Handbook of Clinical Medicine-Mini Edition*. OUP Oxford, 2014.
4. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. *Ann Emerg Med* 1999; 34: 8–18.
5. Plotnick LH, Ducharme FM. Should inhaled anticholinergics be added to β_2 agonists for treating acute childhood and adolescent asthma? A systematic review. *Bmj* 1998; 317: 971–977.
6. Herath SC, Poole P. Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Libr*.
7. Melani AS. Long-acting muscarinic antagonists. *Expert Rev Clin Pharmacol* 2015; 8: 479–501.
8. Mathew R, Altura BM. Magnesium and the lungs. *Magnesium* 1988; 7: 173–187.
9. Mangat HS, D'souza GA, Jacob MS. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. *Eur Respir J* 1998; 12: 341–344.
10. Papiris SA, Manali ED, Kolilekas L, et al. Acute severe asthma. *Drugs* 2009; 69: 2363–2391.
11. Bhandari R, Sharma R. Epidemiology of chronic obstructive pulmonary disease: a descriptive study in the mid-western region of Nepal. *Int J Chron Obstruct Pulmon Dis* 2012; 7: 253.
12. Adhikari TB, Neupane D, Kallestrup P. Burden of COPD in Nepal. *Int J Chron Obstruct Pulmon Dis* 2018; 13: 583.
13. Shrestha B, Dhungel S, Chokhani R. Echocardiography based cardiac evaluation in the patients suffering from chronic obstructive pulmonary disease. *Nepal Med Coll J* 2009; 11: 14–18.
14. Jain P, Kavuru MS, Emerman CL, et al. Utility of peak expiratory flow monitoring. *Chest* 1998; 114: 861–876.
15. Kelly CA, Gibson GJ. Relation between FEV1 and peak expiratory flow in patients with chronic airflow obstruction. *Thorax* 1988; 43: 335.
16. Pearson M. Chronic obstructive pulmonary disease: national clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004; 59: 1–232.
17. Teale C, Morrison JF, Page RL, et al. Dose response to inhaled salbutamol in chronic obstructive airways disease. *Postgrad Med J* 1991; 67: 754–756.
18. Beasley R, Rafferty P, Holgate ST. Adverse reactions to the non-drug constituents of nebuliser solutions. *Br J Clin Pharmacol* 1988; 25: 283–287.
19. González JA, García CH, González PA, et al. Effect of intravenous magnesium sulfate on chronic obstructive pulmonary disease exacerbations requiring hospitalization: A randomized placebo-controlled trial. *Arch Bronconeumol (English Ed)* 2006; 42: 384–387.
20. Amaral AF, Gallo L, Vannucchi H, et al. The effect of acute magnesium loading on the maximal exercise performance of stable chronic obstructive pulmonary disease patients. *Clinics* 2012; 67: 615–622.
21. Noura S, Bouida W, Grissa MH, et al. Magnesium sulfate versus ipratropium bromide in chronic obstructive pulmonary disease exacerbation: a randomized trial. *American journal of therapeutics*, 2014, pp. 152–158.

22. Edwards L, Shirtcliffe P, Wadsworth K, et al. Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: a randomised double-blind placebo-controlled trial. *Thorax* 2013; 68: 338–343.
23. Rowe BH, Bretzlaff J, Bourdon C, et al. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Libr.*
24. Hughes R, Goldkorn A, Masoli M, et al. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial. *Lancet* 2003; 361: 2114–2117.