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Does Magnesium Sulphate have a Role in the Management of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD) in the Emergency Department?

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Abstract

Objective: The objective of this review is to evaluate the current available evidence for the for the efficacy of Magnesium sulphate in COPD.

Methodology: We undertook a literature review and meta-analysis aimed at identifying relevant articles regarding the use of magnesium (IV or nebulised) in the treatment of acute exacerbation of COPD. The outcome measures include; the effect on FEV1, FVC, PERF, rate of admission, rate of NIV or endotracheal intubation and in-hospital mortality.

Result:

- Seven studies were relevant to the review.
- Three evaluated the effect of magnesium on FEV1
- Three studies that examined the effect of magnesium on the FVC.
- Two examined the effect of adding magnesium on oxygen saturation.
- Four studies examined the effect of adding magnesium to the standard treatment of AECOPD.
- Two studies found no significant difference in the requirement for intubation
- Two of three studies subjected to meta-analysis found a reduction in the PEFR and hospital admission with the use of magnesium sulphate.
- The only study that examined the effect of adding magnesium on in-hospital mortality found no effect.

Conclusion: It would appear that the addition of intravenous magnesium sulphate to the standard bronchodilator therapy for AECOPD is beneficial in terms of improving the respiratory functions, oxygen saturation and a reduction in hospital admission. There was no effect in the requirement for intubation and overall hospital mortality.

Keywords: Magnesium; COPD; Acute exacerbation; Nebulisation

Introduction

COPD is a leading cause of death world-wide. Despite many clinical trials regarding the management of the condition, the treatment and management has not changed over the last few decades.

There is no consensus with respect to the management strategies. The mainstay of treatment has been the bronchodilator effect of beta 2 agonists combined with oral steroids. Intravenous magnesium has been used by many physicians as an adjunct to the management of COPD, especially if the first line of treatment has not been effective. Common guidelines and recommendation adopt a stepwise approach to treatment; commencing with bronchodilators, steroids, oxygen, antibiotics and other adjunctive measures depending on the setting and severity.

It has been recognised that magnesium plays a key role in numerous human physiological processes [1,2]. The underlying mechanism of action include calcium antagonism *via* calcium channel regulation of energy transfer and membrane stabilisation.

In the airway, magnesium mediates bronchodilatation through various mechanisms of action including an inhibitory effect on bronchial smooth muscle contraction; mediated by calcium and an inhibitory effect on acetylcholine release from cholinergic nerve terminals and histamine release from mast cells [3,4].

The antecedent for the use of magnesium sulphate in COPD is its effectiveness in asthma. Although asthma and COPD have overlapping clinical features, they represent distinct clinical entities. Despite the proven effectiveness of magnesium in asthma, there is no conclusive evidence of its efficacy in COPD.

Methodology

We undertook a search aimed at identifying relevant articles regarding the use of magnesium (IV or nebulised) in the treatment of acute exacerbation of COPD. The outcome measures include; the effect on FEV1, FVC, PEFR, rate of admission, rate of NIV or endotracheal intubation and in-hospital mortality

We searched the following databases: Embase<1974 to 2020 November 09>, Ovid MEDLINE(R) and Epub ahead of print, in-process and other non-indexed citations and daily <1946 to November 09, 2020>. Others: bestbets.org, google schlolar. The search was checked by 2 of the authors (VA and RK)

Result

A total of 50 papers were identified of which 7 were thought to be relevant and included in the review (Table 1).

Study type	Author and year of publication	No of patients	Methodology	Results, outcome and limitations
RCT	Moradi et al. [5]	77	39 patients in $Mgso_4$ group and 38 patients in placebo group (saline) Intervention given after 60 minutes of salbutamol and ipratropium nebuliser)	Primary outcome: PEFR, DSS and RR
				Secondary outcome: Need for ETT and hospital discharge.
				Following adjunctive use of magnesium following standard treatment with salbutamol on both groups, there was a;
				Significant increase in PEFR (% predicted) in the magnesium group; 10.3. (95% CI 8.68-11.38), P<0.001
				Significant decrease in dyspnoea severity score (DSS) in the magnesium group 1.63 (95% CI 1.14-2.13), P<0.001
				There was no difference in respiratory rate 0.90 (95% CI 0.02-1.78), P=0.04 or Spo2 0.32 (95% CI -1.56-2.20) P=0.734
				There was no difference in endotracheal intubation rate and ED discharge rate.
				Limitations: Highly select group with no co-morbidities, under powered sample size.
RCT	Pishbin et al. [6]	34	17 patients in each group	Outcome measures: PEFR, DSS and $SP0_2$
			All patients received standard bronchodilator	

			treatment for 20 minutes, then given 2 g $MgSO_4$ or placebo	
				Improved dyspnoea severity score (DSS) and Spo_2 in the magnesium group (p=0.001 and 0.004 respectively)
				No difference in PEFR, intubation and admission rate.
				Limitation: Small numbers
RCT (double blind placebo-controlled)	Mukerji et al. [7]	30	17 patients in placebo (saline) group and 13 patients in intervention group (2 g IV $Mgso_4$).	Primary outcome: FEV1 and FVC
			All patients had prior standard bronchodilator treatment then spirometry at T0, T60 and T120	Secondary outcome: Admission rate, length of stay and need for NIV.
				Significant improvement in FEV1=27.07% in magnesium group *vs.* 11.39% in placebo group (95% CI 3.7–27.7, P=0.01)
				Similar improvement noted in FVC at 2 hours in magnesium group
				Limitations: Pilot study, small numbers, single centre.
RCT	Nouira et al. [8]	124	2 groups	Primary outcome: Admission rate, ETT and death rates
			Group 1-62 patients given nebulised ipratropium	Secondary outcome: PEFR, DSS and ABG changes.
			Group 2–62 patients given nebulised plus IV bolus of mgso4	
			All medications given at 30 minutes intervals for 2 hours.	Greater improvement in PEFR AND PaCO2 in patients receiving IV saline and ipratropium than in the magnesium group at 180 minutes.

				No difference in admission, intubation, and mortality rates (95% CI 19 -43) at 180 minutes.
				Limitation: Magnesium used as sole treatment and not as an adjunct
RCT (double blind placebo-controlled)	Edward et al. [9]	116	Group 1 (52) given nebulised magnesium sulphate	Primary outcome: FEV1 at 90 minutes
			Group 2 (64) given nebulised isotonic saline	Secondary outcome: Need for NIV and hospital admission
			All patients received prior initial treatment with nebulised 2.4 mg salbutamol and 500 mcg ipratropium	
				No difference in FEV1 in patients receiving nebulised magnesium and salbutamol versus those receiving nebulised saline with salbutamol (-0.026L, 95% CI 0.15-0.95, P=0.67)
				No difference in admission rate (RR 0.98, 95% CI0.86–1.10, P=0.69)
RCT (double blind, crossover)	Gonzalez et al. [10]	24	Group 1 (12) given IV mgso4 followed by placebo	Outcome measure: Spirometry at 15, 30 and 45 minutes.
			Group 2 (12) given 400 mcg salbutamol nebuliser	
				No improvement in FEV1 at 15, 30 and 45 minutes following administration of IV magnesium.
				Magnesium sulphate found to have no bronchodilator effect alone but enhances the bronchodilator effect of salbutamol.
				Limitation: Single centre, Male bias

RCT (double blind placebo-controlled crossover)	Skorodin et al. [11]	72	2 groups randomised to 1.2g iv magso4 or placebo	Outcome measure: PEFR, DSS Pa02, SPO2 assessed after 45 minutes of treatment.
			All patients given prior treatment with nebulised 2.5 Albuterol.	
				Significant increase in PEFR (mean change 24%) in group given IV magnesium after nebulised salbutamol (p = 0.01)
				No significant difference in dyspnoea severity score (DSS), length of hospital stay (28% in magnesium group versus 42% in placebo group, p = 0.25)
				Limitation: Male bias

Table 1: Studies on the utility of magnesium in acute exacerbation of COPD.

Due to the gross heterogeneity of the studies, only three studies were suitable for meta-analysis of the two of the outcome measures (PEFR and requirement for hospital admission) (Figures 1 and 2).

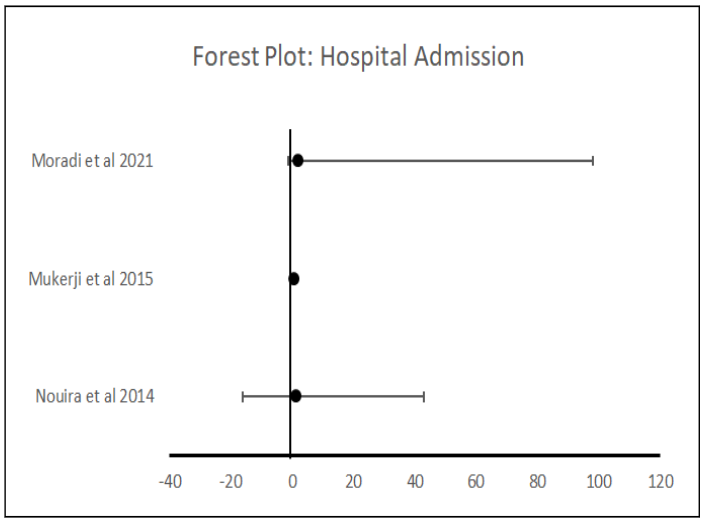

Figure 1: Forest plot: Hospital admission.

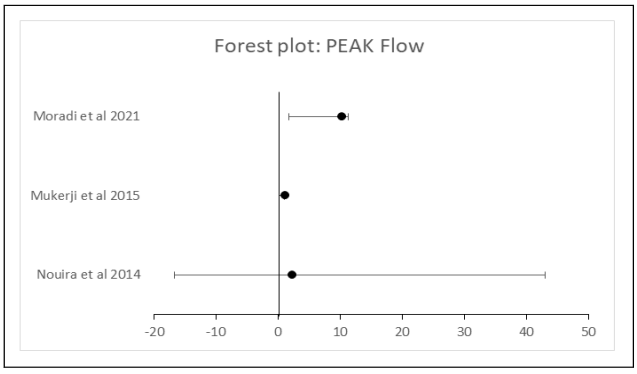

Figure 2: Forest plot: Peak flow.

Discussion

FEV1 (Forced Expiratory Volume in 1 second)

Two of the three studies that evaluated the effect of magnesium on FEV1 found a significant improvement with the addition of magnesium to the standard management of acute exacerbation of COPD. One study found no difference with the addition of magnesium [7,9,11].

FVC (Forced Vital Capacity)

Two studies that examined the effect of magnesium on the forced vital capacity of the lung (FVC) all found a significant improvement with this parameter [7,10].

PEFR (Peak Expiratory Flow Rate)

Four of five studies that examined the effect of magnesium on the PEFR, found a significant difference [5-7,10]. Nouira et al. did not find any significant difference in the PEFR following the use of magnesium [8]. 2 of the three studies subjected to a meta-analysis found a significant improvement in the PEFR following the addition of magnesium.

Oxygen Saturation ($Sp0_2$)

Two studies examined the effect of magnesium on the oxygen saturation. They both found that the addition of magnesium led to an improvement in the oxygen saturation [5,6].

Hospital admission

Five studies examined the effect of adding magnesium to the standard treatment of AECOPD. Two found a significant difference on the admission rate as compared to the group without magnesium. Following a meta-analysis of the three eligible studies, Nouira et al. did not find any difference in the admission rate [5,7-10].

Requirement for Endotracheal Intubation (ETT)

Two studies examined the effect of adding magnesium to the standard treatment of AECOPD on the requirement for endotracheal intubation. They both found no significant difference between the two groups [5,8].

Mortality

Only one study looked at the effect of adding magnesium on in-hospital mortality. The authors found no difference between the group treated with magnesium and the control group [8].

Conclusion

It would appear from the current evidence that the addition of intravenous magnesium sulphate to the standard bronchodilator therapy for acute exacerbation of Chronic Obstructive Airway Disease (COPD) is beneficial in terms of improving the FEV1, FVC, Dyspnoea Severity Score (DSS), PEFR, oxygen saturation and hospital admission in the studies evaluated. However, there was no significant difference when it comes to the requirement for endotracheal intubation and hospital mortality.

The finding of this study is limited by their significant heterogeneity. Only three studies lend themselves to a meta-analysis of only 2 outcome measures; changes in the PEFR and the requirement for hospital admission.

Large scale high quality randomised controlled trials would be required in order to provide conclusive evidence of the utility of adding magnesium sulphate to the standard treatment for acute exacerbation of COPD.

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