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Efficacy of magnesium sulfate in the chronic obstructive pulmonary disease population: A systematic review and meta-analysis

Abstract

Introduction: Magnesium sulfate has been extensively used to treat asthma exacerbations, but its efficacy remains questionable in the chronic obstructive pulmonary disease (COPD) population. Objective is to compare the efficacy of intravenous (IV) magnesium sulfate in COPD.

Material and methods: A systemic review search was conducted on PubMed, Embase, and the Central Cochrane Registry. Randomized clinical trials were included with magnesium sulfate as an intervention arm in the COPD population. For continuous variables, standardized mean difference (SMD) and difference in means (MD) were calculated. For discrete variables, the Mantel-Haenszel (MH) odds ratio was used. For effect sizes, a confidence interval of 95% was used. A p-value of less than 0.05 was used for statistical significance. Analysis was done using both random and fixed effect models. Heterogeneity was evaluated using the I^2 statistic.

Results: Seven studies were included in the final analysis. In patients with acute exacerbations of COPD treated with IV magnesium, a significant increase in forced expiratory volume in one second (FEV_1) was observed (MD = 2.537 [0.717 to 4.357], p = 0.006), as well as in peak expiratory flow rate (PEFR) (SMD = 1.073 [0.748 to 1.397], p < 0.001) using the fixed model. Similarly, residual volume decreased significantly in the IV magnesium group (MD = -0.470 [-0.884 to -0.056], p = 0.026). The hospitalization rate was also lower in the magnesium group, (MH odds ratio 0.453 [0.233 to 0.882], p = 0.020). No statistically significant difference was noted in FEV_1 in the stable COPD population.

Conclusion: IV magnesium was associated with a favorable deviation of FEV_1 and PEFR, decreased residual volume, and decreased odds of admission in the COPD exacerbation population. Therefore, magnesium sulfate can be used as an adjunctive therapy in the treatment of acute exacerbations of COPD.

Key words: magnesium sulfate, COPD, chronic obstructive pulmonary disease, acute exacerbation of COPD

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Introduction

"COPD is a common, preventable, and treatable disease that is defined as persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases", as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [1]. COPD has various subtypes, including chronic bronchitis, chronic obstructive asthma, and emphysema [2]. Risk factors for COPD include smoking, air pollutants, old age, female sex, genetic defects like alpha-1 antitrypsin deficiency, poor socioeconomic status, low birth weight, history of childhood asthma, and recurrent severe lung infections [1].

COPD is a major growing cause of morbidity and mortality globally [3]. COPD is the fourth

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most common cause of death worldwide, and estimates extrapolate that it will be the third most common cause by 2030 [4]. COPD causes high healthcare resource utilization with frequent hospitalizations due to acute exacerbations and the need for chronic treatment [5].

GOLD suggests that COPD treatment should be focused on improving both acute and chronic symptoms, reducing exacerbations, and enhancing patient function and quality of life, and that therapy should be guided by disease severity [1]. The standard of care maintenance therapy for COPD includes inhaled bronchodilators, such as β-blockers and muscarinic blockers, either alone or with the addition of inhaled glucocorticoids. Nonpharmacologic therapies such as smoking cessation, nutrition, the pneumonia vaccine, and pulmonary rehabilitation are also important [1].

Current guidelines recommend using short-acting β-agonists, systemic glucocorticoid therapy, short-acting muscarinic antagonists, and antibiotics [1, 6]. The use of mucoactive agents, methylxanthines, and chest physiotherapy has not proven to be beneficial thus far, though prophylactic N-acetylcysteine is associated with a decrease in the incidence of COPD exacerbations [7, 8].

Magnesium sulfate has been used in both an intravenous and nebulized form to manage severe acute asthma exacerbations. However, the use in severe COPD exacerbations has not been well documented and studied so far. There is limited evidence supporting nebulized or IV magnesium sulfate efficacy in COPD exacerbations [9]. Hence, we have performed a meta-analysis to study the possible role of magnesium sulfate in COPD patients.

Material and methods

Methodology

The databases accessed were the Cochrane central registry of clinical trials, Embase, and PubMed. The reference list of included studies was also checked for any additional studies missed in the initial search. Further, references from included studies were also assessed for any missed articles. Search terms used were chronic obstructive pulmonary diseases, magnesium sulfate, and COPD exacerbation. The deadline for publication was set as December 20, 2020.

Inclusion and exclusion criteria

Papers were included, which:

— were randomized controlled trials with intravenous magnesium sulfate used as an intervention in COPD patients with the standard of care as the control arm;
— enrolled patients 18 years of age or older;
— were available in the English language, without any restrictions regarding date or status of publications.

Those papers which did not meet the above criteria were excluded.

Trial selection and evaluation

Three authors independently reviewed all articles and abstracts and excluded irrelevant articles. The risk of bias for selected papers was assessed using the Cochrane collaborative tool and classified into high, uncertain, and low. Publication bias was assessed using Egger's regression intercept.

Data extraction

Information was extracted using a pre-specified extraction table. Information was extracted from trials reading through text and tables, and a second author reviewed the information collected to ensure its accuracy. The extracted data included the number of patients, post expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), residual volume, and admission rate from the emergency department.

Statistical analysis

The meta-analysis was performed using the comprehensive meta-analysis software version 3. We calculated the mean difference for continuous variables for treatment effect when measurements were all made in the same unit and scale. The standardized mean difference was used in the case of PEFR as measurements were made in different units. MH odd's ratio was calculated for discrete variables (admission rate from emergency). Standard errors were calculated using a 95% confidence interval, and a p-value of 0.05 was used for determining statistical significance. For analysis, results were reported from both random-effects and fixed-effect models. Heterogeneity was evaluated using the I^2 statistic; heterogeneity less than 40 was considered low, 40–60 moderate, and above 60 as high.

Results

Literature search

A total of 358 articles were identified in the initial search. After the removal of duplicates, 332 articles were filtered. The first screening excluded 302 articles. 30 full texts were analyzed.

Six articles were excluded as they were review articles, one did not have an English translation available, five were abstracts, five did not have a relevant intervention, one was a case report, and five were other articles (for example, letters to the editor). Seven randomized control trials were included with a total of 263 patients. The main characteristics are provided in Table 1.

Risk of bias

The results of the risk of bias are shown in Figure 1 and Figure 2.

Results of quantitative analysis

Forced expiratory volume in 1 second (FEV_1): Three studies [10–12] reported a change in FEV_1 percentage after administering IV magnesium sulfate in patients with a COPD exacerbation. The difference was statistically significant when calculated with the fixed model (MD = 2.537 [0.717 to 4.357], p = 0.006,), (I^2 = 68.862 [high heterogeneity]) (Figure 3). The mean difference showed a significant favorable deviation towards the use of magnesium but was statistically insignificant when calculated using the random-effects model (MD = 7.872 [–2.957 to 18.701], p = 0.154).

One study by Abreu Gonzalez *et al.* (2006) reported a change in FEV_1 with salbutamol given after magnesium sulfate infusion. There was a more significant change in FEV_1 (MD = 4.940 [2.599 to 7.281], p ≤ 0.001) [10].

Two studies [13, 14] reported a change in absolute FEV_1 after magnesium loading in stable COPD patients. The results leaned in favor of magnesium sulfate use but were statistically insignificant (MD = 0.045 [–0.003 to 0.094], p = 0.065), (I^2 = 0 [low heterogeneity]) (Figure 4).

Residual volume: Two studies [13, 14] reported a change in residual volume in stable COPD patients after loading with magnesium. There was a decrease in residual volume (MD = –0.470 [–0.884 to –0.056], p = 0.026), (I^2 = 0 [low heterogeneity]) (Figure 5).

Peak expiratory flow rate (PEFR)

Three studies [13–15] reported a change in PEFR after magnesium administration when compared with the standard of care. Two reported [15, 16] the change as a percentage of mean, and the third [11] study reported the absolute difference in PEFR values. Overall, the difference was statistically significant (SMD = 1.073 [0.748 to 1.397], p < 0.001), (I^2 = 91.063 [high heterogeneity]) when calculated using the fixed effects model (Figure 6). The random model showed a strong deviation towards the magnesium group, but it was not statistically significant (SMD = 1 [-0.115 to 2.115], p = 0.079).

Admission rate from emergency

Three studies [12, 15, 16] reported the percentage of patients requiring admission for further treatment. The odds ratio for being admitted in the magnesium sulfate group was significantly lower compared to placebo (MH odds ratio 0.453 [0.233 to 0.882], p = 0.020), (I^2 = 0 [low heterogeneity]) (Figure 7).

Summary of results

IV magnesium sulfate use in COPD exacerbations was associated with a favorable deviation in FEV_1 when used alone and an even more significant increase when used adjunctly with salbutamol. Similarly, a positive deviation favoring IV magnesium was noted in PEFR using IV magnesium when compared to placebo. It was also associated with significantly fewer hospital admissions from the emergency department. There was a significant reduction in residual volume in the stable COPD population, but no significant change in FEV_1 was noted.

Publication bias

Egger's regression intercept was used to ascertain publication bias. The two-tailed p-value for change in FEV_1 was 0.48 and 0.83 for the admission rate from the emergency department. Hence, no significant publication bias was detected in the included studies.

Discussion

Magnesium sulfate, used both intravenously and via nebulization, has been used historically to treat severe asthma exacerbations not responding to β-agonists or systemic glucocorticoids [17]. Magnesium sulfate is cost-effective and readily available at most healthcare centers worldwide. However, its mechanism of action in obstructive lung diseases such as asthma has not been fully understood [18]. It is suggested that it works as a bronchodilator by inhibiting calcium influx into the smooth muscles of bronchioles by inhibiting voltage-dependent calcium channels [19, 20]. Furthermore, magnesium may decrease neutrophilic degranulation during the inflammatory phase [21]. It might play a role in releasing acetylcholine from cholinergic nerve terminals and

Table 1. Main characteristics of studies included in meta-analysis

Study	Participants Analyzed	Intervention	Co-Intervention	Inclusion	Exclusion	Primary Outcome	Secondary Outcomes
Vafadar *et al.* (2020) [16]	IV magnesium (n = 39) vs placebo (n = 38)	2.5 g of magnesium sulfate vs placebo	All patients given O_2 maintain sat > 90%, nebulized ipratropium, IV hydrocortisone, nebulized salbutamol, IV ceftriaxone and oral azithromycin	Adults with a clinical diagnosis of AECOPD	Intubation or mechanical ventilation Hemodynamically unstable Uncooperative or unable to perform peak flow meter Pregnancy Other conditions contributing to dyspnea, or a history suggestive of asthma	Peak expiratory flow rate Dyspnea severity score Respiratory rate	Need for intubation ED discharge rate
Mukerji *et al.* (2015) [12]	IV magnesium (n = 13) vs placebo (n = 17)	2 g magnesium sulfate vs placebo	All patients received 5mg salbutamol, 500 mcg ipratropium, 60 mg prednisone or 100 IV hydrocortisone, Oxygen to maintain sat > 90	Age > 35 Infective or non--infective AECOPD	NIV or mechanical ventilation at admission Unable to cooperate or perform function test Pneumothorax or hypotension	Change in FEV_1 Change in FVC	Hospital admission NIV or MV Length of Stay
Solooki *et al.* (2014) [11]	IV magnesium (n = 15) vs placebo (n = 15)	2 g magnesium sulfate vs placebo	All patients received oxygen, salbutamol 2 puff q6h, ipratropium 2 puff q6h, methylprednisolone 60 mg q12h, azithromycin	Age>40 Non-infective AECOPD	Contraindications to IV magnesium sulfate Unable to perform spirometry Presence of pneumonia Oral temperatures > = 38 °C or SBP < 100	Change in PEFR at 45min at day 3 Change in FEV_1 at 45 min at day 3	None
Abreu Gonzalez *et al.* (2006) [10]	IV magnesium (n = 12) vs placebo (n = 12)	Group A 1.5 g magnesium sulfate IV on day 1 and placebo on day 2 Group B placebo day 1 and 1.5 g magnesium sulfate IV on day 2	All patients given methylprednisolone, fluids, antibiotics (amoxicillin-clavulanic acid or quinolone if allergic), inhaled salbutamol and ipratropium and oxygen to maintain sat > 90%	Men with diagnosed AECOPD who were able to cooperate	Patients with pneumonia, HF, arrhythmia, renal failure Inability to cooperate	FEV1 after magnesium sulfate FEV1 after magnesium sulfate + Salbutamol	Heart rate Blood pressure
Skorodin *et al.* (1995) [15]	IV magnesium (n = 36) vs placebo (n = 36)	1.2 g IV magnesium or placebo after albuterol inhaler	O_2 to maintain sat > 88%, albuterol inhaler	Age > 35 Clinical diagnosis of AECOPD	Temp > 37.9C SBP < 100 CKD or pneumonia	PEFR Dyspnea score Maximal inspiratory and expiratory pressure Vital signs for 45 mins	None
Do Amaral *et al.* (2008) [14]	IV magnesium (n = 22) vs placebo (n = 22) crossover Study	Group A 2 g magnesium IV on day 1 and placebo on day 2 Group B placebo day 1 and 2 g magnesium IV on day 2	100 μg of salbutamol by MDI prior to randomization	COPD diagnosis as per GOLD criteria Stable COPD for 2 months	History of asthma, heart failure, arrythmias, on steroids, diuretics or multimineral supplements	Pulmonary function parameters Arterial blood gas parameters	None
Do Amaral *et al.* (2012) [13]	IV magnesium (n = 20) vs placebo (n = 20) Crossover Study	Group A 2 g magnesium IV on day 1 and placebo on day 2 Group B placebo day 1 and 2 g magnesium IV on day 2	None	COPD diagnosis as per GOLD criteria Stable COPD for 2 months	History of asthma, heart failure, arrhythmias, on steroids, diuretics or multimineral supplements	Pulmonary function parameters Cardiorespiratory parameters at maximal exercise	None

AECOPD — acute exacerbation of COPD; COPD — chronic obstructive pulmonary disease; GOLD — Global Initiative for Chronic Obstructive Lung Disease; MDI — metered dose inhalers; PEFR — peak expiratory flow rate; NIV — non-invasive mechanical ventilation; MV — mechanical ventilation; FVC — forced vital capacity; ED — emitted dose

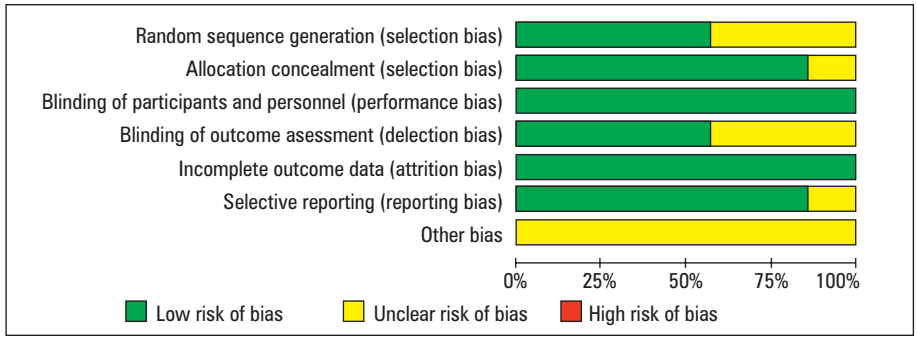

Figure 1. Bias in the studies included

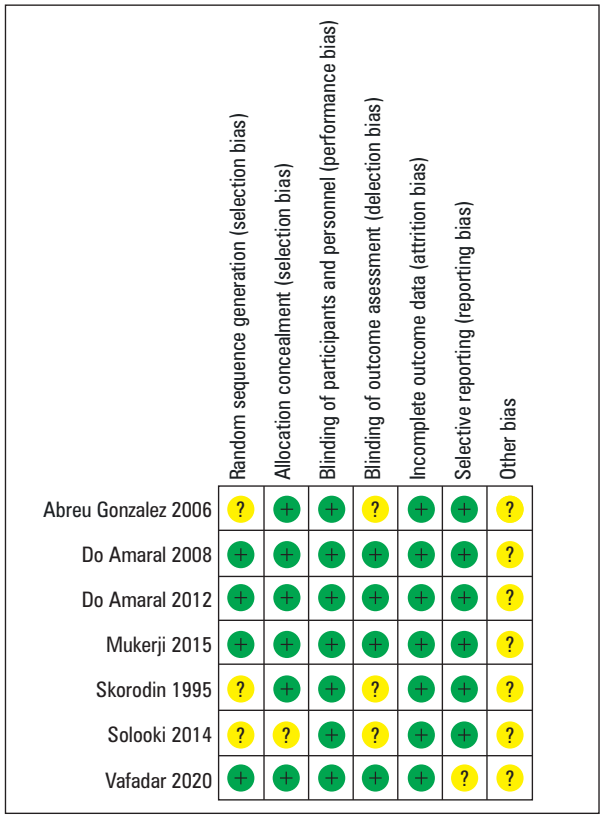

Figure 2. Summary of bias in studies included

histamine from mast cells [22]. Combining these mechanisms improves airflow obstruction and provides the theoretical basis for its efficacy [23]. Therefore, as COPD and asthma have similar first-line treatments in exacerbations, it is reasonable to evaluate the efficacy of magnesium sulfate in acute COPD exacerbations.

Very few studies have explored the bronchodilatory effect of magnesium in COPD [9]. Some studies have reported the efficacy of IV magnesium in acute exacerbations of chronic obstructive pulmonary disease (AECOPD) reporting improved patient symptoms, shorter length of hospital stays [9], increased peak expiratory flow [15], and increased FEV_1 [10]. Edwards *et al.* (2013) found that nebulized magnesium sulfate, as an adjuvant to salbutamol treatment in patients with AECOPD, showed no effect on FEV_1 [9]. Nouira *et al.* (2014) compared ipratropium bromide (IB) versus magnesium sulfate in 124 patients and showed improvement in secondary outcomes of peak expiratory flow rate and arterial blood gas in nebulized IB over magnesium sulfate [24]. However, there was a statistically non-significant difference between both groups regarding primary outcomes of intubations, hospital admissions,

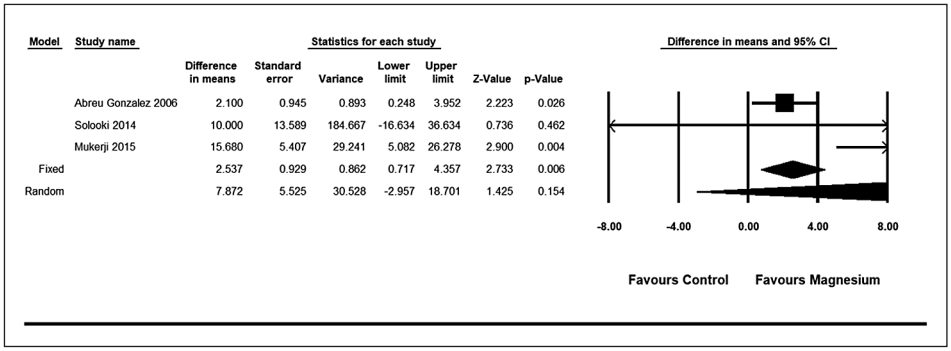

Figure 3. Change in forced expiratory volume in one second (FEV_1) post-intervention in chronic obstructive pulmonary disease (COPD) exacerbation

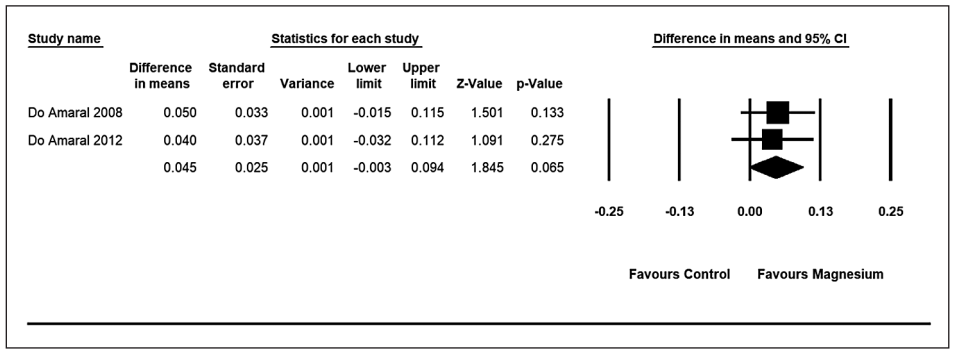

Figure 4. Change in forced expiratory volume in one second (FEV1) post-intervention in stable chronic obstructive pulmonary disease (COPD)

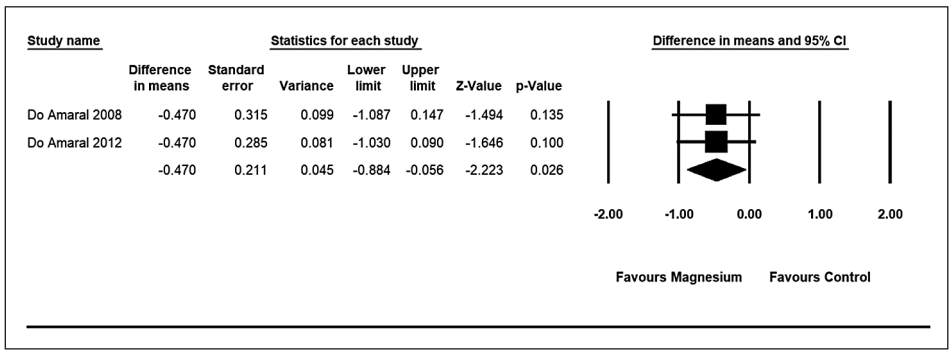

Figure 5. Change in residual volume post-intervention in stable chronic obstructive pulmonary disease (COPD)

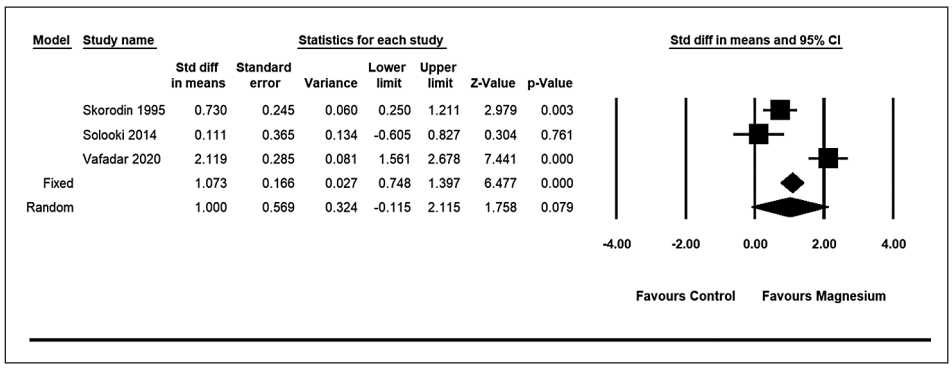

Figure 6. Change in peak expiratory flow rate post-intervention

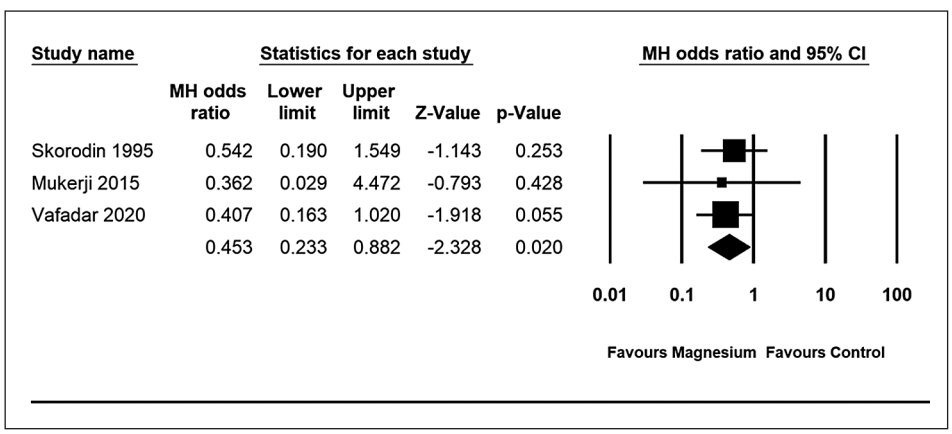

Figure 7. Admission rate from emergency

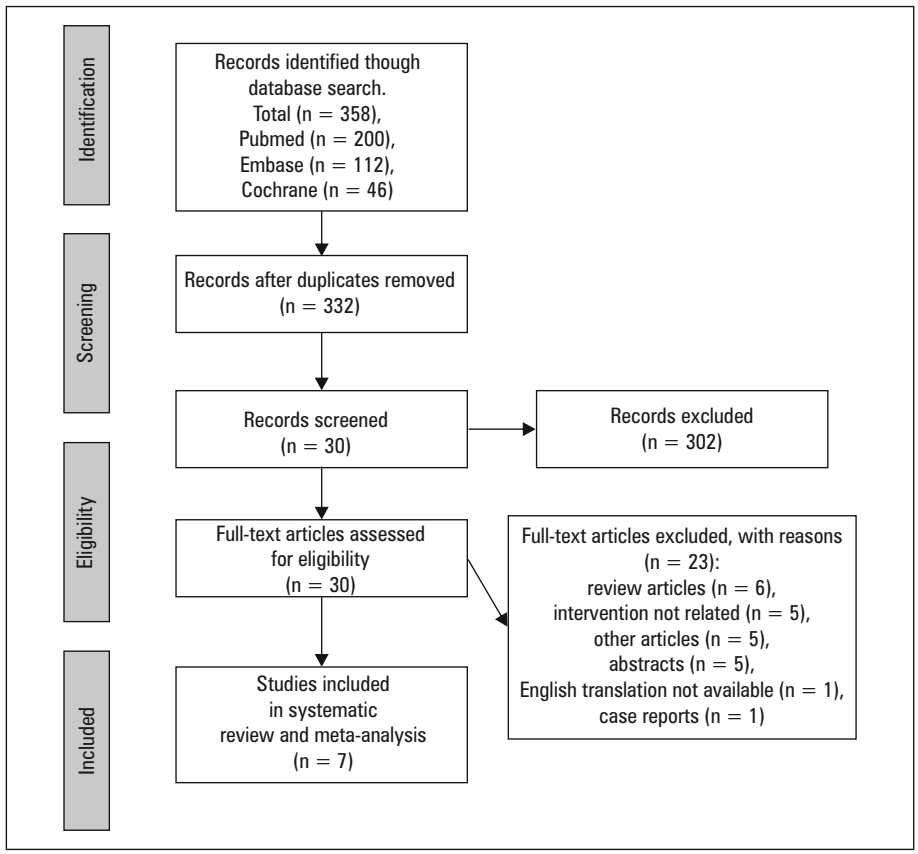

Figure 8. PRISMA figure depicting selection of studies

and hospital death rates in patients with acute COPD exacerbations managed in the emergency department [24].

In our study, cumulative data showed a significant positive deviation towards an increase in FEV_1 percentage and PEFR after infusion of magnesium sulfate in patients with COPD exacerbations. The difference in FEV_1 became more significant when magnesium was used as an adjunct to salbutamol. Given the excellent safety profile of magnesium, these results can be practice-changing. The addition of a cheap, readily-available agent with minimal side effects can lead to improved lung function. The change in lung function was significantly beneficial as lower hospital admissions from the ER (emergency room) were noted in patients treated with magnesium sulfate. Prior, the evidence available on magnesium's efficacy was equivocal, and its practice remains mostly institution and physician preference-based. Hopefully, with our findings, physicians will be more confident in prescribing magnesium when faced with a challenging patient population experiencing COPD exacerbations.

Even though our study showed a reduction in residual volume in stable COPD patients treated with magnesium, which is a new finding compared to earlier available data, it was nonetheless associated with no significant change in FEV_1. Nevertheless, in terms of FEV_1, it is also important to note that there was a favorable deviation towards the magnesium arm when used in stable COPD populations, but it did not reach statistical significance probably secondary to a small patient population. Therefore, it is hard to recommend the regular use of magnesium in stable COPD patients taking into account the current evidence. However, there is a strong possibility that a larger trial may be able to reach statistical significance. Even though the differences in clinical improvement might not appear hugely significant, they will likely positively impact patients and the healthcare system when translated over a large patient population.

As a meta-analysis, this study remains a retrospective chart review and creates the possibility for bias. The small number of trials and a lesser number of people enrolled leads to publication bias. Overall, the utmost effort was undertaken to search, randomize, and extract data from all the published studies. A variety of co-interventions were used with magnesium sulfate in different

trials, affecting the results. Furthermore, the time to measure various respiratory variables in order to observe the treatment response was not standardized and can possibly skew the results in either direction. With meta-analysis, we can overcome some of these limitations by increasing the population size (n) and magnifying the effect of interventions not seen before. We can infer that magnesium can be a good adjunctive therapy in acute exacerbations given the minimal side effect profile and significant bronchodilatation. It is readily available, cheap, and has minimal side effects [9]. This study opens further avenues to study the use of readily available magnesium sulfate in managing COPD exacerbations and standardizing it as part of the treatment regimen.

Conclusion

The use of IV magnesium sulfate in AECOPD likely positively affects FEV_1 and PEFR while significantly reducing hospital admissions. Therefore, we advocate for the regular use of IV magnesium sulfate as an adjunct to therapy with bronchodilators in AECOPD. However, there is currently insufficient evidence to support the routine use of IV magnesium in the stable COPD patient population.

Ethics approval and consent to participate

The data extracted and the manuscript was reviewed by the Research Department and Ethics Committee. No experimental intervention was performed and any specification of guidelines, legislations, or permissions was not required.

Conflict of interest

No competing financial or personal interests were involved for all the authors. The authors have no conflicts of interest to declare.

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