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REVIEW ARTICLE

The benefit of nebulized magnesium sulphate therapy in patients with acute severe asthma: a scoping review

Immad Shahnawaz Qureshi[1], Urooj Fatima[2], Areena Akram[3]

Authors Affiliation:

Cardiff University, United Kingdom[1]

Poonch Medical College, Rawalakot, Pakistan[2,3]

Correspondence to:

dr.amcolian@gmail.com

ABSTRACT

OBJECTIVE

It is known that magnesium sulphate (MgSO4) administered intravenously as an adjunct treatment is effective in treating asthma exacerbations. However, there is limited data available on the use and benefit of nebulized magnesium sulphate.

METHODS

We conducted a scoping review on four databases i.e., Medline, Embase, PubMed, and Cochrane to determine the benefit of using nebulized magnesium sulphate therapy in addition to salbutamol and/or ipratropium in the treatment of patients with severe acute asthma.

RESULTS

A total of 16 articles were included in the study. Based on the literature review, combined nebulized MgSO4 and salbutamol therapy was found to be superior to salbutamol alone in adult patients. There was also a significant reduction in hospital admissions in adult patients with severe asthma exacerbations if they receive nebulized MgSO4. Although some small studies have shown benefit in using it in children and pregnant patients, further studies are needed to address the role of nebulised MgSO4 in such populations.

CONCLUSION

Within the study limitations, magnesium sulphate was found to be beneficial when used in nebulized form in acute asthma exacerbation. Further studies are warranted to establish its role in practice guidelines.

KEYWORDS: Asthma, Magnesium sulphate, Asthma exacerbations, Pulmonary function, β 2-agonists adjunct.

INTRODUCTION

The Global Initiative for Asthma (GINA) 2015 defines bronchial asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation." [1]

Bronchial asthma is very prevalent in Saudi Arabia. The highest prevalence of physician-diagnosed asthma in Saudi Arabia was reported to be as high as 25%. [2] This is a markedly high number when compared to other developed countries where the average burden has been reported to be more than 10%. [3] Braman reports the highest prevalence to be in the United Kingdom (>15%) according to the data then available. [3]

A recent local asthma control survey in Saudi Arabia showed that only 5% of patients were controlled, 31% were partially controlled, and 64% were uncontrolled. In the author's current practice, asthma presentations account for up to 20% of all ER visits. [4]

GINA further details guidelines on the management of asthma in an acute setting. This management comprises mainly of inhaled or nebulised therapy and oxygen as first-line treatment strategies. Steroids are considered as second-line treatment.

The first mention of the use of magnesium for managing asthma was reported in 1936. [5] Individual case reports were published in 1987 and 1989 describing the bronchodilating effect and prevention of intubation in asthmatic patients. [6,7]

The first RCT to investigate the efficacy of IV magnesium sulphate was conducted in 1989 by Skobeloff. [8] Since then, IV magnesium

has been the subject of many RCTs and systematic reviews, while interest has also developed over its use via nebulised route.

Magnesium sulphate is a very cheap drug that is recommended for intravenous (IV) use in acute severe asthma if the above-mentioned treatment does not improve the patient's condition. [1] It however requires IV access and needs to be administered over 20 minutes with cardiac monitoring.

There has been much controversy over the use of magnesium sulphate and the route of administration, and several recent studies have tried to determine whether there is any benefit that can be derived from administration of magnesium sulphate via the inhaled/nebulised route.

The review aims to analyse the current literature regarding use of inhaled/nebulised magnesium in acute setting for asthma exacerbations and compare it to standard treatment with inhaled salbutamol (with or without ipratropium).

METHODS

Data were obtained through a literature review of materials obtained from Medline, Embase, PubMed, and Cochrane databases. The search was refined using keywords such as 'inhaled,' 'nebulised,' 'nebulized,' 'magnesium,' 'salbutamol,' and 'asthma.' The following search strategy was employed: Inhaled [OR] Nebulised [OR] Nebulized) [AND] Magnesium [AND] Salbutamol [AND] Asthma. Articles and studies with a human focus were included from the study duration 2009 -2015. Literature reviews and current guidelines were excluded for analysis and reviewed as background reading. Articles primarily focusing on the 'keywords' were considered necessary for consideration. Exclusion criteria were applied to limit inter-paper confounding variables; improving the applicability of evidence reviewed and avoidance of rhetoric bias.

A total of 86 articles were shortlisted according to the search strategy. Titles and abstracts were screened for relevance; inclusion and exclusion criteria were applied to titles and abstracts with non-qualifying articles excluded. Reference lists of all included papers were reviewed with 'backward chaining' employed to gather pertinent papers for consideration. To select relevant studies, two independent investigators searched for all potentially relevant RCTs and then obtained the full manuscript of the selected articles. A third independent reviewer then formally reviewed these studies against the set inclusion criteria.

A three-point quality assessment was carried out for determining the quality of the included studies. Assessment of allocation concealment, Jadad score [9], the use of an intention-to-treat analysis were determined. Data was extracted independently by two reviewers using a standardized collection form.

All articles were evaluated and 75 were excluded by applying previously mentioned exclusion criteria. The remaining 11 relevant papers consisted of three systematic reviews and eight interventional studies. The references in these papers were backward chained up to 2005 to gain more pertinent articles for review. This identified another three systematic reviews and two interventional studies which account for the 16 articles included in the current literature review.

RESULTS

The summary of the randomised placebo-controlled trials is shown in Table 1 and Table 2.

Table 1. Summary of randomised placebo-controlled trials

RCT	Intervention	Measures of outcome	Study Population	Asthma Severity	Jadad score
Bessmertny et al. (2002)[10]	$MgSO4 + \beta_2$-agonist	FEV_1, %p at 60 min	Adult	Moderate	3
Hughes et al. (2003)[11]	$MgSO4 + \beta_2$-agonist	FEV_1 at 60 min	Adult	Severe	5
Mahajan et al. (2004)[12]	$MgSO4 + \beta_2$-agonist	FEV_1, %p at 20 min	Paediatric	Moderate	3
Mangat et al. (1998)[13]	MgSO4 alone	PEFR, %p at 60 min	Both	Severe	3
Meral et al. (1996)[14]	MgSO4 alone	Ratio increase in PEFR at 60	Paediatric	Moderate	1
Nannini et al. (2000)[15]	$MgSO4 + \beta_2$-agonist	PEFR, %p at 20 min	Adult	Severe	3

Table 1. Summary of randomized placebo-controlled trials

One of the studies measured the outcome as relative change in pulmonary function and attempts to secure absolute values from researchers did not yield the required data. Therefore, the results of this study were not pooled in the analysis. The remaining RCTs all measured pulmonary function at different treatment intervals and thus allowed for pooling of results.

Three of the studies failed to determine any benefit from the use of inhaled MgSO4 and three identified improvements in pulmonary function and one of these three also identified a decrease in admission rate (Gallegos-Solórzano et al. 2010).

Further analysis of the difference in the primary outcomes measured reveals that all the studies that failed to show benefit were measuring improvement in pulmonary function at 120 minutes, and all those that showed

RCT	Study Population (age range)	Intervention	Routine co-treatment	Measures of outcome	Results	Jadad score
Gallegos-Solórzano et al. (2010)[16]	60 severe patients (> 18 yr)	333 mg $MgSO_4$ every 20 min (total 3 doses)	Nebulised: albuterol, ipratropium; Systemic: methylprednisolone	FEV_1 %p, oxygen saturation, admission at 90 min	Improvement in pulmonary function and oxygen saturation, and decrease in admission rate	4
Aggarwal (2006)[17]	100 severe to life threatening patients (13-60 yr)	500 mg $MgSO_4$ every 20 min (total 3 doses)	Nebulised: salbutamol; Systemic: hydrocortisone	PEFR. %p at 120 min	No benefit	5
Kokturk et al. (2005)[18]	26 moderate to severe patients (18-60 yr)	145 mg $MgSO_4$ every 20 min (3 doses for 1st hour), and 4 additional hourly doses	Nebulised: salbutamol; Systemic: methylprednisolone 1 mg/kg	PEFR, %p at 240 min, and duration of achieving target-PEFR 70% predicted	No benefit	2
Hughes et al. (2003)[11]	52 severe patients, FEV1 < 50% predicted after salbutamol treatment (16-65 yr)	151 mg $MgSO_4$ every 20 min (total 3 doses)	Nebulised: salbutamol; Systemic: hydrocortisone 100 mg	FEV_1, % p at 90 min	Improvement in pulmonary function; Enhanced improvement in life-threatening asthma (baseline FEV1 <30%)	5
Bessmertny et al. (2002)[10]	74 mild to moderate patients (18-65 yr)	384 mg $MgSO_4$ every 20 min (total 3 doses)	Nebulised: albuterol; Systemic: hydrocortisone 2 mg/kg every 6 hours	FEV_1, %p at 125 min	No benefit	5
Nannini et al. (2000)[15]	35 patients (> 18 yr)	225 mg $MgSO_4$ (1 dose)	Nebulised: salbutamol	PEFR, %p at 20 min	Improvement in pulmonary function	3

Table 2: Summary of randomized placebo-controlled trials

benefit were measuring pulmonary function at 90 minutes or less. This may suggest that the benefit of MgSO4 is more evident early in the intervention.

The authors also reviewed 2 meta-analyses that looked in to RCTs for the efficacy of MgSO4 as an adjunct therapy for acute asthma in adults (table 3). Both of these meta-analyses were able to pool data and determine that there is weak evidence that nebulised MgSO4 improves pulmonary function and reduces hospitalization.

Both meta-analyses show similar results with similar confidence intervals (CI). Although there is improvement of pulmonary function in both reviews, the CI crosses 0 and therefore cannot be considered statistically signifi-cant. Blitz et al. however show that for more severe cases, the CI does not cross zero and can be considered statisti-cally significant, which leads to their recommendation that nebulised MgSO4 should be considered as an adjunct therapy to β2-agonists in asthma exacerbations, particularly in more severe exacerbations.[20]

Powel et al. (2012) conducted a Cochrane systematic review to determine the efficacy of inhaled MgSO4 administered in acute asthma on pulmonary functions and admission rates. [21] There was no statistically significant improvement in pulmonary function when inhaled MgSO4 and β2-agonist was compared with β2-agonist alone (SMD=0.23; 95% CI -0.27 to 0.74; three studies, n = 188); however, there was considerable study heterogeneity. There was no clear advantage in terms of hospital admissions (RR=0.76; 95% CI 0.49 to 1.16; four studies, n = 249), and there were no serious adverse events reported.

Another study reports that intravenous magnesium sulphate therapy helps in achieving earlier improvement in clinical signs and symptoms of asthma, e.g. respiratory function and significantly reduced hospital admission, in children with acute severe asthma.[22]

Meta-analyses	Number of pooled trials	Outcomes of interest	Results
Mohammed and Goodacre (2007)[19]	7 trials	Pulmonary function	Pulmonary function: SMD 0.17 (CI −0.05 to 0.39)
	(430 adult patients)	Admission rate	Admission rate: RR 0.68 (CI 0.46 to 1.02)
Blitz et al. (2005)[20]	3 trials	Pulmonary function: 20 min, 60 min	Pulmonary function: SMD 0.18 (CI −0.13 to 0.50)
	(161 adult patients)	Admission to hospital	For severe (FEV1 or PEFR <50% predicted): SMD 0.55 (CI 0.12 to 0.98)
			Admission: RR 0.62 (CI 0.38 to 1.02)
			For severe (FEV1 or PEFR <50% predicted): the same

Table 3: Summary of systematic reviews and meta-analyses

DISCUSSION

The use of magnesium sulphate for acute asthma has been studied with many different doses and routes. It remains a controversial therapy for a disease that burdens a large population all over the world. There are theories that suggest how $MgSO_4$ seems to reverse bronchoconstriction in asthma patients. There are several proposed mechanisms by which $MgSO_4$ affects bronchial smooth muscle. It can inhibit calcium influx into the cytosol and cause smooth muscle relaxation. It inhibits release of histamine from mast cells, which is why it may also be beneficial in allergic rhinitis/asthma co-existence. It can inhibit acetylcholine release from cholinergic nerve fibers (which is also calcium dependent). It may increase β2 receptor affinity for β2 agonists.

There is discrepancy between international guidelines on the use of nebulised $MgSO_4$. Clinical data is extremely limited, but new studies have emerged over the last 10 years to lay the controversy to rest. These studies vastly differ in their designs, interventions, target populations, and have great inter-paper heterogeneity. For these reasons, it is difficult to pool results and use the studies for a large meta-analysis. However, some researchers have managed to extrapolate the data and provide some forest plots assessment and shown that there is a significant benefit from adding $MgSO_4$ to the standard nebulisation protocols in acute severe asthma. [20] However, this is the result of one meta-analysis of the same studies that have been used in other reviews. The GINA guidelines state that nebulised salbutamol administered in isotonic magnesium sulphate provides greater benefit than if it is delivered in normal saline.

Combined nebulised $MgSO_4$ and salbutamol therapy is superior to salbutamol alone in adult patients. There is a significant reduction in hospital admissions in adult patients with severe asthma exacerbations if they receive nebulised $MgSO_4$. The latest individual small studies suggest that nebulised $MgSO_4$ may have a role in asthma exacerbation treatment in children and pregnant women. [23,24] Further studies are needed to address the role of nebulised $MgSO_4$ in children and pregnant patients.

Several studies have validated the use of IV $MgSO_4$ for treatment of asthma refractory to standard treatment. The data on nebulised $MgSO_4$ is not as vast. As a result, several systematic reviews have included the same studies and arrived at different interpretations. The author notes that rigorous reviews, that have assessed the quality of the studies they analyse, and those that have searched for unpublished articles or those in another language, have been able to get a larger pool of data which they could use to synthesise their own forest plots and give recommendations. Several systematic reviews were limited to just quoting or reporting the data published by original studies. The author has had the opportunity with this review to assess many different published systematic reviews and see their limitations to inform the author of potential shortcomings in his own review of the literature.

Choice of outcome bias has been evident in many of the studies and leads the author to believe that there is still a need for a more validated study, that can form the basis of future study and analysis. Also, larger studies need to be conducted to inform more reliable results.

CONCLUSION

Considering the evidence critiqued, there remains controversy over the role of nebulised $MgSO_4$ in acute asthma patients in the ED setting, but the following conclusions can be made. A greater benefit is seen in adults with severe – life threatening asthma. A greater effect is seen

in children if the symptoms are of recent onset (<6 hours) or if they have severe features (SpO2 <92%). More research is needed with focused questions to determine the role of nebulised MgSO4 in children and pregnant patients. Inhaled magnesium sulphate is a safe therapy with little to no severe adverse events reported. Further studies are warranted to establish its role in practice guidelines.

REFERENCES

1. Bateman ED, Hurd SS, Barnes PJ, Bousquet J, Drazen JM, FitzGerald M, et al. Global strategy for asthma management and prevention: GINA executive summary. European Respiratory Journal. 2008;31(1):143-78.

2. Sobki SH, Zakzouk SM. Point prevalence of allergic rhinitis among Saudi children. Rhinology. 2004;42(3):137-40.

3. Braman SS. The global burden of asthma. Chest. 2006;130(1 Suppl):4s-12s.

4. Al-Jahdali HH, Al-Hajjaj MS, Alanezi MO, Zeitoni MO, Al-Tasan TH. Asthma control assessment using asthma control test among patients attending 5 tertiary care hospitals in Saudi Arabia. Saudi medical journal. 2008 May 1;29(5):714.

5. Kowal A, Panaszek B, Barg W, Obojski A. The use of magnesium in bronchial asthma: a new approach to an old problem. Archivum Immunologiae et Therapiae Experimentalis. 2007;55(1):35-9.

6. Okayama H, Aikawa T, Okayama M, Sasaki H, Mue S, Takishima T. Bronchodilating effect of intravenous magnesium sulfate in bronchial asthma. JAMA. 1987;257(8):1076-8.

7. McNamara RM, Spivey WH, Skobeloff E, Jacubowitz S. Intravenous magnesium sulfate in the management of acute respiratory failure complicating asthma. Annals of Emergency Medicine. 1989;18(2):197-9.

8. Skobeloff EM, Spivey WH, McNamara RM, Greenspon L. Intravenous magnesium sulfate for the treatment of acute asthma in the emergency department. Jama. 1989 Sep 1;262(9):1210-3.

9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials. 1996;17(1):1-12.

10. Bessmertny O, DiGregorio RV, Cohen H, Becker E, Looney D, Golden J, et al. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. Annals of Emergency Medicine. 2002;39(6):585-91.

11. Hughes R, Goldkorn A, Masoli M, Weatherall M, Burgess C, Beasley R. 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(9375):2114-7.

12. Mahajan P, Haritos D, Rosenberg N, Thomas R. Comparison of nebulized magnesium sulfate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. The Journal of Emergency Medicine. 2004;27(1):21-5.

13. Mangat HS, D'Souza GA, Jacob MS. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. The European Respiratory Journal. 1998;12(2):341-4.

14. Meral A, Coker M, Tanaç R. Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. The Turkish Journal of Pediatrics. 1996;38(2):169-75.

15. Nannini LJ, Jr., Pendino JC, Corna RA, Mannarino S, Quispe R. Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. The American Journal of Medicine. 2000;108(3):193-7.

16. Gallegos-Solórzano MC, Pérez-Padilla R, Hernández-Zenteno RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. Pulmonary Pharmacology & Therapeutics. 2010;23(5):432-7.

17. Aggarwal P, Sharad S, Handa R, Dwiwedi SN, Irshad M. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. Emergency Medicine Journal. 2006;23(5):358-62.

18. Kokturk N, Turktas H, Kara P, Mullaoglu S, Yilmaz F, Karamercan A. A randomized clinical trial of magnesium sulphate as a vehicle for nebulized salbutamol in the treatment of moderate to severe asthma attacks. Pulmonary Pharmacology & Therapeutics. 2005;18(6):416-21.

19. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emergency Medicine Journal. 2007;24(12):823-30.

20. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, et al. Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest. 2005;128(1):337-44.

21. Powell C, Kolamunnage-Dona R, Lowe J, Boland A, Petrou S, Doull I et al. MAGNETIC Study Group. Magnesium sulphate in acute severe asthma in children (MAGNETIC): a randomised, placebo-controlled trial. The Lancet Respiratory Medicine. 2013 Jun 1;1(4):301-8.

22. Albuali WH. The use of intravenous and inhaled magnesium sulphate in management of children with bronchial asthma. The Journal of Maternal-Fetal & Neonatal Medicine. 2014;27(17):1809-15.

23. Badawy M, Hassanin IM. The value of magnesium sulfate nebulization in treatment of acute bronchial asthma during pregnancy. Egyptian Journal of Chest Diseases and Tuberculosis. 2014;63(2):285-9.

24. Mohammadzadeh I, Mohammadi M, Khodabakhsh E. The effect of nebulised salbutamol plus magnesium sulfate in comparison with nebulised salbutamol plus normal saline in acute asthmatic attack in children. Journal of Babol University of Medical Sciences. 2014;16(3):7-12.

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