Effectiveness and Safety of Nebulized Magnesium as Last Line Treatment in Adults with Acute Asthma Attack: A Systematic Review and Meta-Analysis

Danny Darmawan[1], Iris Rengganis[2], Cleopas Martin Rumende[3], Hamzah Shatri[4], Sukamto Koesnoe[2], Yogi Umbarawan[1], Rudi Putranto[4], Sally Aman Nasution[5]*

[1]Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3]Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4]Division of Psychosomatic and Palliative Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo, Jakarta, Indonesia.
[5]Division of Cardiology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo, Jakarta, Indonesia.

Corresponding Author:
Prof. Iris Rengganis, MD., PhD. Division of Allergy and Immunology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: irisrengganis@yahoo.com; dannydarmawan@hotmail.com.

ABSTRACT

Background: *Asthma is a disease characterized by chronic airway inflammation, however one-third of asthmatic cases did not respond adequately. Inhaled magnesium has been proposed as a treatment for unresponsive asthma cases. However, its role remains controversial. This review evaluates the effectiveness and safety of nebulized magnesium compared to standard therapy (Beta Agonist, Anticholinergic, Corticosteroid) in adults with acute asthma attacks.* ***Methods:*** *The protocol has been registered in PROSPERO. A literature search was conducted through PubMed/MEDLINE, Cochrane, ProQuest, and Google Scholar, and using the keywords "inhaled magnesium" and "asthma". Manual searches were carried out through data portals. Journal articles included are randomized controlled trials. The assessment risk of bias was performed using Version 2 of the Cochrane risk-of-bias tool for randomized trials.* ***Results:*** *There are five articles included in this review. There is no significant difference in readmission rate and oxygen saturation in the magnesium group compared to control (RR 1; 95% CI 0.92 to 1,08; p= 0,96 and MD 1,82; 95% CI -0.89 to 4.53; p= 0.19, respectively). There is a significant reduction of respiratory rate and clinical severity in magnesium (MD -1,72; 95% CI -3,1 to 0.35; p= 0.01, RR 0.29; 95% CI 0.17 to 0.69; p <0.001, respectively). There was a higher risk of side effects in the magnesium group (HR 1.56; 95%CI 1.05 to 2.32; p= 0.03). However, the side effects are relatively mild such as hypotension and nausea.* ***Conclusion:*** *Inhaled magnesium improves the outcome of asthmatic patients, especially in lung function, clinical severity, and respiratory rate. Moreover, inhaled magnesium is safe to be given.*

Keywords: *Inhaled Magnesium, Asthma, Adult.*

INTRODUCTION

Asthma is a disease characterized by chronic airway inflammation.[1] Manifestation of the disease includes shortness of breath, wheezing, and tightness in the chest. The symptom of the disease varies in terms of intensity and length. At first, the airflow in the respiratory tract is temporarily obstructed in the acute phase and it becomes irreversible in a later phase. Asthma is related to hyperreactivity of airway disease and inflammation.[2] In 2019, the World Health Organization (WHO) estimated 262 million people had asthma and asthma caused 455.000 deaths annually.[3] Asthma can be found in many countries all over the world, especially in low to middle-income countries. According to Indonesian Basic National Health Research in 2013, the prevalence of asthma reached 4.5%, specifically in Jakarta, the prevalence of asthma was 5.3%. [4] Based on the Global Initiative for Asthma (GINA), the standard treatment of asthma includes short-acting beta-agonists, corticosteroids, and anticholinergics.[4] However, there is 30% of patients unresponsive with these standard treatments.[5]

Magnesium is the fourth largest mineral in the human body. It is involved in 300 enzymatic reactions, especially in the metabolism of Adenosine Triphosphate (ATP). Magnesium is useful for muscle contraction, blood pressure, insulin regulation, and neural transmission. An imbalance of magnesium in the blood may induce abnormality in the neuromuscular and cardiology system.[6,7]

In recent years, magnesium has been studied as an additional medication for asthma. A report from Song et al showed that hypomagnesemia may worsen the severity of asthma.[8-10] Magnesium has an important role in the contraction and relaxation of airway muscle as it has a bronchodilation effect, inhibition of cholinergic, influx of calcium into the cell, and prevents histamine release.[11-14] The usage of magnesium for asthma nowadays is still limited by the intravenous route because it has numerous side effects such as palpitation, flushing, and hypotension. Therefore, nebulized magnesium has been proposed as the preferred route as it has fewer side effects.[9.10]

In previous studies, inhaled magnesium has shown various results. For example, Knightly et al showed that magnesium has a modest beneficial effect on pediatric and adult asthmatic patients. A systematic review published by Su et al concluded that inhaled magnesium had no effect in pediatric population.[15] Therefore, a systematic review of inhaled magnesium for adult asthmatic patients is considered necessary.

METHODS

This systematic review design is based on the 2009 PRISMA guidelines and has been registered in PROSPERO with the number Registration CRD42022362345. A literature search with PICO as follow: Population: Patient with asthma attack, above 18 years old; Intervention: Inhaled Magnesium +SABA+ Anticholinergic+ Corticosteroid; Comparation: SABA+ Corticosteroid+Anticholinergic; Outcome: Clinical Severity, Readmision, Lung Function, Vital Sign, Side Effect was conducted utilising databases namely PubMed/ Medline, Google Scholar, ProQuest, and Cochrane. The keywords of this literature search are "magnesium inhalation" or "magnesium nebulization" or "magnesium inhaled" or "magnesium nebulized" or "mgs04 inhaled" or "mgs04 nebulized" or "mgs04 inhalation" or "mgs04 nebulization" or "magnesium nebules" or "magnesium vaporized" AND "asthma" or asthma attack" or "asthma acute" or "acute asthma" or " asthma exacerbated" in English and Indonesian. Manual searching was conducted in national journal databases and libraries of medical faculty. We included randomized controlled trials comparing inhaled magnesium to standard therapy during asthma attacks in adult patients.

All journals were selected that met the inclusion criteria such as a randomized controlled trial, the sample of population being adult asthmatic patients above 18 years old, a study that compared inhaled magnesium and standard therapy, no limitation in language, and no limitation in a year of publication. The study was excluded such as literature review, and commentary.

Data extracted from each study that met the eligibility criteria included the basic

characteristics of the study, the characteristics of the study population, and the outcomes presented in a descriptive table. The basic characteristics of the study include the name of the main investigator, year of publication, study design, assessment of the asthmatic attack, and duration of the study. The characteristics of the study population consisted of the number of samples, age, sex, disease stage, lung function, and readmission rate. Outcomes collected from the study were readmission rate, clinical severity, mean difference in vital signs, and lung function. The primary outcome is clinical severity, vital signs, lung function, and readmission rate. The secondary outcome is the side effect.

The risk of bias assessment was performed by two independent investigators using Version 2 of the Cochrane risk-of-bias tool (RoB2) for randomized trials. Any conflicting decision would be resolved by consensus with a third investigator. Statistical analysis of this systematic review was conducted using RevMan 5.4 software (*Cochrane Collaboration, the Nordic Cochrane Centre, Copenhagen*). Heterogeneity was analyzed by I^2 test with grading low (0-25), moderate (26-50), substantial (50-75), and significant (>75%). If the analysis shows low and moderate heterogeneity, investigators chose a random effect model. However, if the analysis shows significant heterogeneity, investigators chose a fixed effect model. Investigators did not analyze the publication bias because the amount of articles is less than ten.

RESULTS

Based on the systematic search in four databases, 953 records were collected (**Figure 1**).

Duplications were removed and after a thorough reading of the abstract and title, we excluded 936 studies. Finally, five RCTs were included in this systematic review. The articles were from Ahuja et al, Goodcare et al, Gallegos et al, Hossein et al, and Motamed et al.[16-20]

The reviewer analyzed the risk of bias by using five parameters, such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome measurement, and incomplete outcome data. In the random sequence generation aspect, Ahuja et al have an unclear risk of bias because this article does not mention the randomization method.[17] The study conducted by Goodacre, et al, had a low risk of bias because they used block

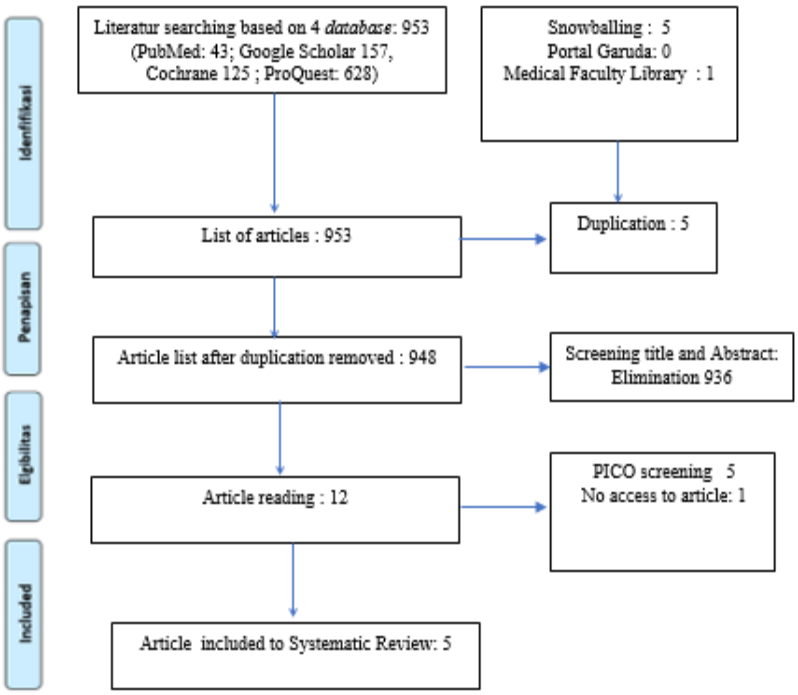

Figure 1. PRISMA chart.

randomization.[19] Study conducted by Motamed, et al, also had a low risk of bias because they used the block method.[20] Hossein et al used computer-generated software.[18] Study from Gallegos et al has a low risk of bias because they randomized the patient on arrival.[16]

Based on the allocation concealment, Study conducted by Ahuja and colleagues had an unclear risk of bias because it stated that this trial does not mention the allocation method[17] Article from Goodacre et al had a low risk of bias because the allocation treatment pack was kept in the emergency department.[19] In Motamed et al, neither the patient nor personnel was granted access to data unless the patient discontinued the research. In Hossein et al, Emergency Physicians were blinded to protocol and allocation of treatment.[18] Article from Gallegos et al shows that allocation was prepared by the physician outside the study.[16]

In the aspect of blinding of participants and personnel, the study from Ahuja et al has a high risk of bias because it used a single-blinded method.[17] The rest of the articles used a double-blinded method in their research. In the blinding of outcome aspect, all of the articles have a low risk of bias. Ahuja et al used a prespecified protocol plan. Goodacre et al observed the outcome sequentially after intervention based on the time previously allocated.[19] The observer in Hossein et al is a blinded emergency physician.[18] Motamed et al used blinded nurses and physicians to become observers. The research was also executed in a prespecified protocol plan.[20]

From the detection of attrition bias, almost all of the studies have a low risk of bias. There is no missing data in the research from Ahuja et al.[17] Missing data in Goodacre et al is below 10%.[19] In Motamed et al, three of 148 subjects discontinued the study.[20] Hossein et al reported all data.[18] However, Gallegos et al have a high risk of bias because almost half of the data was excluded.[16] In the selective reporting parameter, all the article has a low risk of bias. However, an article from Motamed et al did not report complete data such as standard deviation. [20]

Goodacre et al and Gallegos et al show the effectiveness of inhaled magnesium in reducing readmission rates.[16,19] Three RCTs from Ahuja et al, Gallegos et al, and Hossein et al evaluate the effect of inhaled magnesium on patients'

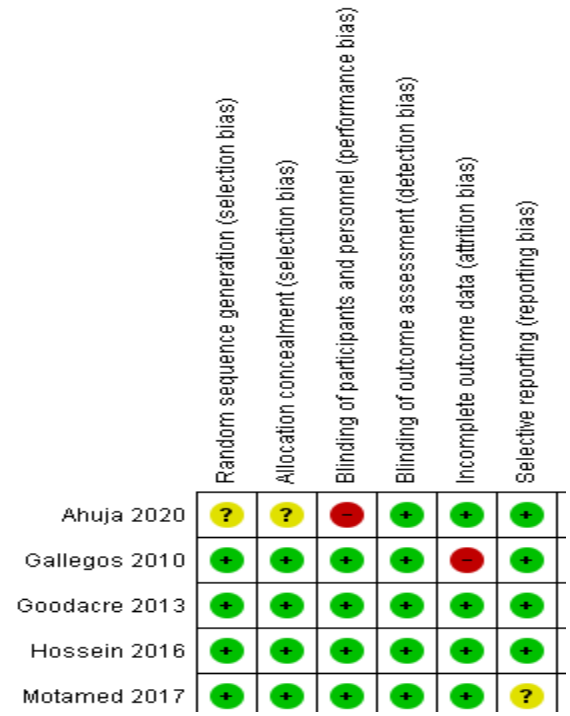

Figure 2. Risk of bias.

vital signs.[16,17,19] Two RCTs from Ahuja et al, and Hossein et al study the effect of inhaled magnesium on the severity of the disease.[17,18]

Studies from Ahuja et al, Gallegos et al, and Hossein et al evaluated the effect of inhaled magnesium on oxygen saturation with total subjects of 225 people. The dose of magnesium varies between 200-333 milligrams. This study showed no significant difference with the addition of inhaled magnesium compared to standard therapy in terms of oxygen saturation level (SMD 1,82; 95% CI -0.89 to 4.53; p =0.19 with random effect model). There was substantial heterogeneity of data in this study I^2=82% (**Figure 3**).[16,17]

Two studies were included in the meta-analysis about the effect of inhaled magnesium on respiratory rate (Ahuja et al and Hossein et al) with total subjects of 165 people.[17,18] Respiratory rates in both studies were measured after 60 minutes of administration of inhaled magnesium. The administration of inhaled magnesium compared to standard treatment improves the respiratory rate of an asthmatic patient (SMD -1,72; IK 95%: -3,1 to -0.35; p= 0.01) with a fixed effect model. Both studies did not have substantial heterogeneity with p=0,37 and I^2=0%. (**Figure 4**)

In the aspect of lung function, there are five studies included. Four of them show that patients' lung function improves after administration of inhaled magnesium. Two of them (Ahuja et al and Hossein et al) were statistically significant.

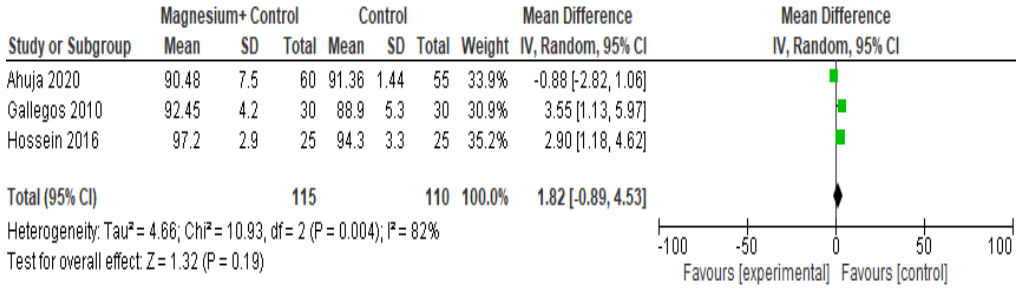

Figure 3. Meta-Analysis on oxygen saturation.

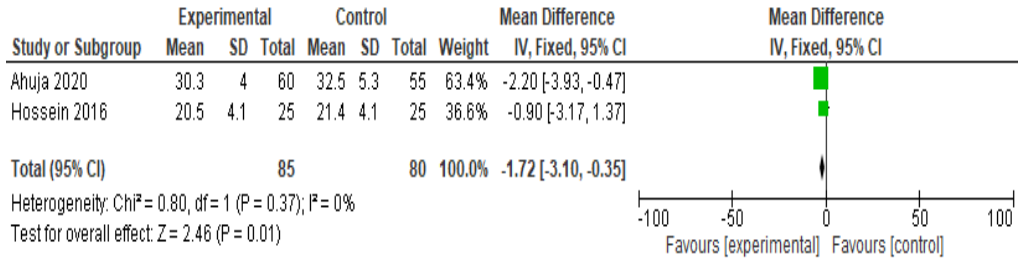

Figure 4. Meta-analysis on respiratory rate.

Table 1. Effect of Magnesium in Lung Function.

	Magnesium Group	Control Group	OR (95% CI)	P	N
Goodacre et al [30] 2013					
ΔPEFR (120 minute)	13.4% (18.0)	14.4% (17.4)	-0.6% (-3.4%-2.1%)	0.652	690
Abuja et al 2020[16]					115
PEFR (60 minute)	108±32	74.5± 19.3		<0.001	
PEFR (120 minutes)	189.3±47.0	103.3± 42.3		<0.001	
Motamed et.al, 2017[31]					148
PEFR 60 minute	333 l/min	280 l/min		NA	
FEV (60 minutes)	2.8 l /min	2.24 l/min		NA	
Gallegos et.al, 2010[10]					60
FEV (60 minutest)	2.16 ± 0.66 l/min	2.01± 0.51 l/min)		NS	
FEV *predicted*	69.7± 13.3 %	61.1 ± 12.7%		<0.01	
Hossein et.al, 2016[33]					55
PEFR *predicted* (60 min)	48.7±23.4 %	36± 28%		0.002	

However, the author only narratively presented because the parameters among the studies were different (**Table 1**).[17,18]

In the aspect of clinical severity, a study from Goodacre et al used dyspnea Visual Analog Scale (VAS) as the parameter. This study shows that magnesium therapy decreased dyspnea VAS in asthmatic patients, however, the difference was not statistically significant (VAS -2.6; -7 to 1.8 mm; p = 0.253).[19] Motamed et al used the Borg Dyspnea Scale as the parameter and it shows statistical improvement in clinical severity in the inhaled magnesium group (p=0.001).[20] However, Motamed et al did not report the exact number of Borg Dyspnea Scale. Ahuja et al and Hossein et al used subjective preferences of patients (yes or no) as parameters to measure the improvement of dyspnea.[17,18] Both studies show that people in the magnesium group have an improvement in clinical severity (RR 0.29; 95% CI 0.17 to 0.69; p = 0.001). Heterogeneity from both studies was statistically non-significant (p=0.87 with I^2=0%.) (**Figure 5)**

In the aspect of readmission rate, two studies were included in this review. Both of them are Goodacre et al and Gallegos et al. The total sample is 750 people.[16,19] There is no significant difference in readmission rate in the magnesium group compared to the control (RR 1; 95% CI 0.92 to 1,08; p= 0,96 and MD 1,82) (**Figure 6)**

The side effect of magnesium is analyzed by two studies from Ahuja et al and Goodacre et al with a total subjects of 805. A study from Goodacre et al shows that 52 out of 332 people in the magnesium group feel the side effects.[19] The example of side effects such as flushing 1%, hypotension 9%, nausea 2% and vomiting 2%. On the other hand, the side effects in the control group are flushing 1%, hypotension 6%, nausea 2%, and vomiting 1%. A trial from Ahuja et al shows no side effects in either group.[17] (Hazard Ratio 1.56; 95% CI 1.05 to 2.32; p= 0.03) using a *fixed effect model.* Heterogeneity from both studies cannot be analyzed.

DISCUSSION

To our knowledge, this is the first systematic review in the adult population to evaluate the effectiveness of inhaled magnesium for asthma in terms of readmission, clinical severity, lung function, and vital signs. In terms of readmission rate, there was no significant difference between the magnesium group and the control group (SMD 1,82; 95%CI to 0.89 - 4.53; p =0.19) with the random effect model. The reason for this phenomenon is magnesium only works within hours (half of life 8.3 hours).[21] The effect of inhaled magnesium on controlling asthma is still questionable. Meral et al show that the effect of inhaled magnesium as a bronchodilator starts one hour after inhalation, and its effect lasts for six hours.[22]

Vital signs of asthmatic patients that were observed in this review are respiratory rate

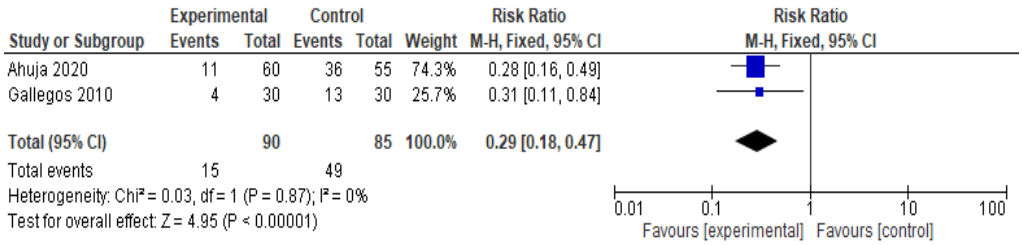

Figure 5. Meta-analysis on clinical severity.

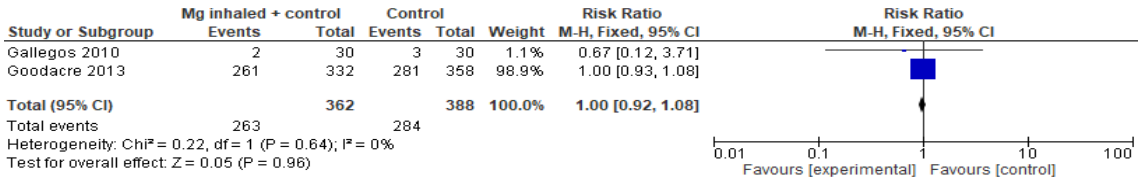

Figure 6. Meta-analysis on readmission.

oxygen saturation and blood pressure just reported in one trial. The trial showed that the administration of magnesium inhalation compared to standard treatment does not affect the oxygen saturation of asthmatic patients. The reason is the administration of oxygen influences the oxygen saturation. All the oxygen treatment was given to achieve oxygen saturation level in the patient. Schuh et al also showed that inhaled magnesium did not affect oxygen saturation.[23]

The administration of inhaled magnesium compared to standard treatment improves the respiratory rate of asthmatic patients. According to Busuttil, nebulized magnesium was beneficial for the stabilization of airway hyperresponsiveness. Inhaled magnesium might decrease bronchoconstriction in stable asthmatic patients. [24]

In the aspect of clinical severity, there are several parameters used by the clinical trials. Goodacre et al show that dyspnea VAS in asthmatic patients was decreased although it is statistically non-significant. Motamed et al showed that improvement in clinical severity in the inhaled magnesium group, although this clinical trial did not report the exact number. Ahuja et al and Hossein et al showed that the magnesium group has an improvement in clinical severity using the random effect model. On the whole, inhaled magnesium improves the clinical outcome of asthmatic patients. According to Knightly et al, the addition of inhaled magnesium in children and adults improves the clinical severity of asthmatic patients.[25]

Nearly all clinical trial results suggested an increasing number of lung functions. This result was supported by a systematic review from Knightly et al showing the promising result of inhaled magnesium.[25] Shan et al also showed that the addition of nebulized magnesium in salbutamol improved lung function.[26] According to Busuttil et al, the combination of inhaled magnesium and SABA has improved lung function in asthmatic patients. A small trial showed inhaled magnesium in combination with inhaled salbutamol and intravenous corticosteroid, to improve airway obstruction and reduce admissions relative to standard bronchodilator therapy.[23]

There is a slight increase in the rate of side effects in terms of hypotension and vomiting (9% vs 6%;2% vs 1% respectively). However, the percentage of side effects was relatively low (below 10%), inhaled magnesium was considered to be safe for asthma. In this case, clinicians should be aware of the side effects and then they should inform the patients. According to Powell et al, there was no good evidence suggesting the use of inhaled magnesium sulfate as a substitute for inhaled short-acting beta agonist (SABA) in first-line therapy.[27] Magnesium appeared to have a positive effect if it is used for last-line treatment due to its synergistic effect with SABA.[28]

CONCLUSION

Inhaled magnesium improves the outcome of asthmatic patients, especially in lung function, clinical severity, and respiratory rate. Moreover, inhaled magnesium is safe to be given.

CONFLICT OF INTEREST

The author declares no conflict of interest

FUNDING

The author declares no sponsorship or funding in developing this review.

REFERENCES

1. Reddel HK, Pedersen S. Global strategy for asthma management and prevention. Global Initiative for Asthma.2022 [Cited 23 Juli 2022]. Available from: www.ginasthma.org
2. World Health Organization. Asthma. 2022 [Cited 23 Jul 2022]. Available from: www.who.int/respiratory/asthma/en/.
3. Global Asthma Report. Global Burden of Disease due to Asthma. 2022 [Cited 3 Oktober 2022]. Available from: http://www.globalasthmareport.org/burden/burden.php
4. Badan Penelitian dan Pengembangan Kementerian Kesehatan RI. Riset Kesehatan Dasar 2013.2013 [Cited 23 Aug 2022]. Available from: www.depkes.go.id/resources/download/general/hasil%20Riskesdas%202013.pdf
5. American Thoracic Society. Asthma Costs the U.S. Economy More than $80 Billion Per Year.2018 [Cited 23 Aug 2022]. Available from: https://www.thoracic.org/about/newsroom/press-releases/journal/asthma-costs-the-us-economy-more-than-80-billion-per-year.php

6. Grober U, Schmidt J, Kisters. K. Magnesium in prevention and therapy. Nutrients.2015;7:8199-226
7. Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J. 2012;5(1):p.3-14.
8. Song WJ, Chang YS. Magnesium sulfate for acute asthma in adults: a systematic literature review. Asia Pac Allergy. 2012;2:76–85.
9. Strauss L, Hejal R, Galan G dkk, Observations on the effects of aerosolized albuterol in acute asthma. Am J Resp Crit Care Med. 1997;155(5):454-8.
10. Mohammed S, Goodacre S. Intravenous and nebulized magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J. 2007;24(12):823-30
11. Allen MJ, Sharma S. Magnesium.2022 [Cited 2022 Mar 3]. In: StatPearls [Internet]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519036/
12. Berair R, Hollins F, Brightling F. Airway smooth muscle hypercontractility in asthma. J Allergy Cairo. 2013.
13. Reuter M, Stasssen M, Taube C. Mast cells in allergic asthma and beyond. Yonsei Med J.2010;51(6):797-807.
14. Coulsen FR, Fryer AD. Muscarinic acetylcholine receptors and airway diseases. Send to Pharmacol Ther. 2003;98(1):59-69.
15. Su Z, Li R, Gai Z. Intravenous and nebulized magnesium sulfate for treating acute asthma in children: A systematic review and meta-analysis. Pediatr Emerg Care. 2018;34(6):390-5.
16. Gallegos MC, Pérez R, Hernández RJ. Usefulness of inhaled magnesium sulfate in the coadjuvant management of severe asthma crisis in an emergency department. Pulm Pharmacol Ther. 2010; 23:432–7
17. Ahuja G, Kumar A, Ghori U, Gohar MA, Nisar M. Effectiveness of nebulized magnesium sulphate as an adjuvant therapy (with Salbutamol) in the management of acute asthma. Pakistan Journal of Medicine and Dentistry. 2020;9(2): p.39-43.
18. Hossein S, Pegah A, Davood F, Said A, Babak M, Mani M, Mahdi R, Peyman H. The effect of nebulized magnesium sulfate in the treatment of moderate to severe asthma attacks: a randomized clinical trial. Am J Emerg Med. 2016;34(5):883-6.
19. Goodacre S. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomized controlled trial. Lancet Respir Med. 2013;1:293–300.
20. Motamed H, Verki MM, Pooladzade. Efficacy evaluation of nebulized Magnesium, as an additional complementary treatment, in clinical and peak flow metric improvements of acute asthma attack: a randomized double-blinded clinical trial. Jundishapur J Nat Pharm Prod. 2017;12:4.
21. Dolberg MKB, Nielsen LP, Dahl R. Pharmacokinetic profile of oral Magnesium hydroxide. Basic Clin Pharmacol Toxicol. 2017;120:264-9.
22. Meral A, Coker M, Tanaç R. Inhalation therapy with magnesium sulfate and salbutamol sulfate in bronchial asthma. Turk J Pediatr. 1996;38(2):169-75.
23. Schuh S, Sweeney J, Rumantir M, et al. Effect of nebulized Magnesium vs placebo added to Albuterol on hospitalization among children with refractory acute asthma treated in the emergency department: a randomized clinical trial. JAMA. 2020;324(20):2038–47.
24. Busuttil M. The role of magnesium in the treatment of acute asthma in adults and its effects on beta-2 adrenergic receptor function.[Disertation]. Adelaide. University of Adelaide; 2019.
25. Knightly R, Milan SJ, Hughes R, et.al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2017;11(11).
26. Shan Z, Rong Y, Yang W, Wang D, Yao P, Xie J, Liu L. Intravenous and nebulized magnesium sulfate for treating acute asthma in adults and children: a systematic review and meta-analysis. Respir Med. 2013;107(3):321-30.
27. Powell C, Dwan K, Milan SJ, Beasley R, Hughes R, Knopp-Sihota JA, Rowe BH. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2012;12:12.
28. Turner DL, Ford WR, Kidd EJ, Broadley KJ, Powell C. Effects of nebulised magnesium sulphate on inflammation and function of the guinea-pig airway. Eur J Pharmacol. 2017;801:79-8.

Supplementary Table. Study characteristics.

Author, Year of Publication Design Study	**Sample Number. Place of Study**	Outcome Measurement	Intervention	**Control**	Sex	Age	**Outcome of Study**	Additional Outcome
Goodacre et.al[30], 2013, *Randomized Controlled Trial*	N:690, Part of 3 Mg Trial in 34 Emergency Department, England	120 minutes after initial therapy For readmission 7 days after admission	MgSO4 500 mg + Salbutamol 5 mg + Ipratropium bromide 500µg + Oral Prednisolone	Salbutamol 5mg + Ipratropium bromide 500µg + Oral Prednisolone	Magnesium Female: 232 Male: 100 Control Female: 252 Male: 106	Magnesium: Median 35(23-47) Control: Median 34.5 (24-47)	There is no association between magnesium and readmission OR 0.96 (0.65-1.4). There is no association between dyspnoea VAS and magnesium -2.6 (-7 to 1.8) There is no statistical difference between inhaled magnesium and ΔPEF -0.6% (-3.4 to 2.1%). There is a higher risk of side effects in the magnesium group. OR 1.67 (1.05-2.66) p=0-0.31)	The side effect of inhaled magnesium is 12% compared to control (10%) In both groups, 1% of patients required ventilation respectively.
Ahuja et, al, [32] 2020, *Single-Blind Randomized Control Study*	N: 115, ED Patient in Karachi	Respiration rate, FEV, and oxygen saturation measured 30,60, 90 dan 120 minutes after the administration of magnesium	MgSO4 333 mg + Salbutamol 2.5 ml + Ipratropium bromide 250 mg + Hydrocortisone 100 mg	Salbutamol 2.5ml + Ipratropium bromide 250 mg + Hydrocortisone100 mg	115 patients Female: 64 Male: 51	N/A	In the 60th minute, the mean respiratory rates in the magnesium and control group are 30.3 and 32.4 times per minute, respectively. In the 120th minute, the mean respiratory rates in the magnesium and control group are 27.4 and 32.16 times per minute respectively (P = 0.003). The mean heart rate in the magnesium and control group are 109.87 and 122.11 times per minute respectively. There is an increasing FEV inpatient in patients with magnesium compared to control (189 and 103, respectively) (P<0.001) The mean of oxygen saturation in the magnesium and control group (90.62 and 91% respectively) Approximately, 72% of patients in the magnesium group feel better after administering drugs. 28% of patients in the control group feel better after administration.	

Motamed et al (2017)[31] *Randomized Controlled Clinical Trial*	N=148, Age 18-65 years old Emergency Department in Iran	PEFR dan FEV1 of patients. It is observed 20,40, and 60 minutes after admission	MgSO4 300 mg + Albuterol 2,5 mg + Ipratropium bromide 0,5 mg + Prednisolone 0.5 mg	Albuterol 2,5 mg + Ipratropium bromide 0,5 mg + Prednisolone 0.5 mg	N/A	Control Median 34.97 (19-60) Magnesium Median 36(21-63)	The mean PEFR of the Magnesium group is 333 L /minute and the Control Group is 280 l/minute (P<0.001). The mean FEV of the magnesium group is 2.8 L per minute and the control group is 2.24 L/min The Borg Dyspnoea scale in the magnesium group is better than the control group (P<0.001). The trial shows no exact number of Borg Dyspnoea scale	
Gallegos et al (2010)[10] *Placebo-controlled, double-blinded clincal trial*	N= 60 Patient above 18 years old. Tertiary Hospital in Meksiko	FEV, readmission rate, Severity of Symptoms	MgSO4 333 mg (3x) + Methylprednisolone 125 mg + Albuterol 7.5 mg + Ipratropium Bromide 1.5 mg	Methylprednisolone 125 mg + Albuterol 7.5 mg + Ipratropium Bromide 1.5 mg	Control Male: 9 Female: 21 Magnesium Male: 9 Female: 21	Control Mean:34.3+/-12.4, Magnesium: Mean 40.2+/ 11	The readmission rate of the control group is 10%, and magnesium group is 7% FEV in the magnesium group is 2.16+/- 0.66L per minute compared to control 2.01+/- 0.51. The relieving of symptoms in the magnesium group occurred in 26 of 30 participants. The relieving of symptoms in the control group occurred in 17 of 30 participants. Oxygen Saturation in the magnesium group is higher than control (92+/- 4.2 and 88.9+/-5.3, respectively)	Side effects that people feel like bitter taste in their mouth and nausea (Not mentioned in the study)
Hossein et al, 2016[33] Randomized Controlled Trial	N=50, Two Emergency Centres in Iran Patient above 16 years old.	Dyspnoea Severity Score, PEFR, Respiration rate, Oxygen Saturation	MgSO4 200 mg (3x) + Salbutamol 2.5 mg + Atrovent 0.5 mg + Oral Prednisolone 50 mg	Salbutamol 2.5 mg + Atrovent 0.5 mg + Oral Prednisolone 50 mg	Magnesium: Male: 14 Female 11 Control Female: 11 Male: 14	Magnesium Mean: 52.4+/16.9 Control Mean: 53+ /- 16.2	The mean respiratory rate in the magnesium group is 20.5±4.8 and the mean of oxygen saturation of the control group is 21.4±4.1 (P =0.229) The mean of oxygen saturation in the magnesium group is 97.2±2.9 and the mean of the oxygen saturation control group is 94.3±3.3 (P <0.001) The mean of PEFR in the magnesium group is 48.7±23.4 and the mean of a control group is 36±28.7 (P <0.002)	