www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v6i5.162

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Effectiveness of Inhaled MgSO4 as an Adjuvant to Initial Treatment of Acute Moderate Asthma in Children: An open Randomized Controlled Trial

Authors
Dr Kiran Raj H[1*], Dr Suman Rath[2]
[1]Senior Resident, Department of Pediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangaluru, India
[2]Consultant Pediatrician, Department of Pediatrics, Bangalore Baptist Hospital, Bengaluru, India.

*Corresponding Author
Dr Kiran Raj H
Senior Resident, Department of Pediatrics, Srinivas Institute of Medical Sciences and Research Centre, Mukka, Mangaluru, India
Krajh999@gmail.com

ORIGINAL RESEARCH ARTICLE

Abstract

Introduction: *Asthma is the most common and best understood chronic disease in childhood, but the diagnosis and management of this disorder is a challenge for pediatricians and for the entire health-care system. Management of asthma depends upon the severity of attack and may include nebulized β2-agonists, anticholinergic agents, inhaled and systemic steroids, Intravenous magnesium sulphate and oxygen supplementation. Use of inhaled magnesium sulphate had been emerging as aninteresting topic for research. Many studies have come up with the conclusion that nebulized MgSO4 in patients with asthma exacerbation results in earlier improvement in clinical signs and symptoms, significant improvement in lung function and consequently a faster recovery. We undertook this study to analyze possibility of any added benefit when nebulized Mgso4 is used in the initial treatment along with the standard drugs in children with acute attack of asthma /wheeze.*

Aims and Objectives

1. *To know the effectiveness of combined inhaled salbutamol and ipratropium in magnesium sulphate over salbutamol and ipratropium in isotonic saline in acute moderate asthma in children.*
2. *To compare the efficacy of combined inhaled salbutamol and ipratropium in magnesium sulphateover salbutamol and ipratropium in isotonic saline in acute moderate asthma in children.*

Materials and Methods: *This was an open-labelled randomized controlled trial consisting of children in the age group of 2 to 14years attending pediatric OPD with wheeze according to GINA guidelines and PRAM scores. 100 children included in this study were divided into 2 groups. Children in Group A received standard treatment of Salbutamol along with Ipratropium and Normal saline while children in group Breceived Salbutamol along with Ipratropium and MgSo4 nebulization as treatment. The effectiveness and*

comparison of efficacy of treatment in these groups were studied. Student 't' test and chi square tests were used to find the significance of study parameters. P value less than 0.05 was considered as significant.

Results: *Out of the 100 children who were included in this study there were 60 (60%) males and 40 (40%) females with a M:F ratio of 1.5:1. Mean age and weights were found to be comparable in both the groups. There was a statistically significant family history in Group A. PRAM scores at 0,20,40 and 60 minutes were statistically significantly higher in patients of Group A than in Group B. Heart rates at 0,20,40 and 60 minutes were comparable in both the groups and there was no statistically significant difference in both the groups. Respiratory rates were statistically significantly higher in Group A at 20,40 and 60 minutes. SpO2 levels were higher at 20 and 40 minutes. Peak expiratory flow rates were found to be comparable in both the groups. The analysis of patients on the basis of need to revisit the hospital showed that there was no statistically significant difference in hospitalrevisit rates in both the groups. There were no cases of treatment failure in any of the groups.*

Conclusion: *Inhaled Magnesium along with the standard treatment gives a significantly better clinical improvement in acute moderate asthma. Hence Inhaled magnesium along with standard treatment given as nebulization may be considered as initial treatment for use in moderate to severe acute asthma in children.*

Keywords: *Acute moderate asthma, inhaled MgSO4, PRAM Scores, Peak Expiratory Flow Rates.*

Introduction

Though asthma is usually defined as a chronic inflammatory disease of the airways resulting in episodic airflow there is no uniform definition of asthma. Revised GINA classification divides it into intermittent, mild persistent, moderate persistent and severe persistent asthma[1]. The analysis of Global burden of asthma indicates that the prevalence has been increasing since last 20 years especially in children. Globally and currently asthma affects ~300 million people and 15% of children are affected by the disease[2]. Childhood asthma seems particularly common in modern metropolitan locales and is strongly linked with other allergic conditions. In contrast, children living in rural areas of developing countries and farming communities are less likely to develop asthma and allergy. Although the cause of childhood asthma has not been determined, contemporary research implicates a combination of environmental exposures and inherent biological and genetic vulnerabilities. Respiratory exposures in this causal environment include inhaled allergens, respiratory viral infections, and chemical and biological air pollutants such as environmental tobacco smoke[3]. Within the general population, asthma affects women more than men; however, among children boys are more commonly affected. Irrespective of the cause of such a hyperresponsiveness of airways asthma results in episodic airflow obstruction. Chronically inflamed airways are hyper-responsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs and increased inflammation) when airways are exposed to various risk factors. Diagnosis is based on several factors including family history, risk factors, symptom patterns, diagnostic tests, and responses to therapy[4].

There are few scoring methods to assess severity of respiratory symptoms in an acute attack. Amongst proposed scores, the Pediatric Respiratory Assessment Measure (PRAM) has been validated for assessing acute asthma exacerbation severity. The PRAM was developed by Chalut, Ducharme and colleagues and has face and criterion validity in pediatric patients with acute asthma exacerbations. It divides asthma into mild moderate or severe asthma on the basis of various factors (suprasternal retractions, Scalene retractions, wheezing, air entry and oxygen saturation). PRAM scores detect significant and clinically meaningful change of severity during the treatment, whereas spirometry does not. This suggests that spirometry and clinical severity scores do not have similar trajectories and that clinical severity scores may be more sensitive to clinical change of acute asthma severity than spirometry[5].

Management of Asthma depends on the severity and classification and may consist of nebulized β2- agonists, anticholinergic agents, inhaled and systemic steroids, Intravenous magnesium sulphate and oxygen supplementation[6]. A single dose of intravenous magnesium sulphate has been shown to be safe and effective in adults and children with acute severe asthma, who have had a poor response to initial therapy[7]. It is a safe drug to administer, but there have been minor side effects reported, such as epigastric or facial warmth, flushing, pain and numbness at the infusion site, dry mouth, malaise, and hypotension[8]. In some cases, severe hypotension may develop. To prevent these complications many researchers have come up with the option of nebulized magnesium sulphate in patients with asthma. Nebulized magnesium sulphate added to inhaled β2-agonists in the treatment of an acute asthma exacerbation has been shown to improve lung function in patients with severe asthma, with a trend towards fewer hospital admissions. Isotonic magnesium sulfate, as a vehicle for nebulized salbutamol is found to have been associated with increased peak flow response to treatment in comparison with salbutamol plus normal saline[9].

There are very few studies on children comparing the standard therapy with inhaled $MgSO_4$[10,11]. Cochrane study database review 2012 has suggested further studies should focus on inhaled MgSO4 in addition to the current guideline treatment for acute asthma (inhaled β2 -agonist and ipratropium bromide)[12]. Therefore, this study was undertaken to analyze any added benefit when nebulized Mgso4 is used in the initial treatment along with the standard drugs in children with acute attack of asthma.

Materials and Methods

This was an open-labelled randomized controlled trial conducted in pediatric department of a tertiary care hospital situate in a metropolitan city. Total 100 children in the age group of 2-14 years coming to outpatient department with wheeze according to GINA guidelines and PRAM scores were included in this study on the basis of predefined inclusion and exclusion criteria. The diagnosis of asthma in children between 2 to 14 yrs was made if they presented with acute wheeze with cough which aggravated in night and early mornings and most of them had viral upper respiratory symptoms. There was a prior history of wheezing and treatment with β2 agonists. Children diagnosed to be having acute moderate asthma on the basis of PRAM scores and GINA Guidelines were included in this study. Informed consent of parents was taken. Children having first episode of wheezing were not included in the study. A detailed family, past, personal and present history was noted down. Detailed clinical examination was done. Patients were randomized to 2 groups.

Group A: Children who receive standard treatment of Salbutamol + Ipratropium+ Normal saline

Group B: Children in this group received Salbutamol+Ipratropium+MgSo4 nebulization.

The dose of salbutamol given was 2.5mg (<5 years) to 5mg (≥6 years), ipratropium- 250 to 500 micrograms, Magnesium sulphate- 0.4 ml of 50%, normal saline 0.9% 3ml. Baseline vitals, Spo2, PEFR (in ≥5years) were taken (best of 3 readings) and PRAM score was determined. Each nebulization was given 3 times for 20 mins each and the vitals, spo2, PEFR and PRAM scores were monitored after each nebulization at 20, 40 and 60 mins.Following 3 nebulizations standard care was given regarding further treatment and discharge medications or admission of the child. The baseline and subsequent parameters after each nebulization were compared and analyzed in both groups. The percentage (%) change in PRAM score in both groups, extent of improvement in heart rate, respiratory rate and SpO_2, change in PEFR and hospitalization rate in each group was compared. Children will be monitored for any side effects throughout the study. In the event of any child developing hypotension normal saline and inotropic support was provided. Data was entered

in Microsoft excel and was analyzed using SPSS version 16.0. Categorical variables were analyzed using chi-square test. A p value of less than 0.05 was considered statistically significant level of difference

Inclusion Criteria

1) Children between 2 to 14 yrs with acute moderate wheeze/asthma
2) Prior history of wheezing, cough with treatment with beta agonists should be present.
3) Parents given Informed Consent.

Exclusion Criteria

1) Critically ill /who need intubation
2) Children who have severe asthma and need immediate treatment.
3) Children with atypical presentation or radiology confirmed pneumonia.
4) Known case of renal, cardiac, neurology, systemic disease.
5) Known hypersensitivity to MgSO4.
6) Parents refused consent.

Results

The study comprised of 100 patients with acute moderate asthma. Out of these 100 patients there were 60 (60%) males and 40 (40%) females with a M:F ratio of 1.5:1. The difference was not found to be statistically significant.

Table 1: Sex distribution in both the groups

Sex	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	p-value
	Number	Percentage	Number	Percentage		
Male	29	58 %	31	62 %	0.16	0.838
Female	21	42 %	19	38 %		

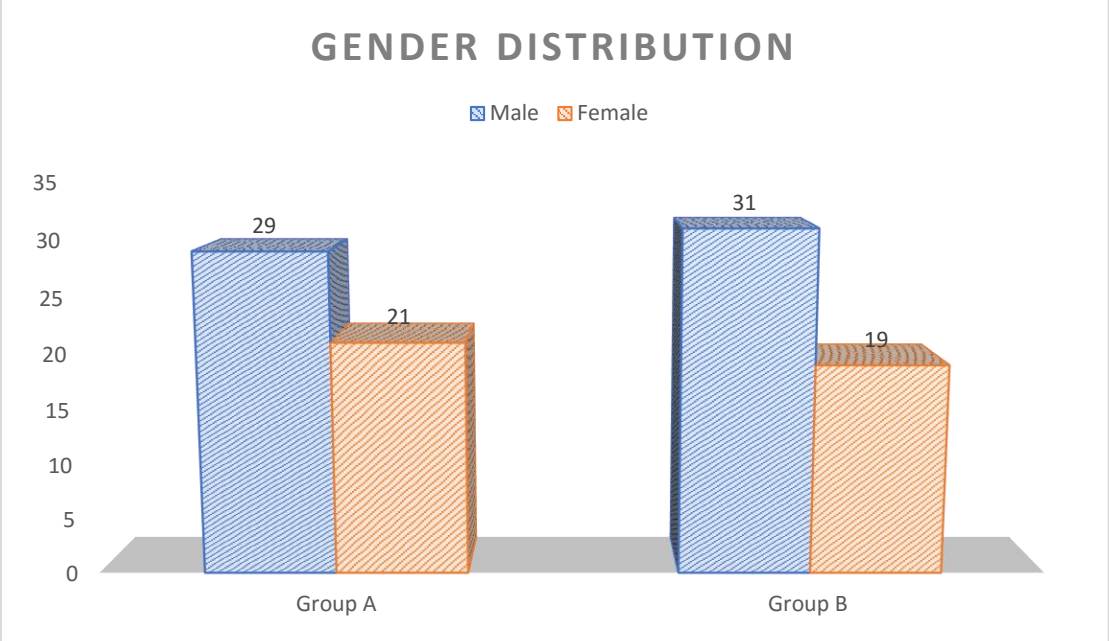

Figure 1: Gender Distribution of the groups

The mean age in Group A and Group B was 6.2 years and 6.4 years respectively. While Mean weight and height was found to be 20.9 and 133.3 in group A and 20.5 and 119 in group B respectively. The comparison of age, weight and height of the patients in both the groups showed that these parameters were comparable in both the groups and there was no statistically significant difference between these 2 groups.

Table 2: Comparison of mean age, height and weight in both the groups

Variable	Group	Mean	Std. Deviation	t value	p value
Age	Normal saline	6.2	3.4	0.4	0.6
	Mag. Sulphate	6.4	2.8		
Weight	Normal saline	20.9	10.6	0.2	0.8
	Mag. Sulphate	20.5	9.5		
Height	Normal saline	133.3	25.2	1.2	0.2
	Mag. Sulphate	119.0	21.1		

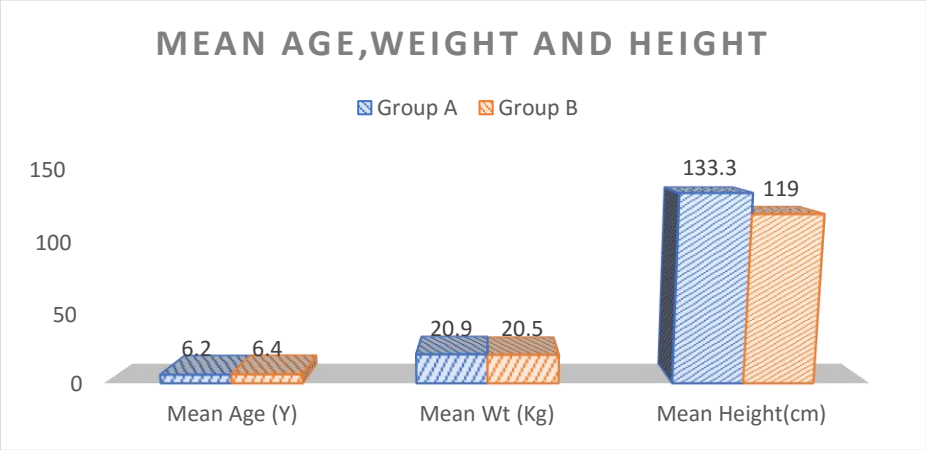

Figure 2: Mean age, height and weight in both the groups

The need for medications like beta agonists and steroids in both the groups showed that out of 50 patients in group A 38 (76%) patients didn't require these medications while in group B 40 (80%) patients didn't need these drugs. Beta agonists and steroids were given in 12 (24%) and 10 (20%) patients in group A and Group B respectively. The difference was not found to be statistically significant (p=0.81).

Table 3: Comparison of need for B2 agonists and steroids in both the groups

Medications (β2 agonists and steroids)	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	p-value
	Number	Percentage	Number	Percentage		
No	38	76 %	40	80 %	0.23	0.81
Yes	12	24 %	10	20 %		

One of the important difference between these 2 groups was presence of family history. In group A there was family history of asthma in 38 % cases while in group B family history was present in 20% of the cases. The difference was found to be statistically significant (p=0.07).

Table 4: Comparison of family history in both the groups

Family history	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	P-value
	Number	Percentage	Number	Percentage		
No	31	62 %	40	80 %	3.9	0.07
Yes	19	38 %	10	20 %		

The analysis of PRAM scores in both the groups at 0,20,40 and 60 minutes showed that there was statistically significant difference in PRAM scores in both the groups and Group A had statistically significantly higher PRAM scores at 0 (P= 0.028),20 (P=0.00),40 (P=0.00) as well as 60 (P=0.00) minutes. The analysis of heart rates in both the groups at 0,20,40 and 60 minutes showed

that there was no statistically significant difference in in both the groups at 0 (P= 0.3),20 (P=0.1),40 (P=0.9) as well as 60 (P=0.5) minutes.

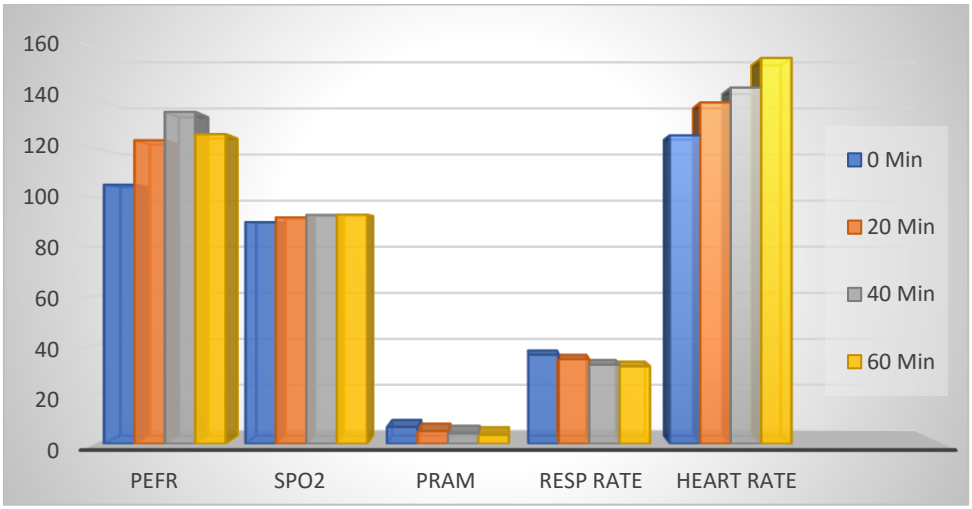

Figure 3: Various parameters at 0,20,40 and 60 Minutes in Group A.

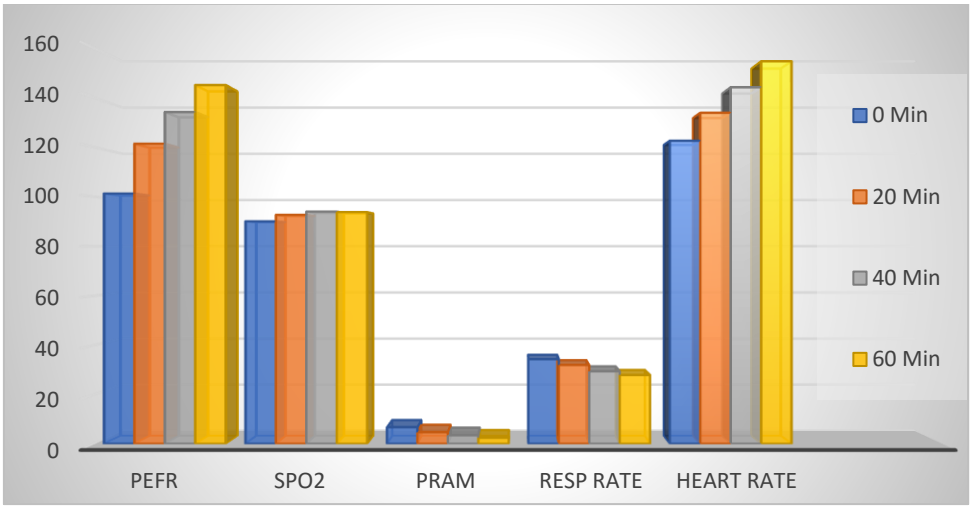

Figure 4: Various parameters at 0,20,40 and 60 Minutes in Group B.

The analysis of respirator rate in both the groups at 0,20,40 and 60 minutes showed that there was no statistically significant difference in in both the groups at 0-minute (P= 0.1) while the statistically significant higher respiratory rates were found in group A at 20 (P=0.05), 40(P=0.02) and 60 (P=0.004) minutes. The analysis of SPO2 in both the groups at 0,20,40 and 60 minutes showed that there was no statistically significant difference in in both the groups at 0-minute (P= 0.82) and 60 minutes (P=0.65) while the statistically significant higher SPO2 levels were found in group B at 20min (P=0.04) and 40 min (P=0.002). Peak Expiratory Flow rates (PEFR) were found to be comparable in both the groups at 0,20,40 and 60 minutes and there was statistically significant difference in PEFR values in both the groups.

Table 5: Comparison of various parameters in both the groups

Variables	Groups	0 min	20 min	40 min	60min
PEFR	NS	105.1±20.1	123.1±21.2	134.6±24.3	145.6±23
	MgSO4	101.3±21.9	121.4±34.3	134.2±37.2	145.1±34.4
	p value	0.46	0.8	0.95	0.9
SPO2	NS	90±2.8	91.9±2.1	92.9±2	93±7.2
	MgSO4	90.1±2.6	92.7±1.8	94±1.3	93.8±9.3
	p value	0.82	0.04	0.002	0.65
PRAM SCORE	NS	6.8±0.96	5.2±1	4.3±1.1	3.7±1
	MgSO4	6.7±1	4.7±1	3.5±1.2	2.5±1.1
	p value	0.028	0.000	0.000	0.000
Respiratory rate	NS	36.2±7.5	34.4±7.2	32.2±7.2	31.5±7
	MgSO4	34.3±4.5	32±4.3	29.4±4.2	27.9±5.1
	p value	0.1	0.05	0.02	0.004
Heart rate	NS	125.1±15.7	138.4±16.4	144.4±24.2	156.4±15.4
	MgSO4	122.6±10.2	133.9±9.6	144.2±10.7	154.7±11.3
	p value	0.3	0.1	0.2	0.5

Comparison of both the groups for re-visits showed that there was no statistically significant difference in incidence of hospital re-visit and both the groups were found to be comparable.

Table 6: Comparison of hospital re-visits in both the groups

Revisit to the hospital	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	p-value
	Number	Percentage	Number	Percentage		
No	41	82 %	39	48 %	0.25	0.8
Yes	9	18 %	11	22 %		

All patients were successfully treated in both the groups since there was no patient who could not be managed in either of the groups. Hence as far as treatment failure was concerned there was no statistically significant difference in both the groups

Table 7: Comparison of treatment failure in both the groups

Treatment failure	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	p-value
	Number	Percentage	Number	Percentage		
No	50	100%	50	100%	0	1
Yes	0	0%	0	0%		

No patient in any of the groups required steroids for treatment (P=1).

Table 8: Comparison of steroid use in both the groups

Steroid use	Normal saline (N=50)		Magnesium sulphate (N=50)		Chi-Square	p-value
	Number	Percentage	Number	Percentage		
No	50	100%	50	100%	0	1
Yes	0	0%	0	0%		

Discussion

Our study comprised of 100 children coming to pediatric outpatient department of our hospital fulfilling the inclusion criteria. Data of Children in Group A and B were analyzed and compared before and after nebulizations at 0, 20, 40 and 60 mins.The sex distribution, anthropometric measurements were comparable in the 2 groups.

The baseline parameters at '0'min. in Group A (Normal saline) and Group B (Magnesium sulphate) respectively were significantly different in terms of PRAM score (mean 6.8 and 6.5 with

p=0.028), Heart rate (mean 125.1 and 122.6 with p=0.35), Respiratory rate (mean 36.2 and 34.3 with p=0.13), SpO2 (mean 90.0 and 90.1 with p= 0.82) and PEFR (mean 105.1 and 101.3 with p=0.46). We observed greater improvement in the magnesium group B over the normal saline group A at 20 mins in respect to significant reduction of PRAM score (mean 4.42 and 5.18 respectively p=0.000) improvement in the respiratory rate (mean 32.0 and 34.4 with p= 0.05) and increase in the Oxygen saturation (mean 92.7 and 91.9 with p=0.04). There was tachycardia in both groups but no significant difference (p=0.1) and the increase in PEFR in both groups was comparable (p=0.46). Similar effects were seen at 40 mins assessment with the magnesium group showing a very significant improvement in the PRAM score (mean 3.18 and 4.22 with p=0.000), Respiratory Rate (mean 29.4 and 32.2 with p=0.002) and Oxygen Saturation (mean 94 and 92.9 with p=0.002). There was no significant difference noticed in the heart rate or the PEFR in the 2 groups. At the end of the study at 60 mins, The PRAM score and Respiratory rate improvement was very significantly more in the magnesium group (PRAM score mean 2.02 and 3.6 with p=0.000 and respiratory rate mean 27.9 and 31.5 with p=0.004 respectively) but the mean heart rate, PEFR and the Oxygen Saturation was nearly same in both groups.

Powell C et al[13] did a similar study in children with acute severe asthma and concluded nebulized isotonic MgSO4, given as an adjuvant to standard treatment, did not show a clinically significant improvement in mean ASS in children with acute severe asthma. However, the greatest clinical response was seen in children with more severe attacks (SaO_2<92%) at presentation and those with preceding symptoms lasting less than 6 h. Our study did show significant improvement in PRAM score in the magnesium group as compared to normal saline group at every point of evaluation in children with moderate asthma.

There are studies done by Mahajan et al[14] and Hughes R J[15] which show improved pulmonary function in the early 20 minutes in the magnesium group in children with severe asthma. In Cochrane systemic review, Blitz M et al[16] showed that Nebulized inhaled magnesium sulfate in addition to β_2-agonist in the treatment of an acute asthma exacerbation, appears to have benefits with respect to improved pulmonary function in patients with severe asthma and there is a trend towards benefit in hospital admission. Our study did not show any significant difference in the revisits in both groups and none of the children needed hospitalization.

Several recent studies are done on use of inhaled mgso4 for management of asthma in children. Albuali WH et[17] al in their study of intravenous and inhaled MgSO4 on hospital admission and pulmonary function in children with asthma found that Intravenous MgSO4 therapy was effective 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. The author recommended that the role of nebulized MgSO4 in asthmatic children requires further investigation.

Gandia F et al [18]conducted a placebo-controlled, double-blind clinical trial with seventy-six patients with bronchial hyperresponsiveness to investigate the effects of inhaled MgSO4 alone and in association with a β2-agonist in the treatment of bronchial hyperresponsiveness. The authors found that Inhaled MgSO4 led to a significant improvement of the FEV1 from the 15th minute after its inhalation. The authors conclude that InhaledMgSO4, in combination with β2-agonist, appears to have benefits in the treatment of bronchial hyperresponsiveness, especially when associated with hypomagnesemia. Similar findings are reported in recent studies conducted by Knightly R[19] who found that treatment with nebulized $MgSO_4$ result in modest additional benefits for lung function and hospital admission when added to inhaled β_2-agonists and ipratropium bromide and Sun YX[20] in their study of Effect of inhaled MgSO4 on FEV1 and PEF in

children with asthma induced by acetylcholine found that nebulized magnesium sulfate alone has a bronchodilator effect and hence can be effective in children with asthma.

Conclusion

Inhaled Magnesium along with the standard treatment in acute moderate asthma gives a significantly better clinical improvement as seen by PRAM score and Respiratory Rate. Children with severe acute asthma may also benefit more if magnesium is added to salbutamol and Ipratropium. Oxygen Saturation improvement is faster if inhaled magnesium is given along with standard treatment. Children in Group B showed significant improvements at 20 and 40 minutes of nebulization. No significant additional benefit in the pulmonary function as seen by peak flow in the magnesium group but mean difference was better in magnesium group.

What is already known?

Intravenous MgSO4 is beneficial in severe/life threatening exacerbations of asthma in children.

What this study adds ?

Inhaled MgSO4 as an adjuvant to standard treatment shows significant clinical improvement in acute moderate asthma in Respiratory Rate, PRAM scoring and SpO2 at 20,40 minutes after the nebulization.

References

1. Global Initiative for Asthma. GINA Report: Global strategy for asthma management and prevention (online). 2013; available from : URL: http://www.ginasthma.com
2. Mani SK. Clinical evaluation and assessment of severity. In: Diagnosis and management of asthma. 4th Edition. United states of America: professional communications,Inc; 2007. p38-39
3. Sheehan WJ, Rangsithienchai PA, Wood RA, et al. Pest and allergen exposure and abatement in inner-city asthma: A Work Group Report of the American Academy of Allergy, Asthma & Immunology Indoor Allergy/Air Pollution Committee. The Journal of allergy and clinical immunology. 2010;125(3):575-581.
4. Brigham EP, West NE. Diagnosis of asthma: diagnostic testing. Int Forum Allergy Rhinol. 2015 Sep;5 Suppl 1:S27-30.
5. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr. 2000 Dec;137(6):762–768.
6. Sarhan HA, EL-Garhy OH, Ali MA, Youssef NA. The efficacy of nebulized magnesium sulfate alone and in combination with salbutamol in acute asthma. Drug Design, Development and Therapy. 2016;10:1927-1933.
7. Reddy AP, Gupta MR. Management of asthma: the current US and European guidelines. Adv Exp Med Biol. 2014;795:81-103. Review.
8. Kokotajlo S, Degnan L, Meyers R, Siu A, Robinson C. Use of Intravenous Magnesium Sulfate for the Treatment of an Acute Asthma Exacerbation in Pediatric Patients. The Journal of Pediatric Pharmacology and Therapeutics : JPPT. 2014;19(2):91-97.
9. Sydow M, Crozier TA, Zielmann S. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus. Intensive Care Med. 1993;19 (8):467–471.
10. Nannini LJ Jr, Pendino JC, Corna RA, Mannarino S, Quispe R. Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. Am J Med. 2000 Feb 15; 108(3):193–7.

11. 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. Ann Emerg Med. 2002 Jun; 39(6):585–91.
12. Mangat HS, D'Souza GA, Jacob MS. Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma: a clinical trial. Eur Respir J. 1998 Aug;12(2):341–4.
13. Powell CV. The role of magnesium sulfate in acute asthma: does route of administration make a difference? :Curr Opin Pulm Med. 2014 Jan;20(1):103-8.
14. 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. J Emerg Med. 2004 Jul;27(1):21–5.
15. Hughes RJ, Goldkorn AL, Masoli M, Weatherall M, Burgess C, Beasley CR. The use of isotonic nebulized magnesium as an adjuvant to salbutamol in the treatment of severe asthma in adults: Randomised placebo-controlled trial. Lancet 2003;361(9375):2114–7.
16. Blitz M, Blitz S, Hughes R, Diner B, Beasley R, Knopp J, Rowe BH. Aerosolized magnesium sulfate for acute asthma: a systematic review. Chest. 2005 Jul;128(1):337-44. Review. Erratum in: Chest. 2005 Nov;128(5):3779.
17. Albuali WH. The use of intravenous and inhaled magnesium sulphate in management of children with bronchial asthma. J Matern Fetal Neonatal Med. 2014 Nov;27(17):1809-15.
18. Gandia F, Guénard H, Sriha B, Tabka Z, Rouatbi S. Inhaled magnesium sulphate in the treatment of bronchial hyperresponsiveness. Magnes Res. 2012 Dec;25(4):168-76.
19. Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2017 Nov 28;11:CD003898.
20. Sun YX, Gong CH, Liu S, Yuan XP, Yin LJ, Yan L, Shi TT, Dai JH. Effect of inhaled MgSO4 on FEV1 and PEF in children with asthma induced by acetylcholine: a randomized controlled clinical trail of 330 cases. J Trop Pediatr. 2014 Apr;60(2):141-7.