Egyptian Journal of Chest Diseases and Tuberculosis (2012) **61**, 29–34

The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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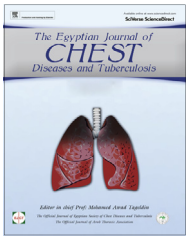

ORIGINAL ARTICLE

Nebulized magnesium sulphate versus nebulized salbutamol in acute bronchial asthma

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Received 2 May 2012; accepted 12 May 2012
Available online 9 February 2013

KEYWORDS

Magnesium sulphate;
Acute asthma;
Salbutamol;
Peak expiratory flow;
Oxygen saturation

Abstract *Aim of work:* The aim of this study is to investigate the efficacy of nebulized magnesium sulphate as a bronchodilator in acute asthma as compared to nebulized salbutamol.

Subjects and methods: This was a randomized controlled study conducted in El-Giza Chest Hospital Emergency Department between January 2010 and June 2011. Randomization was achieved by closed envelope technique. This study involved 48 known bronchial asthma patients presenting with acute or subacute exacerbations. Patients were divided into Control group (A) and Study group (B). Initial assessment of all patients included history, clinical examination (auscultation, respiratory rate (RR), heart rate (HR) and working of accessory muscles). In addition to measurement of peak expiratory flow rate (PEFR) and oxygen saturation (SO_2). Patients received standard treatment for their acute attacks in the form of Sodium hydrocortisone hemisuccinate 100 mg every 6 hours, Supplemental oxygen and nebulized bronchodilator which was salbutamol in group (A) in the form of 4 doses of nebulized solution 0.5 gm% (each dose 1 ml containing 5 mg salbutamol) twenty minutes apart and Magnesium sulphate in group (B) in the form of 4 doses of nebulized solution 10 gm% (each dose 1 ml containing 100 mg magnesium sulphate) twenty minutes apart. Reassessment of the patients was performed after 2 hours to detect improvement.

Results: The percent change in PEFR in Group A was significantly higher than that in Group B (58.90% and 13.92% respectively, *p* value 0.00). There was a statistically significant reduction in the final mean HR in Group B compared to Group A (85 bpm and 96.1 bpm respectively, *p* value

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Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

ELSEVIER **Production and hosting by Elsevier**

 http://dx.doi.org/10.1016/j.ejcdt.2012.10.023

0.011). There was a significant reduction in mean final RR in Group A compared to Group B (22.17 bpm. and 25 bpm respectively, *p* value 0.002).There was a significant increase in oxygen saturation (SO_2) in both groups.

Conclusion: The use of $MgSO_4$ by nebulization in patients with acute asthma attacks results in improvement of clinical condition, increase in peak expiratory flow rate (PEFR), reduction in heart rate (HR), reduction in respiratory rate (RR) and improvement in oxygen saturation (SO_2). The increase in PEFR (bronchodilatory effect) was significantly less than that achieved in patients receiving the usual treatment with Short acting β2 agonists, e.g. salbutamol, when either agents were used alone.

Introduction

Asthma exacerbations are acute or subacute episodes of breathlessness, cough, wheezing, and chest tightness, or any combination of these symptoms. Exacerbations are associated with airways obstruction that should be documented and quantified by PEF or FEV1 measurement [1].

Objective measures of airways obstruction in most asthmatics are considered more reliable to indicate the severity of an exacerbation than changes in the severity of symptoms. The intensity of asthma exacerbations may vary from mild to severe. Among patients attending an emergency department, the severity of obstruction in terms of FEV1 is, on average, 30–35% of predicted normal [1].

In asthmatic subjects who die suddenly of an asthma attack, the peripheral airways frequently exhibit occlusion of the bronchial lumen by inspissated secretions, thickened smooth muscles, and bronchial wall inflammatory infiltration and edema [2].

These changes observed in the asthmatic airways support the hypothesis that peripheral airways occlusion forms the pathologic basis of the gas exchange abnormalities observed in acute, severe asthma [2].

Hypoxemia is therefore common in every asthmatic crisis of some severity; mild hypoxia is easily corrected with the administration of relatively low concentrations of supplemental oxygen. More severe hypoxemia and the need for higher concentrations of supplemental oxygen may relate to some contribution of shunt physiology [3].

Although arterial blood gas analysis is useful in the management of patients with acute, severe asthma, it is not predictive of outcome. Arterial blood gas determinations are necessary in the more severe asthmatic crisis, when oxygen saturation is lower than 90%, and in the case of no response or deterioration. In such cases, analysis of blood gases usually reveals severe hypoxemia with arterial oxygen (PaO_2) lower than 60 mmHg, hypocapnia and respiratory alkalosis with or without compensatory metabolic acidosis. As the severity of airflow obstruction increases, PaCO2 first normalizes and subsequently increases. The transition from hypocapnia to normocapnia is an important sign of severe clinical deterioration and the appearance of hypercapnia probably indicates the need for mechanical ventilation [4].

Clinically, patients with acute, severe asthma appear seriously dyspneic at rest, are unable to talk with sentences or phrases, are agitated and sit upright [5].

Drowsiness or confusion are always ominous signs and denote imminent respiratory arrest. Vital signs in acute severe asthma are: respiratory rate usually >30 breaths/min; heart rate >120 beats/min; wheezing throughout both the inspiration and the expiration; use of accessory respiratory muscles; evidence of suprasternal retractions; and pulsus paradoxus >12 mmHg. Pulsus paradoxus can be a valuable sign of asthma severity but its detection should not delay prompt treatment [5].

Paradoxical thoracoabdominal movement and the absence of pulsus paradoxus suggest ventilatory muscle fatigue and, together with the disappearance of wheeze and the transition from tachycardia to bradicardia, represent signs of imminent respiratory arrest. The usual cardiac rhythm in acute, severe asthma is sinus tachycardia, although supraventricular arrhythmias are not uncommon. Less frequently ventricular arrhythmias may be observed in elderly *patients* [5].

Early treatment of asthma exacerbations should be the best strategy for management [6].

In the emergency department, a brief history regarding time of onset, cause of exacerbation, severity of symptoms (especially in comparison to previous attacks), prior hospitalizations and/or emergency department visits for asthma, prior intubation or intensive care admission, and complicating illness may be useful for treatment decisions. The primary therapies for acute severe asthma include, the administration of oxygen, inhaled β2-agonists, and systemic corticosteroids. The intensity of pharmacological treatment and patient's surveillance should correspond to the severity of the exacerbation [7].

Combining nebulized ipratropium bromide with a nebulized β2 agonist produces significantly greater bronchodilation than a β2 agonist alone, leading to a faster recovery and shorter duration of admission [8].

Oxygen treatment (by nasal cannulae or mask) is recommended for most patients who present with severe exacerbation in order to maintain oxygen saturation $>90\%$ ($>95\%$ in pregnant women and in patients with coexistent cardiac disease) [7].

$MgSO_4$ is an agent that has been proposed as a possible additive treatment in patients with acute asthma and has been shown to be effective in patients with severe acute asthma when delivered parenterally [9].

Magnesium is involved with cellular homeostasis through its role as an enzymatic cofactor, as well as being involved in acetylcholine and histamine release, from cholinergic nerve terminals and mast cells, respectively. Investigators have proposed that the effect of $MgSO_4$ is related to its ability to block the calcium ion influx to the smooth muscles of the respiratory system. Magnesium may increase the bronchodilator response to salbutamol in acute asthma by increasing the affinity of β receptors to salbutamol or by upregulating β receptors [10].

Nebulized magnesium sulphate has bronchodilator effects similar to those of nebulized salbutamol. Nebulized $MgSO_4$ appears to be effective and safe to administer to patients experiencing asthma exacerbations [11].

Intravenous magnesium is contraindicated in patient with renal failure, and systemic toxicity due to high dose of magnesium limits the application in certain circumstances. Nebulized magnesium sulphate may be a solution in such a condition, as high concentration of magnesium may be delivered locally without causing systemic side effect [12].

Aim of the work

The aim of this study is to investigate the efficacy of nebulized magnesium sulphate as a bronchodilator in acute asthma as compared to nebulized salbutamol.

Subjects and Methods

This was a randomized controlled study conducted in El-Giza Chest Hospital Emergency Department between January 2010 and June 2011. Randomization was achieved by closed envelope technique. This study involved 48 known bronchial asthma patients presenting with acute attacks.

Inclusion criteria

Adult cases with acute or subacute exacerbations according to Global Initiative for Asthma (GINA) Guidelines 2010.

Exclusion criteria

1. Fever
2. Smokers
3. COPD patients
4. Pneumonia
5. Cardiac, Renal or Hepatic insufficiency
6. Pregnant or Lactating mothers
7. Respiratory failure

Patients were divided into Control group (A) and Study group (B). Initial assessment of all patients included history, clinical examination (auscultation, respiratory rate, heart rate and working of accessory muscles). In addition to measurement of peak expiratory flow rate and oxygen saturation.

Patients received standard treatment for their acute attacks in the form of:

1. Sodium hydrocortisone hemisuccinate 100 mg every 68 hours.
2. Supplemental oxygen to achieve oxygen saturation more than 90%.
3. Nebulized bronchodilator which was salbutamol in group (A) in the form of 4 doses of nebulized solution 0.5 gm% (each dose 1 ml containing 5 mg salbutamol) twenty minutes apart and magnesium sulphate in group (B) in the form of 4 doses of nebulized solution 10 gm% (each dose 1 ml containing 100 mg magnesium sulphate) twenty minutes apart.

Reassessment of the patients was performed after 2 hours to detect improvement.

Patients whose PEFR did not show any improvement and showed clinical deterioration at the end of the 1 hours were given supplemental treatment immediately which consisted of salbutamol nebulization and aminophylline infusion (5 mg/kg loading dose over 20 min unless on maintenance oral therapy, then infusion of 0.5–0.7 mg/kg/hr). Arterial blood gases (ABG) was withdrawn to assess need for admission to intensive care unit (ICU).

PEFR was monitored with hand held mini-wright peak flow meter with using values mentioned by Gore et al. [13] as a reference range.

Results

Group A = salbutamol group(24 patients)

Group B = magnesium sulphate group(24 patients)

Discussion

Intravenous magnesium sulfate is commonly used as a treatment for an acute asthma attack, but doctors don't typically use the chemical compound as an inhaled medication because potential health benefits have not yet been definitely proven [14].

Most acute asthma attacks improve when treated with an inhaled short-acting beta-agonist, such as albuterol, a commonly used asthma medication that relaxes airway muscles and dilates or enlarges breathing passages. Severe asthma attacks often require additional forms of treatment, which may include corticosteroids, magnesium sulfate and mechanical ventilation, depending on the severity of the symptoms [14].

The results of our study show that the use of $MgSO_4$ by nebulization results in improvement of clinical condition, increase in peak expiratory flow rate (PEFR), reduction in heart rate (HR), reduction in respiratory rate (RR) and improvement in oxygen saturation (SO_2). The increase in PEFR was significantly less than that achieved in patients receiving the usual treatment with short acting β2 agonists (see Table 1).

Looking at Tables 2 and 3 the PEFR in group (A) before treatment was significantly less than that in group (B). This denoted that patients had a more degree of airway obstruction in the salbutamol group. After treatment there was no significant difference, once again indicating that the increase in PEFR in salbutamol group was high.

Tables 4 and 5 showed that there was a statistically significant improvement in PEFR% in both groups. Thus, the use of either inhaled salbutamol or $MgSO_4$ improved airway obstruction.

Table 1 Statistical comparison between group A and group B regarding age.

	Group A	Group B	Man-Whitney U	*p* Value
Age mean	30.08	33.08	238	0.301
N	24	24		
Std. Deviation	12.003	8.345		

N = number of cases.

Table 2 Statistical Comparison between group A and group B regarding basal peak expiratory flow rate (PEFR) percentages.

	Group A	Group B	Man-Whitney U	*p* Value
Age mean	48.46	61.13	169.5	**0.014**[a]
N	24	24		
Std. Deviation	12.914	16.369		

[a] Statistically significant = *p* value < 0.05.

Table 3 Statistical comparison between group A and group B regarding final PEFR percentages.

	Group A	Group B	Man-Whitney U	*p* Value
Age mean	86.96	68.25	225	0.194
N	24	24		
Std. Deviation	65.972	17.048		

Table 4 Statistical Comparison between basal and final PEFR percentages in group A.

	Basal	Final	*p* Value
PEFR% mean	48.46	86.96	< 0.001[a]
N	24	24	
Std. Deviation	12.914	65.972	

[a] Statistically significant = *p* value < 0.05.

Table 5 Statistical Comparison between basal and final PEFR percentages in group B.

	Basal	Final	*p* Value
PEFR% mean	61.13	68.25	< 0.001[a]
N	24	24	
Std.Deviation	16.369	17.048	

[a] Statistically significant = *p* value < 0.05.

However, according to Table 6 the percent change in PEFR in group (A) was significantly higher than that in group (B). This denoted that salbutamol was more effective as a bronchodilator than $MgSO_4$ with a much higher effect on airway obstruction.

The results obtained in Tables 4–6 agreed with a single blind study conducted by Tanmaya et al.[15]. They evaluated the efficacy of nebulized magnesium sulphate in the treatment of severe asthma in comparison to nebulized salbutamol. 49 patients participated in this study and were divided into two groups, 25 patients received 4 nebulizations of salbutamol and 24 patients received $MgSO_4$ nebulizations. Patients were monitored with respect to PEFR, HR, RR, blood pressure, presence of cyanosis, SO_2, clinical examination of respiratory system and fischl index (at 0 and 120 min) .The fischl index includes 7 clinical and symptomatic findings such as: dyspnea, accessory muscle use, wheeze, heart rate $\geqslant$120/min, respiratory rate $\geqslant$30, pulsus paradoxicus $\geqslant$18 mmHg and PEFR $\leqslant$120 l/min. The presence of each finding scores 1 point and a total score of 4 or more imply severe asthma. Patients in both groups showed significant improvement in all the above mentioned parameters. However, comparison between the 2 groups revealed that salbutamol was better than $MgSO_4$ in the management of acute exacerbations of bronchial asthma.

Table 6 Statistical comparison between group A and group B regarding percent change in PEFR.

	Group A	Group B	Man-Whitney U	*p* Value
PEFR%change mean	58.90	13.917	53.5	< 0.001[a]
N	24	24		
Std.Deviation	44.2914	15.7445		

[a] Statistically significant = *p* value < 0.05.

The results of our study as shown in Tables 4 and 5 also agreed with a study conducted by Mangat et al. [16] whom investigated the efficacy of nebulized $MgSO_4$ as a bronchodilator in acute asthma as compared to nebulized salbutamol. Their study was a randomized, double-blind, controlled clinical trial. They enrolled 33 asthmatic patients aged 12-60 years in acute exacerbation. Patients were randomized to receive treatment with serial nebulization of either 3 ml (3.2% solution, 95 mg) $MgSO_4$ solution or 3 ml (2.5 mg) salbutmol solution. They noted a significant improvement in PEFR and decrease in RR in each group separately but there was no significant difference between both groups which disagree with our study as shown in Table 6. This may be explained by the fact that as they used half the dose of salbutamol that we used in our study; similar doses of salbutamol could have caused a much more significant bronchodilator effect.

Our results in Table 6 disagreed with Dadhich et al. [17] whom conducted a study to assess the efficacy of nebulized magnesium sulphate in acute severe asthma. They randomly allocated 71 patients into 3 groups. Group A was nebulized with salbutamol, Group B with salbutamol & $MgSo_4$ and Group C by $MgSo_4$ alone. Parameters measured included PEFR, FEV1, FVC FEV1/FVC at baseline, 10 & 20 min interval along with vital parameters and side effects.

They observed an insignificant increase in all parameters (PEFR, FEV1, FVC, FEV1/FVC) in all three groups. However, the mean% increase over baseline was quite significant at 10 & 20 min interval in Group B & Group C where $MgSo_4$ was used. $MgSo_4$ induced greater bronchodilation in those patients having baseline PEFR < 50% in contrast to salbutamol. No significant changes in vital parameters were noticed.

They concluded that $MgSo_4$ induced greater bronchodilation in patients with acute severe asthma. No additional side effects were noticed either alone or with salbutamol. Results were good & early but unsustainable. So $MgSo_4$ may be used as an adjunct for standard treatment in management of acute severe asthma.

In the two studies by Blitz et al. [10] and Rowe et al. [11], the efficacy of nebulized salbutamol was found to be equal to that of nebulized magnesium sulphate with no treatment benefit of either agent used alone. Thus, treatment with nebulized $MgSo_4$ should be considered as an addition to that with inhaled B2 agonists in patients experiencing asthma exacerbations [10].

The combination of nebulized $MgSo_4$ and salbutamol was also dealt with in a study by Hughes et al. [18]. 52 patients with severe exacerbations of asthma presenting to the emergency departments were enrolled in a randomised double-blind placebo-controlled trial. The patients received 2·5 mg nebulized

salbutamol mixed with either 2·5 ml isotonic magnesium sulphate or isotonic saline on three occasions at 30 min intervals. The primary outcome measure was FEV1 at 90 min. They concluded that use of isotonic magnesium as an adjuvant to nebulized salbutamol results in an enhanced bronchodilator response in treatment of severe asthma.

Nannini et al. [19] enrolled 35 patients suffering from asthma. The patients were randomized to receive a one-time dose of 2.5 mg of albuterol. The albuterol dose was diluted in 3 ml of 0.9% sodium chloride or 3 ml of isotonic magnesium sulfate. The magnesium group demonstrated significant improvements in PEFR compared with the control group. They concluded that when nebulized magnesium and albuterol were used together, a higher peak flow could be achieved in comparison to albuterol plus 0.9% sodium chloride.

In our study Table 7, the mean basal heart rate (HR) in salbutamol group was significantly higher than that in $MgSo_4$ group. This denoted that in general the asthmatic attack was more severe in patients of the salbutamol group. This also explains why the mean basal PEFR in that group was much lower than Group B.

In Tables 8–10, the HR decreased in both groups. The reduction was statistically significant in Group B but not in Group A. This could be explained by stimulation of ß2-receptors of the heart, as a side effect, in patients receiving salbutamol (Group A). This agreed with Mangat et al. [16] whom also found a significant reduction in HR in patients treated with inhaled $MgSo_4$ only. This finding illustrates the fact that nebulized $MgSo_4$ can be used safely in cardiac patients (see Table 11).

In Table 12 we noted a significant reduction in mean final respiratory rate (RR) in Group A compared to Group B, correlating with better clinical improvement in that group (see Tables 13–15).

In Tables 16–18 there was a significant increase in oxygen saturation (SO_2) in both groups. This confirms the efficacy of both drugs as effective bronchodilators.

Looking to Table 19 there were 4 patients in group A whom presented with a severe attack (PEFR < 50%). They were distressed with working accessory respiratory muscles. They needed supplementel therapy in the form of frequent salbutamol nebulization and aminophylline infusion (5 mg/kg loading dose over 20 min, then infusion of 0.5–0.7 mg/kg/hr). This ex-

Table 7 Statistical comparison between group A and group B regarding basal HR.

	Group A	Group B	Man-Whitney U	*p* Value
HRbasal mean	97.08	89.17	188	**0.039**[a]
N	24	24		
Std.Deviation	14.569	10.865		

[a] Statistically significant = *p* value < 0.05.

Table 8 Statistical Comparison between basal and final HR in group A.

	Basal	Final	*p* Value
HR mean	97.08	96.13	0.071
N	24	24	
Std. Deviation	14.569	14.220	

Table 9 Statistical comparison between basal and final HR in group B.

	Basal	Final	*p* Value
HR mean	89.17	85	**0.005**[*]
N	24	24	
Std. Deviation	10.865	11.018	

[*] Statistically significant = *p* value < 0.05.

Table 10 Statistical comparison between group A and group B regarding final HR.

	Group A	Group B	Man-Whitney U	*p* Value
HR final mean	96.13	85.00	165	**0.011**[a]
N	24	24		
Std. Deviation	14.220	11.018		

[a] Statistically significant = *p* value < 0.05.

Table 11 Statistical comparison between group A and group B regarding basal RR.

	Group A	Group B	Man-Whitney U	*p* Value
RR basal mean	28.08	26.25	230.5	0.234
N	24	24		
Std. Deviation	5.500	6.095		

Table 12 Statistical comparison between group A and group B regarding final RR.

	Group A	Group B	Man-Whitney U	*p* Value
RR final mean	22.17	25.00	135	**0.002**[a]
N	24	24		
Std.Deviation	12.433	5.357		

[a] Statistically significant = *p* value < 0.05.

Table 13 Statistical comparison between basal and final RR in group A.

	Basal	Final	*p* Value
RR mean	28.08	22.17	< 0.001[a]
N	24	24	
Std. Deviation	5.500	12.433	

[a] Statistically significant = *p* value < 0.05.

Table 14 Statistical comparison between basal and final RR in group B.

	Basal	Final	*p* Value
RR mean	26.25	25.00	0.106
N	24	24	
Std. Deviation	6.095	5.357	

Table 15 Statistical comparison between group A and group B regarding basal SO_2.

	Group A	Group B	Man-Whitney U	*p* Value
SO_2 basal mean	93.33	94.38	162.5	0.0113
N	24	24		
Std.Deviation	1.377	8.365		

Table 16 Statistical comparison between group A and group B regarding final SO_2.

	Group A	Group B	Man-Whitney U	*p* Value
SO_2 final mean	96	96.46	218	0.132
N	24	24		
Std.Deviation	0.933	1.414		

Table 17 Statistical comparison between basal and final SO_2 in group A.

	Basal	Final	*p* Value
SO_2 mean	94.38	96	< 0.001[a]
N	24	24	
Std.Deviation	1.377	0.933	

[a] Statistically significant = *p* value < 0.05.

Table 18 Statistical Comparison between basal and final SO_2 in group B.

	Basal	Final	*p* Value
SO_2 mean	93.33	96.46	**0.014**[a]
N	24	24	
Std. Deviation	8.365	1.414	

[a] Statistically significant = *p* value < 0.05.

Table 19 Statistical Comparison between group A and group B regarding number of cases with atopy, accessory muscle working, need for supplemental therapy and need for admission.

	Group A	Group B	$\chi 2$	*p* Value
Atopy	2	1	0.355	1
Accessory muscle working	4	1	2.000	1
Need supplemental therapy	4	1	1.020	1
Need admission	0	1	2.000	1

plains the significantly lower mean basal PEFR and significantly higher mean basal HR in group A shown in Tables 2 and 7 of our study.

Conclusion

Nebulized $MgSo_4$ has a significant bronchodilatory effect in acute bronchial asthma. This effect is however significantly less than that of nebulized salbutamol when either are used alone. The combination of $MgSo_4$ and salbutamol however can produce more superior bronchodilation.

Nebulized $MgSo_4$ improves the clinical condition in patients with acute attack of bronchial asthma reflected by increase in peak expiratory flow rate (PEFR), oxygen saturation (SO_2) and decrease in heart rate (HR) and respiratory rate (RR).

Nebulized $MgSo_4$ is well tolerated without adverse effects especially regarding HR, thus can be considered in cardiac patients.

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