

Magnesium Sulphate Nebulization versus Salbutamol Nebulization in Acute Asthmatic Attacks in Adults

Original
Article

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ABSTRACT

Background: Short acting β_2 -agonist is considered the main stay of therapy in acute asthma episodes, but it could not completely relieve the bronchospasm and reduce dyspnea. One of the other treatments is magnesium sulphate (MgSO₄). Nebulized MgSO₄ effect has been less evaluated in asthmatics.

Aim of the Work: To compare the effects of nebulized MgSO₄ in higher doses versus salbutamol nebulization in severe asthmatic attacks in adults.

Patients and Methods: Two hundreds asthmatic patients with acute severe attacks were included in an interventional study. Following initial clinical evaluation and spirometric measurements; peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV₁%) measurements, patients were divided into two equal groups; group I: nebulized salbutamol and group II: nebulized MgSO₄. Salbutamol group received salbutamol (2.5 ml) + isotonic saline (2.5 ml) while MgSO₄ group received MgSO₄ (500mg), 7.5 ml (2 mmol vial), through a jet nebulizer. The nebulization was given three times for the first two hours, 20 minutes apart, and then every hour for the remaining four hours. After that clinical reevaluation, PEF and FEV₁% measurements were done.

Results: The pre-nebulizer clinical parameters, PEF and FEV₁ were nearly similar between groups I and II: (PEF: 376.45±49.88 vs. 388.46±43.22, FEV₁%: 57.06±9.03 vs. 56.51±9.18,). The post-nebulizer PEF and FEV₁% between groups I and II were also nearly similar: (PEF: 410.98±273.82 vs. 391.24±39.81, p=0.47, and FEV₁%: 62.22±9.52 vs. 61.78±9.41, p= 0.74). However, the clinical parameters post-nebulization was different: group I developed more tachycardia, palpitation and tremors as side effects while group II develop nausea, taste changes, numbness and dizziness as a side effects.

Conclusion: Nebulized magnesium sulphate provides nearly equal response to salbutamol in the treatment of acute severe asthmatic attacks in adults.

Key Words: Acute asthma in adults, magnesium sulphate nebulization.

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INTRODUCTION

Standard treatments for acute asthmatic attacks include short acting β_2 -agonists, anticholinergics, systemic corticosteroids and supplemental oxygen. In spite of being quite effective for most patients, rapid and sustained improvement is not achieved by these treatments in a significant proportion of patients^[1]. Asthmatic attacks that are refractory to this standard therapy require additional treatment option like magnesium sulphate (MgSO₄)^[2]. While there are guidelines stating the safety and effectiveness of a single dose of intravenous MgSO₄ in adults with life threatening or acute severe asthma not responding to initial treatments, nebulized MgSO₄ has not been mentioned in these situations^[3].

Magnesium as an intracellular cation (being the 4th most abundant among body cations) is a physiological

calcium antagonist. It is, also, essential for the activation of adenylyl cyclase and more than 300 other enzymes^[4,5]. Magnesium by blocking intracellular calcium entry, activating the sodium calcium pump, and inhibiting the endoplasmic reticulum release of calcium, leads to decreased intracellular calcium with subsequent calcium and myosin interaction inhibition leading to smooth muscle cell relaxation. In addition, magnesium reduces inflammatory mediators through T cell stabilization and inhibition of mast cell degranulation. Also, magnesium inhibits acetylcholine release, depressing muscle fiber excitability. Moreover, magnesium is thought to reduce asthma severity by stimulating synthesis of nitric oxide and prostacyclin^[6,7]. Lastly, magnesium increases the bronchodilator effect of β_2 adrenergic agonists through β_2 receptors upregulation, and through the increase of the agonists affinity to their receptors^[8,9].

The advantages of the inhalation route include that it is noninvasive, with less toxicity potential, and provides targeted delivery of medication to the lower airways^[10]. Nebulized MgSO₄ gives its effect in milligrams and requires efficient aerosol delivery system like breath-enhanced nebulizer, with inhalation of the patient through a mouthpiece^[11]. In order to maximize the delivery of MgSO₄ to the airways, and avoid bronchospasm from aerosol hyperosmolarity, and hypotension due to systemic absorption, Coates *et al.*^[11], recommended nebulization of 6 mL of MgSO₄ and albuterol solution for 16 minutes, using Aeroneb Go/Idehaler nebulizer and a face mask for severe asthma treatment in children.

As regards to nebulize MgSO₄, there are scant data provided from limited numbers of studies with contradictory results^[12,27]. Therefore, the issue of effectiveness of administration of higher doses of nebulized MgSO₄ in the treatment of acute severe asthma should be explored.

AIM OF THE STUDY

To compare the effectiveness of nebulized MgSO₄ in higher doses vs. nebulized salbutamol on the clinical and respiratory function parameters especially peak expiratory flow (PEF) and forced expiratory volume in the first second (FEV1%) measurements in adults with severe acute asthmatic attacks.

PATIENTS AND METHODS

Ethical considerations

Informed written consent was taken from each participant before enrollment into the study. The study was approved by ethical committee of our institute (ADIMIRB09082018).

Inclusion criteria

Both male and female patients older than 18 years with severe acute asthmatic attack.

Exclusion criteria: Patients with chronic obstructive lung disease, chronic respiratory failure, congestive heart failure, intractable hypertension, renal and hepatic failure, arrhythmia, pregnancy, and lactation, and allergy to MgSO₄ or salbutamol were excluded from the study.

Study Design

This interventional study was carried out at emergency department (ER), Al-Azhar University hospital, New Damietta, during the period from October 2018 to July 2019. It included 200 known bronchial asthma patients presented by symptoms and signs of acute attacks according to Global Initiative for Asthma (GINA) 2018. A short medical history including illness duration, symptoms, drug history was taken. Vital signs (conscious level, temperature, heart rate, blood pressure, respiratory rate, and pulsus

paradoxus), dyspnea grade, FEV1%, PEF, arterial blood gas (ABG) parameters and C-reactive protein (CRP) were evaluated and registered. According to updated GINA 2018 criteria, the severity of asthmatic attacks was evaluated^[13]. After initial evaluation, the patients were randomly divided into two groups based on treatment they will receive. Group I patients (n=100) were treated by nebulized salbutamol (2.5 ml), diluted in isotonic saline (2.5 ml) and group II patients (n=100) were treated by nebulized MgSO₄ (500mg); 7.5 ml (2 mmol vial). Two DeVilbiss jet nebulizers (DeVilbiss Health Care, Inc., Somerset, PA) were used for the nebulization. Both salbutamol and MgSO₄ were given three times, 20 minutes apart during the first two hours, and then every hour for the next three hours. After five hours the symptoms, spirometry and ABG parameters were reevaluated. The PEF and FEV1 $\geq 70\%$ of predicted with oxygen saturation $\geq 90\%$ were considered the end point of the study and subsequently the patients were considered either improved (discharged home) or not improved (admitted to the hospital).

During the evaluation process, all patients were received immediate oxygen therapy (46- l/minute) to keep oxygen saturation above 90% to reduce hypoxic pulmonary vasoconstriction which interferes with the ventilation-perfusion mismatch that characterize severe bronchoconstriction. They, also, received IV methylprednisolone (1 mg/kg) which had been considered to decrease the hospitalisation need and days, and reduce the relapse risk. Recognition of side effects of nebulized medications by questioning and examination was done.

Spirometry

Following the standards of American Thoracic Society/European Respiratory Society^[14], and using ZAN MeBgerate GmbH D-97223 Oberthulba, Schlimpfhoferstr, Messgeraete GmbH Germany, spirometry; all patients underwent standard spirometry. Pre and post nebulization (MgSO₄ or salbutamol), special measurement of: a) FEV1%, (b) Forced vital capacity (FVC), (c) FEV1/FVC ratio, and (d) PEF were done. The spirometric indices were recorded in % predicted value.

Arterial blood gases

Heparinized blood gas syringe was used to collect an ABG specimen anaerobically and was analyzed within few minutes.

Statistical methodology

The recorded data were revised then coded to be analyzed using the IBM Statistical Package for Social Science (IBM SPSS) version 20. Qualitative variables were presented in the form of numbers and percentages, while quantitative variables with parametric distribution in the form of means \pm SD and

ranges. Comparison of qualitative data between two groups was done using Chi-square test. Quantitative variables were compared between two groups using student *t*-test. When *p*-value < 0.05, it was considered statistically significant, < 0.001: highly statistically significant, and ≥ 0.05 : non statistically significant.

RESULTS

The mean age of the patients was 52.0417.07 \pm years for group I and 50.4216.98 \pm for group II. Both studied groups were matched regarding age, sex, hypertension, diabetes mellitus, hepatic, renal or cardiac disease, or chest x-ray findings (normal or hyper inflated) (Table 1). In this study, also, there was no statistically significant difference between studied groups regarding CRP, pH, PaO₂, or SaO₂ (Table 2).

While there was no statistically significant difference between studied groups regarding clinical

and spirometric parameters in the pre-nebulization stage, there were statistically significant differences between studied groups in the post-nebulization stage: as HR, palpitation and tremors were significantly higher in nebulized salbutamol treated group (110.49, 10.20 \pm 22.0% and 15.0% respectively), compared to nebulized MgSO₄ treated group (104.8711.0%, 8.12 \pm and 0.0% respectively) [*P* value 0.001, 0.036 and 0.01 respectively]. On the other hand, nausea, taste changes, numbness and dizziness (6.0%, 6.0%, 7.0% and 7.0% respectively), were significantly higher in nebulized MgSO₄ treated group compared to nebulized salbutamol treated group [p value 0.013, 0.013, 0.007 and 0.007 respectively] (Table 3).

The effectiveness of nebulized salbutamol was 93.0% vs. 92.0% for nebulized MgSO₄ (*p* = 0.78), accordingly, there was no statistically significant difference between both (Table 3).

Table 1: Comparison of age, sex, co morbidities, and chest-x-ray findings between both studied groups

Variable		Salbutamol	MgSO ₄	Total	Test	<i>p</i> value
Age	Mean \pm SD	52.04 \pm 17.07	50.42 \pm 16.98	51.23 \pm 17.00	0.67	0.51
	Range	19 -84	19-84	19-84		
Sex	Male	81 (81.0%)	82 (82.0%)	163 (81.5%)	0.03	0.85
	Female	19 (19.0%)	18 (18%)	37 (18.5%)		
Hypertension		60 (60.0%)	56 (56.0%)	116 (58.0%)	0.32	0.56
Diabetes mellitus		66 (66.0%)	64 (64.0%)	130 (65.0%)	0.08	0.76
Hepatic disease		22 (22.0%)	16 (16.0%)	38 (19.0%)	1.17	0.27
Renal disease		14 (14.0%)	12 (12.0%)	26 (13.0%)	0.17	0.67
Cardiac disease		14 (14.0%)	16 (16.0%)	30 (15.0%)	0.15	0.69
Chest x-ray	Normal	41 (41.0%)	45 (45.0%)	86 (43.0%)	0.32	0.56
	Hyper inflated	59 (59.0%)	55 (55.0%)	114 (57.0%)		

*Statistical significance was defined as $p \leq 0.05$. MgSO₄: magnesium sulphate

Table 2: Comparison of C-reactive protein and arterial blood gases indices between both studied groups

		Mean \pm SD	Range	Test	<i>p</i> value
CRP	Salbutamol	19.68 \pm 12.56	6.00 - 48.00	1.81	0.07
	MgSO ₄	16.68 \pm 10.81	6.00 - 48.00		
pH	Salbutamol	7.41 \pm 0.11	7.23 - 7.58	0.17	0.84
	MgSO ₄	7.41 \pm 0.11	7.25 - 7.58		
PaO ₂	Salbutamol	68.20 \pm 9.64	31.00 - 90.00	1.47	0.14
	MgSO ₄	70.08 \pm 8.35	31.00 - 88.00		
PaCO ₂	Salbutamol	31.00 \pm 4.68	20.0 - 42.0	0.95	0.34
	MgSO ₄	30.44 \pm 2.14	25.0 - 41.0		
SaO ₂	Salbutamol	90.66 \pm 4.73	77.00 - 98.00	1.03	0.30
	MgSO ₄	91.36 \pm 4.83	77.00 - 98.00		

*Statistical significance was defined as $p \leq 0.05$.

Table 3: Comparison of effects and side effects of nebulized salbutamol and nebulized magnesium sulphate in both studied groups

Item	Pre-nebulization			Pre-nebulization		
	Salbutamol	MgSO ₄	<i>P value</i>	Salbutamol	MgSO ₄	<i>P value</i>
HR Mean ±SD	104.68±10.32	104.65±7.75	0.98	110.4±910.20	104.8±78.12	0.001*
RR Mean± SD	28.42±2.36	28.93±2.42	0.13	25.78±3.04	25.46±1.70	0.36
FEV1/FVC	57.29±9.44	55.70±5.65	0.15	85.58±7.95	84.77±5.19	0.39
FEV1 % Mean± SD	57.06±9.03	56.51±9.18	0.67	62.22±9.52	61.78±9.41	0.74
PEF Mean ±SD	376.45±49.88	388.46±43.2	0.07	410.98±273.8	391.24±39.8	0.47
Palpitation No. (%)	13(13.0%)	14(14.0%)	0.83	22(22.0%)	11(11.0%)	0.036*
Nausea No. (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	6(6.0%)	0.013*
Dyspnea No. (%)	13(13.0%)	15(15.0%)	0.68	10(10.0%)	8(8.0%)	0.62
Tremors No. (%)	0(0.0%)	0(0.0%)	-	15(15.0%)	0(0.0%)	0.001*
Taste No. (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	6(6.0%)	0.013*
Numbness No. (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	7(7.0%)	0.007*
Dizziness No. (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	7(7.0%)	0.007*
Cough No. (%)	13(13.0%)	15(15.0%)	0.68	10(10.0%)	8(8.0%)	0.62
Knee jerk No. (%)	0(0.0%)	0(0.0%)	-	0(0.0%)	2(2.0%)	0.15
Outcome No. (%)	Improved (discharged home)			93(930%)	92(92.0%)	0.78
	Not improved (hospital admission)			7(7.0%)	8(8.0%)	

*Statistical significance was defined as $p \leq 0.05$.

MgSO₄: magnesium sulphate; HR: heart rate; RR: respiratory rate; FEV1:forced expiratory volume in first second; FVC: forced vital capacity; PEF: peak expiratory flow

DISCUSSION

Our study revealed that in severe asthmatic attacks MgSO₄ nebulization in higher doses is as effective as salbutamol-saline nebulization. The improvement in clinical, PEF, FEV1%, and ABG parameters were nearly similar between both groups. Although side effects had happened with both groups as palpitation (22%) and tremors (15%) were higher in nebulized salbutamol treated group, and nausea (6%), taste changes (6%), numbness (7%) and dizziness (7%) were higher in nebulized MgSO₄ treated group, accordingly both drugs are well tolerated by the patients. In agreement with our results, Sun *et al.*^[15], concluded that nebulized MgSO₄, used alone, had a bronchodilator effect in acetylcholine induced asthma in children. Kew *et al.*^[16], concluded that inhaled magnesium consequential in improvement of severe asthma attacks, but highlight that limited improvement could be related to severe airway obstruction. Inhaled magnesium is thought to induce its bronchodilating effect through reduction of the bronchial hyperreactivity induced by methacholine and reduction of histamine release^[17,18]. Additionally, Meral *et al.*^[19], concluded that while nebulized MgSO₄ improved PEFR nearly in five minutes in asthmatic attacks in adults, it lasted up to one hour in asthmatic attacks of children.

Moreover, Mohammadzadeh *et al.*^[20], compared MgSO₄ as a vehicle to nebulized salbutamol versus

nebulized salbutamol-saline in severe asthmatic attacks in children and concluded that nebulized MgSO₄ plus salbutamol was more effective. In addition, Akter *et al.*^[21], found that nebulization with the combination provided early and better response than salbutamol alone. Their finding can be explained by that the use of magnesium in adjunction to nebulized salbutamol may increase β -receptors affinity to agonists or upregulate the receptors, thus augmenting the bronchodilator effect of salbutamol. In contrast, Bessmertny *et al.*^[22], and Kokturk *et al.*^[12], showed no added benefit from adjunction of magnesium to salbutamol. In addition, nebulized salbutamol was shown by a study to provide longer bronchodilation effect up to six hours^[19].

The dose of nebulized magnesium varied significantly between different studies. A dose-response study found no difference between (90/ 135/ 180/ 360 mg) doses and placebo on respiratory function^[23], indicating that even if nebulized magnesium is beneficial, its dose remains unclear^[24]. Goodacre *et al.*^[25], reviewed nebulized magnesium trials in adults and children and concluded that the dose of MgSO₄ ranged from 95 - 500 mg, repeated up to four times, 2030- minutes apart. However, these studies did not provide evidence for the role of nebulised MgSO₄ in acute asthma. According to Shan *et al.*^[2], nebulized MgSO₄ in adults was shown by 8 studies to be associated with significant improvement of respiratory function and reduction

of hospital admission. However, nebulized MgSO₄ in children, in one study, showed no significant effect on the respiratory function. This difference between the effect of nebulized MgSO₄ in adults and in children might be explained by the difference in doses used, or in the smooth muscle susceptibility to MgSO₄^[2].

According to Rady *et al.*^[26], intravenous and nebulized MgSO₄ had beneficial effects in the treatment of infants and children with wheezy chest, due to asthma or other diseases, who were critically ill. Su *et al.*^[27], in their systematic review discussed the efficacy of MgSO₄ (IV or nebulized) for acute asthmatic attacks in children, and concluded that IV MgSO₄ was effective in improving pulmonary functions, decreasing hospitalization, and the need for other treatments, while nebulized magnesium showed no significant effect. However, the limitations of these results were the small sample size, and may be use of small doses of nebulized MgSO₄.

The limitations of this study include: PEFr has poor reproducibility and highly effort dependent.

Conclusion and recommendation: Higher doses of MgSO₄ (500mg) nebulization is effective as salbutamol nebulization in the treatment of acute asthmatic attacks in adults in the form of improvement of clinical, spirometric indices, and ABG parameters. However, the side effects of both drugs were significantly different as tachycardia, palpitation and tremors were common in salbutamol nebulization, while nausea, taste changes, numbness and dizziness were common in MgSO₄ nebulization. Therefore, if the patient with acute asthmatic attack is at higher risk for side effects of one drug, the other drug is recommended.

FINANCIAL SUPPORT

No financial support

CONFLICTS OF INTEREST

There are no conflicts of interest

Abbreviations

MgSO₄: Magnesium Sulphate, GINA: Global Initiative for Asthma, ABG: Arterial Blood Gases, PEF: Peak Expiratory Flow, FEV₁: Forced Expiratory Volume in the first second.

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المخلص العربي

دراسة مقارنة استنشاق مادة ماغنسيوم سلفات والساليوتامول في نوبات الحساسية الشديدة في البالغين

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الخلفية: يعتبر المادة المنبه للبيتا ٢ أهم دواء في نوبات الحساسية لذا هل يعتبر مادة الماغنسيوم سلفات موسع للشعب ويقلل النهجان وتفايدي الأثار الجانبية للساليوتامول حيث تم استخدام مادة الماغنسيوم سلفات كعلاج وريدي في نوبات الحساسية المقاوم للعلاج لكن الاستنشاق لم يستخدم من قبل أال قليل لكن جرعاته تستخدم بالمليجرامات عكس الآخرين يستخدم بالميكروجرام.

الغرض من البحث: مقارنة استنشاق مادة ماغنسيوم سلفات والساليوتامول في نوبات الحساسية الشديدة في البالغين. **طريقة البحث:** تم تقسيم المرضي الي مجموعتين كل مجموعة تحتوي علي ١٠٠١ مريض يعني من نوبة حساسية حسب الجينا ١٠٢ ٨١ وتم أخذ التاريخ المرضي وفحصه وعمل وظائف تنفس وغازات بالدم وتم اعطاء المجموعة الأولي استنشاق ساليوتامول (٢.٥ ملي ساليوتامول + ٢.٥ ملي محلول ملح) والمجموعة الثانية ماغنسيوم سلفات (٠.٥ مجم ماغنسيوم سلفات + ٧.٥ ملي محلول ملح) وكان استخدامه ثلاثة مرات في الساعة ثم كل ساعة ولمدة اربع ساعات ثم يتم اعادة تقييم المريض.

النتائج: كان ال يوجد فروق احصائية بين المرضي في وظائف التنفس قبل وبعد الاستنشاق مما يدل علي أن الدواء ان مثل بعضهم لكن الأثار الجانبية في المجموعة الأولي (سرعة ضربات القلب - الرعشة) كانت أكثر أما الغثيان والتنميل

والدوخة كانت في المجموعة الثانية أكثر.

الاستنتاجات: استخدام مادة ماغنسيوم سلفات يؤدي نفس كفاءة مادة الساليوتامول في نوبات الحساسية الشديدة في

البالغين.