Nebulized Magnesium Sulfate in Acute Moderate to Severe Asthma in Pediatric Patients

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Abstract—A prospective double-blind placebo controlled trial carried out on 60 children known to be asthmatic who presented to the emergency department at Alexandria University of Children's Hospital at El-Shatby with acute asthma exacerbations to assess the efficacy of adding inhaled magnesium sulfate to β-agonist, compared with β-agonist in saline, in the management of acute asthma exacerbations in children. The participants in the study were divided in two groups; Group A (study group) received inhaled salbutamol solution (0.15 ml/kg) plus isotonic magnesium sulfate 2 ml in a nebulizer chamber. Group B (control group): received nebulized salbutamol solution (0.15 ml/kg) diluted with placebo (2 ml normal saline). Both groups received inhaled solution every 20 minutes that was repeated for three doses. They were evaluated using the Pediatric Asthma Severity Score (PASS), oxygen saturation using portable pulse oximetry and peak expiratory flow rate using a portable peak expiratory flow meter at initially recorded as zero-minute assessment and every 20 minutes from the end of each nebulization (nebulization lasts 5-10 minutes) recorded as 20, 40 and 60-minute assessments. Regarding PASS, comparison showed non-significant difference with p-value 0.463, 0.472, 0.0766 at 20, 40 and 60 minutes. Regarding oxygen saturation, improvement was more significant towards group A starting from 40 min with significant p-value=0.000. At 60 min p-value=0.000. Although mean PEFR significantly improved from zero-min in both groups; however, improvement was more significant in group A with significant p-value = 0.015, 0.001, 0.001 at 20 min, 40 min and 60 min, respectively. The conclusion this study suggests is that inhaled magnesium sulfate is an efficient add on drug to standard β- agonist inhalation used in the treatment of moderate to severe asthma exacerbations.

Keywords—Nebulized, magnesium sulfate, acute asthma, pediatric.

I. INTRODUCTION

ASTHMA causes significant morbidity and mortality worldwide in children [1]. Asthma is affecting up to 10% of adults and 30% of children in the western world [2]. Severe acute asthma exacerbation is a medical emergency that must be quickly diagnosed and treated [3]. Patients with moderate/severe persistent asthma who had exacerbations had higher total and asthma-related health care costs than those without exacerbations [4]. Asthma exacerbation should be classified first as mild, moderate, severe or life threatening and managed according to that by immediate care, and close

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repeated measurement of lung function [5]. Emergency management of asthma includes supplemental oxygen, administration of short acting beta-2 agonists (SABA) and systemic corticosteroids (CS) to maintain oxygen saturation, decrease obstruction and prevent future relapses [6].

Administration of intravenous theophylline, β-agonists and magnesium sulfate may be used in selected cases [5]. The use of magnesium sulfate intravenously during acute exacerbation showed improvement in the treatment of moderate to severe asthma in children, although still there is currently no overall clear understanding of the role of inhaled magnesium sulfate [7], [8].

This study focused on the assessment of the efficacy of adding inhaled magnesium sulfate to β-agonist in the management of moderate to severe acute asthma exacerbations.

II. MATERIAL AND METHODS

A. Study Design

The study was carried out during the period from May to December 2015. About 150 where examined, only 60 involved as 90 did not fit the inclusion criteria.

The children included in the study were divided randomly in two groups; Group **A** (Study group): included 30 asthmatic children who received inhaled salbutamol solution (Farcolin respirator solution, PHARCO, Alexandria, Egypt), (0.15 ml/kg) plus isotonic magnesium sulfate (magnesium sulfate, EIPICO, Alexandria, Egypt (2 ml) in a nebulizer chamber.

Group B (Control group). Included 30 asthmatic children who received inhaled salbutamol solution (Farcolin respirator solution, PHARCO, Alexandria, Egypt), (0.15 ml/kg), diluted with placebo (normal saline, Haidyl, Alexandria, Egypt) 2ml.

Each patient received an inhaled solution using nebulizer mask that lasts for 5-10 minutes. Inhalation was repeated for three doses. Assessment was done before starting treatment and recorded as zero-minute assessment then every 20 minutes from the end of the inhalation (neglecting time of inhalation) and repeated after each session recorded at 20, 40 and 60 minute assessments.

B. Sample Size

Sample size was calculated using PASS program version 14. PASS 14 Power analysis and Sample Size Software (2015). Group sample sizes of 50 patients with acute exacerbation of asthma (25 patients per each group) achieve 81% power.

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C. Inclusion Criteria

– Children diagnosed as asthmatic in accordance to the Global Initiative for Asthma (GINA) guidelines [4].
– Age 5-14 years old of both genders that are capable of measuring PEFR.
– Asthmatic children presented by moderate to severe acute exacerbation according to the PASS and PEFR.

D. Exclusion Criteria

– Severely ill patients requiring immediate hospital care.
– Any evidence of bacterial infection that can worsen asthma.
– Any history of associated serious chronic disease (cardiac, renal or hepatic dysfunction).
– Use of bronchodilator within 8 hours.
– Use of systemic steroids within 72 hours.
– Children known to have immunodeficiency.
– History of previous asthmatic attacks managed by ICU admissions.

All participating patients continued in the study. Every patient's record included information with special emphasis on:

– Age, gender.
– Personal history of other allergies.
– Past histories of previous severe attacks and its management.
– Family history of asthma.
– Social history: Smoking parents, living near industrial factories, as well as socioeconomic level.

E. Clinical Examination

A clinical examination was done with regards to vital signs (pulse, blood pressure, respiratory rate and temperature), signs of respiratory distress (retractions, working accessory muscles, level of consciousness, cyanosis,) as well as local chest findings, including the PASS.

Recording of PEFR at zero, 20, 40 and 60 minutes was done (when age and condition allowed) to assess the initial severity and degree of improvement. The average of the best three readings was recorded using a handheld Peak Flow Meter (Omron -PFM20).

The children were instructed to use the handheld Peak Flow Meter as follows: Inhale as deeply as possible holding in all the air while placing the lips tightly around the sterile mouth piece, and without:

– Coughing.
– Valsalva (glottis closure).
– Early termination of expiration.
– Leak.
– An unsatisfactory start of expiration characterized by excessive hesitation or false start.
– Obstructed mouth piece due to tongue.

A handheld pulse oximetry (Jumper, JPD-500A) was used to evaluate the improvement of oxygen saturation with treatment at zero, 20, 40 and 60 minutes.

F. Method of Preparation

– Identical bottles were labeled serially from one-60, each bottle contained 13 ml of solution (either saline or magnesium sulfate).
– A coding sheet was used to distribute the bottles to the two groups, either the solution with isotonic magnesium sulfate or with normal saline.
– Salbutamol was given 15ml/kg with 2ml from a bottle that contained either normal saline or isotonic magnesium sulfate.
– The coding sheet was seen only at the time of data analysis (the study was double blind).

G. Ethical Consideration

The protocol of the study was approved by the Ethical Committee, Alexandria University, Egypt. Its local serial number is 01028032 approved March 2016. It complies with the Helsinki declaration. ISRCTN 61336225 registered as a retrograde study.

H. Statistical Methods

Statistical analysis was done using IBM SPSS statistics program version 21. Quantitative data were described by mean and median as measures of central tendency and standard deviation, and range as measures of dispersion. Statistical comparisons of continuous variables were carried out using either student's t-test or the Wilcoxon rank-sum test depends on data distribution by Kolmogorov–Smirnov (K-S) test. Statistical comparisons of continuous variables measured at different time periods was done by either repeated measures ANOVA test or Friedman test depending on the data distribution given by the K–S test.

III. RESULTS

The study consisted of 24 males and 36 females, ranging in age from 5 years to 11 years, with a mean of 7.283 ± 1.7907 years. The participants were divided into two groups: Group A (study): included 30 children who were treated with inhaled salbutamol solution diluted with isotonic magnesium sulfate (2 ml) in a nebulizer chamber and Group B (control), which included 30 children who were treated with inhaled salbutamol solution diluted with placebo (normal saline 2ml).

Table I shows the personal characteristics of the patients of the two groups: the differences between the groups regarding age, weight and height, were not statistically significant.

TABLE I
PERSONAL CHARACTERISTICS OF STUDIED PATIENTS

	Group A (Study) (n=30)	Group B (Control) (n= 30)		P value
Mean Age (years)	7.400 ±1.6836	7.167±1.9134	t=0.501	0.618
Male / Female	11/ 19	13/17	X^2=0.278	0.598
Mean Weight (kg)	27.550±6.6051	27.400±8.0026	t=0.079	0.937
Height (cm)	124.667±9.0528	121.233±11.4521	t=1.288	0.203

Data presented as mean ±standard deviation (SD), t = student t-test, X2 = chi-square test.
p< 0.05 significant.

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Table II shows the comparison between Group A (study group) and Group B (control group) regarding the clinical score for asthma severity during the observation period after treatment. The comparison showed no significant difference with p-values 0.996, 0.463, 0.472, 0.0766 at zero, 20, 40 and 60-minutes assessment, respectively.

TABLE II
PASS TOTAL SCORE OVER TIME

	Group A (Study) (n= 30)	Group B Control (n= 30)	t	p-
PASS total score 0 min	7.433±1.0400	7.233±9353	-0.001	0.996
PASS total score 20 min	5.667±1.4933	5.967±1.6501	0.738	0.463
PASS total score 40 min	4.200±1.7889	4.533±1.7760	-0.724	0.472
PASS total score 60 min	2.567±1.5687	3.433±2.1121	1.80	0.076

Data presented as mean ±standard deviation (SD) used t-test and $p < 0.05$ significant.

TABLE III
OXYGEN SATURATION ASSESSMENT DURING THE OBSERVATION PERIOD AND AFTER TREATMENT IN STUDIED PATIENTS

	Group A (Study) (n= 30)	Group B Control (n= 30)	t	p- value
SaO_2 0 min	90.400±1.5447	90.200±1.2149	-0.557	0.579
SaO_2 20 min	94.367±2.4280	93.067±3.3726	1.713	0.092
SaO_2 40 min	95.967±1.3257	93.833±2.6533	3.939	0.000
SaO_2 60 min	97.467±0.8604	95.033±2.2512	5.530	0.000

Data presented as mean ±standard deviation (SD)
$p < 0.05$ significant, t = student t-test

Table III shows comparison between group A (study group) and group B (control group) in oxygen saturation assessment during the observation period after treatment at 20, 40, 60 minutes from initial assessment. The p-value was reached by unpaired student t-test. At 20 mins: SaO2 was 94.367±2.4280 in Group A and 93.067±3.3726 in Group B and the p-value=0.092, which means it was not significant between both groups. At 40 mins: SaO2 was 95.967±1.325793 in Group A and 93.833±2.6533 in Group B and p-value=0.000, which means it was significant. At 60 mins: SaO2 was 97.467±.8604 in Group A and 95.033±2.2512 in Group B and p-value=0.000, which means it was significant.

Table IV shows a comparison between Group A (study group) and Group B (control group) in the PEFR assessment during the observation period after treatment at 20, 40, 60 minutes from initial assessment. It indicates that mean PEFR improvement over time was more significant in Group A. The p-value was reached by unpaired student t-test. At 20 mins: PEFR was 165.9890±38.8426 in Group A and 141.7780± 35.57603 in Group B and p-value=0.015, which means it was significant. At 40 min: PEFR was 181.5557±39.6994 in Group A and 146.5567±36.57195 in Group B and p-value=0.001, which means it was significant. At 60 mins: PEFR was 206.6673±41.3100 in Group A and 168.1100±41.31688 in Group B and p-value=0.001, which means it was significant.

Fig. 1 shows that PEFR was improved in both groups. But in Group A (study group), there was better improvement.

TABLE IV
PEFR ASSESSMENT DURING THE OBSERVATION PERIOD AFTER TREATMENT IN STUDIED PATIENTS

	Group A (Study) (n= 30)	Group B Control (n= 30)	t	P
PEFR 0 min	138.9997±32.3907	127.5239±28.1931	-1.464	0.149
PEFR 20 min	165.9890±38.8426	141.7780±35.57603	2.518	0.015
PEFR 40 min	181.5557±39.6994	146.5567±36.57195	3.551	0.001
PEFR 60 min	206.6673±41.3100	168.1100±41.31688	3.615	0.001

Data presented as mean ±standard deviation (SD)
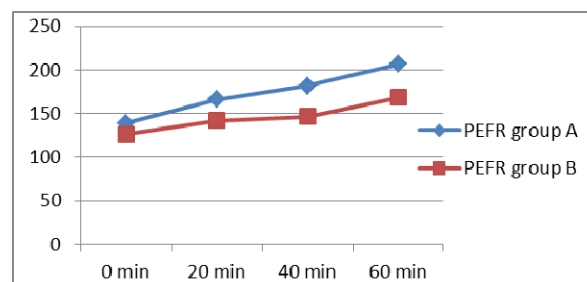$p < 0.05$ significant, t = student t-test

Fig. 1 Repeated measures of PEFR in MgSO4 and saline chart

Out of 30 cases, 13 patients in Group A (study group) required systemic steroids and intravenous magnesium sulfate, while in Group B, about 17 cases required systemic steroids and intravenous magnesium sulfate. The chi-square statistic was 3.09 and THE p-value was 0.787 which was not significant. All cases from Group A (study group) were discharged home with follow up schedule as recommended by GINA. The 26 cases from Group B (control group) were discharged home with a follow up schedule, while four cases were admitted to a ward for further management, as recommended by GINA. The chi-square statistic was 1.66 and p-value was 0.197, which was not significant.

IV. DISCUSSION

The role of magnesium sulfate in the treatment of asthma has been studied over many years. Blitz et al. studied the role of Nebulized inhaled magnesium sulfate in addition to β agonist in the treatment of acute asthma exacerbation, while Torres et al. studied the role of intravenous infusion of magnesium sulfate during the first hour of hospitalization. Both included randomized or pseudo-randomized trials in patients presenting with acute asthma. Both found that magnesium appeared to have benefits with respect to improved pulmonary function in patients with severe asthma and there was a trend towards benefits in hospital admissions [8], [9].

The potential clinical benefits of inhaled MgSO4 have been studied and research publications have produced conflicting results [9]. Powell et al. recommended further studies to focus on inhaled MgSO4 in addition to the current guideline treatment for acute asthma [10].

This study used standard therapy protocol in severe exacerbations of asthma and examined the efficacy of adding inhaled MgSO4 to β-agonist inhalation in a double blind study of 60 children with acute severe asthma exacerbation who

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were divided into two groups; Group A (study group) included 30 cases who received inhaled salbutamol with 2 ml of magnesium and Group B (control group) which included 30 children who received inhaled salbutamol with 2ml of saline In this study; we used a clinical score (PASS) , pulse oximetry reading and handheld peak flow meter assessment as separate items to assess asthma severity concisely and to avoid miss scoring. Assessment was done initially then repeated every 20 minutes (at zero, 20, 40 and 60 minutes) to see the effect of three doses of nebulization from the start point as recommended for initial acute asthma management. Other investigators assessed the effect of nebulization by different intervals. Haqq et al. reported that in practice, the first measurement should not be taken earlier than 15-20 minutes from the start point. His study assessed patients every 10 minutes [11], while Akter et al. assessed them every 20 minutes [12].

With a non-significant baseline difference in both study groups regarding the clinical score, oxygen saturation and PEFR, this study illustrated that there was a linear improvement in the clinical score, oxygen saturation and PEFR from zero mins and with each 20 min assessment up to 60 mins in both groups, but more significant towards Group A. Regarding the clinical score, the results of the current study showed better improvement towards the magnesium group with p=0.015, 0.001, 0.001 at 20, 40 and 60 minute assessment, respectively, which is in agreement with the findings of the study by Zadeh et al. (used pulmonary index for evaluation of the clinical condition) that showed improvement in clinical assessment towards the magnesium group with p=0.000 [13].

Oxygen saturation assessment showed better improvement in Group A (study group) with p=0.092, 0.000, 0.000 at 20, 40 and 60-minute assessment, respectively, which is consistent with the study of Akter et al. that included children from 6-12 years that showed p >0.05 at 20-minute assessment and <0.05 at 40-minute and 60-minute assessments, respectively [12]. Our study showed that the mean PEFR was significantly better in Group A than in Group B at 20, 40 and 60-minute assessment. This is consistent with Haqq et al. (2006), who concluded that combining magnesium sulfate solution 2ml with salbutamol for nebulization, resulted in early response and great improvement in PEFR [11], [12].

Sun et al. concluded that the combination of MgSO4 and albuterol did not have a synergistic effect. Although the study was conducted on 330 children, asthma attack was induced by acetylcholine and did not include a severe form, and also, assessment was done at 10 minutes and 20 minute intervals only [14]. Almost no side effects were recorded in the present study. This confirms the conclusions of the study by Shan Z et al. Considering the low risk of serious side effects from magnesium sulfate and the readily availableness of it, it would seem reasonable to use intravenous and nebulized magnesium sulfate to treat patients with severe life-threatening asthma attacks [15]. Inhaled drugs are given in a lower dose than is necessary with systemic delivery (oral or injection), and thus have fewer and less severe adverse effects [16].

The study of Watanatham et al. demonstrated similar safety and clinical benefits of nebulized and intravenous MgSO4 among children and adults suffering from severe asthmatic attacks, with no recorded side effects following nebulizer or intravenous magnesium [17]. The discharge rate in Group A (study group) was better than Group B (control group). All patients in Group A were discharged, while four in Group B were in need of ward admission and p-value was 0.197 (non-significant).

In conclusion, this study suggested that using magnesium sulfate as an additive to β- agonist showed more significant improvement in clinical scores, and oxygen saturation and PEFR more than saline. This conclusion is also consistent with the findings of [18], [19] and meta-analysis [20], [15].

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