ORIGINAL ARTICLE

Effectiveness of Nebulized Magnesium Sulphate as an Adjuvant Therapy (With Salbutamol) in the Management of Acute Asthma

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ABSTRACT

Background: Although the treatment of acute asthma in the emergency department varies, the administration of magnesium sulfate ($MgSO_4$) is usually recommended adjacent to corticosteroids and bronchodilators. This study aims to ascertain the influence of inhaled $MgSO_4$ as complement treatment with salbutamol regarding treatment of urgent asthma exacerbations.

Methods: A single-blind randomized control study was carried out, from 1st January 2017 to 30th June 2017, involving asthmatic patients presenting to Ziauddin Hospital and Jinnah Hospital in Karachi, with severe acute asthma exacerbations. The Sealed Envelope calculator was used to calculate a sample size of 84 patients, and data was collected through non-probability consecutive sampling. Both batches were administered salbutamol and ipratropium, with Batch A patients also receiving nebulization with $MgSO_4$. Dyspnea, respiratory rate, pulse, peak expiratory flow rate, and oxygen saturation were recorded for each participant. An independent sample t-test was used to assess the effectiveness of $MgSO_4$, as a significant means of improving asthma treatment, with a $p<0.05$ interpreted as significant.

Results: A sum of 115 patients was included in the research, out of which 63.5% had a family history of asthma. Treatment with $MgSO_4$ was seen as significant ($p<0.01$). $MgSO_4$ administration showed significant improvement in mean pulse rate ($p = 0.001$), peak expiratory flow rate ($p = 0.004$) and mean respiratory rate ($p = 0.003$), as compared to treatment with salbutamol only.

Conclusion: Treatment outcomes between the two groups differed significantly. Intervention with $MgSO_4$ showed significant improvement in pulse rate, respiratory rate, dyspnea, and peak flow, without any observed side effects.

Keywords: Asthma; Magnesium Sulfate; Dyspnea; Expiratory Peak Flow Rate.

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doi.org/10.36283/PJMD9-2/008

INTRODUCTION

Asthma is a chronic respiratory condition that leads to difficulty breathing and can precipitate coughing, chest tightness and shortness of breath. In recent decades, its prevalence has increased dramatically and it is now acknowledged as a significant inducer of medical expense, disability, and mortality[1]. Developed countries have 5% prevalence of asthma and of the asthmatics presenting at emergency departments (ED), 27% require admission. This is despite the conventional medical treatment with beta-adrenergic agonists, anticholinergic and corticosteroids[2]. In Pakistan,

the asthma prevalence is 10% in adults and 20% in children[3].

Although the treatment of acute asthma in the ED varies, the administration of magnesium sulfate ($MgSO_4$) is usually recommended adjacent to corticosteroids and bronchodilators[4]. $MgSO_4$ is anti-inflammatory, promotes bronchodilation, and is presently a popular therapy in EDs, with more than 80% of patients with severe, life-threatening asthma having undergone the treatment[5-7]. However, few studies have been conducted on the effectiveness of $MgSO_4$ on asthmatic patients and the literature so far is inconclusive. Some studies have found a higher mean forced expiratory volume percentage (FEV %) and overall improved pulmonary functions among those managed with $MgSO_4$, in contrast to the reference group [8]. However, a recent review found only marginal benefits of $MgSO_4$ on pulmonary functions [9], while other studies found no improvement in its incorporation at all[10]. We, therefore, aimed to assess and compare treatment with salbutamol alone and with the addition of $MgSO_4$, and to evaluate the influence of each treatment on the respiratory functions of asthmatic patients.

METHODS

A single blind, randomized control study was carried out for six months at the ED of Ziauddin Hospital and the Pulmonology department at Jinnah Hospital in Karachi. The Ethics Committee of Ziauddin Hospital and Jinnah Hospital approved the study with the reference code (0010116GAEM).

Patients, 18 to 60 years of age, who came to the ED with severe acute asthma exacerbations, and who were willing to participate in the study after informed consent, were included in the study that was conducted from 1st January 2017 to 30th June 2017. Patients were labeled with acute asthma if they had a previous history of asthma and presented with any two of the following; dyspnea at rest or exertion, respiratory rate (RR) > 25/min, and PEFR <80% of predicted. We did not include patients with any of the following conditions; near-fatal asthma, fever >99°F, other respiratory disorders such as bronchiectasis and tuberculosis, a history of pulmonary or thoracic surgery, current smokers, chronic diseases like hypertension. Breastfeeding or pregnant patients, patients taking systemic steroids, patients using dietary supplements with $MgSO_4$ and patients with hypersensitivity to $MgSO_4$ were also excluded from the study.

The principal investigator started data collection after taking informed written consent from the eligible patients. Peak expiratory flow rate (PEFR) was recorded using a peak expiratory flow meter, and modified Medical Research Council (mMRC) Dyspnea Scale was used to measure dyspnea. The RR of each participant was also recorded (baseline at 0 minutes and final at 120 minutes). Readings were registered using a portable PEFR, while the NHANES III prediction equations were utilized to calculate predicted values[11]. Since, 84 patients were randomly divided into group, A which received $MgSO_4$ treatment, and group B that stood as the placebo group. All asthmatic participants were initially administered IV hydrocortisone, 100 mg, and thereafter tended to in accordance with the subsequent protocol.

Both groups received salbutamol and ipratropium (2.5 ml of 2.5% and 250 mg of 1.5 ml respectively) administered in normal saline (2.5 ml) via wet nebulizer with 100% oxygen at 0, 20 and 40 minutes after initiation. After half an hour, group A patients received nebulization with 333 mg of 10% isotonic $MgSO_4$, whereas group B patients were given the placebo i.e. nebulization with normal saline. The PEFR and clinical findings of a respiratory exam were documented at four 30-minute intervals, starting from the 0-minute mark. The staff in the ED, blinded about the patient and group assignment, would then decide whether to discharge or hospitalize the patient, at the 120 minute mark. Name, age, gender, residence, family history of asthma, duration of disease, previous history of asthmatic exacerbations was recorded for each patient. Further data on the pulse rate (HR), blood pressure (BP), RR, oxygen saturation (SaO_2), and PEFR was also noted at 30-minute intervals. The primary outcome variable was to determine improvement in PEFR.

Data was entered on SPSS version 20 and descriptive analysis was done. Effectiveness of salbutamol with and without nebulized $MgSO_4$ was labeled 'positive' and 'negative' respectively (on the basis of the criteria given with effectiveness at 120 minutes) and associated with a mean improvement in PEFR clinical status. A student's t-test was applied to compare the improvement regarding the two batches, before and after treatment, with a p-value less than 0.05 interpreted as significant.

RESULTS

The study involved 115 patients of which 60 made up the intervention group and 55 made up the non-intervention group. From these groups 64 were females and 51 were males. A family history of asthma was noted in 63.5% (n = 73) of the participants and acute exacerbations occurred in 88.7% (n = 102) of them. No side effects of $MgSO_4$ use were observed in the patients involved in the study.

Table 1 illustrates a comparison between the two groups, through the independent sample t-test,

 doi.org/10.36283/PJMD9-2/008

with RR, HR, PEFR, and paO_2 assessment after treatment at baseline and 30-minute intervals. Mean RR improvement overtime was more significant in the intervention group. At 60 minutes RR was calculated to be 30.33 in the $MgSO_4$ category and 32.38 in the comparison category (p = 0.01). At 90 minutes RR was 29.28 in the $MgSO_4$ category and 32.91in the comparison category (p = 0.007) and at 120 minutes RR was 27.40 in the $MgSO_4$ category and 32.16 in the comparison category (p=0.003).

Table 1: Comparison of respiratory rate, pulse rate, PEFR and paO2 over time in both groups.

Parameters		$MgSO_4$ Group (n=60)		Comparison Group (n=55)		p-Value
		$\tilde{x}$	σ	$\tilde{x}$	σ	
Respiratory Rate	**RR at presentation**	31.72	4.12	32.61	5.54	0.322
	RR at 30 minutes	32.12	5.21	33.22	5.33	0.265
	RR at 60 minutes	30.33	4.04	32.38	5.38	0.010*
	RR at 90 minutes	29.28	5.19	32.91	6.51	0.007*
	RR at 120 minutes	27.40	8.23	32.16	8.33	0.003*
Pulse Rate	**Pulse at presentation**	120.51	15.36	122.05	19.91	0.646
	Pulse 30 minutes	119.23	13.89	120.20	24.47	0.798
	Pulse 60 minutes	116.40	13.26	122.24	18.27	0.055
	Pulse at 90 minutes	114.37	14.49	120.56	23.59	0.097
	Pulse at 120 minutes	109.87	13.53	122.11	23.49	0.001*
PEFR	**PEFR at presentation**	61.50	8.987	58.55	10.077	0.099
	PEFR at 30 minutes	71.33	13.712	71.09	11.812	0.920
	PEFR at 60 minutes	108.17	32.806	74.55	19.703	<0.001*
	PEFR at 90 minutes	137.33	35.695	72.73	13.396	<0.001*
	PEFR at 120 minutes	189.33	47.044	103.31	42.392	<0.001*
SaO_2	**SaO_2 at presentation**	89.73	7.44	91.25	1.69	0.142
	SaO_2 at 30 minutes	89.85	7.38	91.36	1.71	0.141
	SaO_2 at 60 minutes	90.48	7.50	91.36	1.44	0.394
	SaO_2 at 90 minutes	90.62	7.49	91.98	2.09	0.194
	SaO_2 at 120 minutes	91.33	7.46	92.15	2.45	0.443

**Data presented as mean (x) ± standard deviation (σ) used t-test and p < 0.05 as significant Abbreviations: RR=Respiratory Rate, /PEFR = Peak Expiratory Flow Rate, SaO_2 = oxygen saturation of arterial blood.*

With reference to HR, there is no statistically significant change was observed at baseline 30, 60 and 90 minutes but at 120 minutes HR was 109.87 in the $MgSO_4$ category and 122.11 in the comparison category (p = 0.001).

A comparison between the $MgSO_4$ category and the reference category in the PEFR after treatment

shows that the average PEFR improvement over time was comparatively more significant in the $MgSO_4$ batch. At 60 minutes PEFR was 108.17 in the $MgSO_4$ batch and 74.55 in the comparison batch ($p < 0.001$) and at 90 minutes PEFR was 137.33 in the $MgSO_4$ batch and 72.73 in the comparison batch ($p<0.0001$). At 120 minutes, PEFR was 189.33 in the $MgSO_4$ batch and 103.31 in the comparison batch ($p < 0.001$). Regarding SO_2, no significant change was observed on comparing the $MgSO_4$ batch with the reference batch.

When the effectiveness of $MgSO_4$ was assessed, using the independent t-test, a significant difference in the mean pulse rate at 120 minutes was observed in the batch receiving treatment as compared to comparison batch ($p<0.001$). Similarly, a significant difference in the mean respiratory rate at 120 minutes was also observed in the batch receiving treatment ($p = 0.003$). When SaO_2 was assessed at 120 minutes no difference in the mean SaO_2 was observed in the batch receiving treatment ($p = 0.443$) (Table 2).

Table 2: Difference in means of pulse rate, respiratory rate and SAO_2 at 120 minutes in both groups.

Parameters	Intervention with Magnesium Sulphate	N	$\tilde{x}$	σ	p-Value
Pulse Rate (120 mins)	Positive	60	109.8	13.5	0.001*
	Negative	55	122.1	23.5	
Respiratory Rate (120 mins)	Positive	60	27.4	8.2	0.003*
	Negative	55	32.2	8.3	
SaO_2 Rate (120 mins)	Positive	60	91.3	7.5	0.443
	Negative	55	92.1	2.4	

**p <0.05 is significant*
Abbreviations: SaO2 = oxygen saturation of arterial blood

When the effectiveness of treatment with $MgSO_4$ was assessed in association with peak expiratory flow measurements, from baseline to 120 minutes using the paired t-test, significant difference was found in both intervention and comparison groups, with double the improvement in the intervention group.

A significant association was found when effectiveness of treatment with $MgSO_4$ was assessed in association with dyspnea at 120 minutes using the chi square test. $MgSO_4$ intervention relieved dyspnea at 120 minutes in 72% (n= 49) of the patients while in the comparison group only 28% (n=19) experienced relief from dyspnea ($p<0.001$).

DISCUSSION

In our study $MgSO^4$ intervention showed significant improvement in four parameters; HR, RR, dyspnea and PEFR. A review of previous equivalent trails shows variable results. Alansari and colleagues have demonstrated that adding to steroid therapy magnesium provides no benefit regarding moderate to severe exacerbations of asthma[12]. In a similar trial conducted in Iran by Bijani et al. In 2001, 81 patients were taken who were not responding to routine therapy and were given 25 mg/kg $MgSO_4$ with nebulized salbutamol and systemic corticosteroids. Improvement in pulmonary function was observed when predicted PEFR% was assessed at 180 minutes[13]. This finding is consistent with our study where a significant association was found between treatment and effectiveness as compared to the comparison group.

In a study done by Silverman, an improved FEV1 was demonstrated within 20 minutes of magnesium therapy, and a 20% improvement in PEFR was seen with sustained therapy for 110 minutes[14]. Nannini et al. also reported similar findings when magnesium was used supplementary to salbutamol for the acute management of asthma. They demonstrated a higher PEFR after treatment in patients with severe airflow obstruction who received combined therapy, as compared to those on salbutamol alone[15]. A study comparing nebulized salbutamol versus nebulized magnesium sulfate also found a reduced HR in the group receiving magnesium therapy in contrast to the comparison group (85 for the former and 96.1 for the latter, $p = 0.011$) as well as lowered mean respiratory rate (22.17 for the former and 25 for the latter, $p = 0.002$). However, both categories showed a rise in oxygen saturation[16].

A similar finding was observed in another study that showed improved PEFR when nebulized $MgSO_4$ was added to conventional treatment. The group receiving $MgSO_4$ demonstrated higher post-bronchodilator PEFR ($p < 0.014$) and SpO2 ($p < 0.006$)

 doi.org/10.36283/PJMD9-2/008

than the reference group. In addition, it was also demonstrated that treatment with this therapy was also useful in reducing emergency department admissions ($p < 0.047$)[17]. In isolated use $MgSO_4$ bronchodilation is significantly reduced but when used in combination with inhaled salbutamol this effect is enhanced, as seen by a rise in PEFR and SO_2 and a drop in RR and HR[16, 18] . Another clinical trial conducted in New Zealand which studied the effect of $MgSO_4$ combined with salbutamol in patients with an attack of severe asthma (PEFR 50% predicted) showed an improvement of PEFR at 90 minutes and a higher discharge rate as compared to the salbutamol alone group[19]. In severe asthma crisis, it has been found that inhaled $MgSO_4$ improves PEFR as well as oxygenation (SpO_2), when given in addition to standard asthma treatment, with reduced emergency department admission rates[20, 21].

Our study also showed that a decrease in HR in the intervention, which is consistent with Mangat et al. illustrating that $MgSO_4$, is safe to be used in cardiac patients[19, 22]. However, a significant reduction was not observed in the comparison group, which could be attributed to the side effects of salbutamol as it stimulates the B2 heart receptors. Studies indicate that nebulized $MgSO_4$ as a complementary to salbutamol can induce a heightened in severe asthma through bronchodilation. A significant difference was shown in our study by twice an increase in FEV1 after administration of salbutamol with $MgSO_4$ as compared to salbutamol alone. Heart rate, however, did not vary significantly between the two categories[18].

In a similar trial comparing standard therapy consisting of nebulized salbutamol, atrovent and prednisolone, alone and with $MgSO_4$, dyspnea decreased in severity with the $MgSO_4$ intervention at 20, 40 and 60 minutes ($p = 0.004$). In addition, SpO_2 at 20 minutes of treatment was more raised than that of the comparison group ($p = 0.002$). A corresponding recovery in RR was also seen in the treatment group ($p = 0.018$) along with a reduction in hospitalization rates. This reduction in dyspnea and improvement in respiratory rate is consistent with the findings of our study[23].

However, when nebulized $MgSO_4$ is given alone the increase in PEFR is comparable to that of salbutamol alone[24]. A study done in Egypt showed that inhaled $MgSO_4$ shows clinically significant improvement in acute asthma, when used in isolation, or combined with salbutamol, with a rise in PEFR and a reduction in HR and RR in both situations[25]. Another study done in Thailand found that both routes of administration have the same effects, and they found no side effects of $MgSO_4$[26]. According to Cochrane review 2017, the evidence that inhaled $MgSO_4$ with salbutamol may be beneficial for people with severe asthma exacerbations is insufficient. Recent randomized controlled trial also has not shown significant benefits[27-29]. In another systematic review, the capacity of inhaled $MgSO_4$ is less apparent because of limited evidence. It has however been observed that with appropriate administration of $MgSO_4$, the resultant safety profile is excellent[30]. Our study showed a significant effect on the PEFR ($p = 0.004$) when treated with $MgSO_4$. In order to further, validate the suitability of $MgSO_4$ in emergency department management of asthma it is suggested that a similar study be carried out on a larger sample size.

CONCLUSION

Intervention with $MgSO_4$ had significant improvement in HR, RR, Dyspnea, and PEFR with nebulized $MgSO_4$ being safe and without any observed side effects.

ACKNOWLEDGEMENTS

The authors acknowledged the Dr. Ziauddin University Hospital for facilitating the research study.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

ETHICS APPROVAL

The ERC of Ziauddin University approved the study with the Reference Code: 0010116GAEM.

PATIENT CONSENT

All patients gave their informed consent before inclusion in the study. All participants had the ability to withdraw from the study at any time.

AUTHORS' CONTRIBUTION

GA, AK and UG designed the study, did the bench work, while MA and VM wrote the manuscript.

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