ORIGINAL ARTICLE

Treatment of Acute Severe Asthma by Intravenous Magnesium Sulfate in Patients Non-responsive to Established Therapy

*Naveed Inayat, **Rashid Ahmed Khan, ***Anwar Ahmed Shaikh, ****Rubina Sahito

ABSTRACT

Objective: To appraise the use of magnesium sulfate in improving pulmonary function thereby eliminating the need for hospitalization during severe asthma attack.

Methods: A Randomized Placebo controlled trial was performed at the Liaquat University Hospital, Pulmonary ward Jamshoro / Hyderabad. Patients between the ages of 18-60, reporting to the emergency or intensive care unit were recruited to participate in the study after signing of the consent form. Inclusion criteria was, acute asthmatics with forced expulsion volume (FEV)1 $\leq$ 30% on arrival at the emergency department. As an emergency treatment, all patients received nebulized salbutamol, Ipratropium Bromide and intravenous hydrocortisone hemi succinate. A total of two gram (2gm) of intravenous magnesium sulfate or placebo were administrated 30 minutes after arrival at emergency department. Change in FEV1 at 180 minutes was used to measure the efficacy of magnesium sulfate instead of conventional therapy. Data was analyzed using statistical software.

Results: A total of 44 participants were recruited for the study. The mean FEV1 was measured at the time of admission to the emergency department. The mean FEV measured post-emergency department arrival was found to be 24.9%. Patients receiving magnesium sulfate showed an FEV of 46.2% in comparison to 41.5% in group treated with the placebo. Patients with lower initial FEV1 showed the most different after magnesium sulfate infusion, where FEV1 increased from < 25%.The effect of magnesium Sulfate compared to placebo was greater in patients with a lower initial FEV1, where FEV1 increased from < 25% expected, to 47.2% predicted in group treated with Magnesium as compared to 36.8% expected in the group treated with placebo. Administration of magnesium sulfate to patients with FEV1 $\geq$ 25 resulted in increase in FEV1 that was comparable to the placebo group (52.2% in magnesium sulfate group compared to 55.6% in placebo group).

Conclusion: Our results indicated that inclusion of magnesium sulfate to the therapeutic regimen facilitated pulmonary function by significantly improving FEV1 in server acute asthma patients that were previously non-responsive to conventional treatment.

Key words: Asthma, Magnesium Sulfate, FEV1.

Article Citation: Inayat N, Khan RA, Shaikh AA, Sahito R. Treatment of Acute Severe Asthma by Intravenous Magnesium Sulfate in Patients Non-Responsive to established Therapy. J Peoples Uni Med Health Sci. 2016;6(4):197-202.

INTRODUCTION:

Sever acute asthma is a life threatening condition which if left untreated could result in respiratory failure and death. As a result, sever acute asthma is considered a medical emergency and should be treated in a timely manner. Guidelines defined by the Global Initiative for Asthma (GINA) recommends administering oxygen, ß2 agonists, anticholinergics and corticosteroids, during severe exacerbations. The recommended treatment stabilizes most acute asthma patient[1]. Although this combination therapy is effective, nonetheless it has its drawbacks, where broncodilation may occur in minutes, corticoids will take hours to have an

* *Associate Professor Pulmonology, LUMHS, Jamshoro.*
** *Assistant Professor Pulmonology, LUMHS , Jamshoro*
*** *Registrar Pulmonology, LUMHS, Jamshoro*
**** *Research Officer, LUMHS, Jamshoro*

Correspondence to:
Dr. Naveed Inayat
Associate Professor Pulmonology
LUMHS, Jamshoro.
Email: naveedinayat64@yahoo.com

effect, which may have deleterious effect of sever acute asthma patients. Alternate therapies are therefore required to treat patients with severe acute asthma and prevent fatalities due to exacerbation of asthma. Previous reports demonstrated that magnesium sulfate induce bronchial smooth muscle relaxation in a dose dependent manner[4] by inhibiting calcium influx into the cytosol[5], histamine release from mast cells[6], or acetylcholine release from cholinergic nerve endings[7], and lastly enhancing the effect of ß2 agonists by increasing the receptor affinity[8]. Lastly, magnesium sulfate stimulates nitric oxide and prostacyclin synthesis, which might reduce asthma severity[9]. Given the bronchodilatory properties of magnesium sulfate it can be used as an adjuvant therapy for severe and life threatening asthma exacerbation[2]. Use of magnesium sulfate in patients with acute exacerbation is also recommended in the current guidelines[10,11], according to which intravenous (I/V) magnesium sulfate can be used as an adjuvant therapy to improve pulmonary function and subsequently reduce the number of admissions to the hospital. Unfortunately, despite combination therapy (adjuvant plus conventional), a third of asthma patients might still die due to poor quality emergency care[3].

The aim of this study was to determine if administration of intravenous magnesium sulfate together with conventional therapy, improves symptoms of breathlessness and pulmonary function (FEV1) and reduce the need for hospital admission in acute severe asthma.

METHODS:

Placebo controlled, randomized study was conducted at pulmonology department, Liaquat University Hospital, Jamshoro (Sindh), Pakistan, during the period of 1st January 2016 to 30th June 2016.

Selection of Patients:

A total of 44 patients were selected from chest OPD and ward after confirming acute severe asthma based on history and clinical examination.

Inclusion Criteria:

Patients previously diagnosed with asthma. Asthmatics having medication for at least 6 months. FEV1 ? 30 predicted on arrival at the emergency department (ED). Patients having low response after first 3 doses of nebulized salbutamol administered at an interval of 20 minutes over a period of an hour.

Exclusion Criteria:

Individuals with history of chronic obstruction pulmonary disease (COPD), congestive heart failure, coronary artery disease, diabetes mellitus, hypertension, renal insufficiency, pneumonia, pregnant female, patients unable to perform spirometry, and with temperature $\geq$ 38.9°C.

Patients were treated with the conventional therapy according to the GINA guideline.

Demographic and clinical information (physical examination, vital sign, pulse oximetry, and spirometry) was recorded prior to[12]. Patients were then randomized to two group using 1:1 ratio. After the initial emergency (ED) evaluation, patients randomized to either

** I/V MgSO4 2gm in 50ml normal saline given over 20 minutes.

** I/V normal saline, 50ml given over 20 minutes (in placebo)

Standard therapy was provided in accordance with guidelines of the British thoracic society and Scottish intercollegiate guidelines network (sign) and comprised of oxygen, nebulized Salbutamol, nebulized Ipratropium bromide and I/V hydrocortisone 250mg given during recruitment, followed by up to 5mg of Salbutamol added to each trial.

Treatment was started in placebo and test group by administering 2 gm Magnesium Sulfate in 50ml solution of normal saline, or a placebo I/V for 20 to 30 minutes.

On arrival to emergency department, salbutamol was re-administered at 30 minutes intervals for upto 120. Clinical assessment, with spirometry was done before each treatment and repeated at 180 minutes, at the time when a decision was made to hospitalize or not. The criteria for admission were standardized FEV1 <50% expected, respiration rate $\geq$25 Breath /minute, no progress in shortness of breath or wheezing or substantial dyspnoea on ambulation. Once the patient was admitted the protocol was

terminated. The patients, when discharged were advised to carry on their medication, they were also instructed for the use of salbutamol inhalation after each 60 hours or when there is a need and to continue 30mg prednisone for one week.

RESULTS:

A total of 44 adults were enrolled in the study of which complete data set of six-month was available for 40 participants. Two participants were excluded from the study based on the FEV1 which was greater than 50% of the predicted value. The remaining two participants requested early withdrawal because of lake of satisfactory improvement. Participants who continued with the study were divided into two equal groups. The demographic and baseline characteristic of these patients are shown in Table-1

In control group there were 16 (80%) males and 4 (20%) female while in treatment group there were 14 (70%) males and 6 (30%) female with mean Age of 36.5± 7.72 years (18-60 years). All patients had a history of asthma varying from 8 to 12 years and were on asthmatic medications. Out of 40, eight patients were smoker, who smoked less than eight packs per year, all smokers in the study were male participants who visited emergency department twice in past year and were admitted to the hospital at least twice in part five years.

No significant difference was observed between the placebo and treatment group for any of the demographic or clinical variable measured. Baseline FEV1 for treatment group range from 0.74-0.22 while for placebo group baseline FEV1 ranged from 0.75-0.21 and FEV1 22.6% (5.6) controlled and 23.2% (4.8) in treatment group at 0 minutes (on arrival). Difference in the mean of the baseline FEV1 before treatment was not statistically significant.

Assessment in outcome was analyzed by following ways.

Analysis on difference between magnesium sulphate treated group and controlled group in mean change in FEV1 and PEFR from baseline was calculated and shown in Table-2.

FEV1 at baseline revealed a difference in change in FEV1 at 60 minutes and 180 minute 29.2 V/s 30.6 and 43.6 V/s 48.4 respectively. A significant improvement in PEFR were observed in patients taking Magnesium Sulphate at 60 minute and 180 minutes were 160 v/s 170 and v/s 276 respectively, the advantage of treatment group over controlled group remained significant

Further analysis was then undertaken to assess the difference between treatment group and controlled group in mean change in FEV1 in patients having severe asthma FEV1 < 25% and FEV1 > 25% to 30% predicted. Observation in 14 Patients (8 controlled 6 Treatment) having and FEV1 of less than 25% Exhibited a significant benefit from magnesium sulphate therapy 49.8 compare to controlled group 38.6 mean difference was 11.2%.

However, patients with FEV1 > 25% to 30%, exhibited no benefit from treatment as shown in Table- 3 (FEV1 of treatment group =51.4 as compared with 59.9 in controlled group) (mean difference - 3.5, not significant).

The overall hospitalization rate at 8 hours was identical in patients receiving magnesium sulphate 2 out of 20 patients in treatment group and 10 out 20 patients in controlled group were admitted in hospital.

DISCUSSION:

Our results demonstrated an increase in the FEV1 of upto 40% in severe acute asthma patients treated with magnesium sulfate. Moreover, the observed increase in FEV1 and subsequent progress in respiratory function persisted for many hours after treatment with Magnesium Sulfate. A possible explanation for the observed increase in the FEV1 could be the anti inflammatory activity of Magnesium Sulfate. Evidence for the anti inflammatory effect of Magnesium Sulfate were provided by the experimental data demonstrating that treatment with magnesium sulfate results in lowering superoxide assembly in neutrophils acquired from adult asthmatic patients[13]. In addition to the ability of Magnesium Sulfate to increase respiratory function, there are several other factors such as the cost effectiveness, availability and ease of administration that makes this treatment more attractive. Side effects of minor importance includes light-headedness lethargy, nausea, transient flushing, or burning at the I/V site. Improvement in transient urticaria has

Table-1: Demographic & Baseline Characteristic of Patients.

Characteristics / Variables	Control Group n-20	Treatment Group n-20
Age		
Mean	36.5±7.72 years	38.5±7.62 years
Range	18-60 years	18-60 years
Sex		
Male	16 (80%)	14 (70%)
Female	4 (20%)	6 (30%)
Smoker		
Male	4 (20%)	4 (20%)
Duration of Asthma (Years)	5-10	6-12 years
Baseline FEV_1 (L)		
On 0 minute arrival		
FEV_1, L	0.74 (0.28)	0.75 (0.21)
FEV1 %	22.6 (5.6)	23.2 (4.8)
PEFR (L/min)	140 (72)	140 (70)
PEFR (%)	31.0 (12.0)	32.4 (16.0)

Table-2: Difference between Magnesium Sulphate Treated Group & Controlled Group

Mean Change in FEV1 and PEFR from Baseline	Control Group (n=20)	Treatment Group
After 60 minutes		
FEV1, L	0.94 (0.38)	1.0 (0.38)
FEV1 %	29.2 (12.0)	30.6 (10.0)
PEFR L/min	160 (66)	170 (68)
PEFR %	37.2 (12.4)	32.2 (12.6)
After 180 minutes		
FEV1, L	1.40 (0.64)	1.62 (0.18)
FEV1 %	43.6 (18.4)	48.4 (18.0)
PEFR L/min	238 (124)	276 (146)
PEFR %	54.1 (20.8)	62.8 (22.6)

Table-3: Comparison of FEV1 in Treatment and Controlled Group

Variable	0 Minute (Arrival)	60 Minutes	180 Minutes	Mean difference between treatment group at final assessment
Initial FEV1				
25 to 30% predicted				
Controlled (n-12)	29.2 (3.4)	37.1 (9.2)	54.9 (14)	-3.5
Magnesium (n-14)	26.2 (2.4)	35.2 (9.6)	51.4 (16.4)	(-9.2 to 3.5)
Initial FEV1				
20 to 24.9% expected				
Controlled (n-8)	29.2 (1.5)	28.3 (7.2)	38.6 (12)	11.2
Magnesium (n-6)	24.0 (1.0)	31.5 (7.3)	49.8 (16.2)	(-1.3 to 13.2)

been observed after withdrawal of Magnesium[14]. No main side effect was noted in current study. Magnesium sulphate is a safe and cheap medication with some bronchodilator effect[15].

Magnesium sulfate, is predominantly intracellularly located, where it serves as an important co-factor for several enzymatic reaction and is maintains cellular haemostasis. Moreover, magnesium sulfate is also essential for functionality of smooth muscle cells, and low levels of magnesium can cause contraction of muscles whereas high levels lead to relaxation of smooth muscles, thus producing bronchodilation[16]. Magnesium competes with calcium for entry into smooth muscles cells[17]. Inhabitants, such as histamine, released from mast cells, cause release of calcium from the sarcoplasmic reticulum[18,6]. Thus I/V Magnesium sulphate can be considered for patients with acute severe asthma who don't respond to standard therapeutic i.e. regular anti-asthmatics. The final FEV1 of 46.2% was achieved in patients having Magnesium in comparison to 41.5% expected for patient receiving placebo therapy (mean difference 4.7%). The maximum response of Magnesium was observed in cases having severe compromised airway on their arrival at emergency department, while cases with FEV1 closes to 30% predicted, on arrival at emergency department had no obvious advantage. Current study supports the use of Magnesium Sulfate to increase the respiratory functions and reduce severity of asthma in patient.

Many studies demonstrate the usefulness magnesium for the treatment of acute severe asthma[19-21]. Taking into consideration disease severity, Bloch et al[22], managed 145 cases having varying degree of airflow obstruction with 2 gm of magnesium (or placebo). Data was analyzed by stratifying pulmonary function. When the presenting FEV1 was >25% predicted there was no improvement in pulmonary function of the 35 randomized patients whose initial FEV1 was ≥ 25% predicted. Administration of magnesium sulfate decreased hospitalization rates by improving pulmonary function.

Our current study demonstrated that magnesium treatment improves pulmonary function in patents with sever acute asthma. Our results were in agreement with previous observation indicating that the improvement with Magnesium is associated with initial FEV1. Our study demonstrated that in patients with severe airway compromise, a 2 gm of I/V magnesium may prove useful in combination with b-agonist. Magnesium results in greatest improvement in respiratory function in cases having initial FEV1 at lowest levels.. Our data are consistent with reports of recent studies, which demonstrated improvement in lung functions 4, 5 and decrease in hospitalization in adult with severe asthma who recovered.

CONCLUSION:

In conclusion we have shown that a combination of I/V magnesium sulfate therapy along with standard GINA recommended therapy may facilitate bronchodilation and subsequent improvement in air flow obstruction as compared to conventional therapy alone.

RECOMMENDATION:

I/V MgSO4 as a safe and effective adjacent to conventional Broncho dilation therapy in acute severe asthma in adult.

REFERENCES:

1. Cheuk DK, Chau TC, Lee SL. A Meta-Analysis on intravenous Magnesium Sulfate for treating acute asthma. Arch Dis Child. 2005; 90(1):74-7.
2. Muhammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: a systematic review and meta-analysis. Emerg Med J. 2007; 24(12): 823-30.
3. Carroll W, Lenney W. Drug therapy in the management of acute asthma. Arch Dis Child Educ Pract Ed.2007; 92(3): ep82-6.
4. Spivey WH, Skobeloff EM, Levin RM. Effect of magnesium chloride on rabbit bronchial smooth muscle. Ann Emerg Med. 1990; 19:1107-12.
5. Gourgoulianis KI, Chatziparasidis G, Chatziethimou A, Molyvdas PA. Magnesium As relaxing Factor of Airway Smooth muscles. J Aerosol Med. 2001; 1(3):301-7.

6. Bois P. Effect of Magnesium Deficiency on mast Cells and urinary Histamine in Rats. Br J Exp Pathol. 1963;44:151-5.
7. Del Castillo J, Engbeak L. The nature of the neuro muscular block produced by Magnesium. J Physiol. 1954;124(2):370-84.
8. Classen HG, Jacob R, Schimatischek H. Interaction of Magnesium with direct and indirect acting sympathomimetic amines. Magnes Bull. 1987;9:80-7.
9. Skobeloff EM, Spivey WH, Mc Namara RM, Greenspon L. Intravenous Magnesium Sulfate for the treatment of acute asthma in the emergency department. JAMA. 1989; 262(9):1210-3.
10. Global strategy for asthma management and prevention global initiative for asthma (GINA) updated 2010. Available from www.ginasthma.org.
11. British guidelines on the management of asthma 2008. British thoracic society, Scottish intercollegiate guidelines network revised 2011. Available from; http://www.globalasthmanetwork.org/management/guides/bosnia_and_herzegovina/British%20guideline%20for%20asthma.
12. Mahler DA, Dyspnoea. London, UK: Futura Publishing,1990; 122.
13. Cairns CB, Kraft M. Magnesium attenuates the neutrophil respiratory burst in adult asthmatic patients. Acad Emeg Med. 1996;3(12):1093-7.
14. Thorp JM Jr, Katz VL, Combell D, Cefalo RC. Hypersensitivity to magnesium sulphate. Am J Obstect Gynecol. 1989;161(4):889-90.
15. Okayma H, Aikwa T, Okayma M, Sasaki H, Meu S, Takis ST. Bronchodilating effects of intravenous magnesium sulphate in bronchial asthma. JAMA. 1987;257(8):1076-8.
16. Noppen M, Vanmaele L, Impens N, Schandevyl W. Bronchodialtion effect of intravenous magnesium sulphate in acute severe broncodial asthma. Chest.1990; 97(2):373-6.
17. Altura BM, Atura BT. Biochemistry and pathophysiology of congestive heart failure: is there a role for magnesium? Magnesium. 1986;5(3-4):134-43.
18. Dunnet J, Nayler WG. Calcium effelux from cardiac sacroplasmic reticulum: effects of calcium and magnesium. J Mol Cell Cardiol. 1978:10(5):487-98.
19. Rosello HJ, Pla JC. Sulphato de magnesio en la crisis de asma. Prensa Med Argent. 1936;23:1677-80.
20. Kuitert LM, Kletchko SL. Intravenous magnesium sulphate in acute, life threatening asthma. Ann Emerg, Med. 1991;20(11):1243-5.
21. Schiermeyer RP, Finkelstein JA. Rapid infusion of magnesium sulphate obviates need for instuation in stuatus asthmaticus AM J Emerg Med. 1994;12(2):164-6.
22. Bloch H, Silverman R, Mancherje N, Grant S, Jagminas L, Scharf SM. Intravenous magnesium sulphate as an adjunct in the treatment of acute asthma. Chest.1995; 107(6):1576-81.