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Study of Broncho-Dilating Effect of Nebulized Magnesium Sulfate, as a Vehicle for Salbutamol or as an Individual Agent, In Patients of Acute Asthma.

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ABSTRACT

Magnesium is a calcium antagonist which reduces movement of Calcium ion across cell membrane, thus relieving bronchial constriction. It also reduces mucous glands secretions and release of histaimine by mast cells. Our study analysed the bronchodilating effects of Magnesium sulphate, along with its safety profile in acute asthma. Total 71 asthmatics were randomly allocated into 3 groups. Group A (n=26) was nebulised with salbutamol alone, Group B (n=24) with salbutamol mixed in isotonic magnesium sulphate (MgSO4 7.5% w/v) and group C (n=21) treated with magnesium sulfate alone. Parameters measured were PEFR at baseline, 10 minute and 20 minute interval along with vital parameters and side effects, if any. In all three groups, we observed an increase in PEFR , Mean % increase over baseline was quite significant (P<0.01) at 10 and 20 minute interval in Group B and Group C in whom, magnesium sulfate was nebulized. Magnesium sulfate induced greater bronchodilation in those patients having baseline PEFR<50% [Acute Severe Asthma] in contrast to plain salbutamol. No significant changes in vital parameters were noticed and side effects were also self-limiting. With bronchodilating properties, Magnesium sulfate may be used in acute attacks of asthma, to buy time, till other standard Bronchodilatiors may act. However, further clinical trials are needed to establish the optimum dose-response relationship.

INTRODUCTION

In recent past there has been a great increase in knowledge about immune pathology, disease characteristics and the treatment of asthma. There is no cure of bronchial asthma, morbidity and mortality is continuously increasing despite of positive research. Magnesium is one of the important intracellular cation, has potential significance to the airways [1]. Many studies have shown that magnesium is important in the regulation of Broncho vasomotor tone [2] and it's low dietary intake has been shown to be associated with airway hyper-responsiveness [1,3]. It has smooth muscle relaxant [4], broncho-dilating [5,6,7] and anti-inflammatory effects [7] and so may have role in therapy of asthma. When magnesium is deficient, the action of calcium is enhanced. In contrast, an excess of magnesium blocks calcium and it is very important as the intracellular influx of calcium causes bronchial muscle constrictions. Several studies indicated the effect of I/V magnesium sulfate in acute and stable asthma [8,9,10,11,12], it improves PEFR and also reduced hospital admission rates [8]. More recently inhaled magnesium sulfate has also been found safe in patients with stable asthma and also as an adjuvant therapy in emergency department. Magnesium

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sulfate is considered to augment the bronchodilator effect of salbutamol, possibly through increased affinity of B2 receptors [13]. Inhaled magnesium has also shown to have inhibitory effect on histamine, methacholine and metabisulphite induced bronchoconstriction in asthmatic patients [14,15,16]. Some studies have shown that isotonic MgSO4 as vehicle for nebulized salbutamol increases the peak expiratory flow response to treatment in comparison to salbutamol with normal saline [17,18].

Aims and Objectives

To determine effect of nebulized isotonic magnesium sulfate on peak flow rate as a vehicle for salbutamol solution or as an individual agent and to confirm its safety and suitability as a first line treatment in acute asthma.

MATERIAL AND METHODS

This study was conducted on diagnosed patients of acute asthma, reporting in emergency room as well as outpatient department of medicine and chest-TB dept at Gandhi Medical College and Hamidia Hospital, Bhopal. Study plan was approved by the departmental ethical committee. Patients between age of 15 years to 65 years, who gave informed consent were included. Those excluded were on the basis of smoking, pregnancy, concomitant medical illnesses like renal, cardiac or other diseases, lower respiratory infection, who have taken oral or parental corticosteroid/B2 agonist in preceding 12 hours and in-cooperation in measuring peak expiratory flow. Patients of asthma with acute exacerbation were recorded for their age, sex, height, weight, occupation, other addiction, present complaints, duration, history of past illness and treatment , aggravating and relieving factors, personal and family history. A thorough physical examination was done to know the general condition, respiratory rate, pulse rate, pulse character and blood pressure. A complete systemic examination, especially respiratory system, was done in all patients, oxygen saturation was recorded. All other relevant investigations as chest radiograph, electrocardiogram etc. were also done, when needed. Peak expiratory flow rate (best of three attempts with mini wright peak flow meter [Element Clark Ind. Ltd.]) was recorded as baseline value before nebulization treatment, then 10min after treatment and 20min after treatment. Simultaneously patients were assessed for subjective improvement or worsening. Duration of treatment at emergency room were also recorded. Changes in vital parameters as respiratory rate, pulse rate, blood pressure SpO2 were recorded and predicted values of PEFR were calculated on the basis of age, gender, height, and weight and as per the standards of Indian population. The same nebulizer (OMRON-CX Compressor, Singapore) was used throughout the study, driven by electricity power(mean particle size of 5.2+/- , nebulization rate 400mg/min). No medication was used during the study except oxygen. When additional treatment needed, status at the time of intervention was used as end study point. In the study, a total of 71 patients with acute bronchial asthma were randomly categorized in three groups, group A (n=26), patients in this group were treated with salbutamol nebulization 0.5ml(2.5mg salbutamol) diluted in 3ml of normal saline. Group B patients(n=24) were treated with salbutamol 0.5 ml(2.5mg) in 3ml of 7.5%(w/v) magnesium sulfate isotonic solution [17,19] and group C (n=21) were nebulized with only 3ml of 7.5%(w/v) isotonic magnesium sulfate solution [19].

Results were expressed as mean+/-SD for all parameters in all groups, results were compared to each other by statistical analysis and their significance was tested and considered significant statistically at p value of <0.05.

RESULTS

Table 1: Pre-treatment characteristics of patients in all study groups

Characteristics	Group A(n=26)	Group B(n=24)	Group C(n=21)
Age	46.5±16.1	42.3±12.3	42±13.8
Male	14(53.8%)	12(50%)	9(42.8%)
Duration of asthma	5.92±5.38	7.5±7.17	7.83±6.38
Respiratory rate	24±5	20±6	22±4
Pulse rate	94±17	96±19	98±16
Systolic pressure	130±20	136±14	132±18
Diastolic pressure	84±12	84±8	84±10
Medication used			
Steroids	4(15.3%)	10(41.6%)	6(28.5%)
B2 agonists	20(76.9%)	12(50%)	12(57.1%)
Salbutamol	2(7.6%)	3(12.5%)	2(9.5%)
Theophylline	6(23%)	8(33.3%)	7(33.3%)

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Table 2: Symptom Characteristics of all the study group patients

Symptoms	Group A	Group B	Group C
Episodic breathlessness	24(92%)	19(79%)	15(15%)
Nocturnal breathlessness	12(12%)	12(50%)	11(52%)
Dry cough	14(54%)	9(38%)	9(43%)
Productive cough	6(23%)	7(30%)	7(33%)
Wheze	16(62%)	18(76%)	16(76%)
Chest tightness	16(62%)	15(63%)	13(62%)
Nasal symptoms	14(54%)	7(30%)	7(33%)

Patients from all three study groups were matched in age, sex, duration, symptoms, previous medications usage and vital parameters, so all the groups were statistically comparable to each other($p>0.05$). All the patients had typical symptoms of bronchial asthma, 81% had episodic breathlessness, 49% nocturnal breathlessness, 45% dry cough, chest tightness was present in 62%, wheezing in 70% among all patients.

Though, the mean baseline peak expiratory flow rate was little higher in the group A patients as compared to the groups B and C, but the difference was found statistically insignificant ($p>0.05$). When significance of mean percentage increase over baseline, after 10 minutes of nebulization tested, this change was statistically highly significant in all the three groups($p<0.001$) and these changes were more significant in groups B and C as compared to group A ($p<0.01$). When significance of mean percentage increase after 20 minutes over baseline were tested, these changes were statistically highly significant in all groups ($p<0.001$). At 20 min, Group B and C patients had more than 50% increase in flow rate over baseline as compared to about 30% in group A. On comparision, change in PEFR between group A and B, A and C was significant ($p<0.01$) but was insignificant among groups B and C ($p>0.05$).

Table 3 : Effect of treatment on the peak expiratory flow rates

(At 10 minutes)

PEFR(L/Min)	Group A	Group B	Group C
Predicted	399.23+-75.88	390.42+-67.47	379.52+-66.82
Baseline mean(% of predicted)	218.46+-101.15 (53.43+-20.12)	171.88+-82.29 (44.41+-19.27)	169.05+-73.27 (45.57+-1872)
After 10min(% of predicted)	261.54+-105.58 (64.82+-20.79)	235.83+-90.02 (61.17+-21.68)	230.95+-75.16 (62.30+-19.62)
Mean % increase over baseline	24.29+-11.92	44.37+-34.52	40.82+-22.88
P value	P< 0.001	P <0.001	P <0.001

(At 20 minutes)

After 20 min (% of predicted)	276.92+-113.68 (69.60+-22.37)	245.42+-90.26 63.63+-22.32)	245.24+-72.91 (66.15+-19.27)
Mean % increase over baseline	31.08+-11.68	51.25+-39.90	52.94+-25.08
P value	P <0.001	P<0.001	P<0.001

Side Effects

Almost 35% patients group A felt some adverse effect, 6 patients (23%) had palpitation, 2(8%) had facial flushing, malaise, tremors, 1(4%) felt facial warmth. In the group B, 30% had one or more side effect mainly sweating(20%), facial warmth(8%), facial flushing(2%), tremors(9%) and palpitation was complained by 2(8%), few patients also complained of nausea, bed smell. In the group C, 10% had palpitation, 14% sweating and 10% dizziness, so as compare the side effect, palpitation was present in more number in group A while group B and C complained of sweating and dizziness. In this regard the side effects in each groups could not be compared, however the incidence of tremor was similar in group A and B but there were no patient complained tremor in group C. Minor changes were recorded on these vital signs post treatment but these were found statistically insignificant ($p>0.05$). Table 4 shows that there were no significant changes in different vital parameters at all times pre and post treatment.

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Table 4: Changes in vital parameters in all study groups

	Group A	Group B	Group C
Respiratory rate (Pre treatment)	24+-5	20+-6	22+-4
Post treatment	24+-6	19+-5	21+-5
P value	p>0.05	p>0.05	p>0.5
Pulse rate (pretreatment)	94+-17	96+-19	98+-16
Pulse rate (post treatment)	98+-15	98+-16	100+-15
P value	p>0.05	p>0.05	p>0.05
Systolic pressure (pre treatment)	130+-20	136+-14	132+-18
Systolic pressure (post treatment)	132+-18	136+-12	132+-14
P value	p>0.05	p>0.05	p>0.05
Diastolic pressure, (pretreatment)	84+-12	84+-8	84+-10
Diastolic pressure, (posttreatment)	84+-10	82+-8	84+-8
P value	p>0.05	p>0.05	p>0.05

DISCUSSION

Relaxation effect in asthma by ionic magnesium was reported previously. It has also been estimated that 50% of asthmatic patients have low level of serum magnesium and these patients improve significantly after IV magnesium sulfate therapy. More recently magnesium sulfate has been used through inhaled route for treatment of asthma and it is claimed to augment the bronchodilatory effects of traditionally used salbutamol. Little is known about the effects of nebulised magnesium sulfate on airway reactivity in response to a direct or indirect acting broncho-constricting agents. Hyperosmolar solutions delivered by nebulizer might induce bronchoconstriction, so isotonic solution of magnesium sulfate was used in these studies [17,19].

In our study, nebulization therapy induced quick symptomatic relief, bronchodilating effect of different treatment schemes was assessed by rise in PEFR at 10 and 20 min over baseline and changes were statistically significant in all the three groups. On comparison of individual groups to each other there were more percent changes in mean PEFR in group B (51.25+_39.90) and C (52.94+_25.08), which was more than 50% increase over baseline as compared to about 30% increase in group A (31.08+-11.68), after 20min post-nebulization. There were significant comparative changes in PEFR between group A and B, A and C (P<0.01) but it was insignificant between group B and C(P>0.05). The maximum bronchodilating effect was observed during first 10 minutes and was maintained at 20minutes. In severe asthma category (baseline PEFR</=50%), there were significant improvement after 20 minutes post nebulization, in all groups (p<0.001), but the improvement in group B and C was highly significant (p<0.001) as compared to group A, however, the difference between group B and C was not significant (P>0.05). The above result suggests that nebulized magnesium sulfate with B2 Agonist had produced maximum improved pulmonary functions in the form of mean percentage increase over baseline PEFR. So, there is over all benefit of nebulising magnesium sulfate in acute asthma but combining nebulized magnesium sulfate with nebulized salbutamol in patients of acute asthma dosen't make any significant difference (>0.05) as compared to plain magnesium sulfate.

Rolla et al [13] previously in their study, observed the effect of mild increase in ionic serum magnesium level, on bronchodilatory response to salbutamol in asthmatics with normal serum magnesium level. This was a double blind placebo controlled study. They confirmed that Magnesium sulfate may augment the bronchodilator action of salbutamol in acute asthma by increasing the affinity of B2 agonist or by upregulating the receptors. Other potential mechanism may include potentiation of beta 2 agonist effects on magnesium requiring enzymes such as adenyl cyclase and sodium-potassium ATPase, or purhaps by offsetting beta agonist tachyphyllaxis [17].

Nannini et al [17] studied istonic magnesium sulfate as vehicle for nebulized salbutamol in patients of acute asthma. They enrolled 35 patients with acute asthma and concluded that in patients with acute asthma, isotonic magnesium sulfate as a vehicle for nebulized salbutamol, increased the peak flow

response to treatment in comparision with salbutamol plus normal saline. This inference was similar to that of our study.

In 2006, Rodrigo et al [18] studied aerosolised magnesium sulfate in combination with inhaled beta-2 agonist compared to beta-2 agonist alone in treatment of asthma in a randomised control trial. They found that patients who received magnesium sulphate, showed non-significant improvement in pulmonary function(p=0.18). The advantage of use of magnesium sulfate was demonstrated only in patients with life threatening acute asthma with baseline PFR<30% of predicted (p=0.002). Also, nebulised magnesium sulfate with beta 2 agonist showed a reduction in admission rate compared to single beta 2 agonist agent. These findings are also similar to the observation of our study.

Blitz M et al had studied efficacy of inhaled magnesium sulfate. In this randomised control trial, they included the patients with acute asthma and treated with nebulised magnesium sulfate alone, and in combination with beta-2 agonist. They also concluded that nebulised magnesium sulfate in addition to beta 2 agonist produced improved pulmonary functions in these patients [20].

Meral et al [21] compared the effect of inhaled magnesium sulfate and salbutamol in patients with acute asthma. The evaluation of patients was done using respiratory score, respiratory rate, heart rate, blood pressure and peak expiratory flow rate. Although, bronchodilating effect of magnesium sulfate continued for approximately one hour, but treatment of acute asthma using salbutamol inhalation was found to be more effective and successfull with continued effect lasting upto six hours.

The palpitation was the major side effect in group A (6 out 26; 23%) while facial warmth, facial flushing, bed smell, sweating, malaise, weakness, dizziness and tremors were complained by few of the patients to whom magnesium sulphate was given with or without salbutamol nebulization treatment. Also, no significant adverse effect and changes in vital parameters were noted in our all groups. More so, these side effects were minor and short lasting. These results were similar and comparable with study of Agrawal P et al [22] and Cochrane database [23]. None of the patients in our study groups showed depressed deep tendon reflexes, which is one of the first clinical sign of magnesium toxicity [24]. So, nebulised magnesium sulfate could be considered as a safe and effective treatment alternative for acute asthma, particularly acute severe asthma group.

CONCLUSION

Magnesium sulfate induced greater bronchodilation in patients of acute severe asthma. Nebulization route did not adversely affect action of salbutamol; no added side effects were noted. Therefore, magnesium sulphate nebulization may be used as an adjuvant or an alternative to standard treatment of acute severe asthma. However, Further clinical trials are needed to establish the benefits and optimal dose response relationship.

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