ORIGINAL ARTICLE

Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study

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Objective: To test the hypothesis that combined administration of multiple doses of nebulised salbutamol and magnesium sulphate provides additional benefit compared with salbutamol alone in adult patients with acute asthma.

Design: Randomised, double blind, prospective study.

Methods: A total of 100 patients presenting to an emergency department with an acute attack of bronchial asthma were randomised to two groups: nebulisation with a combination of salbutamol and magnesium sulphate (group A) and nebulisation with salbutamol only (group B). Both groups received nebulisation thrice at intervals of 20 minutes. Salbutamol and magnesium sulphate were administered in doses of 0.5 mg and 500 mg, respectively, and the solutions were made isotonic to plasma osmolality. Pulse rate, blood pressure, and peak expiratory flow rate (PEFR) were measured at baseline and at 15, 60, 75, and 120 minutes. Serum magnesium levels and blood gases were measured at 0 and 120 minutes in both groups.

Results: All patients had either acute severe or life threatening asthma. The baseline characteristics were comparable in the two groups. Both groups showed significant rise in PEFR at all time intervals, however, there was no significant difference between the groups in rise in PEFR at any time point. Serum magnesium levels remained within normal limits, and there was no difference in requirement of additional medication during the study or hospital admission rates in both groups. No significant side effects were noted.

Conclusion: This study suggests that there is no therapeutic benefit of adding magnesium sulphate to salbutamol nebulisation in the treatment of patients with acute severe or life threatening asthma.

Acute exacerbation of bronchial asthma is a frequently encountered problem in emergency departments worldwide. According to data from Australia and Canada, acute asthma accounts for 1–12% of all adult emergency department visits.^{1,2}

Standard treatment of an acute asthmatic attack includes β adrenergic agents and steroids. The addition of multiple doses of nebulised ipratropium to β adrenergic agents and steroids has been shown to reduce the rates of hospitalisation and associated morbidity in patients with acute severe asthma.^{3–5} A substantial reduction of 30–60% in hospital admissions was shown with combined treatment with β adrenergic agents and ipratropium.^{4,5} In patients with mild to moderate acute asthma, there is no apparent benefit from adding a single dose of an anticholinergic medication. Despite the efficacy of these agents, many patients do not respond adequately and may require hospitalisation. There are an estimated 1.8 million annual emergency department visits for acute asthma in the USA, and nearly 500 000 patients are hospitalised each year.⁶ Other studies have shown admission rates of 20–30% in patients with acute asthma.^{7,8}

Several studies and case reports have demonstrated benefits of the use of intravenous magnesium sulphate in acute severe asthma. In adults, the use of intravenous magnesium sulphate improved pulmonary function but did not reduce hospitalisation rates.⁹ A meta-analysis on the use of intravenous magnesium sulphate in acute asthma in children showed additional benefits in moderate to severe asthma, both in terms of pulmonary function tests and rates of hospitalisation.¹⁰

Few studies have been published on the use of nebulised magnesium in such patients.^{11–14} Studies comparing nebulised magnesium sulphate with salbutamol in patients with acute

asthma have shown the bronchodilator response of magnesium to be either similar¹⁵ or of lower magnitude and duration as compared with salbutamol.¹⁶ Again only a few studies have been conducted comparing the combination of nebulised magnesium sulphate and salbutamol with salbutamol alone. These studies, which included small numbers of patients, concluded that the addition of magnesium sulphate to nebulised salbutamol produced either greater bronchodilation compared with salbutamol alone^{11–13} or no benefit.¹⁴

Therefore we conducted a double blind, randomised trial to evaluate whether addition of magnesium sulphate to nebulised salbutamol provides greater bronchodilation compared with standard therapy with nebulised salbutamol in patients with acute asthma.

PATIENTS AND METHODS

The Ethics Committee of the All India Institute of Medical Sciences, New Delhi, approved the study.

Eligibility criteria

We included patients between 13 and 60 years of age with acute bronchial asthma who presented to our emergency department in 2003 when either of the two investigators, PA or SS, was available. Patients were considered asthmatic if they had been previously diagnosed or treated for bronchial asthma, or the history and examination findings were suggestive of bronchial asthma as defined by the British Thoracic Society guideline.¹⁷

We excluded patients if any of the following conditions was present: first episode of wheezing; history suggestive of chronic bronchitis or emphysema; history of congestive heart failure, angina, or renal insufficiency; temperature $>38^{\circ}\text{C}$; requirement of endotracheal intubation as judged by the

attending emergency physician; failure to use peak expiratory flow meter; or failure to get consent for participation in the study. Pregnant women were also excluded.

Initial management and assessment

On arrival in the emergency room, a patient was administered oxygen and an intravenous line inserted. A detailed history was taken and clinical examination was performed to rule out any associated illness. Informed consent was obtained from patient's relatives. Any medications received by the patient within 24 hours of their visit were noted.

Pulse, blood pressure, respiratory rate, and presence of pulsus paradoxus above 10 mm Hg were recorded. The degree of spasm was assessed by peak expiratory flow rate (PEFR), which was recorded as the best of three readings using a mini Wright's peak flow meter (Airmed Ltd, Harlow, England). The same instrument was used throughout the study. Blood gas and acid-base status were analysed in all patients using AVL auto-analyser (AVL List GmbH, Austria). For estimation of serum magnesium levels, the serum taken before the start and after the completion of the study was separated and stored at -70°C until it was assayed.

Randomisation and medications

After enrolment patients were randomly allocated to one of the two study groups. We used random number tables for the randomisation. The individual random numbers were kept in separate envelopes so that concealment could be maintained until the patient was included in the assigned group. The medications were prepared by a doctor who was not a part of the study and were labelled as A (combination of magnesium sulphate and salbutamol) or B (salbutamol only). Thus the patients and investigators (PA and SS) were blinded to the nature of the treatment given to a patient.

Patients in both groups received nebulisation at 0, 20, and 40 minutes. For nebulisation, the medications were constituted as follows:

- Group A – 10 ml solution consisting of 1 ml of salbutamol nebulisation solution + 1 ml of magnesium sulphate (intravenous preparation containing 500 mg of magnesium sulphate per ml) + 8 ml distilled water with final osmolality of 295 mosmol/kg
- Group B – 1 ml of salbutamol nebulisation solution was diluted with 1.5 ml of distilled water and 7.5 ml of normal saline with final osmolality of 287 mosmol/kg.

The drugs were administered by ultrasonic nebulisation over a period of seven to eight minutes. As mentioned above, all the patients were also administered oxygen at a flow rate of 6 l/min. The attending emergency physicians were free to administer intravenous hydrocortisone and additional doses of salbutamol nebulisation if judged to be required.

Assessment of response

All clinical variables and PEFR were recorded at 0, 15, 60, 75, and 120 minutes. The primary objective was to determine whether changes in PEFR produced by the two interventions would be significantly different in the two study groups. Blood gases and electrolytes were determined before the start of the study and at the end of 120 minutes. Any side effects noted by the patient or physicians were recorded. The decision to discharge a patient was taken by the attending emergency physician and was usually made once the PEFR was greater than 65% of predicted value for more than four to six hours. A patient whose PEFR was below 65% after 12 hours of emergency department treatment or who had an unsatisfactory response to treatment, as judged by the attending physician, was admitted.

Statistical methods

When we were planning this study, we found only two published studies comparing multiple doses of nebulised salbutamol plus magnesium sulphate and salbutamol alone.^{11–14} Hence, to derive meaningful and valid results, we decided to include at least 100 patients in the study. We felt this would be a realistic number for us to be able to recruit in the study period. We did not perform a power calculation before conducting the study.

Descriptive statistical parameters (mean and standard deviation) were calculated for each quantitative variable. Between group comparisons of qualitative data were done using χ^2 tests (with Yates' correction) or Fisher's exact test. As normality assumption and equality of variance were satisfied for most of the quantitative variables, between group comparisons of means were done using unpaired *t* test/*z* test. Otherwise, if necessary, Wilcoxon's rank sum test was used. As a comparison of the baseline data of the two study groups did not reveal any significant difference ($p > 0.05$), the results at a given point of time between two groups were also compared with the same methods to assess the comparative changes. For within group comparison of quantitative data over time we used two way analysis of variance (ANOVA)/Friedman's test. In case of significant results, Tukey's multiple range test was used to identify the pairs of observations with significantly different results. The results were considered significant at the 5% level ($p < 0.05$).

RESULTS

Figure 1 shows the enrolment and allocation of the patients to the two study groups. Of 136 patients with acute asthma, 36 patients were excluded. Thus a total of 100 patients were recruited and randomly allocated to the two study groups, with 50 patients in each group. The groups did not differ significantly as regards their age, age of onset of asthma, history of smoking in the past, duration of present episode of acute asthma and, medications received before presentation to the emergency department (table 1). The symptoms of acute exacerbation in these patients mainly included increased cough, dyspnoea, and wheeze. Before presentation, most patients had received medications in the form of inhaled β agonists (43 and 45 in groups A and B, respectively), oral steroids (8 and 7 in groups A and B, respectively), and antibiotics (36 and 33 in groups A and B, respectively). The baseline pulse, blood pressure, respiratory rate, and PEFR of the two groups were not significantly different. On analysis of PEFR values and clinical features, the patients fell into two categories of acute asthma as defined by British Thoracic Society guideline—acute severe asthma (29 and 30 in groups A and B, respectively) and life threatening asthma (21 and 20 in groups A and B, respectively).¹⁷ No patient had moderate exacerbation of their asthma.

With treatment, the pulse rate declined significantly ($p < 0.05$) in each group at 120 minutes but there was no significant change in the systolic or diastolic blood pressure. The PEFR rose significantly within each study group starting at 15 minutes ($p = 0.000$) and the highest reading of PEFR was noted at 120 minutes ($p = 0.000$). When the PEFR of the two groups was compared, there was no significant difference ($p > 0.05$) at the various time points during the study (table 2; fig 2). On including patients with life threatening asthma only (29 in group A and 30 in group B), again no significant difference in response was found between the two groups at any time point.

PaO_2 , Paco_2 , and serum magnesium levels before and at the completion of study are shown in table 3. The rise in arterial oxygen tension at 120 minutes was significant in both treatment groups. Basal values of serum magnesium in both groups were within normal range (reference range

Figure 1 Flow diagram showing enrolment and allocation of patients to the nebulised salbutamol plus magnesium sulphate or salbutamol alone group. *Two patients had both fever and first episode of asthma.

1.7–2.7 mmol/l) although the difference was statistically significant (unpaired *t* test). After the interventions, the magnesium levels were still within the normal limits, though the difference between the two groups remained statistically significantly different. Using the paired *t* test, the changes in magnesium levels between baseline and 120 minutes within each group were also significant. In the group receiving magnesium nebulisation, there was a significant fall in magnesium levels at 120 minutes.

Additional medications were given by the attending emergency physicians during the study period if the PEFR did not rise above the previous value and the patient still had respiratory distress. Steroids and β agonists were given to 23 and 20 patients in group A, and 21 and 23 patients in group B, respectively. Patients in group A who received β agonists ($n = 20$) also received steroids. Similarly in group B, all the patients who received steroids ($n = 21$) also received β agonists. This difference was not statistically significant. Only one dose of the additional medications was given. Importantly, none of the patients received additional medications within the first hour of treatment. Hydrocortisone was administered intravenously in a dose of 100 mg while nebulised salbutamol was given in a dose of 500 μ g.

We further divided the patients in both groups into two subgroups—those who received and those who did not receive additional medications during the study. Table 4 shows the PEFR in the subgroups of both study groups. Within the same group, variations in PEFR in the two subgroups were statistically significant at most time points (*p* values at 0, 15, 60, 75, and 120 minutes were 0.002, 0.005, 0.0001, 0.015, and 0.017 in group A and 0.093, 0.011, 0.090, 0.058, and 0.030 in group B, respectively). However, a comparison between groups A and B, of patients receiving no additional medications and those receiving additional medications, showed that the PEFR were not significantly different at any time point.

Table 1 Baseline characteristics of the patients in the two study groups*

	Group A	Group B	<i>p</i> value
Age (years)†	46.26 (13.96)	41.00 (16.66)	0.117
Men : women	27:23	33:17	0.307
Duration of asthma (years)†	10.66 (8.20)	13.00 (11.97)	0.237
Previous hospitalisation‡	7	6	1.000
Duration of present attack in days†	4.16 (1.69)	4.28 (1.99)	0.746
Received medications before arriving at hospital‡	48	50	0.495
Smoker‡	9	5	0.110

*Group A: nebulised magnesium sulphate + salbutamol; group B: salbutamol alone. †Mean (SD). ‡No. of patients.

Palpitations and tremors were noted in 13 and 7 patients in group A, and 11 and 7 patients in group B, respectively. None of the patients had any adverse effects severe enough to warrant withdrawal from the study.

Eighty-one patients (41 from group A and 40 from group B) were discharged after further treatment in the emergency department. Although patients were generally discharged when the PEFR was greater than 65% of the predicted value for more than four to six hours, there was some variability among the attending emergency physicians, as in 16 patients the PEFR was not recorded at the time of discharge. The mean (SD) duration of stay in the emergency department was 16.4 (5.5) hours. A total of 19 patients (9 from group A and 10 from group B) required hospital admission, of which 11 were sent to another hospital due to lack of beds (according to our hospital policy). Thus we were unable to follow up the patients after hospitalisation.

DISCUSSION

We conducted the present study to investigate the role of nebulised magnesium sulphate combined with salbutamol versus salbutamol alone in patients with acute severe asthma. The study showed that nebulisation of combination of magnesium sulphate and salbutamol had no significant beneficial effect compared with plain salbutamol nebulisation in patients with life threatening and acute severe asthma. Further, there were no significant differences between the two groups with regard to side effects and rates of hospitalisation. Group A (nebulised magnesium sulphate combined with salbutamol) showed significant fall in magnesium levels, whereas in group B (salbutamol alone) there was a rise in magnesium levels, even though the final levels were still within the normal range. None of the included patients had moderate exacerbation of asthma, possibly because patients with acute asthma attend an emergency department only when the asthma worsens despite taking medications prescribed by family doctors/general practitioners. This may also be the reason for the mean duration of asthma attack of more than four days before presentation.

We used an isotonic solution of magnesium sulphate because hyperosmolar magnesium sulphate can cause bronchoconstriction¹⁸ or increased airway reactivity to histamine.¹⁹ Magnesium may increase the bronchodilator response to salbutamol in acute asthma by increasing the affinity of β receptors to salbutamol²⁰ or by upregulating β receptors. Other effects of magnesium which may produce bronchodilation include:

- Magnesium relieves bronchoconstriction by decreasing the uptake and release of calcium in bronchial smooth muscle.²¹

Table 2 Variables measured during the study*†

	Time (min)				
	0	15	60	75	120
Pulse					
Group A	107.8 (8.8)	102.6 (8.2)	100.4 (8.1)	97.4 (7.2)	94.6 (8.4)
Group B	110.9 (13.8)	108.7 (12.4)	105.0 (11.5)	100.6 (10.2)	97.3 (9.2)
Systolic pressure					
Group A	133.6 (11.1)	136.2 (10.4)	136.7 (9.6)	136.8 (8.7)	138.8 (8.7)
Group B	134.8 (16.4)	136.3 (11.8)	137.7 (11.6)	137.7 (11.7)	138.2 (10.5)
Diastolic pressure					
Group A	86.3 (5.5)	87.3 (5.2)	88.0 (5.3)	89.3 (5.3)	89.3 (5.5)
Group B	84.8 (8.4)	87.9 (7.0)	89.0 (6.0)	88.7 (6.3)	88.7 (5.6)
Peak expiratory flow rate (PEFR)					
Group A	118.6 (41.3)	142.8 (40.2)	172.4 (43.7)	204.0 (50.4)	237.8 (56.3)
Group B	111.6 (43.3)	133.2 (44.9)	168.2 (54.6)	202.4 (51.8)	236.2 (61.7)
p value for PEFR (group A v B)	0.410	0.263	0.672	0.876	0.893

*Group A: nebulised magnesium sulphate + salbutamol; group B: salbutamol alone. †Values are mean (SD).

- Magnesium decreases excitability of muscle membrane by inhibiting the release of acetylcholine from cholinergic nerve terminals, thereby producing bronchial smooth muscle relaxation.²²
- Magnesium inhibits histamine release from mast cells and may stimulate nitrous oxide generation and prostacyclin synthesis.²³

The role of magnesium sulphate in the treatment of acute asthma has been evaluated in several studies. In most of the studies magnesium was administered intravenously. Only a limited number of studies of nebulised magnesium sulphate in acute asthma have been conducted. A Cochrane review showed that intravenous magnesium sulphate was effective in the treatment of acute bronchial asthma.²⁴ A recent meta-analysis in children with acute asthma also concluded that intravenous magnesium sulphate provided additional benefit when given along with other agents.¹⁰

The first studies of nebulised magnesium sulphate with salbutamol given as individual agents in patients with acute asthma showed the bronchodilator response of magnesium to be of either similar¹⁵ or lower magnitude and duration compared with salbutamol.¹⁶

Only a few studies have compared a combination of nebulised magnesium sulphate and salbutamol with salbutamol alone. Nannini *et al*'s¹¹ study on 35 patients showed that, compared with a single dose of salbutamol, there was a greater increase in peak flow rate when a single

dose of magnesium sulphate was added to nebulised salbutamol. In another study conducted on 52 patients with severe asthma,¹² nebulisation of three doses of magnesium sulphate plus salbutamol was found to produce more bronchodilation compared with three doses of salbutamol alone. Mahajan *et al*'s¹³ showed modest benefit of adding one dose of nebulised magnesium sulphate to salbutamol in the treatment of acute asthma in children. However, they did not give the subsequent course of the acute episode, including responses to repeat dosing with magnesium sulphate and salbutamol. In contrast, a study conducted in adults with mild to moderate acute asthma showed no benefit of administering three doses of magnesium sulphate along with salbutamol as compared with placebo plus salbutamol.¹⁴ Thus the results of these few studies, which included small numbers of patients, are conflicting with regard to the role of additional nebulisation of magnesium sulphate in acute asthma.

Our study, the largest to date, failed to show any benefit of the addition of nebulised magnesium sulphate to conventional treatment of acute asthma in patients with acute severe or life threatening asthma. We are unable to explain the marked differences in the initial magnesium levels between the two groups, and the fall in magnesium levels in the group receiving magnesium and the rise in the group receiving salbutamol.

There are some limitations of this study. Firstly, the mean duration of the asthma attack in both the groups was more than four days, which may be more than that seen in patients attending other emergency departments. This longer duration of the acute episode indicates that a marked amount of the bronchoconstriction would have been due to bronchial wall oedema, which would have limited the response to

Figure 2 Mean PEFR (l/min) at various time points in the two groups.

Table 3 Blood gas and serum magnesium measurements of the two study groups*†

	0 min	120 min	'p' value
PaO ₂ (mm Hg)			
Group A	81.0 (8.9)	89.3 (4.3)	0.000
Group B	82.2 (8.6)	90.2 (4.0)	0.000
PaCO ₂ (mm Hg)			
Group A	33.5 (6.8)	37.3 (5.4)	0.000
Group B	34.5 (8.5)	37.3 (4.6)	0.001
Magnesium (mmol/l)			
Group A	2.02 (0.18)	1.92 (0.21)	0.002
Group B	1.94 (0.21)	2.12 (0.25)	0.000
p value (group A v B)	0.042	0.000	

*Group A: nebulised magnesium sulphate + salbutamol; group B: salbutamol alone. †Values are mean (SD).

Table 4 Mean (SD) peak expiratory flow rate (PEFR) in patients receiving additional or not receiving additional medications during the study*

	Time (min)				
	0	15	60	75	120
PEFR in patients receiving no additional medications					
Group A (n = 27)	134.1 (39.4)	160.0 (34.1)	198.5 (28.8)	235.9 (29.0)	273.0 (31.4)
Group B (n = 27)	120.7 (35.7)	147.1 (36.7)	188.6 (32.4)	225.4 (32.2)	269.6 (33.9)
p value (group A v B)	0.193	0.184	0.235	0.207	0.708
PEFR in patients receiving additional medications					
Group A (n = 23)	100.4 (36.2)	122.6 (37.8)	141.7 (38.1)	166.5 (44.2)	196.5 (51.0)
Group B (n = 23)	100.0 (49.8)	115.5 (48.9)	142.3 (66.0)	173.2 (57.8)	193.6 (63.4)
p value (group A v B)	0.973	0.585	0.974	0.665	0.867

*Group A: nebulised magnesium sulphate + salbutamol; group B: salbutamol alone.

bronchodilator therapy. Despite this limitation, most of our patients did show a significant response to nebulised therapy. Secondly, most of the patients had received inhaled β agonists, oral steroids, and antibiotics before arrival at our emergency department. Thirdly although the dose of magnesium sulphate used in our study was higher than has been used in any other study, it is possible that even this higher dose was not adequate to produce significant bronchodilation. Fourthly, we did not continue nebulisation of magnesium sulphate beyond three doses although further doses of salbutamol are recommended if a patient shows only partial response to initial doses. Fifthly, many patients received additional medications (steroids and nebulised salbutamol) during the study. However, as the number of patients who received additional medications did not differ significantly between the two groups, we feel that this did not have any major effect on the results of the study. Furthermore, all the additional medications were administered after one hour of the start of study, and even at one hour, there was no significant difference in PEFR between the two groups. Finally, the study was underpowered (power 0.152 with a high β error). Therefore, a possible difference between the two groups could have been masked by the small sample size.

As the most important aspect of treatment of acute asthmatic patients is to reduce the rate of hospitalisation, future studies should be performed (with calculation of sample size) based on an event rate (hospitalisation rate) in the control group of 20% and a power of 0.80. The reduction in the event rate in the treatment group could be kept as 5% as this reduction will translate into a huge benefit. The large number of patients required warrants a multicentric study to answer the question whether addition of nebulised magnesium sulphate is beneficial in patients with acute asthma.

CONCLUSION

The present study showed that there may not be any therapeutic benefit of addition of magnesium sulphate to salbutamol nebulisation in the treatment of life threatening and acute severe asthma. However, an adequately powered study needs to be conducted to support this conclusion.

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