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A Randomized Controlled Trial of Intravenous Magnesium Sulphate as an Adjunct to Standard Therapy in Acute Severe Asthma

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ABSTRACT

Though intravenous (IV) Magnesium Sulphate ($MgSO_4$) has additive effect to beta-2 agonists, its additive benefit in face of combination therapy with beta-2-agonists and ipratropium (standard therapy of severe acute exacerbation of asthma) remains unaddressed. The aim of this investigation was to evaluate the role of IV $MgSO_4$ when used as an adjunct to standard therapy of severe exacerbations of asthma.

Randomized, single blinded, placebo-controlled study was carried out in Emergency Department (ED). Patients aged 18-60 years presenting with acute asthma and $FEV_1 \leq 30\%$ predicted (pred.) were included. All patients received IV Hydrocortisone on arrival.

In group1 (controls), patients were nebulised with salbutamol and ipratropium thrice at 20 minutes interval and were given 2g IV $MgSO_4$ at 30 minutes. In group2 patients were nebulised similarly, but were given IV normal saline at 30 minutes for blinding. FEV_1 was evaluated at baseline and at 30 minutes intervals. The primary efficacy end point was $FEV_1\%$ pred. at 120 mins and pooled discharge rate (derived from comparing proportion of groups attaining $PEFR \geq 60\%$ pred. and relief in dyspnea at 30,60,90,120 minutes). Both groups of 30 patients each, were matched with respect to demographic and pulmonary parameters (Baseline $FEV_1\%$: $22.0 \pm 5.1\%$ in group2 vs. $22.07 \pm 5.2\%$ in group1, $p=0.87$). At 120 minutes, there was a higher mean $FEV_1\%$ pred ($62.84 \pm 4.73\%$ vs. $56.7 \pm 4.5\%$) and %improvement from baseline of ($40.7 \pm 9.2\%$ vs $34.77 \pm 7.3\%$), in group 2 as compared to group1 (Mean Difference = 6.07%, C.I. 1.87-10.62., $p < 0.01$). The pooled discharge rate in group2 with respect to group1 was positive and significant (log rank = 6.8, $p < 0.05$). Thus IV $MgSO_4$ improves pulmonary function and discharge rates, when used as an adjunct to standard therapy in severe acute asthma.

Magnesium sulfate as an adjunct to standard therapy in patients with severe exacerbation of asthma could cause improvement in pulmonary function and decrease in hospital admission.

Key words: Acute severe asthma; Magnesium sulfate; Treatment

INTRODUCTION

Asthma is prevalent in 4-5% of the population of the developed countries and almost 27% asthmatics

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Intravenous Magnesium Sulphate in Acute Severe Asthma

presenting at emergency departments require admission despite standard therapy with beta adrenergic agonists, anti-cholinergics and corticosteroids.^{1,2} Presently, the mainstay of therapy in the Emergency Department (ED) are inhaled beta α -2-agonists and systemic steroids. The beneficial effects of beta agonists occur minutes after administration, while steroids may take a number of hours to improve pulmonary function. In the search for additional therapeutic options, intravenous (IV) Magnesium sulphate ($MgSO_4$) has been proposed as an effective and safe adjunct in treatment of acute asthma due to its low cost, widespread availability and low incidence of side effects.

Of the several randomized controlled trials using IV magnesium in acutely ill adults, results have been mixed with some studies demonstrating a benefit^{3,4,5} and others not.^{6,7} Studies, which have reported a positive outcome, have shown a benefit predominantly in those classified as severe exacerbations.^{3-5,8} Two recent reviews supported its use as an adjunct in severe exacerbation in adult and paediatric age groups respectively^{9,10}. However both these reviews consist mainly of studies in USA emergency rooms in 1990's and due to limitation of individual studies, the reviews are unable to address factors such as the clinical setting of the study or concomitant therapy such as pre-existing inhaled corticosteroid, or additional therapies such as anti-cholinergics. Despite proven benefit of IV $MgSO_4$ to beta-2 agonist, its additive benefit in patients receiving treatment including ipratropium in addition to beta-2-agonists, (standard therapy of exacerbation of asthma), and those already taking inhaled corticosteroids remains unclear and unaddressed.¹⁰⁻¹²

Though Magnesium has been recommended as adjunct in international guidelines for management of severe exacerbations, some investigators argue that potential bronchodilator and anti-inflammatory benefits of $MgSO_4$ might be eroded in these common clinical settings of a treatment protocol including ipratropium¹² and pre-treatment with steroids¹¹, rendering it ineffective as an adjunct. Many researchers emphasise the need for a study with design including ipratropium bromide as part of standard therapy for severe exacerbation of asthma as well as enrolling patients already receiving inhaled corticosteroids, to properly evaluate the role of Magnesium Sulphate as an adjunct in severe exacerbations of asthma.¹⁰⁻¹⁴

We did a MEDLINE search before commencing this study and did not find any trial evaluating role of

IV $MgSO_4$ as adjuvant to standard therapy in acute severe asthma patients, including ipratropium as a part of the protocol. This is the first study in medical literature (to the best of our knowledge) to evaluate the role of IV $MgSO_4$ in severe exacerbation of asthma by adopting design taking ipratropium as a part of standard therapy of severe exacerbations to do away with the critical limitation of above mentioned earlier works.^{12,13} The aim of the study was to measure the improvement in pulmonary function as well as the preventive risk of hospitalization in adjunct IV $MgSO_4$ group compared to control group. The aim was thus to explore, both physiologically and clinically significant effects of $MgSO_4$ as an adjunct, if there are any.

PATIENTS AND METHODS

Study Patients

Patients between the ages of 18 years and 60 years presenting with acute asthma to the ED of Vallabhbhai Patel Chest Institute, Delhi, India were considered for enrollment. Patients were eligible if asthma was diagnosed in the past by a clinician with spirometry records showing a reversibility of 12%, and asthma medication was used during the previous 6 months. Patients were included if they had an $FEV_1 < 30\%$ predicted on presentation to the ED, were willing to remain in the Emergency Room for 3 h, and fulfilled most of the criteria for severe exacerbations as according to GINA.¹⁵ Exclusion criteria were a history of COPD or other chronic lung disease, and other known cardiac, renal and hepatic dysfunctions. Patients were excluded if they were pregnant or lactating. Patients requiring intubation or unable to perform spirometry were also excluded. The study was approved by the human subjects ethical committee at vallabhbhai patel chest institute.

Initial Management and Assessment

On arrival in the emergency room, 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. The parameters measured were: 1. Spirometry, 2. Respiratory rate, 3. Heart rate and blood pressure, 4. Presence of cyanosis, 5. Arterial oxygen saturation using a pulse oxymeter 6. Clinical examination of respiratory system and 7. Borg Dyspnea score (At 0 and 120 minutes). Borg dyspnea scale is a rating from 0 through

10 that allows patients to self-assess breathlessness, where 0 indicates no dyspnea and 10 represents the most severe dyspnea.¹⁶

A portable spirometer was used to measure pulmonary function (KoKo legend peak model Ferraris, Louisville). Since patients with acute severe asthma may not be able to perform spirometry according to accepted standards, we accepted spirometry in which the forced expiration lasted at least 2 seconds, a sharply defined peak flow was, present early in expiration. Lack of significant glottic closure was present in the first second, and the patients appeared to be offering their best effort. (detected by spirometer). Patients were encouraged to give at least three acceptable efforts at each time period where the FEV₁ measures from the two best efforts were within 10% of each other. However only one effort was required on arrival for enrollment¹¹. FEV₁ and peak expiratory flow rate (PEFR) measures were recorded from the spirometer, predicted values were calculated from the NHANES III prediction equations for Caucasians. The same instrument was used throughout the study.

Randomization and Treatment Protocol

This was a placebo-controlled, randomized, single-blinded trial. Patients were allocated to the two groups using a 1:1 ratio randomization table. 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. After randomisation and group allocation patients in both groups were given 100 mg IV hydrocortisone at arrival (0-minute), and there after treated according to following protocol.

A nebulising solution consisted of 1ml of 2.5% salbutamol (2.5 mg of beta-2 agonist), 1.5 ml of ipratropium bromide (anticholinergic) and 2.5 ml of normal saline aerosolized via a wet nebuliser with 100 % oxygen. The patients in one group received 2 ampules of 2ml of 50% MgSO₄ (2g) diluted in 250 ml of normal saline and given slowly over 20 minutes to prevent central nervous side effects and flushing. Similar-looking placebo was given to other group.

Group A (IV MgSO₄ group): Patients received 1 mL of 2.5% salbutamol (2.5 mg), 250 micrograms of 1.5 ml ipratropium administered in 2.5 mL of normal saline via wet nebulizer with 100% oxygen at 0,20,40 minutes after admission into the protocol. At 30 min,

the patient received 2 g magnesium sulfate in 250 mL of normal saline solution given slowly over 20 minutes.

Group B (control group): Patients received 1 mL of 2.5% salbutamol (2.5 mg), 250 micrograms of 1.5 ml ipratropium administered in 2.5 mL of normal saline via wet nebulizer with 100% oxygen at 0,20,40 minutes after admission into the protocol. At 30 min, the patient received like-appearing placebo in 250 mL of normal saline solution.

Assessment of Response

All clinical parameters were recorded at 0, 30,60, 90, and 120 minutes. Spirometry and clinical examination of respiratory system were done at every assessment. The primary objective was to determine whether changes in FEV₁ produced by the two interventions would be significantly different in the two study. Any side effects noted by the patient or physicians were recorded. At 120 min, a decision to hospitalize or discharge was made by respective ED unit staff, blinded to group allocation. Hospital admission criteria were standardized: PEFR < 60% predicted, or significant dyspnea on walking. when protocol ended, All patients discharged from the ED were instructed to continue their regular medications, to use inhaled salbutamol every 3 to 4 h as needed, and to take prednisone, 30 mg OD, for 7 days along with antibiotics if deemed suitable.

Statistical Analysis

The primary outcome variable was FEV₁ percent predicted at 120 min, and hospital admission rates. Secondary outcome measures included, change in Borg dyspnea ratings, pulse rate and respiratory rate. All data were analyzed with a "SPSS 15.0 software package (SPSS Inc. Chicago, IL). Estimations from power calculations showed that the use of 60 subjects was sufficiently sensitive to detect a 0.32 L difference in FEV₁, and 15 % difference in hospital admissions, with $\alpha = 0.05$ and $\beta = 0.20$ (i.e., with 80% power). From a previous study result in subgroup of severe exacerbation FEV₁ \leq 30% we could estimate the mean (\pm SD) final FEV₁ value (in liters) to be expected at 2 h to be 1.62 ± 0.64 .¹⁴ Changes in FEV₁ were evaluated using repeated-measures analysis of variance (ANOVA), with one between-subject factor (IV MgSO₄ control) and one within-subject factor (time). One-way repeated-measures ANOVA was used to compare baseline values for each variable, after assessing normality of distributions. When the F value indicated significant dif-

Intravenous Magnesium Sulphate in Acute Severe Asthma

ferences between group means, post hoc pairwise multiple comparisons were performed using the Bonferroni test. To provide a graphic summary, Kaplan-Meier curves of the proportion of patients who reached the discharge threshold during the 2 hours of treatment were used.

RESULTS

Study Population

A total of 75 patient visits were screened, 5 patients were excluded, 10 patients randomized had protocol violations (Figure 1). Baseline historical and clinical variables were similar in both groups (Tables 1, 2). There was significant difference in height between both groups.

Improvement in Pulmonary Function

The improvement in pulmonary function over baseline was significant in both groups ($p < 0.01$). There was a significant difference between both groups ($p=0.01$). Subjects receiving IV MgSO₄ had a

40.77±9.2% improvement from baseline, and control subjects showed a 34.7±7.3% improvement from baseline. Thus Patients receiving IV MgSO₄ showed an overall greater improvement of .607%, (95%.C.I. 1.87-10.62., $p<0.01$) in FEV₁ from that of the control group. The mean FEV₁ % predicted values at 0, 30, 60, 90, 120min, were 22.0±5.1%, 44.27±7.65%, 54.93±7.54, 57.83±8.96% and 62.84±10.02%, respectively, in the IV MgSO₄ group, and 22.07±5.2%, 47.47±7.45%, 50.97±6.14% 54.37±4.73 and 56.7±6.20% in the control group (Figure 2).

Hospital Admission

The overall hospital admission rate at 2 hour was higher in patients receiving placebo (9 \ 30 patients) than IV MgSO₄ (2\30). Kaplan-Meier estimated curves of the proportion of patients who reached the discharge threshold during the 2 h of treatment showed a significant difference in favor of the IV MgSO₄ group (log-rank test =6.38, $p=0.011$) (Figure 3).

Table 1. Population characteristics in both groups. Data are presented as mean (SD).

Population characteristics	Magnesium group (n=30)	Controls(n=30)
1.Age(years)	34.79 (8.05)	35.9(8.76)
2.Sex (male\female)	14\16	15\15
3.Height(cm)	151.73(3.81)	155.07(5.09)*
4.Weight(kg)	60.03(8.92)	58.03(7.65)
5.Duration of Asthma(yrs.)	12(4)	11(6)
6.History of Atopy	7\30	5\30
7.Smoker	2\30	3\30
8.Number of patients with Past emergency visits	20\30	21\30
9. a) Reliever beta-2-agonist use in Past 24 hr	22\30	20\30
b) Theophylline use in 24 hr	8\30	10\30
c) Steroid use in 24 hr	4\30	6\30

There were significant differences in height between two groups. (*= $P<0.05$)

Table 2. Clinical Measures According to Study Group on Emergency Room Arrival, and 120 min after Arrival (Discharge).

Topics Variables	0 minute(Arrival)		120 minute(Discharge)		Mean difference between groups (95% C.I.)
	Placebo	Magnesium	Placebo	Magnesium	
1. Respiratory rate, Breaths\ min	38.70(3.40)	38.20(2.56)	21.60(2.46)	21.83(1.55)	-0.733_(-2.32- 0.85)
2. Pulse rate, beats\ minute	126.47(11.47)	127.97(10.19)	106.27(8.34)	100(7.43)	7.76_(0.24-15.29)*
3. Mean arterial Pressure mm Hg	104.5(5.28)	103.17(16.48)	97.83(2.60)	94.5(16.7)	1.93_(-0.15 - 4.02)
4. Borg Dyspnea Scale	9.66(0.484)	9.67(0.50)	2.40(1.35)	2(0.83)	0.4_(-0.2 - 1.0)
5. FEV ₁ % predicted	22.0(5.1)	22.07(4.77)	56.70(6.20)	62.84(10.02)	6.07_(1.87-10.62)**

Data are presented as mean (SD) unless otherwise indicated. Borg dyspnea index scaled from 0 (no symptoms) to 10 (most severe symptoms). Placebo or magnesium were administered immediately after the 30-min assessment. Magnesium was administered 2 g IV. (* $p < 0.05$, ** $p < 0.01$)

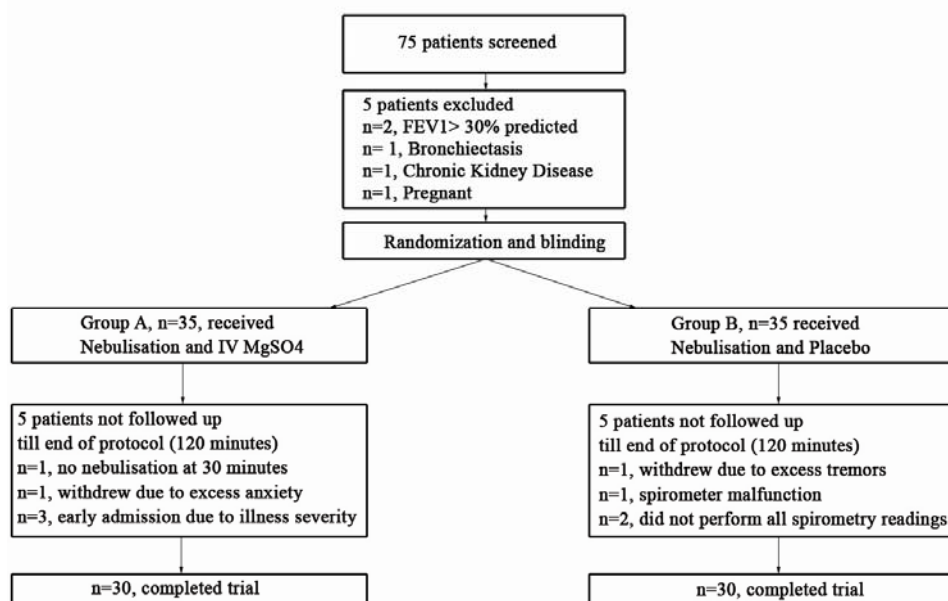


Figure 1. Consort flow diagram showing enrolment and allocation of patients to the nebulisation plus IV magnesium sulphate or nebulisation alone (control)

group. 75 patients were screened, 5 excluded. 10 randomized patients had protocol violation

Group A (N=35)

Received Nebulisation and IV MgSO4

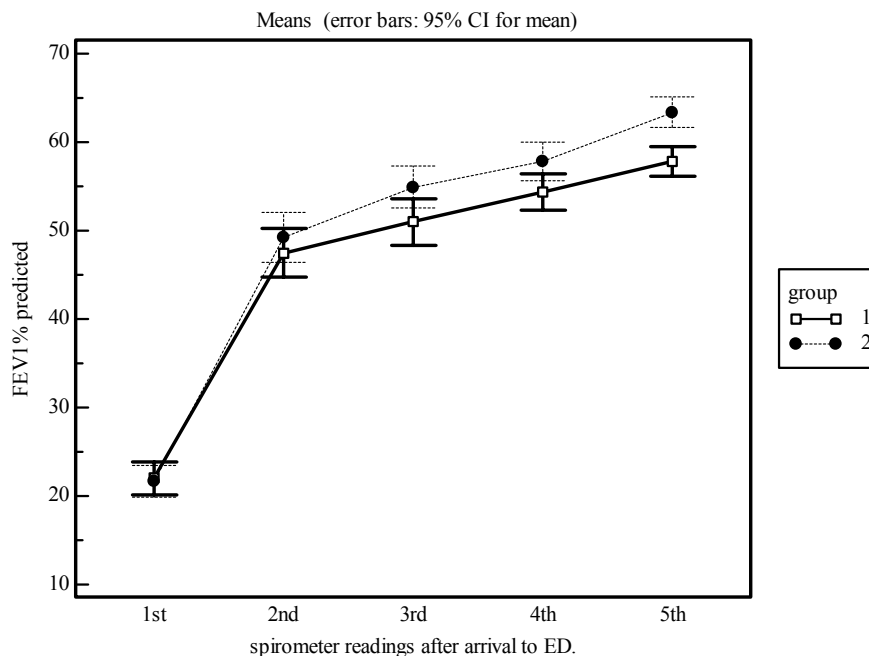


Figure 2. FEV₁ percent predicted expressed as mean Spirometry readings were performed at ED arrival (1st reading), 30 min (2nd), 60 min (3rd), 90 min (4th) and 120 min (5th). Three nebulisations with salbutamol and ipratropium were performed at 0, 20, 40 minutes after arrival in each group. Magnesium (group 1) or placebo (group 2) was administered after spirometry measurement at 30 min. At 120 min, final spirometry was performed and the treatment protocol ended

Intravenous Magnesium Sulphate in Acute Severe Asthma

The IV MgSO₄ group showed higher rates of patients who obtained the discharge threshold than the control group at 60, 90 and 120 min. The proportions (95% CI) at these treatment times were 60% (42 to 78%), 83.3% (69 to 97%), 93% (79 to 97%), in the IV MgSO₄ group and 33.3% (16 to 50%), 54.3% (36 to 72%), 70% (54 to 86%) respectively, in the control group. The O.R. (odds ratio) for admission in IV MgSO₄ with respect to placebo was lower and significant. (O.R=0.16, C.I=0.05-0.77, p<0.05). The absolute risk reduction (ARR) in hospitalization in IV MgSO₄ group was also significant at 23% (C.I. 4.6%-146.2 % p=0.045). The average number of patients needed to treat (NNT) to prevent one hospitalization in MgSO₄ group was 4.2 and significant (C.I.-0.05 to maximum of 11.2).

Other Clinical Response Variables

The 120-min pulse rate was lower in the magnesium-treated group as compared to control treatment, while other clinical variables including respiratory rate and Borg dyspnea index did not significantly differ (Table 2).

Side Effects

In adjunct IV MgSO₄ group, there were complaints of anxiety (8/30), palpitations (4/30), tremors (15/30), headache (6/30), dry mouth (16/30), and non-specific nausea (2/30). In placebo-controlled group, there were complaints of anxiety (10/30), palpitations (6/30), tremors (14/30), headache (5/30), dry mouth (17/30), and non-specific nausea (1/30). There was no statistically significant difference in any of these side effects. No Magnesium specific side effects like arrhythmia, hypotension or loss of deep tendon reflexes were noted in the study.

DISCUSSION

This is the first study to demonstrate that 2 g of IV MgSO₄ when administered as an adjunct to standard therapy of acute severe asthma including ipratropium as a part of its protocol, improves pulmonary function and decreases hospital admission rates in patients presenting to the ED with severe exacerbations of asthma. There is also a higher decrease in pulse rate and a larger increase in oxygen saturation in IV MgSO₄ group as compared to controls.

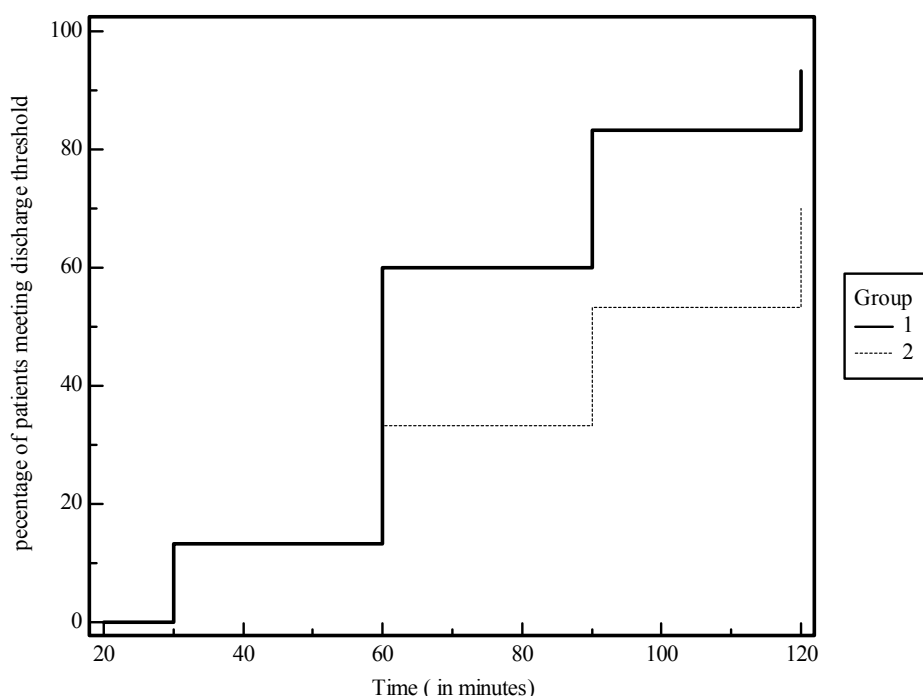


Figure 3. Kaplan-Meier estimated curves showing the percent of patients in the IV MgSO₄ (group 1) and control (group 2) groups who obtained the discharge threshold (PEFR_≥ 60% and relief in dyspnea) during the treatment time. Log-rank test =6.38, p=0.011

Outcomes and Possible Mechanisms

FEV₁% Improvement. In this study patients in group receiving salbutamol, Ipratropium, steroids and adjunct IV MgSO₄ had an improvement in FEV₁ of 40.77±9.2% from baseline. Thus Patients receiving IV MgSO₄ showed an overall greater improvement of .6.07 %, (95%.C.I .1.87-10.62.,p<0.01) in FEV₁ from that of placebo-controlled group In a severe subgroup (PEFR<50%) of a recent study by Bradshaw et. al¹⁷ using ipratropium, steroids and lower dose of IV MgSO₄ (1.2 g) as adjuvant to salbutamol ,there was no difference in percent predicted PEF between groups at end point (MgSO₄ 63.7 cf. placebo 61.6; mean difference,2.1; 95% CI, _6.7 to 11.0; p =0.63) .The dose of MgSO₄ in the above study was 1.2 g whereas our study and the majority of others demonstrating a response used 2g. Researchers ⁵ have reported a dose dependent improvement in pulmonary function in response toMgSO₄, suggesting optimal bronchodilation may be achieved using higher doses of MgSO₄. The positive response in our study and other studies ^{5,11} may have been influenced by the choice of dosing at the higher end of the recommended range (2g) as compared to study by Bradshaw et al.¹⁷ Also, a lower threshold of pulmonary function, FEV₁ ≤ 30% predicted was used for inclusion in this study as compared to study by Bradshaw et. al. (PEFR< 75% predicted) and a more sensitive indicator (FEV₁ %vs. PEFR%) for assessing change in pulmonary function might have been the other cause of the discrepancy between the results, since IV MgSO₄ has been shown to cause larger improvement in more severe subgroup (FEV₁ ≤ 30% of acute asthma.⁵ In another study by Silverman *et al.* there was an FEV₁ % change of 25.1 ± 11% from baseline in patients with severe exacerbations (FEV₁ < 30%)receiving salbutamol ,steroids and IV MgSO₄ group¹¹. In another study, which was similar to control group in our study, there was a mean FEV₁ % change of 34 ± 12% from baseline after 2hrs in patients receiving salbutamol and ipratropium in severe exacerbations (FEV₁ <30%).¹² The higher improvement in FEV₁ in this study as compared to above studies is due to cumulative effects of salbutamol, ipratroipum and MgSO₄ used in this study design. This also goes on to show that IV MgSO₄ exerts a positive outcome even in face of standard treatment including ipratropium and in patients already pre-treated with steroids. Thus the additional benefit of MgSO₄ is not eroded when these factors are taken in account as had been doubted by some

investigators.^{11,12} Meta-analyses have shown that IV MgSO₄ exhibits a varying levels of improvement (strongly significant to weakly significant) in pulmonary functions ^{9,10,18} The results of these meta-analyses differ due to different number of individual studies included and the heterogeneity in design of studies. Various factors might have contributed to a larger improvement in pulmonary function in our study group using adjunct IV MgSO₄. Magnesium causes relaxation of bronchial smooth muscle via modulation of calcium ion movement within the cell¹⁹ and prostaglandin and G-protein mediated vascular smooth-muscle relaxation.²⁰⁻²³ Its anti-inflammatory action via decreased super-oxide production in neutrophils probably leads to sustained improvement in pulmonary function.²⁴

Hospital Admission Risk. The discharge rate at 120 min in adjunctive IV MgSO₄ group (28\30) was higher than placebo (26\30) and both were clinically and statistically significant.. The absolute risk reduction in hospitalization in IV MgSO₄ group in this study is statistically significant at 23% (C.I. 4.6% - 146.2 %) as well as clinically significant since in search for newer therapeutic options for treatment of severe exacerbations, even a 5% decrease in hospitalization assumes much importance.²⁵ The significant pooled discharge rate implies that effect threshold starts early and thus if MgSO₄ is used routinely in severe exacerbations,it can result in earlier discharge of the patient. The average number of patients needed to treat (NNT) to prevent one hospitalization in MgSO₄ group was only four. This represents a substantial reduction in cost given a much higher cost of example compared with drug.. The significantly lesser hospitalization rate in our study as compared to study by Bradshaw et al. (MgSO₄ 70% (21/30) placebo= 84% (26/31) p=0.32) might be due to higher dose of MgSO₄ (2g) and lower threshold (FEV₁ ≤ 30%) of inclusion. Meta-analyses differ on preventive risk of admission conferred by use of IV MgSO₄ as adjunct. One meta-analysis of trials in children shows a preventive risk¹⁰ (OR 0.290, 95% CI 0.143 to 0.589), while meta-analyses of trials in adults by Goodacre²⁴ and Rowe⁹ showed a non-significant benefit.. This heterogeneity in hospitalization risk seen in meta-analyses as compared to uniform benefit in pulmonary function might have been due to the subjective nature of guidelines for admission and different number of trials included. The wide range of confidence intervals of absolute risk of reduction of hospitalization rates and odds ratio are due to the logarithmic distribution of confi-

Intravenous Magnesium Sulphate in Acute Severe Asthma

dence intervals of odds ratio and absolute risk reduction and lesser number of patients in this study. While these results are still significant ($p < 0.05$) and can be generalised, a study with larger number of subjects and hence higher power might have narrower range of confidence intervals.

Decrease in Pulse Rate. A significant higher decrease in pulse rate in adjunctive IV $MgSO_4$ group as compared to placebo group is similar to the findings by Gaur et al in comparison of inhaled Magnesium versus inhaled salbutamol²⁶ and is probably due to negative dromotropic action of $MgSO_4$ in tachy-arrhythmias. It also confers $MgSO_4$ an advantage as an adjunct over IV aminophylline which has definite arrhythmogenic properties and a narrow therapeutic window.²⁷

Side Effects. The lack of Magnesium related and additional side effects in this study is similar to the results of meta-analyses.^{9,10} No major side effects were noted in this study. The side effects of tremor, palpitation, headache might have been due to use of beta-2-agonist action of salbutamol while dry mouth might have due to anti-secretory action of ipratropium. Serious side effects of Magnesium at the dose administered in this study are extremely uncommon in patients with adequate renal function

Limitations of the Study

Single-blindedness of this study is source of potential bias and in future double-blind design should be used to verify findings of this study. Study is also needed to determine if repeat doses or continuous infusions of magnesium benefits ED or hospitalized patients with asthma. Another consideration is whether protocol bronchodilator therapy was sub-optimal for this subject population. However, In support of this study regimen, 7.5 mg of nebulised salbutamol is as effective as 22.5 mg (7.5 mg every 20 min) and continuous nebulisation is not more effective than intermittent nebulisation.²⁸⁻³⁰

Clinical and Research Implications

This study used the recommended design⁹⁻¹⁴ taking ipratropium and steroids as part of standard therapy of acute severe asthma to properly evaluate the role of 2 g $MgSO_4$ as an adjuvant, and it was found that 2 g IV $MgSO_4$ causes improvement in pulmonary function even when ipratropium is a part of standard therapy protocol in severe exacerbations of asthma. Larger double blind studies with this design should be done to

find potential benefit of IV $MgSO_4$ as adjunct to salbutamol and ipratropium in both adults and children.

In summary, 2 g of IV magnesium sulfate administered as an adjunct to standard therapy in patients presenting to ED with severe exacerbation of asthma causes improvement in pulmonary function and decrease in hospital admission and it should be used as an adjunct to systemic steroids and nebulisation with beta-2-agonists and anticholinergics in patient who present to the ED with severe airway obstruction.

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