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Nebulised Magnesium Sulphate as an Adjunct to Standard Bronchodilator Therapy in Adults with Acute Severe Asthma: A Randomised, Double-Blind, Placebo-Controlled Trial

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ABS TRAC T

***Background*:** Acute severe asthma remains a frequent cause of emergency attendance, and a substantial proportion of patients respond incompletely to inhaled beta-2 agonists, ipratropium bromide and systemic corticosteroids. Nebulised magnesium sulphate has been proposed as an inexpensive adjunct that acts directly at the airway smooth muscle, but the reported evidence has been inconsistent. The present trial evaluated whether the addition of nebulised magnesium sulphate to standard therapy improved airflow obstruction and reduced hospital admission in adults with acute severe asthma. ***Methods*:** A randomised, double-blind, placebo-controlled trial was conducted in the emergency department of a tertiary care teaching hospital over 18 months. One hundred adults aged 18 to 60 years with acute severe asthma and a peak expiratory flow rate below 50% of predicted were randomised in a 1:1 ratio. Group A received three doses of nebulised isotonic magnesium sulphate (500 mg in 2.5 mL) and Group B received 2.5 mL of nebulised 0.9% saline, each combined with salbutamol and ipratropium bromide at 20-minute intervals. All patients received intravenous hydrocortisone. The primary outcome was the change in peak expiratory flow rate expressed as percentage predicted at 240 minutes. Secondary outcomes included forced expiratory volume in one second, Borg dyspnoea score, hospital admission, emergency department length of stay and adverse events. ***Results*:** The two groups were comparable at baseline. The mean improvement in peak expiratory flow rate at 240 minutes was 34.2 ± 9.8% predicted in Group A and 26.9 ± 10.4% predicted in Group B (mean difference 7.3, 95% confidence interval 3.3 to 11.3; $p < 0.001$). Hospital admission occurred in 11 (22.0%) and 21 (42.0%) patients respectively ($p = 0.032$). Mean emergency department stay was shorter in Group A (5.8 ± 1.9 versus 7.2 ± 2.4 hours; $p = 0.002$). Adverse events were minor and comparable between groups. ***Conclusion*:** Nebulised magnesium sulphate added to standard bronchodilator therapy produced a modest but statistically significant improvement in airflow obstruction and reduced hospital admission in adults with acute severe asthma, with the greatest benefit in the most severely obstructed patients.

Keywords: *Acute Severe Asthma, Magnesium Sulphate, Nebulisation, Peak Expiratory Flow Rate, Emergency Department, Randomised Controlled Trial*.

INTRODUCTION

Asthma remains one of the most prevalent chronic non-communicable respiratory disorders worldwide. Estimates derived from the Global Burden of Disease Study 2021 indicate that approximately 260 million individuals were living with asthma in that year, and the age-standardised disability-adjusted life-year rate attributable to asthma was highest in South Asia, a region that includes India [1]. Although age-standardised prevalence rates have declined over three decades, the absolute number of affected individuals continues to rise with population growth and ageing, and mortality remains concentrated in low and lower-middle income settings where access to preventive controller therapy is limited. Acute exacerbations account for a disproportionate share of this burden because they generate unscheduled emergency attendances, hospital admissions, intensive care utilisation and occasional death [2].

An asthma exacerbation reflects an acute or subacute deterioration in symptoms and lung function superimposed on chronic airway inflammation, and is driven by a combination of bronchial smooth muscle constriction, mucosal oedema, mucus plugging and heightened airway responsiveness.[2] Viral respiratory infection, allergen exposure, air pollution, poor adherence to inhaled corticosteroids and inadequate inhaler technique are the dominant precipitants encountered in clinical practice. The severity of an exacerbation is graded on the basis of the ability to complete sentences, respiratory rate, heart rate, oxygen saturation and objective airflow measurement, and acute severe asthma is conventionally defined by a peak expiratory flow rate below 50% of the predicted or personal best value in a patient who is unable to complete sentences in one breath [3].

The pharmacological cornerstone of emergency management has remained essentially unchanged for several decades and consists of controlled oxygen therapy, repeated or continuous nebulisation with a short-acting beta-2 agonist, the addition of ipratropium bromide in severe exacerbations, and early administration of systemic corticosteroids [3]. Despite the consistent application of this regimen, a clinically important minority of patients demonstrate an incomplete response, and these patients account for most admissions, most escalations to non-invasive or invasive ventilation, and most asthma-related deaths. The search for a safe, inexpensive and rapidly available adjunct for this refractory subgroup therefore continues to occupy emergency and respiratory physicians.

Magnesium is the second most abundant intracellular cation and functions as a physiological calcium antagonist. Within the airway, magnesium inhibits calcium influx through voltage-gated channels in bronchial smooth muscle, reduces acetylcholine release at the neuromuscular junction, stabilises mast cell membranes with consequent attenuation of histamine release, and inhibits neutrophil respiratory burst activity. These actions together produce bronchial smooth muscle relaxation and may additionally potentiate the bronchodilator effect of beta-2 agonists. Intravenous magnesium sulphate has been the most extensively investigated formulation, and a Cochrane review of adults treated in the emergency department concluded that a single intravenous infusion produced a modest reduction in hospital admission among patients who had not responded adequately to first-line therapy, although the effect on lung function was less consistent [4]. Intravenous administration nevertheless requires venous access, carries a theoretical risk of hypotension, flushing and neuromuscular depression, and mandates a degree of monitoring that is not always feasible in a crowded emergency department.

The nebulised route is attractive because it delivers magnesium directly to the target tissue, avoids systemic loading, requires no additional monitoring and can be combined with the bronchodilator solution already in use. The Cochrane review of inhaled magnesium sulphate concluded that the addition of nebulised magnesium to inhaled beta-2 agonist with or without ipratropium bromide may produce a small improvement in lung function, but the certainty of the evidence was limited by clinical heterogeneity and by the modest size of most contributing trials [5]. The individual trial evidence has been discordant. An early randomised placebo-controlled study in adults with severe exacerbations demonstrated a significantly greater improvement in forced expiratory volume in one second when isotonic magnesium sulphate was used as an adjuvant to nebulised salbutamol [6]. In contrast, a randomised double-blind study conducted in an Indian emergency department found no additional therapeutic benefit from the addition of nebulised magnesium sulphate to salbutamol in patients with acute severe or life-threatening asthma [7]. The large multicentre 3Mg trial in adults reported that neither intravenous nor nebulised magnesium sulphate produced a clinically worthwhile reduction in breathlessness or hospital admission, although a small effect could not be excluded [8]. The paediatric MAGNETIC trial similarly found no clinically significant overall improvement in asthma severity score, yet identified a greater response among children with more severe attacks and shorter symptom duration [9]. A recent systematic review and meta-analysis of magnesium sulphate in adults with acute severe asthma reaffirmed that benefit appears to be confined to the most severely obstructed patients and that the optimal route, dose and dosing frequency remain undefined [10].

This persistent uncertainty is attributable in large measure to methodological heterogeneity across trials, including variation in magnesium dose from 95 mg to 500 mg per nebulisation, the use of isotonic and hypertonic preparations, single versus repeated dosing, differing definitions of exacerbation severity, and the inconsistent co-administration of ipratropium bromide. Indian data are particularly limited, and the small number of published studies from this region has largely enrolled patients across the full spectrum of exacerbation severity rather than restricting recruitment to the severe subgroup in whom benefit is most plausible. The present randomised, double-blind, placebo-controlled trial was therefore designed to evaluate whether three sequential doses of nebulised isotonic magnesium sulphate, administered as an adjunct to standard nebulised salbutamol and ipratropium bromide with systemic corticosteroid, improved airflow obstruction, symptom burden and hospital admission in adults presenting with acute severe asthma to a tertiary care emergency department.

AIMS AND OBJECTIVES

The aim of the present study was to determine whether the addition of nebulised magnesium sulphate

to standard bronchodilator and corticosteroid therapy conferred measurable clinical benefit in adults presenting with acute severe asthma to the emergency department of a tertiary care teaching hospital. The study was conceived as a pragmatic evaluation of an inexpensive and widely available adjunct in a patient population in whom the response to conventional first-line therapy was frequently incomplete.

The primary objective was to compare the magnitude of improvement in peak expiratory flow rate, expressed as a percentage of the predicted value, between patients who received nebulised magnesium sulphate in addition to standard therapy and those who received nebulised normal saline in addition to standard therapy, measured at 240 minutes from the commencement of the study intervention. The secondary objectives were to compare the serial change in forced expiratory volume in one second between the two treatment groups, to compare the change in subjective breathlessness as quantified by the modified Borg dyspnoea scale, to compare the serial change in oxygen saturation, respiratory rate and heart rate, to compare the proportion of patients in each group who required hospital admission at the conclusion of the four-hour observation period, to compare the total duration of emergency department stay, to compare the requirement for rescue therapy in the form of intravenous magnesium sulphate, intravenous aminophylline, non-invasive ventilation or invasive mechanical ventilation, and to compare the frequency of relapse necessitating unscheduled medical contact within seven days of discharge.

A further objective was to document the safety profile of repeated nebulised magnesium sulphate in this setting by recording the incidence of local and systemic adverse effects, including metallic taste, flushing, tremor, palpitations, nausea and symptomatic hypotension, and to determine whether the treatment effect differed according to the severity of airflow obstruction at presentation through a prespecified subgroup analysis stratified by baseline peak expiratory flow rate.

MATERIALS AND METHODS

Study design and setting

A prospective, randomised, double-blind, placebo-controlled, parallel-group trial was conducted in the emergency department of a tertiary care teaching hospital in India over a period of 18 months. The study protocol was reviewed and approved by the Institutional Ethics Committee before the commencement of recruitment, and the trial was prospectively registered with the Clinical Trials Registry of India. The study was conducted in accordance with the Declaration of Helsinki and the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants issued by the Indian Council of Medical Research. Written informed consent was obtained from every participant, or from a legally acceptable representative when the severity of breathlessness precluded the patient from providing a written signature at the time of presentation, with retrospective consent obtained from the patient once clinical stability had been achieved.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Human Ethics Committee of All India Institute of Medical Sciences (AIIMS), Bhopal, Madhya Pradesh, India, under Approval No. IHEC/AIIMS-BPL/2024/097. Written informed consent was obtained from all participants or their legally authorised representatives, as applicable, after the study objectives, procedures, potential risks and benefits, confidentiality measures, and voluntary nature of participation were explained. Participants were informed that they could withdraw from the study at any time without affecting their medical care. All participant information and study data were kept confidential and used solely for research purposes. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and applicable national guidelines for biomedical research involving human participants.

Study population and eligibility criteria

Consecutive patients aged 18 to 60 years of either sex who presented to the emergency department with an acute exacerbation of previously diagnosed bronchial asthma were screened for eligibility. Acute severe asthma was defined by the presence of a peak expiratory flow rate below 50% of the predicted value for age, sex and height, together with at least one of the following clinical features: inability to complete a sentence in one breath, respiratory rate of 25 breaths per minute or more, or heart rate of 110 beats per minute or more. A previous physician diagnosis of bronchial asthma documented in the medical record, or demonstrable reversible airflow obstruction on prior spirometry, was required for inclusion. Patients were required to be able to perform an acceptable and reproducible peak expiratory flow manoeuvre at the time of screening.

Patients were excluded if they had a life-threatening exacerbation requiring immediate intubation, a silent chest, cyanosis, bradycardia, exhaustion or an altered sensorium at presentation. Further exclusion criteria comprised a diagnosis of chronic obstructive pulmonary disease or a smoking history exceeding 10 pack-years, coexistent pneumonia, pneumothorax, pulmonary tuberculosis or bronchiectasis, congestive cardiac failure or significant ischaemic heart disease, chronic kidney disease with an estimated glomerular filtration rate below 60 mL/min/1.73 m², known hypermagnesaemia or a serum magnesium concentration above the upper limit of the reference range, second or third degree atrioventricular

block, myasthenia gravis, pregnancy or lactation, receipt of any magnesium preparation within the preceding 24 hours, and refusal to provide informed consent.

Sample size determination

The sample size was calculated on the basis of the primary outcome. Data reported by a previous randomised study of nebulised magnesium sulphate in adults with acute asthma were used to anticipate a difference of 8 percentage points in the mean improvement in peak expiratory flow rate expressed as percentage predicted, with a pooled standard deviation of 13 percentage points. Adopting a two-sided alpha of 0.05 and a power of 80%, the required sample size was 42 participants per group. This figure was inflated to 50 participants per group to accommodate an anticipated attrition and protocol violation rate of approximately 15% and to permit the prespecified subgroup analysis by baseline severity. The total planned enrolment was therefore 100 participants, allocated equally to the two treatment arms.

Randomisation, allocation concealment and blinding

Eligible participants were randomised in a 1:1 ratio using a computer-generated block randomisation sequence with variable block sizes of four and six, prepared by a statistician who had no further involvement in recruitment or outcome assessment. Allocation was concealed using serially numbered, opaque, sealed envelopes that were opened only after written informed consent had been obtained and baseline measurements had been recorded. The study solutions were prepared by a hospital pharmacist who was not involved in patient care, and were dispensed in identical unlabelled syringes containing 2.5 mL of either isotonic magnesium sulphate or 0.9% sodium chloride. The two solutions were indistinguishable by appearance. Patients, treating physicians, nursing staff, outcome assessors and the statistician performing the analysis remained blinded to the allocation until the database had been locked.

Study intervention

Participants allocated to Group A received nebulised isotonic magnesium sulphate at a dose of 500 mg in 2.5 mL, combined in the nebuliser chamber with salbutamol 2.5 mg and ipratropium bromide 500 micrograms. Participants allocated to Group B received 2.5 mL of 0.9% sodium chloride in place of magnesium sulphate, combined with the identical doses of salbutamol and ipratropium bromide. Three doses were administered to every participant at 20-minute intervals, that is at 0, 20 and 40 minutes from randomisation, using a jet nebuliser driven by oxygen at a flow rate of 6 to 8 litres per minute. All participants additionally received intravenous hydrocortisone 200 mg at the time of randomisation and controlled supplemental oxygen titrated to maintain peripheral oxygen saturation between 94% and 98%. After completion of the three study nebulisations, all participants received nebulised salbutamol 2.5 mg alone at hourly intervals until the end of the four-hour observation period, in accordance with departmental protocol.

Outcome measures and data collection

The primary outcome measure was the change from baseline in peak expiratory flow rate expressed as a percentage of the predicted value at 240 minutes. Peak expiratory flow rate was measured with a calibrated mini-Wright peak flow meter, and the best of three technically acceptable attempts was recorded at baseline and at 20, 60, 120 and 240 minutes. Forced expiratory volume in one second was measured with a portable spirometer at baseline and at 60, 120 and 240 minutes and was expressed as a percentage of the predicted value derived from Indian reference equations. Subjective breathlessness was graded on the modified Borg scale from 0 to 10 at the same time points. Oxygen saturation by pulse oximetry, respiratory rate and heart rate were recorded at baseline and at every subsequent assessment. Serum magnesium, serum electrolytes, random blood glucose, complete blood count and chest radiography were obtained at baseline in all participants. A twelve-lead electrocardiogram was recorded at baseline and repeated at the end of the observation period.

Secondary clinical outcomes comprised the requirement for hospital admission, which was determined at 240 minutes by a treating physician blinded to allocation using prespecified departmental criteria; the total duration of emergency department stay measured from triage to disposition; the requirement for rescue therapy in the form of intravenous magnesium sulphate, intravenous aminophylline, non-invasive ventilation or invasive mechanical ventilation; and admission to the intensive care unit. Adverse events were recorded prospectively on a structured proforma at each assessment point and at the time of disposition.

Follow-up protocol

Participants who were discharged from the emergency department were reviewed in the respiratory outpatient clinic on the seventh day after discharge. At this visit, symptom recurrence, adherence to prescribed controller and reliever therapy, unscheduled medical contact, repeat emergency attendance and hospital admission occurring within the seven-day interval were documented. Participants who did not attend the scheduled review were contacted by telephone using a standardised script, and the same information was obtained. Participants who were admitted to hospital were followed until discharge, and the duration of hospital stay together with any in-hospital complication was recorded. Follow-up data were complete for all randomised participants.

Statistical Analysis

Data were entered into a spreadsheet and

analysed using standard statistical software. Analysis was performed on an intention-to-treat basis. The normality of continuous variables was assessed using the Shapiro-Wilk test and by inspection of histograms and normal quantile-quantile plots. Normally distributed continuous variables were summarised as mean with standard deviation and were compared between the two groups using the independent samples t test. Continuous variables that departed from normality were summarised as median with interquartile range and were compared using the Mann-Whitney U test. Categorical variables were summarised as frequency with percentage and were compared using the Pearson chi-square test, with the Fisher exact test applied when the expected cell frequency was below five. Serial measurements of peak expiratory flow rate, forced expiratory volume in one second and Borg score were analysed using repeated measures analysis of variance, with treatment group entered as the between-subject factor and time as the within-subject factor, and the group by time interaction term was taken as the test of differential response. The Greenhouse-Geisser correction was applied when the assumption of sphericity was violated. The between-group difference in the primary outcome was expressed as a mean difference with a 95% confidence interval. The effect of treatment allocation on hospital admission was additionally examined using binary logistic regression with adjustment for age, sex, baseline peak expiratory flow rate and duration of the current exacerbation, and results were reported as adjusted odds ratios with 95% confidence intervals. A prespecified subgroup analysis was performed according to baseline peak expiratory flow rate above and below 40% of predicted. A two-sided p value of less than 0.05 was considered statistically significant.

RESULTS

Participant flow and baseline characteristics

A total of 168 patients presenting with an acute exacerbation of bronchial asthma were screened during the study period, of whom 68 were excluded because they did not meet the criteria for acute severe asthma, satisfied one or more exclusion criteria, or declined participation. One hundred participants were randomised, with 50 allocated to nebulised magnesium sulphate (Group A) and 50 allocated to nebulised normal saline (Group B). All 100 participants received the allocated intervention, completed the four-hour observation period and were available for seven-day follow-up, and all were therefore included in the intention-to-treat analysis.

The baseline demographic, clinical and physiological characteristics of the two groups are presented in Table 1. The mean age was 38.4 ± 12.1 years in Group A and 37.6 ± 11.7 years in Group B (p = 0.735). Men constituted 27 (54.0%) of Group A and 29 (58.0%) of Group B (p = 0.687). The mean duration of physician-diagnosed asthma was 9.2 ± 5.8 years and 8.7 ± 5.4 years respectively (p = 0.657), and the mean duration of the presenting exacerbation before emergency attendance was 14.6 ± 8.9 hours and 15.3 ± 9.4 hours respectively (p = 0.703). The baseline peak expiratory flow rate was 38.6 ± 7.4% predicted in Group A and 39.2 ± 7.8% predicted in Group B (p = 0.694), and the baseline forced expiratory volume in one second was 41.2 ± 8.1% predicted and 40.6 ± 8.4% predicted respectively (p = 0.717). The mean serum magnesium concentration was 0.82 ± 0.09 mmol/L in Group A and 0.84 ± 0.10 mmol/L in Group B (p = 0.297). None of the baseline variables differed significantly between the two groups, confirming the adequacy of randomisation.

Table 1: Baseline demographic, clinical and physiological characteristics of the two study groups

Variable	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	Test statistic	p value
Age (years), mean ± SD	38.4 ± 12.1	37.6 ± 11.7	t = 0.339	0.735
Male sex, n (%)	27 (54.0)	29 (58.0)	$\chi^2 = 0.162$	0.687
Body mass index (kg/m²)	23.8 ± 3.4	24.1 ± 3.6	t = 0.429	0.668
Duration of asthma (years)	9.2 ± 5.8	8.7 ± 5.4	t = 0.446	0.657
Current or former smoker, n (%)	9 (18.0)	11 (22.0)	$\chi^2 = 0.250$	0.617
Duration of present attack (hours)	14.6 ± 8.9	15.3 ± 9.4	t = 0.383	0.703
Regular inhaled corticosteroid use, n (%)	31 (62.0)	29 (58.0)	$\chi^2 = 0.165$	0.685
≥ 1 exacerbation in preceding year, n (%)	22 (44.0)	24 (48.0)	$\chi^2 = 0.161$	0.689
PEFR (% predicted)	38.6 ± 7.4	39.2 ± 7.8	t = 0.395	0.694
FEV_1 (% predicted)	41.2 ± 8.1	40.6 ± 8.4	t = 0.364	0.717
SpO_2 on room air (%)	91.8 ± 2.1	92.1 ± 2.3	t = 0.682	0.497
Respiratory rate (breaths/min)	28.4 ± 3.6	28.9 ± 3.8	t = 0.675	0.501
Heart rate (beats/min)	112.6 ± 11.4	110.8 ± 12.1	t = 0.766	0.446
Modified Borg dyspnoea score	6.8 ± 1.2	6.9 ± 1.3	t = 0.400	0.690
Serum magnesium (mmol/L)	0.82 ± 0.09	0.84 ± 0.10	t = 1.050	0.297

$MgSO_4$, magnesium sulphate; PEFR, peak expiratory flow rate; FEV_1, forced expiratory volume in one second; SpO_2,

peripheral oxygen saturation; SD, standard deviation. Continuous variables compared using the independent samples t test and categorical variables using the Pearson chi-square test.

Primary outcome: serial change in peak expiratory flow rate

The serial values of peak expiratory flow rate expressed as percentage predicted are summarised in Table 2. Both groups demonstrated progressive improvement over the observation period. The difference between the groups was not significant at 20 minutes (47.8 ± 8.6% versus 46.2 ± 8.9%; t = 0.915, p = 0.362), but became significant from 60 minutes onward. At 60 minutes the peak expiratory flow rate was 58.9 ± 9.7% predicted in Group A and 53.4 ± 10.2% predicted in Group B (t = 2.762, p = 0.007). At 120 minutes the corresponding values were 66.4 ± 10.3% and 59.8 ± 11.1% (t = 3.081, p = 0.003), and at 240 minutes they were 72.8 ± 10.9% and 66.1 ± 11.6% (t = 2.977, p = 0.004).

The primary outcome, defined as the change in peak expiratory flow rate from baseline to 240 minutes, was 34.2 ± 9.8 percentage points in Group A and 26.9 ± 10.4 percentage points in Group B, yielding a mean difference of 7.3 percentage points (95% confidence interval 3.3 to 11.3; t = 3.615, p < 0.001). Repeated measures analysis of variance confirmed a highly significant effect of time (F = 284.63, p < 0.001) and a significant group by time interaction (F = 6.84, p = 0.001), indicating that the trajectory of recovery differed between the two treatment arms. The main effect of treatment group was also significant (F = 7.92, p = 0.006).

Table 2: Serial peak expiratory flow rate (% predicted) in the two study groups

Time point	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	t value	p value
Baseline (0 min)	38.6 ± 7.4	39.2 ± 7.8	0.395	0.694
20 minutes	47.8 ± 8.6	46.2 ± 8.9	0.915	0.362
60 minutes	58.9 ± 9.7	53.4 ± 10.2	2.762	0.007
120 minutes	66.4 ± 10.3	59.8 ± 11.1	3.081	0.003
240 minutes	72.8 ± 10.9	66.1 ± 11.6	2.977	0.004
Change, baseline to 240 min	34.2 ± 9.8	26.9 ± 10.4	3.615	< 0.001

Values are mean ± standard deviation. Repeated measures analysis of variance: effect of time F = 284.63, p < 0.001; group by time interaction F = 6.84, p = 0.001; effect of group F = 7.92, p = 0.006. Mean difference in change from baseline 7.3 percentage points (95% confidence interval 3.3 to 11.3).

Secondary outcomes: spirometry and symptom score

The serial values of forced expiratory volume in one second and of the modified Borg dyspnoea score are presented in Table 3. The forced expiratory volume in one second was comparable at baseline (41.2 ± 8.1% versus 40.6 ± 8.4% predicted; p = 0.717) but was significantly higher in Group A at 60 minutes (59.6 ± 9.4% versus 54.7 ± 10.1%; t = 2.510, p = 0.014), at 120 minutes (66.8 ± 10.1% versus 61.2 ± 10.8%; t = 2.677, p = 0.009) and at 240 minutes (73.4 ± 10.6% versus 67.5 ± 11.3%; t = 2.696, p = 0.008). The mean improvement in forced expiratory volume in one second at 240 minutes was 32.2 ± 9.5 percentage points in Group A compared with 26.9 ± 10.1 percentage points in Group B (t = 2.706, p = 0.008).

Subjective breathlessness improved more rapidly in the magnesium group. The modified Borg score fell from 6.8 ± 1.2 at baseline to 4.2 ± 1.1 at 60 minutes in Group A, compared with a fall from 6.9 ± 1.3 to 4.8 ± 1.2 in Group B (t = 2.605, p = 0.011). The difference persisted at 120 minutes (3.1 ± 1.0 versus 3.7 ± 1.1; t = 2.851, p = 0.005) and at 240 minutes (2.2 ± 0.9 versus 2.8 ± 1.0; t = 3.155, p = 0.002). Repeated measures analysis of variance for the Borg score demonstrated a significant group by time interaction (F = 5.47, p = 0.004).

Table 3: Serial forced expiratory volume in one second (% predicted) and modified Borg dyspnoea score

Parameter and time point	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	t value	p value
FEV_1, baseline	41.2 ± 8.1	40.6 ± 8.4	0.364	0.717
FEV_1, 60 minutes	59.6 ± 9.4	54.7 ± 10.1	2.510	0.014
FEV_1, 120 minutes	66.8 ± 10.1	61.2 ± 10.8	2.677	0.009
FEV_1, 240 minutes	73.4 ± 10.6	67.5 ± 11.3	2.696	0.008
FEV_1, change to 240 min	32.2 ± 9.5	26.9 ± 10.1	2.706	0.008
Borg score, baseline	6.8 ± 1.2	6.9 ± 1.3	0.400	0.690
Borg score, 60 minutes	4.2 ± 1.1	4.8 ± 1.2	2.605	0.011
Borg score, 120 minutes	3.1 ± 1.0	3.7 ± 1.1	2.851	0.005
Borg score, 240 minutes	2.2 ± 0.9	2.8 ± 1.0	3.155	0.002

Values are mean ± standard deviation. FEV_1, forced expiratory volume in one second. Repeated measures analysis of variance for FEV_1: group by time interaction F = 5.92, p = 0.003. Repeated measures analysis of variance for Borg

score: group by time interaction F = 5.47, p = 0.004.

Physiological parameters

The serial changes in oxygen saturation, respiratory rate and heart rate are shown in Table 4. Oxygen saturation was significantly higher in Group A at 60 minutes (95.4 ± 1.6% versus 94.6 ± 1.8%; t = 2.348, p = 0.021) and at 240 minutes (96.8 ± 1.3% versus 96.2 ± 1.5%; t = 2.140, p = 0.035). The respiratory rate was lower in Group A at 60 minutes (22.6 ± 3.1 versus 24.1 ± 3.4 breaths per minute; t = 2.304, p = 0.024) and at 240 minutes (19.4 ± 2.6 versus 20.8 ± 2.9 breaths per minute; t = 2.541, p = 0.013). Heart rate declined comparably in both groups, and the difference did not reach statistical significance at 60 minutes (108.2 ± 10.6 versus 110.4 ± 11.2 beats per minute; t = 1.010, p = 0.315) or at 240 minutes (96.4 ± 9.8 versus 99.1 ± 10.4 beats per minute; t = 1.336, p = 0.185), indicating that the addition of magnesium sulphate did not aggravate beta-agonist related tachycardia.

Table 4: Serial oxygen saturation, respiratory rate and heart rate in the two study groups

Parameter and time point	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	t value	p value
SpO_2 (%), baseline	91.8 ± 2.1	92.1 ± 2.3	0.682	0.497
SpO_2 (%), 60 minutes	95.4 ± 1.6	94.6 ± 1.8	2.348	0.021
SpO_2 (%), 240 minutes	96.8 ± 1.3	96.2 ± 1.5	2.140	0.035
Respiratory rate, baseline	28.4 ± 3.6	28.9 ± 3.8	0.675	0.501
Respiratory rate, 60 minutes	22.6 ± 3.1	24.1 ± 3.4	2.304	0.024
Respiratory rate, 240 minutes	19.4 ± 2.6	20.8 ± 2.9	2.541	0.013
Heart rate, baseline	112.6 ± 11.4	110.8 ± 12.1	0.766	0.446
Heart rate, 60 minutes	108.2 ± 10.6	110.4 ± 11.2	1.010	0.315
Heart rate, 240 minutes	96.4 ± 9.8	99.1 ± 10.4	1.336	0.185

Values are mean ± standard deviation. SpO_2, peripheral oxygen saturation measured by pulse oximetry. Respiratory rate expressed as breaths per minute and heart rate as beats per minute.

Clinical outcomes

The clinical outcomes are summarised in Table 5. Hospital admission at the conclusion of the four-hour observation period was required by 11 participants (22.0%) in Group A and 21 participants (42.0%) in Group B, a statistically significant difference (χ^2 = 4.593, p = 0.032). The relative risk of admission with magnesium sulphate was 0.52 (95% confidence interval 0.28 to 0.98), corresponding to an absolute risk reduction of 20.0% and a number needed to treat of 5. Binary logistic regression adjusting for age, sex, baseline peak expiratory flow rate and duration of the presenting exacerbation confirmed an independent protective effect of magnesium sulphate on hospital admission, with an adjusted odds ratio of 0.39 (95% confidence interval 0.16 to 0.94; p = 0.036).

The mean duration of emergency department stay was 5.8 ± 1.9 hours in Group A and 7.2 ± 2.4 hours in Group B (t = 3.232, p = 0.002). Rescue therapy with intravenous magnesium sulphate was required by 6 participants (12.0%) in Group A and 15 participants (30.0%) in Group B (χ^2 = 4.882, p = 0.027). Intravenous aminophylline was administered to 4 participants (8.0%) and 11 participants (22.0%) respectively, a difference of borderline significance (χ^2 = 3.804, p = 0.051). Non-invasive ventilation was required by 2 participants (4.0%) in Group A and 5 participants (10.0%) in Group B (Fisher exact p = 0.240), and intensive care admission by 1 participant (2.0%) and 3 participants (6.0%) respectively (Fisher exact p = 0.617). One participant in Group B required invasive mechanical ventilation, and no participant in Group A did so (Fisher exact p = 1.000). Among participants discharged from the emergency department, relapse requiring unscheduled medical contact within seven days occurred in 4 of 39 (10.3%) in Group A and 9 of 29 (31.0%) in Group B (χ^2 = 4.427, p = 0.035). There were no deaths in either group.

Table 5: Clinical outcomes in the two study groups

Outcome	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	Test statistic	p value
Hospital admission, n (%)	11 (22.0)	21 (42.0)	χ^2 = 4.593	0.032
Duration of ED stay (hours)	5.8 ± 1.9	7.2 ± 2.4	t = 3.232	0.002
Rescue intravenous $MgSO_4$, n (%)	6 (12.0)	15 (30.0)	χ^2 = 4.882	0.027
Intravenous aminophylline, n (%)	4 (8.0)	11 (22.0)	χ^2 = 3.804	0.051
Non-invasive ventilation, n (%)	2 (4.0)	5 (10.0)	Fisher exact	0.240
Intensive care admission, n (%)	1 (2.0)	3 (6.0)	Fisher exact	0.617
Invasive mechanical ventilation, n (%)	0 (0.0)	1 (2.0)	Fisher exact	1.000

Duration of hospital stay (days)*	2.6 ± 1.1	3.4 ± 1.5	t = 1.759	0.089
Relapse within 7 days, n (%)†	4/39 (10.3)	9/29 (31.0)	$\chi^2 = 4.427$	0.035
In-hospital mortality, n (%)	0 (0.0)	0 (0.0)	–	–

*ED, emergency department; $MgSO_4$, magnesium sulphate. *Calculated only for admitted participants (11 in Group A and 21 in Group B). †Calculated only for participants discharged from the emergency department (39 in Group A and 29 in Group B). Relative risk of hospital admission 0.52 (95% confidence interval 0.28 to 0.98); adjusted odds ratio from logistic regression 0.39 (95% confidence interval 0.16 to 0.94), p = 0.036.*

Prespecified subgroup analysis and adverse events

The prespecified subgroup analysis stratified by baseline severity demonstrated that the treatment effect was concentrated among the most severely obstructed participants. Among the 56 participants with a baseline peak expiratory flow rate below 40% of predicted, the improvement at 240 minutes was 36.8 ± 9.4 percentage points in Group A (n = 27) compared with 25.4 ± 10.1 percentage points in Group B (n = 29), a mean difference of 11.4 percentage points (t = 4.361, p < 0.001), and hospital admission was required by 6 of 27 (22.2%) and 15 of 29 (51.7%) participants respectively ($\chi^2 = 5.126$, p = 0.024). Among the 44 participants with a baseline peak expiratory flow rate of 40% predicted or above, the improvement was 31.1 ± 9.9 percentage points in Group A (n = 23) and 28.9 ± 10.6 percentage points in Group B (n = 21), which was not significant (t = 0.712, p = 0.481), and admission rates were 5 of 23 (21.7%) and 6 of 21 (28.6%) respectively ($\chi^2 = 0.265$, p = 0.607).

Adverse events are detailed in Table 6. A transient metallic taste during nebulisation was reported more frequently in Group A, occurring in 7 participants (14.0%) compared with 1 participant (2.0%) in Group B, although the difference did not attain statistical significance (Fisher exact p = 0.059). Tremor was reported by 9 participants (18.0%) in Group A and 11 participants (22.0%) in Group B ($\chi^2 = 0.250$, p = 0.617), and palpitations by 6 participants (12.0%) and 8 participants (16.0%) respectively ($\chi^2 = 0.332$, p = 0.564). Facial flushing occurred in 4 participants (8.0%) in Group A and 1 participant (2.0%) in Group B (Fisher exact p = 0.362). One participant (2.0%) in Group A developed transient asymptomatic hypotension that resolved without intervention. The overall incidence of any adverse event was 19 (38.0%) in Group A and 17 (34.0%) in Group B ($\chi^2 = 0.175$, p = 0.676). No serious adverse event, clinically significant arrhythmia or neuromuscular complication was recorded in either group, and no participant discontinued the study intervention because of an adverse event.

Table 6: Adverse events recorded during the study period

Adverse event	Group A ($MgSO_4$) n = 50	Group B (Saline) n = 50	Test statistic	p value
Metallic taste, n (%)	7 (14.0)	1 (2.0)	Fisher exact	0.059
Tremor, n (%)	9 (18.0)	11 (22.0)	$\chi^2 = 0.250$	0.617
Palpitations, n (%)	6 (12.0)	8 (16.0)	$\chi^2 = 0.332$	0.564
Facial flushing, n (%)	4 (8.0)	1 (2.0)	Fisher exact	0.362
Nausea, n (%)	3 (6.0)	2 (4.0)	Fisher exact	1.000
Headache, n (%)	3 (6.0)	4 (8.0)	Fisher exact	1.000
Transient hypotension, n (%)	1 (2.0)	0 (0.0)	Fisher exact	1.000
Any adverse event, n (%)	19 (38.0)	17 (34.0)	$\chi^2 = 0.175$	0.676
Serious adverse event, n (%)	0 (0.0)	0 (0.0)	–	–
Withdrawal due to adverse event, n (%)	0 (0.0)	0 (0.0)	–	–

$MgSO_4$, magnesium sulphate. Participants could report more than one adverse event. Categorical comparisons performed using the Pearson chi-square test, with the Fisher exact test applied where the expected cell frequency was below five.

DISCUSSION

The present randomised, double-blind, placebo-controlled trial demonstrated that the addition of three sequential doses of nebulised isotonic magnesium sulphate to standard therapy with salbutamol, ipratropium bromide and systemic corticosteroid produced a modest but statistically significant improvement in airflow obstruction in adults with acute severe asthma. The mean difference of 7.3 percentage points in the improvement in peak expiratory flow rate at 240 minutes was accompanied by concordant differences in forced expiratory volume in one second, subjective breathlessness, oxygen saturation and respiratory rate, and translated into a clinically meaningful reduction in hospital admission from 42.0% to 22.0%. The prespecified subgroup analysis indicated that this benefit was concentrated among participants presenting with a peak expiratory flow rate below 40% of predicted, in whom the mean difference in improvement rose to 11.4 percentage points and the admission rate fell from 51.7% to 22.2%.

These findings are consistent with the earliest

adequately powered randomised evidence in this field. Hughes and colleagues randomised 52 adults with severe exacerbations to isotonic nebulised magnesium sulphate or saline as an adjuvant to salbutamol and reported a significantly greater improvement in forced expiratory volume in one second in the magnesium arm, with the difference emerging progressively over the treatment period rather than after the first nebulisation [6]. The temporal pattern observed in the present trial mirrored that observation closely, in that no significant separation was evident at 20 minutes but a clear divergence had appeared by 60 minutes and widened thereafter. This pattern is biologically plausible, since the initial improvement in both arms is attributable predominantly to the beta-2 agonist, whereas any incremental contribution from magnesium requires cumulative deposition across repeated nebulisations. The systematic review by Mohammed and Goodacre similarly concluded that nebulised magnesium sulphate improved pulmonary function when added to standard therapy, with the effect most apparent in patients with severe exacerbations [11].

A number of smaller trials employing magnesium sulphate as a vehicle for nebulised salbutamol have reported comparable findings. Nannini and colleagues demonstrated a significantly greater improvement in peak expiratory flow rate when salbutamol was diluted in isotonic magnesium sulphate rather than saline, and the benefit in that study was likewise most evident in the subgroup with the most severe baseline obstruction [12]. Kokturk and colleagues, in a randomised trial of patients with moderate to severe attacks, found greater improvement in spirometric indices with magnesium as the vehicle for salbutamol [13]. Sarhan and colleagues reported that nebulised magnesium sulphate combined with salbutamol produced superior improvement in pulmonary function and a shorter duration of emergency treatment compared with salbutamol alone [14]. The dose employed in the present trial, 500 mg per nebulisation given on three occasions, lay at the upper end of the range used in these studies and may partly explain the consistency of the effect observed here.

The results nevertheless stand in contrast to several influential negative studies, and this discordance merits careful consideration. Aggarwal and colleagues, in a randomised double-blind trial of 100 adults conducted in an Indian emergency department, found no therapeutic benefit from the addition of nebulised magnesium sulphate to salbutamol in patients with acute severe or life-threatening asthma [7]. Two methodological differences are relevant. That trial did not include ipratropium bromide in the standard regimen, and it enrolled a proportion of patients with life-threatening features who were excluded from the present study. The large multicentre 3Mg trial similarly reported that nebulised magnesium sulphate did not produce a clinically worthwhile improvement in breathlessness or a reduction in hospital admission in adults with acute severe asthma, although the confidence intervals in that trial did not exclude a small beneficial effect on admission [8]. The paediatric MAGNETIC trial found no clinically significant overall improvement in asthma severity score, yet reported that the greatest response occurred in children with oxygen saturation below 92% at presentation and with symptom duration of less than six hours [9]. The internal consistency between that observation and the subgroup finding of the present trial is notable, and suggests that the true effect of nebulised magnesium is real but restricted to a narrow band of severity that is easily diluted when trials recruit across the full severity spectrum.

The two Cochrane reviews addressing this question have reached appropriately cautious conclusions. The review of inhaled magnesium sulphate found that the addition of nebulised magnesium to inhaled beta-2 agonist with or without ipratropium bromide may produce a small improvement in lung function, but graded the certainty of evidence as low on account of clinical heterogeneity and imprecision [5]. The parallel review of intravenous magnesium sulphate in adults concluded that a single infusion reduced hospital admission modestly in patients refractory to first-line therapy [4]. A more recent systematic review and meta-analysis of magnesium sulphate for acute severe asthma in adults reaffirmed that benefit is largely confined to the most severely obstructed patients and that the optimal route and regimen remain unsettled [10]. A meta-analysis of intravenous magnesium sulphate in children reached a similar conclusion regarding the concentration of benefit in severe disease [15]. Taken together with the present findings, the accumulated evidence supports a position in which nebulised magnesium sulphate is regarded not as a routine addition to every exacerbation but as a targeted adjunct for the severely obstructed patient who has not responded adequately to the first cycle of conventional nebulisation.

An important practical consideration is the comparison between the nebulised and intravenous routes. The reduction in the requirement for rescue intravenous magnesium sulphate from 30.0% to 12.0% observed in the present trial suggests that adequate airway delivery by the nebulised route may obviate the need for systemic administration in a proportion of patients, with consequent avoidance of intravenous cannulation, monitoring requirements and the risk of systemic magnesium toxicity. The safety profile documented here supports this proposition. Apart from a transient metallic taste, which was the only adverse effect more frequent in the magnesium arm, the incidence of tremor, palpitations, flushing and nausea did not differ between the groups, no serious adverse event occurred, and heart rate declined comparably in both arms, indicating that the addition of magnesium

did not aggravate beta-agonist related tachycardia. This favourable tolerability, combined with the very low acquisition cost of magnesium sulphate and its universal availability in Indian hospital pharmacies, renders the intervention particularly attractive in resource-constrained emergency settings [3].

Several limitations of the present study warrant acknowledgement. The trial was conducted at a single tertiary care centre and the sample size, although adequate for the primary outcome, was insufficient to detect differences in infrequent events such as intensive care admission, invasive ventilation or mortality. The subgroup analysis, although prespecified, was not powered as a formal test of interaction, and the corresponding finding should therefore be regarded as hypothesis-generating rather than definitive. The observation period was restricted to four hours, and although seven-day follow-up was complete, longer-term outcomes such as time to next exacerbation were not captured. Patients with life-threatening features requiring immediate ventilatory support were excluded on ethical grounds, and the findings cannot be extrapolated to that population, which is arguably the group in greatest need of an effective adjunct. Finally, serum magnesium concentrations were measured only at baseline, and the study therefore cannot describe the pharmacokinetic relationship between the nebulised dose and systemic magnesium exposure. Multicentre trials that restrict recruitment to severely obstructed patients, standardise the magnesium dose and dosing interval, and incorporate patient-centred outcomes are required before nebulised magnesium sulphate can be incorporated into routine guideline recommendations [10, 16].

CONCLUSION

In adults presenting to the emergency department with acute severe asthma, the addition of three sequential doses of nebulised isotonic magnesium sulphate to standard therapy with salbutamol, ipratropium bromide and systemic corticosteroid produced a modest but statistically significant improvement in peak expiratory flow rate and forced expiratory volume in one second, a more rapid reduction in subjective breathlessness, and a significant reduction in the requirement for hospital admission from 42.0% to 22.0%. The benefit was concentrated among patients with a baseline peak expiratory flow rate below 40% of predicted, in whom both the physiological and the clinical differences were substantially larger than in the cohort as a whole. The intervention was well tolerated, with a transient metallic taste as the only adverse effect attributable to magnesium and with no serious adverse event in either group.

These findings support the selective use of nebulised magnesium sulphate as an inexpensive, safe and readily available adjunct in the emergency management of severely obstructed adults with asthma who have not responded adequately to the first cycle of conventional bronchodilator therapy, rather than as a routine addition for all exacerbations. Given the discordance between the present results and several larger negative trials, adequately powered multicentre studies that restrict enrolment to patients with severe airflow obstruction, standardise the magnesium dose and dosing schedule, and evaluate patient-centred and longer-term outcomes are required before this practice can be endorsed in international management guidelines.

DECLARATIONS

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