
Original Articles

INTRAVENOUS MAGNESIUM SULFATE IN ACUTE SEVERE ASTHMA NOT RESPONDING TO CONVENTIONAL THERAPY**Pullela Rama Devi, Lata Kumar, Sunit C. Singhi, Rajendra Prasad and Meenu Singh**

From the Departments of Pediatrics and Biochemistry, Postgraduate Institute of Medical Education and Research, Chandigarh 160 012.

Reprint requests: Prof. Lata Kumar, Head, Department of Pediatrics, PGIMER, Chandigarh 160 012.

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Objective: To evaluate the effectiveness of early administration of intravenous Magnesium sulfate (IV MgSO₄) in children with acute severe asthma not responding to conventional therapy.

***Design:** Randomized double-blind, placebo-controlled trial. **Setting:** Pediatric emergency service of a large teaching hospital. **Subjects:** 47 children aged between 1-12 years with acute severe asthma showing inadequate or poor response to 3 doses of nebulized salbutamol given at an interval of 20 min each. **Intervention:** The MgSO₄ group received 0.2 ml/kg of 50% MgSO₄ as intravenous (IV) infusion over 35 minutes and the placebo group received normal saline infusion in the same dose and at the same rate. MgSO₄ solution and normal saline were coded and dispensed in identical containers. Decoding was done at the completion of the study. All the patients received oxygen, nebulized salbutamol, IV aminophylline and corticosteroids.*

***Results:** MgSO₄ group showed early and significant improvement as compared to placebo group in PEFr and SaO₂ at 30 min and 1, 2, 3 and 7 hours after stopping the infusion (*p* ranging from <0.05 to <0.01). The clinical asthma score also showed significant improvement in the MgSO₄ group 1, 2, 3 and 11 hours after stopping the infusion (*p* <0.01). **Conclusion:** Addition of MgSO₄ to conventional therapy helps in achieving earlier improvement in clinical signs and symptoms of asthma and PEFr in patients not responding to conventional therapy alone.*

Key words: Bronchial asthma, Magnesium sulfate.

ASTHMA is a common disease in childhood. A recent analysis of childhood asthmatic deaths found that the major contributing factor for mortality was inadequate medical response(1). Bronchodilators and corticosteroids have been the primary drugs for the emergency room (ER) management of acute asthma(2). However, some patients show inadequate response to the above therapy. In such situations other drugs which reverse airway obstruction would be of great benefit. One drug that

has been reported to successfully reverse bronchospasm in patients refractory to β_2 agonists is intravenous Magnesium sulfate (IV MgSO₄). Magnesium (Mg) acts as a physiological antagonist of calcium and inhibits smooth muscle contraction(3). Few reports that documented the bronchodilator effect of IV MgSO₄ in adult asthmatic patient were carried out in experimental situation(4,5). Literature search revealed only two controlled trials in children with acute asthma, wherein aerosolized MgSO₄

was used and found ineffective(6,7). There is a paucity of controlled trials in children with acute severe asthma where IV MgSO₄ was used(7). We designed this study to evaluate: (i) if IV MgSO₄ could reverse or reduce bronchospasm not responding to initial hour of (3₂ agonist therapy; and (ii) if addition of IV MgSO₄ shortened the duration of hospital stay in children with an acute attack of asthma.

Methods

Study Design

A randomized double-blind, placebo-controlled trial was planned.

Study Subjects

All the children between 1-12 years of age with acute severe asthma admitted to the Pediatric Emergency (ER) of Nehru Hospital, Post Graduate Institute of Medical Education and Research, Chandigarh between January 1994 to January 1995 were eligible for inclusion in the study.

Inclusion Criteria

Patients were included in the study if they met the following criteria: (i) inadequate or poor response to initial 3 doses of nebulized salbutamol given at an interval of 20 minutes over a period of one hour, and (ii) where a written consent could be obtained from the parents accompanying the child.

Exclusion Criteria

These included: (i) Children with axillary temperature greater than 38° C, and (ii) Subjects with blood pressure less than 50th percentile for the age (as IV MgSO₄ can cause hypotension).

Study Protocol

In all the patients, clinical severity of the disease was assessed at admission and monitored subsequently by using the fol-

lowing parameters: respiratory and heart rates, pulsus paradoxus, accessory muscle usage, dyspnea, color, wheeze, peak expiratory flow rates (PEFR) in children 5 years or older and oxygen saturation (SaO₂).

Respiratory rate was counted manually for one minute when the child was at rest. Heart rate and oxygen saturations were monitored with the help of pulse oximeter. Pulsus paradoxus was measured by a sphygmomanometer and stethoscope as the difference in systolic blood pressure between the pressure at which the first sporadic, faint pulse sounds were heard and the pressure at which all sounds were heard. Dyspnea was assessed semiquantitatively as follows(8): (i) In younger children (<2 yr) the assessment was based on quality of cry and ability to speak; and (ii) in subjects between 2-5 years, either of the above two criteria, whichever was feasible, was considered (*Table 1*). Peak Expiratory Flow Rates (PEFR) were obtained with the help of Mini Wright Peak Flow Meter. The patients were first demonstrated and explained the method of blowing into the peak flow meter. Then they were asked to blow out as hard as possible. The process was repeated thrice. The highest of the three numbers achieved was recorded. The predicted PEFR (baseline) was determined by referring to standard table of values in patients where the personal best was not available(9). No attempt was made to obtain the readings in patients who had severe asthma and were unable to move the needle of the peak flow meter.

The severity of asthma attack was graded into mild, moderate or severe based on the criteria laid by National Heart, Lung and Blood Institute, National Asthma Education Program Expert Panel Report(8) (*Table 1*).

Uniform initial therapy was given to all

TABLE I—*Estimation of Severity of Acute Exacerbations of Asthma.*

Sign/Symptom	Mild	Moderate	Severe
Respiratory rate	Normal to <1 standard deviation from the norm (SD) for age	Normal to <2 SD for age	Normal to >2 SD for age
Dyspnea	Absent or mild; speaks in complete sentences	Moderate; speaks in phrases or partial sentences	Severe; speaks only in single words or short phrases
Pulsus paradoxus	<10 mm Hg	10-20 mm Hg	20-40 mm Hg
Accessory muscle usage	No intercostal to mild retractions.	Moderate intercostal retraction with tracheosternal retractions; use of sternocleidomastoid muscles	Severe intercostal retractions, tracheosternal retractions with nasal flaring
Color	Good	Pale	Possibly cyanotic
Auscultation	End expiratory wheeze only	Wheeze during entire expiration and inspiration	Breath sounds becoming inaudible
Oxygen saturation	>95%	90-95%	<90%
PEFR	70-90% predicted or Personal best	50-70% predicted of personal best	<50% predicted of personal best

Based on guidelines for diagnosis and management of asthma recommended by National Heart, Lung and Blood Institute, National Asthma Education Program(8).

patients. The details are shown in *Fig 1*. At the end of one hour, 49 patients with inadequate or poor response (for definitions see *Fig 1*). were randomly assigned to placebo or MgSO₄ group. At the time of entry into study 0.2 ml/kg of placebo or Magnesium sulfate (50%) was given as infusion in 30 ml of one fifth normal saline in 5% dextrose over 35 minutes. Magnesium sulfate and placebo solutions (normal saline) were prepared in the hospital pharmacy, coded and dispensed in identical vials. All the patients in both groups were treated with salbutamol nebulization, aminophylline infusion and hydrocortisone as per protocol (*Fig 1*).

Assessment and Monitoring

To assess the clinical progress all the

parameters listed earlier were recorded just before starting the infusion (baseline), immediately after giving the infusion (0 hour), half an hour, one, two and three hours after stopping the infusion and every four hourly thereafter till the time of discharge from ER. Blood pressure and knee jerks were monitored at five minute intervals throughout infusion, and at 30 min post-infusion.

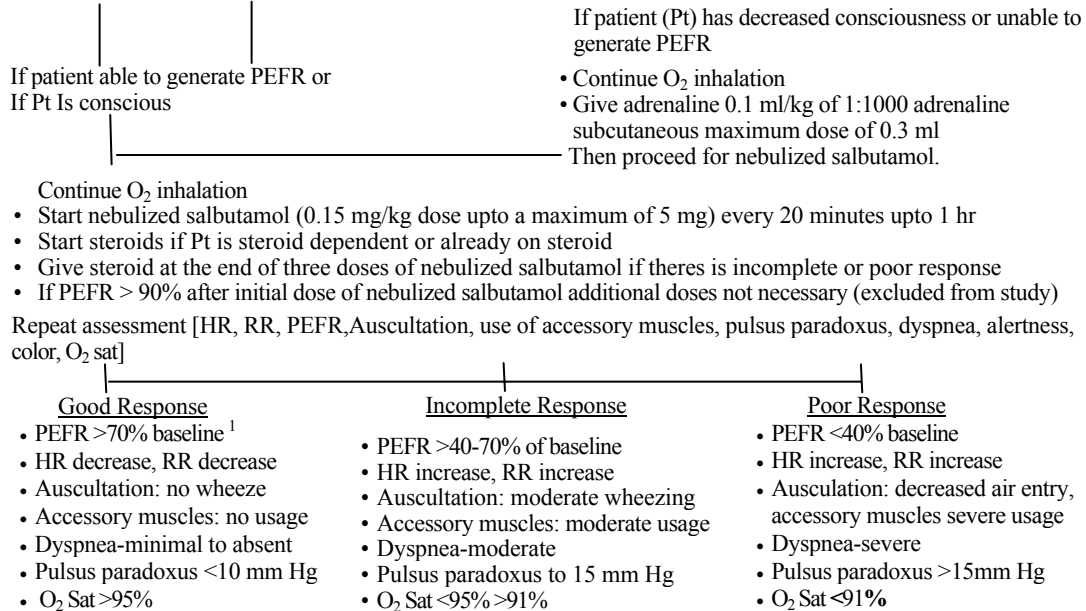
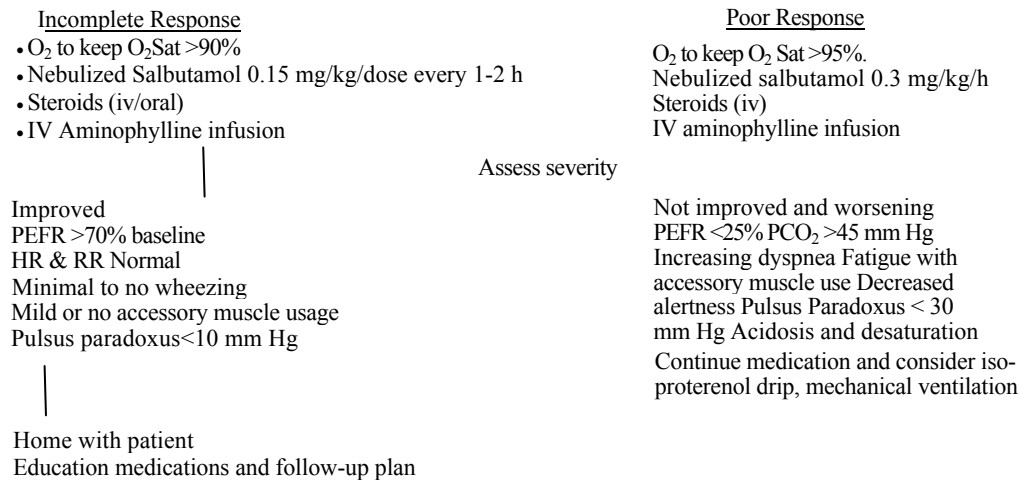
The following criteria were used to discharge the patients from ER: (i) PEFR >70% of the predicted value; (ii) Normal heart rate; (in) Pulsus paradoxus <10 mm Hg; (iv) Normal respiratory rates; (v) Minimal to no wheeze; (vi) Mild to no accessory muscles usage; and (OH) Minimal to absent dyspnea.

Fig 1. Protocol for Management of Acute Severe Asthma

INITIAL ASSESSMENT (PHASE I)

Heart rate (HR), respiratory rate (RR), PEFR, Auscultation, use of accessory muscles, pulsus paradoxus, dyspnea, alertness, color, O₂ saturation.

[Start on O₂ 6 Liters Flow (aim at keeping O₂ Sat > 95%)]

**PHASE II**

Phase I: Assessment & treatment in the first hour of admission

Phase II: Treatment after giving IV MgSO₄ or placebo.

* None of the children in our study required mechanical ventilation or isoproterenol

Serum Magnesium Estimation

Three ml venous blood was collected before starting the infusion and soon after stopping the infusion in acid washed mineral free glass test tubes. Serum Magnesium estimation was done spectrophotometrically using Methyl thymol blue(10).

Statistical Analysis

The between group comparison of frequency distribution, Chi square test (with Yates correction, wherever applicable) was used. For between group comparison of numeric variables unpaired 't' test, and for categorical data Mann-Withneys U test was used. For within group comparison of paired observations at individual time points with respect to baseline values, paired 't' test was used. Multivariate ANOVA (MANOVA) was used to compare percentage saturation values.

Results

The data of the two groups was compiled. Two children were excluded during the study period as they became febrile. When decoding was done by the pharmacist, it was found that 24 children had been assigned to MgSO₄ and 23 to placebo

group. For this sample size calculated Z (1 — b) was 1.05 corresponding to a power of 0.85.

The MgSO₄ group had a mean (SD) age of 6.7 (3.62) years and placebo (normal saline) group of 6.75 (3.5) years. Boys predominated in both groups (19 in MgSO₄ and 17 in placebo group). PEFR could be monitored in 15 and 16 children in MgSO₄ and placebo groups, respectively. After tabulating the data, clinical asthma scores were calculated at all time interval as shown in *Table 11(11)*. There was no significant difference in both groups with respect to clinical asthma scores, heart rates, oxygen saturation and PEFR, before starting the infusion (p >0.05) (*Table III*).

The use of MgSO₄ resulted in early and significant improvement in clinical asthma score, per cent of Predicted Peak Expiratory Flow Rate (PPEFR), and SaO₂. The clinical asthma scores in MgSO₄ group were significantly lower at 1,2,3 and 11 hours after infusion (p <0.01) (*Table IV*). The mean PPEFR was significantly higher in MgSO₄ group at 30 minutes and 1,2,3 and 7 hours after stopping the infusion (p <0.01) (*Fig 2*). The number of patients who achieved a

TABLE II—Clinical Asthma Score"

Score	RR ⁺	Wheeze	Accessory muscle usage	Dyspnea
0	<30	Nil	Nil	Nil
1	31 to 45	Mild	Mild	Mild
2	46 to 60	Moderate	Moderate	Moderate
3	>61	Severe	Severe	Severe

+ Respiratory rate scoring in children above 6 years of age.

Score	Rate
0	<20
1	20-35
2	36-50
3	>50

* Modified from pulmonary index score(11).

TABLE III- Comparison of Baseline Characteristics Between MgSO₄ and Placebo Groups.

Parameter	MgSO ₄ group	Placebo group
Median clinical asthma score	11	11
Heart rates	142.29 ± 14.65	137.57 ± 19.20
Pulsus paradoxus	15.58 ± 3.53	15.30 ± 2.80
SaO ₂	92.08 ± 2.34	91.35 ± 1.90
PPEFR	30.08 ± 13.96	27.14 ± 18.42

None of the differences between the two groups were statistically significant. Except for asthma score, values are depicted as mean ± SD.

PEFR of >70% of predicted at 11 hours after stopping the infusion was significantly higher in MgSO₄ group; 8 out of 15 as compared to 2 out of 16 in placebo group ($p < 0.05$) (Table V). Mean SaO₂ was significantly higher in MgSO₄ group at 30 minutes and 1,2,3 and 7 hours after stopping

the infusion ($p < 0.05$) (Fig 2). The analyses of variance revealed that the interaction effect and within subject effects were not significant. The hospital stay was appreciably less in the MgSO₄ group (13.6 ± 6.8 h) as compared to controls (18.9 ± 7.7 h; $p < 0.05$).

In the MgSO₄ group, serum magnesium concentration increased significantly from preinfusion (0.61 ± 0.15 mmol/L) to post-infusion (1.71 ± 0.21 mmol/L; $p < 0.001$). In contrast, the concentration remained unchanged in the placebo group (preinfusion 0.69 ± 0.20 mmol/L and post-infusion 0.71 ± 0.23 mmol/L). The serum magnesium concentration in normal healthy children ranges between 1.5 to 1.8 mEq/L(12).

Children experienced only minor side effects like epigastric warmth (12.5%), pain (16.6%) and tingling and numbness (12.5%) at the site of infusion. All these side effects started within 2 to 3 minutes after initiating the infusion. Epigastric warmth lasted for maximum period of 5 minutes and mild pain lasted for maximum period of 10 minutes. No other significant side effects (hypotension or respiratory depression) were noted.

TABLE IV- Comparison of Median Clinical Asthma Scores in MgSO₄ and Placebo Groups.

Time in hours	Median clinical asthma score		Pvalue
	Placebo group	MgSO ₄ group	
Before infusion	11	11	>0.05
Soon after infusion	11	10	>0.05
Hours after infusion			
1	10	9	<0.01
2	10	8	<0.01
3	10	7	<0.01
7	8	6	>0.05
11	7	6	<0.01

*Mann-Whitney u-test

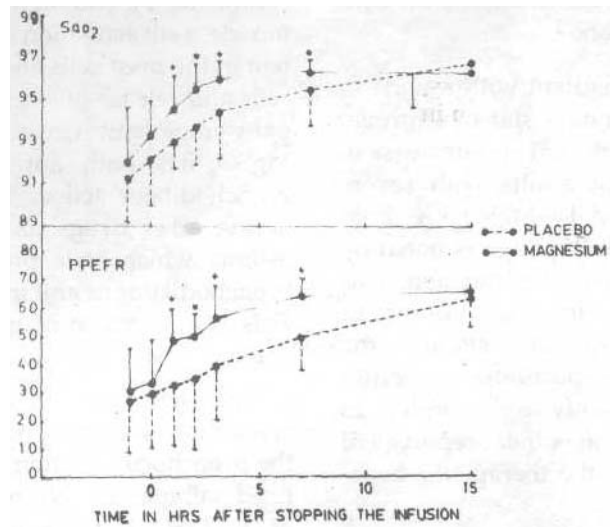


Fig 2. Serial percentage oxygen saturation (SaO₂) and per cent peak expiratory flow rate (PPEFR) (+ $p < 0.01$; and * $p < 0.05$).

TABLE V- Comparison of Number of Patients with Predicted PEFR of $\geq 70\%$ at Various Time Intervals in MgSO₄ and Placebo Groups

Time after infusion (h)	No. of patients	
	MgSO ₄	Placebo
2	0	1
3	1	1
7	6	1
11*	8	2
15	10	7

* $p < 0.05$

Discussion

To date there have been no randomized, double blind controlled trials on the use of IV MgSO₄ in acute severe asthma in children(7). Our study is one of the first double blind placebo controlled trial of its kind to evaluate the role of IV MgSO₄ in naturally exacerbated severe acute asthma

in children and adolescents. In the only other published report on its use, IV MgSO₄ was used in four children with acute severe asthma who failed to respond to conventional therapy(13). All of them showed improvement in their clinical asthma score after 40-50 mg/kg MgSO₄ IV. However, this was not a controlled study and the sample size was too small to draw any definite conclusion. Other reports with MgSO₄ used nebulized form of this drug in children with acute asthma in whom no beneficial effect was demonstrated(6,7).

We found that use of intravenous MgSO₄ therapy was associated with significant improvement in PPEFR and SaO₂ starting within 30 minutes of infusion and significant improvement in clinical asthma scores starting from one hour after infusion. The maximal response was seen in the early phase of treatment. These findings suggest that early institution of IV MgSO₄ along with conventional therapy may facilitate bronchodilation and thus result in ear-

lier relief of airflow obstruction than conventional therapy alone.

Our data are consistent with reports of recent studies which have shown improvement in lung functions(4,5) and decrease in hospitalization(14) in adults with severe asthma who received IV MgSO₄. A rapid decay of the effect of MgSO₄ was noted by some observers after the infusion was stopped(4,5). Unlike others we did not notice any decline in PEFr after stopping the MgSO₄ infusion. The post-infusion serum Mg levels in our study were similar to those documented in other reports(4,5) which demonstrated the therapeutic benefit of IV MgSO₄.

Except for minor side effects like tingling and numbness, none of the children experienced major life threatening complications. It has been seen that symptoms of hypermagnesemia occur at serum Mg levels >5 mEq/L (2.5 mmol/L)(15). They include hyporeflexia (the earliest manifestation), hypotension and drowsiness. At higher levels, other hazardous side effects like respiratory depression (12-15 mEq/L), coma and death can occur. These can be rapidly reversed by intravenous administration of calcium(15).

The postulated mechanism of action of MgSO₄ is due to its modulatory role in calcium ion movement. Magnesium inhibits calcium uptake by cells thus inhibiting smooth muscle contraction(3,16). Calcium mediates bronchospasm by activation of the contractile system in the airway smooth muscle wall and activates secretory system in the mast cells and mucus producing cells. Apart from this, Mg⁺⁺ ions also inhibit release of acetylcholine from motor nerve terminals, inhibits histamine release from mast cells and depresses the excitability of muscle fiber membrane(17). Calcium mediates bronchospasm by activation of the

contractile system in the airway smooth muscle wall; activation of the secretory system in the mast cells and mucus producing cells and release of neurotransmitter at the parasympathetic nerve endings(18). Thus MgSO₄ has both anti-inflammatory and bronchodilator action. This is unlike most of the other drugs used in acute severe asthma which have predominantly either bronchodilator or anti inflammatory action. This unique action coupled with its safety and low cost offers an advantage.

In conclusion, our study clearly indicates that IV MgSO₄ helps in overcoming the bronchoconstriction refractory to nebulized salbutamol. We recommend the use of IV MgSO₄ as a safe and effective adjunct to conventional bronchodilator therapy in acute severe asthma in children. Its use is likely to achieve early improvement in clinical asthma score, peak expiratory flow rates and SaO₂.

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