A comparative analysis of the effectiveness of Magnesium Sulfate in treating acute bronchial asthma in children: Nebulized versus intravenous administration.

Ayesha Shafiq[1], Hina Batool Siddiqui[*,2], Madiha Ikram[3], Nasreen Ali[4], Faiqa Nazir[5], Madiha Noor[6].

ABSTRACT:

Objective: To compare the mean PRAM score between Nebulized Magnesium Sulphate and IV Magnesium Sulphate in children with acute bronchial asthma.

Methodology: This prospective Comparative study was conducted between6th February 2024 to 15th August 2024 at Pediatric ER Dept. PAF Hospital Islamabad. A total of 70 children of acute moderate and severe asthma of either gender in age 2 to 12 years old were included. Patients were “divided into two groups”. “Group A” received IV Magnesium Sulfate and “Group B” received nebulized Magnesium Sulphate. PRAM score was recorded at and 60 minutes after the presentation.

Results: The mean age of children in Group A was 7.06 ±2.27 & in Group B were 7.66 ±2.44 years. Most of patients 44 (62.8%) were between 7 and 12 years of age. Out of these 70, 43 (62%) males and 27 (38%) females with male to female ratio of 1.6:1. Mean baseline PRAM in Group A was 6.37±1.46 and in Group B was 7.06± 1.55. The mean PRAM at 60 minutes in Group A was 2.63±1.17 and in Group B was 5.31± 1.23 (p value=0.0001)

Conclusion: Mean PRAM score is improved with intravenous MgSO4 as compared to nebulized MgSO4 in children presenting with acute severe asthma

Keywords: Magnesium sulfate, High dose infusion, Severe asthma, Pediatric Emergency department, PRAM Score

Introduction: Asthma is an emerging health condition around globe. Worldwide 334 million people are afflicted by asthma and this is anticipated to increase to additional 100 million by the year 2025.[1] It ranks as 26th among cases associated with years of life lost in South-east Asia with 1 in 250 deaths around the world are attributed to asthma.[2]

Asthma represents a significant public health concern, with its prevalence rising continuously. According to Global Initiative for Asthma (GINA), asthmatic patients are estimated to be 9.7 million in Pakistan i.e., 5.4% of the population. About 6% of the school going children in south Punjab and 15.8% in Karachi bear asthma. Overall, the prevalence in Pakistani teenagers is 6-9% in urban population.[3] The rising incidence of asthma is linked to a rise in atopic sensitization. This is close to rise in other allergic disorders like eczema and allergic rhinitis. The hike in rate of asthma is related to urbanization. It is expected that it will upsurge in coming years with shifting of communities from rural to urban areas i.e., 45 to 59% in 2025.[2] Asthma exacerbations can range in severity from "mild" to "life-threatening," often resulting in numerous visits to general practitioners and emergency departments, frequently necessitating hospitalization. While such cases may lead to limited admissions to the intensive care unit, instances of ventilation and fatalities due to status asthmaticus still arise. Therefore, effective management and prevention of acute episodes are essential for individuals with severe asthma.[4]

Children presenting to paediatric emergency with acute moderate and severe asthma deserve immediate intensive therapy. Despite rigorous treatment, some asthmatics remain critically sick and are at increased risk for respiratory failure, intubation and ventilation. Several therapies are in use among which Magnesium sulfate (MgSO4) is a relative safe choice. MgSO4 given at a dose of 20-75 mg/kg (max dose 2.5g) given IV over 20 minutes have shown some benefit as additional therapy in patient with severe asthma. Although, administration of MgSO4 requires monitoring of cardiovascular status.[5] MgSO4 is suggested as an accessory therapy in acute asthma. MgSO4 augments the B receptor response to salbutamol. MgSO4 has been seen to relax visceral muscle cells by reducing Ca+2 influx. It inhibits histamine and acetylcholine emission from cholinergic nerve endings & mastocytes respectively. It also encourages synthesis of nitric oxide and Prostacyclin who are responsible for bronchodilatation and vasodilation. Mg+2 also have an anti-inflammatory part, reducing neutrophil initiation in patients with asthma.[4]

MgSO4 is available both in intravenous and nebulized forms. It has the benefit of easy availability, reasonable cost and with less side effects. Other benefit of Magnesium Sulfate is the ability to block β 1-adnergic effects of Ventolin, thereby preventing palpitations.[6] IV MgSO4 in addition to Salbutamol & Steroids has shown to improve lung function tests in both grownup and children along with decreased prevalence of hospital admissions to up to 30%. There is limited data available regarding the outcome of nebulized MgSO4 in children. Studies are being carried out to prove the part of IV and Nebulized MgSO4 in addition to usual therapy in children & adults especially who do not respond to standard care. Given its accessibility, affordability, and minimal side effects, magnesium sulfate (MgSO4) appears to be a viable treatment option for children suffer-

1: Pediatrician PAF Hospital Peshawar
2: Assistant Professor Pediatrics PAF Hospital Mushaf Sargodha.
3: Assistant Professor Pediatrics KRL Hospital Islamabad.
4: Assistant Professor Pediatrics. Fazaia Medical College Islamabad.
5: Assistant Professor Pediatrics. Rawal Institute of Sciences. Islamabad.
6: Assistant Professor Medicines. PAF base Nur Khan.
*=corresponding author:
Email. hinairtaza14@gmail.com

ing from acute asthma. Metanalysis conducted by Shan Z et al with 25 trials (16 intravenous, 9 nebulized) involving 1754 patients showed that although in adults' intravenous treatment was associated with a significant effect upon respiratory function but weak evidence of effect upon hospital admission. While in children with beneficial effects upon both respiratory functions also reduce hospital admission.[7] Inhaled MgSO4 is unexpected to be related with a crucial increase in serious adverse effects.4 Advance administration of IV MgSO4 with ample dose i.e., 50-75 mg/kg decreases hospital stay in patients with severe asthma. More ever intravenous MgSO4 was found to be safe with few adverse effects in comparison to other drugs.[8] Nebulized ipratropium bromide is frequently used along with salbutamol for acute asthma. Nebulized magnesium sulfate is designated in the Global Initiative for Asthma (GINA) 2015 as an adjunctive therapy for life threatening cases. But the data is very limited showing the success of above drugs in childhood status asthmaticus.[9] Therefore the motive to conduct this research is to work on the outcome of both forms of MgSO4 in severe asthma to decrease the severity of acute asthma.

Objective:

To compare the efficacy of intravenous vs nebulized magnesium sulfate in pediatric patients using PRAM score.

Methodology:

This comparative clinical study was conducted at Pediatric Emergency, Pakistan Air Force Hospital Islamabad from 16th February 2024 to 15th August 2024. Total of 70 cases were taken as a sample size by using OpenEpi software with level of significance 5%, and power of study is 80%. Input for group A was mean 29 SD±19 and for group B it was 13 ±SD16.[7] For this study patients with age 2-12 years with status asthmaticus of both genders presented at pediatric emergency were included. Children with acute pneumonia, chronic lung disease, known cardiac or renal disease, cystic fibrosis, immunodeficiency and consolidation patch on chest x-ray were excluded from the study. Non-probability consecutive sampling was used and cases were allocated in group on alternate basis. Current study was performed after taking consent from ethical committee and parents. Group A had intravenous magnesium sulfate and Group B with nebulized Magnesium sulphate. All children selected were evaluated using a PRAM score upon presentation to classify their condition as acute, moderate, or severe asthma.

PEDIATRIC RESPIRATORY ASSESSMENT MEASURE (PRAM): It is a scoring system, comprising of 12 points to record the patient's asthma severity.[10] For the current study PRAM score was recorded at presentation and then 60 minutes after the initiation respective treatment in both Groups. The outcome was determined on the basis of mean ±SD decrease in PRAM score in two groups at presentation and after 60 minutes. All Children from both Groups A and B received standard care, which included bronchodilator therapy consisting of salbutamol 0.15 mg/kg/dose combined with Ipratropium bromide at a dosage of 500 µg/dose, administered every 20 minutes. All patients were also provided with oxygen supplementation, and baseline times were documented. Group A was treated with intravenous MgSO4 at a dosage of 25 mg/kg, while Group B received nebulized MgSO4 at a volume of 2 ml.[11] PRAM score was recorded at 60 minutes of presentation. Descriptive analysis of qualitative and quantitative variables was conducted. Qualitative variables; gender and drugs were measured in percentages and frequencies. Qualitative variables; age, weight and PRAM score measured as mean and standard deviation. The data was analysed using SPSS version 25. Comparison of mean ±SD PRAM score in between two groups was measured by using sample t-test (independent samples) Effect modifiers were controlled by stratification like age, weight, gender. Post stratification independent sample t-test applied, p value ≤ 0.05" was considered as significant.

PRAM SCORE:

Emergent & Urgent Care Asthma Clinical Score (PRAM)*

Signs	0	1	2	3
Suprasternal Indrawing	absent		present	
Scalene Retractions	absent		present	
Wheezing	absent	expiratory only	inspiratory and expiratory	audible without stethoscope/ silent chest with minimal air entry
Air entry	normal	decreased at bases	widespread decrease	absent/ minimal
Oxygen saturation on room air	> 93%	90% - 93%	< 90%	

Severity Classification	PRAM CLINICAL Score
Mild	0 - 4
Moderate	5 - 8
Severe	9 - 12
Impending Respiratory Failure	12+ following lethargy, cyanosis, decreasing respiratory effort, and/or rising pCO_2

Results:

Age range of study participants (n=70) was 2-12 years; 43 (62%) were boys & 27 (38%) girls. 62.8% participants were between 7-12 years. Mean age for group A participants was 7.06 years ±SD 2.27, for group B it was 7.66 years ±SD2.44. Mean body weight (kg) of study participants in group A was 18.03±5.56 kg and in Group B 18.80±4.463. Mean PRAM score with ±SD, both at arrival and at 60 mins is shown in table no 1, while stratification of PRAM scores with respect to age groups and gender is shown in table no 2.

Table No 1: PRAM score between two groups.

PRAM Score	Group A n=35	Group B n=35	p value
At presentation	6.37 ± 1.46	7.06 ± 1.55	0.059
At 60 minutes	2.63 ± 1.17	5.31 ± 1.23	0.0001

Table No 2: PRAM SCORE after stratification of age in two groups

Age in Years	Group A (n=35)		Group B (n=35)		p value
	Mean	±SD	Mean	±SD	
2-6 Years	2.33	1.29	5.82	1.25	0.0001
7-12 Years	2.85	1.04	5.08	1.18	0.0001

Discussion: Asthma is characterized by reversible airway obstruction caused by bronchial spasms and increased mucus production.[12] Patients who continue to exhibit clinical symptoms despite receiving standard pharmacological treatment are classified as having severe acute asthma,[13] which is associated with a higher frequency of hospital admissions. This condition is widely prevalent globally.[14] The standard treatment for acute asthma typically involves oxygen inhalation, β2 agonists, and nebulization with Ipratropium bromide, along with intravenous corticosteroids.[15] Additional treatment options may include inhaled or subcutaneous epinephrine, intravenous or inhaled magnesium sulfate, and intravenous aminophylline.[16] According to the "Global Initiative for Asthma" and the "British Thoracic Society guidelines," the use of intravenous and inhaled magnesium sulfate can be beneficial in asthma management.[17] While intravenous magnesium sulfate is well recognized as the preferred treatment, the efficacy of inhaled magnesium sulfate remains unverified.[18]

It has been shown by researcher that intravenous MgSO4 in adults presenting with acute asthma result in marked improvement of spirometry functions as well.[19,20] Numerous studies highlighting the positive effects of magnesium sulfate therapy in patients suffering from acute asthma have yielded encouraging findings; however, the precise nature of its efficacy remains somewhat ambiguous.[21-26] In this context, two meta-analyses evaluated the effectiveness of intravenous magnesium sulfate as an adjunctive treatment alongside inhaled salbutamol and intravenous steroids in paediatric emergency settings.[27,28]

The data collected indicated that intravenous magnesium sulfate shows potential as an adjunct therapy for preventing hospital admissions, with an odds ratio of 0.290 and a 95% confidence interval ranging from 0.143 to 0.589. Furthermore, the analysis of PRAM scores demonstrated a significant improvement. The administration of intravenous magnesium sulfate in the Accident & Emergency department was generally well-tolerated, with minimal adverse effects reported. Both meta-analyses concluded that intravenous magnesium sulfate is a viable adjunct therapy for patients with severe acute asthma who do not respond adequately to standard treatments. Additionally, another study found that administering IV magnesium sulfate during the first hour of hospitalization was associated with a significantly lower percentage of patients requiring intubation and mechanical ventilation in cases of severe asthma.[29] Singhi et al.[30] evaluated the efficacy of intravenous magnesium sulfate, terbutaline, and aminophylline in patients with severe acute asthma who were not adequately responding to standard treatment, the administration of a single dose of intravenous MgSO4 alongside inhaled salbutamol and steroids was found to be more effective and safer than the use of aminophylline or terbutaline as supplementary therapy.

A recent Cochrane review examined the effectiveness of intravenous magnesium sulfate in treating patients with acute asthma.[31] The review indicated that treatment with IV magnesium sulfate reduced the likelihood of hospital admission by 68% (odds ratio: 0.32, 95% confidence interval: 0.14 to 0.74). However, the overall reduction in the number of admissions had a wide confidence interval ranging from 86% to 26%. Additionally, the review noted a reduction of 5.3 hours in the length of hospital stay for patients receiving IV magnesium sulfate. It also identified further advantages of magnesium sulfate therapy, including a decrease in paediatric intensive care unit admissions, improved patient monitoring, enhanced pulmonary function, and better Paediatric Respiratory Assessment Measure (PRAM) scores. Nevertheless, the authors concluded that it remains challenging to determine whether this constitutes sufficient evidence of safety or if it justifies the prescription of this treatment, given the limited effect size and small sample sizes in the studies reviewed.

Research involving intravenous magnesium sulfate as an adjunct treatment for acute asthma often supports its early application. A combined analysis of randomized controlled trials involving 425 patients, which compared magnesium sulfate to placebo or other parenteral medications, demonstrated that the administration of parenteral magnesium sulfate resulted in significant clinical improvements, reduced hospital stays, decreased need for mechanical ventilation, and expedited discharge from the emergency department.[32] However, it is important to note that these trials were limited by small sample sizes and a broad range of outcome measures. Similar conclusions were drawn in a previous meta-analysis regarding magnesium sulfate therapy in the emergency department.[33] The concurrent administration of IV magnesium sulfate with inhaled β-2 agonists and systemic steroids has been associated with a decrease in clinical scores, suggesting that the early introduction of IV magnesium sulfate may enhance the bronchodilatory effects of first-line therapies.

Two systematic reviews have highlighted the significant benefits of intravenous magnesium sulfate (MgSO4) in improving spirometry outcomes and reducing hospitalization rates among patients.[34,35] However, nebulized magnesium sulfate did not show a similar effect on hospitalization rates. Specifically, intravenous magnesium sulfate was associated with a 68% reduction in the likelihood of hospital admission. The use of mechanical ventilation in cases of acute asthma is challenging and is typically reserved for children who do not respond to initial medical treatment and subsequently experience respiratory failure. Torres et al [29] found a notable decrease in the need for mechanical ventilation among patients with acute severe asthma who received intravenous magnesium sulfate within the first hour of treatment in the emergency department, compared to those who only received standard therapy, which included nebulization with β2 agonists and steroids. While the study presents compelling evidence, it does have some potential limitations, including the lack of blinding and its open-label design. The control group exhibited a 33% intubation rate, which is considerably high. Given the significant implications of mechanical ventilation on both patient outcomes and hospital costs, these findings suggest a potential for substantial savings in hospital resources and a positive impact on child health. Another latest open intervention research with IV magnesium sulfate only given to all the patients presenting with severe acute asthma before having nebulized beta 2 agonists or steroids revealed a marked reduction in pulmonary function tests.[36] This data indicates that IV Magnesium sulfate has bronchodilator effects even when implemented as a main drug in the opening therapy of asthma. High dose infusion of magnesium sulfate has been used in A&E dept. This approach has a response of earlier disposal from the ER. An open label, randomized prospective study on [37] patients in a study

from Paraguay 50mg/ kg bolus over one hour was compared with high dose of MgSO4 infusion of 50mg/kg for 4 hours (max 8gms over 4 hour).[37] 47% in a high dose MgSO4 infusion" group (9/19) versus 10% (2/21) in the short bolus group (p =0.032) were disposed in 24 hours with a marked risk reduction of 37% (95% CL 10-63) and a no needed to treat of 2.7 (95% CI 1.6-9.5) to facilitate a disposal at or before 24 hours. Length of stay was reduced in the high dose MgSO4 infusion group.[38]

Conclusion:

This study concluded that the average PRAM score is more favourable with intravenous magnesium sulfate compared to inhaled magnesium sulfate in patients experiencing life-threatening asthma. Therefore, we recommend that intravenous magnesium sulfate be routinely administered to children suffering from acute moderate to severe asthma to decrease associated morbidity and mortality.

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