Clinical outcomes of children with acute asthma managed with intravenous magnesium sulfate outside intensive care setting

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Abstract

Asthma in children constitutes a well-known respiratory condition with significant mortality. In poorly controlled asthma, multiple adjunct therapies, including magnesium sulfate (MS), are recommended to decrease the likelihood of intubation; however, limited evidence exists to support their routine usage in day-to-day situations. The aim of this study is to determine the outcomes of pediatric patients treated with MS during exacerbations of asthma admitted at a tertiary care unit. A retrospective study was conducted at the Aga Khan University Hospital, Karachi, Pakistan, from January 2019 to December 2021. Patients aged 6 years to 15 years who presented with acute asthma through the emergency room, having a clinical respiratory score of more than 5, and were admitted to the high-dependency unit (HDU) were included in the study. Patients who were started on MS within 24 hours of admission were categorized in the MS group. Patients receiving all standard acute asthma treatment but were not started on magnesium therapy within 24 hours of admission were categorized in the non-MS group. Different outcome variables were compared between the groups. A total of 110 patients with asthma were enrolled. A total of 54 patients were categorized into the MS group, while 56 were included in the non-MS group. Fewer patients were transferred from HDU to the pediatric intensive care unit (PICU) (24.07%) in the MS group compared to the non-MS group (42.85%), (p=0.02). In the MS group, the mean number of days spent on oxygen in HDU was 2.38±0.81, while the non-MS group spent more days (3.10±0.84) (p<0.01). This study demonstrates that for pediatric patients with severe asthma exacerbations, administration of intravenous MS (within 24 hours) is beneficial, results in fewer admissions to PICU, and reduces the mean number of days spent on oxygen therapy.

Introduction

Asthma constitutes a well-known respiratory condition that is predominant in all age groups. In 2019, Global Burden of Disease (GBD) collaborators estimated that over 260 million people globally had poorly controlled asthma (diagnosed asthma with wheezing within the past 12 months) [1]. In Pakistan, the asthma burden is estimated to be around 15 million in children and 7.5 million in adults [2]. While in India, the GBD (1990-2019) estimated that asthma constituted a total burden of 34.3 million, accounting for 13.09% of the global burden [3].

The significant mortality incurred in asthmatics, despite the availability of well-established guidelines on asthma management, occurs due to asthma exacerbations, which remain a cause of concern. A range of risk factors contributes to asthma exacerbations,

such as treatment non-adherence, exposure to environmental triggers, low-income households, exposure to chronic stress, child psychological problems, parental stress, family functioning, obesity, physical inactivity, and unhealthy diets [4].

Poor asthma control not only confers uncertainty to the patient of acute exacerbations but also to the family, adding a significant financial burden to the patients and society [5]. Therefore, better treatment approaches to asthma exacerbations are the need of the hour to ease the over-burdened healthcare system.

Inhaled bronchodilator therapy, in combination with systemic corticosteroids, achieves optimal control during episodes of asthma exacerbations based on their safety and efficacy [6]. Moreover, exacerbations of asthma management require oxygen, bronchodilators (salbutamol and multiple doses of ipratropium bromide), and systemic corticosteroids for most patients. In case asthma remains poorly controlled, multiple adjunct therapies are recommended to decrease the likelihood of intubation. These therapies include magnesium sulfate (MS) ($MgSO_4$), heliox-driven albuterol nebulization, intravenous (IV) β_2-agonists, leukotriene receptor antagonists, and noninvasive ventilation; however, limited evidence exists to support their routine usage in day-to-day situations [7]. With regard to MS therapy, recent studies have demonstrated the benefit of using MS before intubation [8,9]. However, no such evidence has been generated from Pakistan. Magnesium works efficiently with direct bronchodilation by decreasing the uptake of calcium at bronchial smooth muscles and reducing neutrophil bursts associated with an inflammatory response [10].

We aimed to determine the outcomes of pediatric patients treated with MS during exacerbations of asthma admitted at a tertiary care unit.

Materials and Methods

A retrospective study was conducted at the Aga Khan University Hospital, Karachi, Pakistan, from January 2019 to December 2021. All patients aged between 6 years to 15 years presented with acute asthma through the emergency room (ER) having a clinical respiratory score (CRS) of more than 5 and admitted to the high-dependency unit (HDU) were included in the study. Patients started on MS within 24 hours of admission were categorized in the MS group. Patients receiving all standard acute asthma treatment but were not started on magnesium therapy within 24 hours of admission were categorized in the non-MS group.

Patients who were intubated or started on pressure ventilation (bilevel positive airway pressure/ventilator support) in the ER or directly transferred to the pediatric intensive care unit (PICU) were excluded from the study. Similarly, patients who were directly admitted from outpatient clinics were excluded. Patients admitted with concurrent pathologies such as bronchiolitis, bronchopneumonia, and upper airway obstruction and/or previously diagnosed with cystic fibrosis, tuberculosis, chronic lung disease, congenital cardiac diseases, and immune deficiency syndrome were also excluded.

The CRS is a reliable tool comprising six clinical features assessed in asthmatic patients during acute exacerbations. It comprises variables that are assessed and subsequently scored from 0, 1, and 2 according to the findings shown in Table 1. Based on the CRS, asthma exacerbations are classified as mild (<3), moderate (4-7), and severe (8-12) [11]. We employed this tool in our study to classify asthmatics and assess disease severity to make clinical management decisions.

The standardized acute asthma protocol: National Institute for Health and Care Excellence/British Thoracic Society guidelines used in our institution included back-to-back/continuous salbutamol nebulization (0.15-0.5 mg/kg/h), IV methylprednisolone 2 mg/kg then subsequently 0.5-1 mg/kg every 4-6 hours, and oxygen therapy. IV $MgSO_4$ is usually started in patients as per response to initial nebulization, especially patients with incomplete response to conventional therapy during the first 1 to 2 hours. Magnesium is administered at a dose of 25-75 mg/kg over 30 minutes with blood pressure monitoring [12].

Outcome variables that were compared between the group includes length of stay (LOS), shifting to PICU, number of days on oxygen, return to ER for asthma within 7 days of discharge and 30-day readmission rates.

Patients in these two groups were further compared for their use of controller medications for the past 6 months from their first documented exacerbation during the study period. This included the use of oral montelukast, inhaled corticosteroids (ICS) only and long acting β agonist with ICS (LABA+ICS). For this study and to establish uniformity, we had chosen 2021 Global Initiative for Asthma guidelines [13,14].

Asthma exacerbation, as defined by the American Thoracic Society and European Respiratory Society, is a worsening in symptoms and/or lung function and/or increased rescue bronchodilator use for at least 2 days. We classify it as moderate exacerbation if no hospital admission or ER visit is required, whereas an admission or ER visit, along with oral corticosteroid treatment for at least 3 days, denotes a severe exacerbation [15].

Table 1. Clinical respiratory score. Mild (<3), moderate (4-7), severe (8-12).

Assess	Score 0	Score 1	Score 2
Respiratory rate	Age 1-5 years: <30 Age >5 years: <20	Age 1-5 years: 30-40 Age >5 years: 20-30	Age 1-5 years: >40Age >5 years: >30
Auscultation	Good air movement, expiratory scattered wheezing or loose rales/crackles	Depressed air movement, inspiratory and expiratory wheezes, or rales/crackles	Diminished or absent breath sounds, severe wheezing or rales/crackles or marked prolonged expiration
Accessory muscle usage	Mild to no use of accessory muscles. Mild to no retractions or nasal flaring on inspiration	Moderate intercostal retractions, mild to moderate use of accessory muscles, nasal flaring	Severe intercostal and substernal retractions; nasal flaring
Mental status	Normal to mildly irritable	Irritable, agitated, restless	Lethargic
Room air SpO_2	>95%	90-95%	<90%
Color	Normal	Pale to normal	Cyanotic, dusky

SpO_2, oxygen saturation.

Statistical analysis

Data was analyzed using IBM Corp. released 2013, IBM SPSS Statistics for Windows, Version 22.0. (IBM, Armonk, NY, USA). Categorical variables were reported in frequency and percentages, while continuous variables were reported in mean and standard deviation. Means were analyzed using the Student *t*-test and categorical data was analyzed using the Chi-square test, to assess for significant differences between the groups. A p-value ≤0.05 was considered significant, with a type I error of 5%.

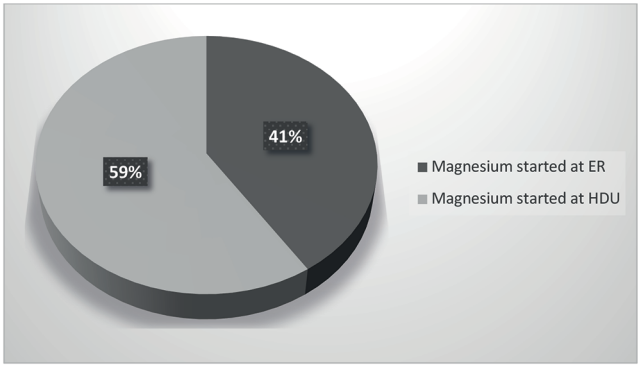

Figure 1. Site of magnesium therapy introduction. ER, emergency room; HDU, high-dependency unit.

Results

A total of 110 patients with asthma who met the eligibility criteria were included in our study during the designated period. 54 patients who were started on MS therapy within 24 hours of admission were categorized as the MS group. 56 patients who received standard acute asthma treatment but did not receive magnesium therapy within 24 hours of admission were classified as the non-MS group. Figure 1 shows percentages of patients who received IV $MgSO_4$ in the ER and HDU. The difference in the mean age of both groups (the mean age for the MS group was 8.58 years to 9.01 years for the non-MS group) was insignificant (p=0.14). Both groups were dominated by male gender. The difference between the average duration of diagnosis with asthma, the mean number of ER visits last year, and the mean number of hospitalizations with asthma exacerbations last year was insignificant between the two groups. For the MS group, the mean CRS score in the ER at arrival was 6.81±0.85, for the non-MS group, the score was 6.5±0.76; the difference between the scores was insignificant (p=0.20). In terms of the use of controller medications in the number of patients, the difference in the use of inhaled LABA+ICS, ICS only, and montelukast between the two groups was also insignificant (Table 2). As seen in Table 3, fewer patients were transferred from HDU to PICU (24.07%) in the MS group compared to the non-MS group (42.85%), with a significant difference (p=0.02). For patients who were given IV $MgSO_4$ within 24 hours of admission (MS group), the mean number of days they spent on oxygen in HDU was 2.38±0.81, while the non-MS group spent more days (3.10±0.84); the difference was significant (p<0.01). There was no significant difference in terms of the average LOS per admission (3.88 days in

Table 2. Demographic distribution and clinical characteristics between the groups.

	MS group	Non-MS group	p-value for comparison between MS and non-MS
Patients, (n)	54	56	-
Mean age (years)	8.58±3.09	9.01±2.27	0.14
Male:female	1.3:1	1.4:1	-
Average duration of diagnosis with asthma (years)	3.89±1.72	4.79±1.39	0.16
Mean CRS score in ER at arrival	6.81±0.85	6.5±0.76	0.20
Previous year mean ER visits last year (n)	1.59±0.56	1.78±0.48	0.19
Patients with last year hospitalizations with asthma, n (%)	9 (16.66)	11 (19.64)	0.13
Use of inhaled LABA with ICS (LABA+ICS), n (%)	10 (18.51)	9 (16.07)	0.32
Use of ICS only, n (%)	18 (33.33)	15 (26.78)	0.14
Use of Monteleukast, n (%)	48 (88.88)	45 (80.835)	0.17

MS, magnesium sulfate; CRS, clinical respiratory score; ER, emergency room; PICU, pediatric intensive care unit; LABA, long-acting β agonist; ICS, inhaled corticosteroid.

Table 3. Outcome variables between the groups.

	MS group	Non-MS group	p
Number (n)	54	56	-
Average LOS per admission (days)	3.88±1.25	3.92±1.24	0.86
Mean number of days on oxygen support	2.38±0.81	3.10±0.84	<0.01
Number of patients transferred from HDU to PICU, n (%)	13(24.07)	24 (42.85)	0.02
Return to ER for asthma within 7 days of discharge, n (%)	2 (3.70)	3 (5.35)	0.51
Re-admission for asthma within 1 month of discharge, n (%)	4 (7.40)	5 (8.92)	0.523

MS, magnesium sulfate; LOS, length of stay; HDU, high-dependency unit; PICU, pediatric intensive care unit; ER, emergency room.

the MS group to 3.92 days in the non-MS group), number of re-admissions for asthma within 7 days (3.70% in the MS group to 5.35% in the non-MS group) and 1 month of discharge (7.40% in the MS group to 8.92% in the non-MS group) between the MS and the non-MS group. Figure 2 shows certain side effects of magnesium noticed in our cohort; 5.50% of patients experienced hypotension, 3.30% headache, 9.20% nausea/ vomiting, 7.40% rash or allergic skin reactions, while 3.30% of patients experienced muscle weakness from IV $MgSO_4$ treatment.

Discussion

Our study reports that the infusion of IV $MgSO_4$in asthma exacerbations in the first 24 hours results in fewer admissions to PICU from HDU and a significant reduction in the mean number of days spent on oxygen therapy in HDU. However, intervention with MS does not result in reduced LOS per admission and does not, comparatively, decrease readmissions due to asthma exacerbations within the first 7 days and 1 month after discharge (Table 3). We did not find the independent variables that confounded the results (Table 2).

The use of IV $MgSO_4$ as an adjunct therapy is encouraged in children whose forced expiratory volume (FEV1) does not improve to 60% of the predicted within 1 hour of care during an acute asthma attack [16,17]. Our study focused on the administration of IV $MgSO_4$ within 24 hours from the time of admission. The patients were then given magnesium after the standard care of management during an asthma attack.

In the ED, asthma exacerbation patients with CRS scores of more than 5 were enrolled, which denoted a severe attack and led to the patients being admitted into HDU [11]. Patients with worsening asthma symptoms were transferred from the HDU to the PICU for intensive management as needed. The study showed that 24.07% of patients in the MS group were shifted to the PICU, while 42.85% of patients in the non-MS group were shifted to the PICU, with a significant difference (p=0.02). These findings are consistent with a retrospective cohort study by Delaroche *et al.* on children aged 5-11 years. The effect of early (within 60 minutes) and delayed administration of IV $MgSO_4$ was studied; the study observed that early administration was associated with reduced need for hospitalization in asthma exacerbation. Our study also found that early administration of IV $MgSO_4$ was associated with more timely delivery of first-line asthma therapies [18]. A review of three articles out of eight studies by Johnson *et al.* reported a reduction in PICU transfers after using continuous MgSO4 infusions in status asthmaticus in children [19]. The effect of MS therapy in acute severe asthma also proved to be beneficial in another study involving children over the age of 2. A total of 40 patients were given 4 hours of infusion magnesium in a pediatric ER; remarkably, magnesium dramatically improved clinical outcomes, and only 5% of the children were transferred to the PICU [20]. In the review of 53 articles to study the effect of IV $MgSO_4$ in asthma exacerbation in patients under 18, Irazuzta *et al.* reported a reduction in the need for hospitalization and intensive care admission following IV $MgSO_4$ infusion [21].

Nonetheless, there is a paucity of studies to effectively conclude the effect of IV $MgSO_4$ and the need for PICU admissions. Meta-analysis results from three studies suggest a reduction in the need for hospitalization following IV $MgSO_4$ infusion (a statistically significant 68% decrease in the odds), however, the study sample size of 115 children limited the generalizability of the findings [22]. Foster *et al.* evaluated the effectiveness of IV $MgSO_4$ in managing severe asthma exacerbations, administered within 60 minutes of presentation to the ER in the pediatric age group. Contrary to our report, this study concluded to have found no significant reduction in PICU admissions following early IV $MgSO_4$ administration [calculated odds ratio (OR) of PICU admission subcategorized by respiratory clinical score (RCS): RCS 10 (OR 2.52), RCS 11 (OR 2.19), and RCS 12 (OR 4.12)] [23]. Also, another double-blinded randomized controlled trial by Schuh *et al.* in 816 children observed an increase in the need for hospitalization following IV $MgSO_4$ administration in asthma exacerbation [24]. Hence, our study results strengthen the recommendation that the administration of IV $MgSO_4$ improve clinical outcomes and reduces PICU admissions.

A retrospective cohort analysis of the pediatric asthmatic popu-

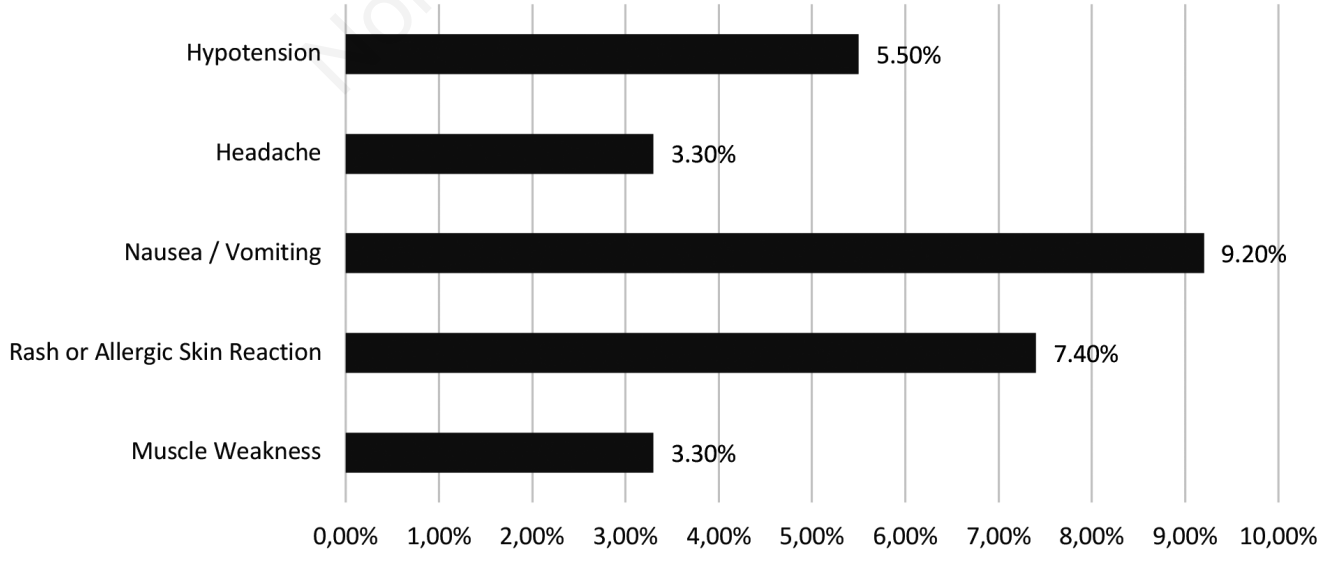

Figure 2. Side effects experienced from intravenous magnesium sulfate treatment.

lation on continuous albuterol outside the intensive care unit setting (ICU) and magnesium concluded that, in fact, the administration of magnesium contributed to longer LOS at the hospital [25]. On the contrary, in our study, the subjects enrolled were given magnesium after the standard care of management during asthma exacerbation, but no significant correlation could be established between the MS group and LOS at the hospital.

Oxygen therapy improves clinical symptoms in asthma exacerbations like heart rate and PCO_2 [26]. Our study shows MS results in a significant reduction in the mean number of days spent on oxygen therapy in HDU. Owed to the bronchodilation effect of IV $MgSO_4$, it was reiterated that, in fact, it improved FEV1 and lung function in severe asthma [27]. However, interestingly, these findings were promising in patients with acute severe asthma as opposed to no correlation in patients with moderate asthma [25]. Rates of readmission within 7 days and 1 month of an asthma exacerbation remained unaffected in both groups. This brings us to highlight another study that was conducted in pediatric emergency care applied research network and concluded after a review of 61,854 ER visits that the revisit rates among children discharged from ER after administration of IV $MgSO_4$ did not differ from those among children who did not receive this medication [28]. However, no studies have been conducted to measure rates of readmission after magnesium use in an inpatient setting as done in our study.

We observed minimal side effects of treatment with IV $MgSO_4$ administered at a dose of 25-75 mg/kg over 30 minutes. Minor side effects requiring minimal to no medical attention, including facial flushing with warmth, headache, nausea, and vomiting, are most common with magnesium therapy. Due to the vasodilatory effect, most patients given IV $MgSO_4$ at high doses or rapidly experience hypotension and neuromuscular weakness [29]. Supratherapeutic doses lead to serious side effects, including cardiac conduction abnormalities and muscle weakness [30]. In our study, serious side effects like hypotension and muscle weakness were observed only in 5.50% and 3.30% of patients, respectively.

Limitations

Our results were subject to some limitations. Since in our study, patients with severe asthma attacks, as denoted by a CRS of more than 5, were enrolled, it indirectly hints that patients with high disease severity were likely to receive better medical attention as compared to the better individuals. Moreover, factors such as initial management before presenting at our center and the dose of medication administered were not recorded, which might have had an effect on clinical outcomes. Due to the retrospective nature of the study design, the past history of pediatric patients involving drug compliance and exposure to trigger factors prior to an asthma exacerbation was not evaluated.

Conclusions

Our study demonstrates that for pediatric patients with severe asthma exacerbations, administration of IV $MgSO_4$ (within 24 hours) is beneficial and results in fewer admissions to the PICU and reduces the mean number of days spent on oxygen therapy. However, no reduction in LOS per admission and readmissions within 7 days and 1 month after discharge from the ER was seen with $MgSO_4$ use. There is a need for further prospective studies to effectively evaluate the benefits of IV $MgSO_4$ with regard to the timings of administration.

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