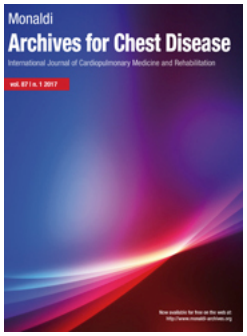

Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2023 [Online ahead of print]

To cite this Article:
Aziz DA, Sajjad MA, Iftikhar H. **Clinical outcomes of children with acute asthma managed with intravenous magnesium sulphate outside intensive care setting.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2023.2664

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

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Contribution: DA, and HI helped in conception and design of the study, **AS and HI** did analysis and interpretation of data, **AS and DA** contributed in drafting the work and revising it critically for important intellectual content. All authors approved the Final version for publication and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare they have no competing interests, and all authors confirm accuracy (Disclosure forms attached separately)

Grant support & financial disclosures: None

Article category: Original Article

Declarations: None

Ethical Considerations, informed consent and Consent for publication: Approval was received by the Ethics Review Committee at Aga Khan University Hospital with protocol number ERC: 6228-18471. All mentioned ethical aspects and related consents were taken into consideration during the conduct of this study.

Acknowledgement: IT and medical record Departments, Aga Khan University Hospital, Karachi, Pakistan

Abstract

Asthma in children constitutes a well-known respiratory condition with significant mortality. In poorly controlled asthma, multiple adjunct therapies including magnesium sulphate ($MgSO_4$), are recommended to decrease the likelihood of intubation; however, limited evidence exists to support their routine usage in day-to-day situations. Aim of this study is to determine the outcomes of pediatric patients treated with magnesium sulphate 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 presented with acute asthma through Emergency Room (ER) having clinical respiratory score (CRS) more than five, admitted in high-dependency unit (HDU) were included in the study. Patients who were started on magnesium sulfate within 24 hours of admission were categorized in magnesium sulfate (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-magnesium sulfate (non-MS) group. Different outcome variables were compared between the groups. A total of 110 patients with asthma were enrolled. Fifty-four patients were categorized into MS group while 56 were included in non-MS group. Fewer patients were transferred from HDU to pediatric intensive care unit (PICU) (24.07%) in MS group compared to non-MS group (42.85%), ($p=0.02$). In MS group, the mean number of days spent on oxygen in HDU were 2.38±0.81, while 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 IV $MgSO_4$ (within 24 hours) is beneficial and results in fewer admissions to PICU and reduces the mean number of days spent on oxygen therapy.

Key words: acute asthma exacerbation; magnesium sulphate therapy; oxygen dependency.

Introduction

Asthma constitutes a well-known respiratory condition which 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 past 12 months) [1]. In Pakistan, asthma burden is estimated to be around 15 million in children and 7.5 million in

adults [2]. While in India, the Global Burden of Disease (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 contribute 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 does to the family, adding 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 achieve 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 sulphate (MgSO4), heliox-driven albuterol nebulization, intravenous beta $_2$ -agonists, intravenous leukotriene receptor antagonists (LTRAs), and noninvasive ventilation; however, limited evidence exists to support their routine usage in day-to-day situations [7]. With regards to magnesium sulphate therapy recent studies have demonstrated benefit in using of magnesium sulphate prior to intubation with [8,9]. However, no such evidence has been generated from Pakistan. Magnesium works efficiently with direct bronchodilation by decrease uptake of calcium at bronchial smooth muscles and reduces neutrophil burst associated with inflammatory response. [10]

We aimed to determine the outcomes of pediatric patients treated with magnesium sulphate 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 Emergency Room (ER) having clinical respiratory score (CRS) more than five, admitted in high-dependency unit (HDU) were included in the study. Patients started on magnesium sulfate within 24 h of admission were categorized in magnesium sulfate (MS) group. Patients receiving all standard acute asthma treatment but were not started on magnesium therapy within 24 h of admission were categorized in the non-magnesium sulfate (non-MS) group.

Patients who were intubated or started on pressure ventilation (BIPAP/ ventilator support) in the ER or directly transferred to pediatric intensive care unit (PICU) were excluded from the study. Similarly, patients who were directly admitted from outpatient clinic were excluded. Patients admitted with concurrent pathology 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 of six clinical features assessed in asthmatic patients during acute exacerbations. It comprises of variables which 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), 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: NICE/BTS guidelines-used in our institution included back-to-back/ continuous salbutamol nebulization (0.15-0.5 mg/kg/h), intravenous methylprednisolone 2 mg/kg then subsequently 0.5-1 mg/kg every 4-6 h, and oxygen therapy. Intravenous magnesium sulphate 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 h. Magnesium is administered at a dose of 25-75 mg/kg over 30 min with blood pressure monitoring [12].

Outcome variables that were compared between the group includes length of stay, 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 on controller medications for the past 6 months from their first documented exacerbation during the study period. This included use of oral montelukast, inhaled corticosteroids (ICS) only and long-acting beta agonist with inhaled corticosteroids (LABA+ICS). For this study in particular and to establish uniformity, we had chosen 2021 GINA guidelines [13,14].

Asthma exacerbation, as defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS), is a worsening in symptoms and/or lung function, and/or increased rescue bronchodilator use, for at least two 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 three days, denotes a severe exacerbation [15].

Statistical analysis

Data was analyzed using IBM Corp. released 2013, IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. 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 Chi-square test, to assess for significant difference between the groups. The p-value ≤ 0.05 was considered significant, with a type I error of 5%.

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 magnesium sulfate therapy within 24 hours of admission were categorized as MS group. 56 patients who received standard acute asthma treatment but did not receive magnesium therapy within 24 hours of admission were classified as non-MS group. Figure 1 shows percentages of patients who received IV $MgSO_4$ in ER and HDU. The difference in mean age of both groups (mean age for MS group 8.58 years to 9.01 years for non-MS group) was insignificant ($p=0.14$). Both groups were dominated by male gender. Difference between average duration of diagnosis with asthma, mean number of ER visits

last year and mean number of hospitalizations with asthma exacerbations last year, was insignificant, between the two groups. For MS group mean CRS score in the ER at arrival was 6.81±0.85, for non-MS the score was 6.5±0.76, the difference between the scores was insignificant (p=0.20). In terms of use of controller medications in number of patients, difference in use of inhaled LABA with ICS (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 MS group compared to non-MS group (42.85%), with significant difference (p-value 0.02). Patients who were given IV magnesium sulfate within 24 hours of admission (MS group), mean number of days they spent on oxygen in HDU were 2.38±0.81, while non-MS group spent more days (3.10±0.84), difference was significant ($p<0.01$). There was no significant difference in terms of average length of stay (LOS) per admission (3.88 days in MS group to 3.92 days in non-MS group), number of re-admissions for asthma within 7 days (3.70% in MS to 5.35% in non-MS group) and 1 month of discharge (7.40% in MS to 8.92% in non-MS) between MS and 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% patients experienced muscle weakness from IV $MgSO_4$ treatment.

Discussion

Our study reports the infusion of IV magnesium sulfate in asthma exacerbations in first 24 hours results in fewer admissions to PICU from HDU, and a significant reduction in mean number of days spent on oxygen therapy in HDU. However, intervention with magnesium sulfate does not result in reduced length of stay per admission and does not, comparatively, decrease readmissions due to asthma exacerbations within first seven days and one 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 one hour of care during an acute asthma attack [16,17]. Our study focused on administration of intravenous magnesium sulfate (IV MgSO4) 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 score of more than five were enrolled which denoted a severe attack and led to the patients being admitted into a high dependency unit (HDU) [11]. Patients with worsening asthma symptoms were transferred from HDU to the PICU for intensive management as per need. The study showed that 24.07% of patients in MS group were shifted to PICU while 42.85% patients in non-MS group were shifted to PICU, with 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 min) 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 Mg was associated with more timely delivery of first-line asthma therapies [18]. In a review of three articles out of eight studies by Johnson PN et al reported a reduction in PICU transfers after using continuous MgSO4 infusions in status asthmaticus in children [19]. The effect of magnesium sulfate therapy in acute severe asthma also proved to be beneficial in another study involving children over the age of two years. A total of 40 patients were given 4 hours of infusion magnesium in a pediatric emergency room; 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 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. A meta-analysis results from three studies suggest reduction in need for hospitalization following IV $MgSO_4$ infusion (statistically significant 68% decrease in the odds), however, according to the study sample size of 115 children limited the generalizability of the findings [22]. Foster *et al.,* who evaluated the effectiveness of IV $MgSO_4$ in managing severe asthma exacerbations, administered within 60 min 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 administration of IV $MgSO_4$ improve clinical outcome and reduce PICU admissions.

A retrospective cohort analysis of the pediatric asthmatic population on continuous albuterol outside the intensive care unit setting (ICU) and magnesium concluded that in fact, 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 MG group and LOS at the hospital.

Oxygen therapy improves clinical symptoms in asthma exacerbations like heart rate, PCO_2 [26]. Our study shows Magnesium Sulfate results in a significant reduction in the mean number of days spent on oxygen therapy in HDU. Owed to 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 seven days and one month of an asthma exacerbation remained unaffected in both groups. This brings us to highlight another study which was conducted in a 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 magnesium 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, and nausea and vomiting are most common with magnesium therapy. Due to 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 attack as denoted by a CRS of more than five were enrolled, 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 prior to presenting at our center, and dose of medication administered was not recorded which might have had an effect on clinical outcomes. Due to retrospective nature of the study design, past history of pediatric patients involving drug compliance and exposure to trigger factor 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 PICU and reduces the mean number of days spent on oxygen therapy. However, no reduction in LOS per admission and readmissions within seven days and one month post discharge from 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 regards to timings of administration.

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Table 1. Clinical respiratory score (CRS). 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: >40 Age > 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

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

CRS: Clinical Respiratory Score, ER: Emergency Room, PICU: Pediatric Intensive Care Unit, LABA: Long-acting beta agonist, ICS: Inhaled Corticosteroid.

Table 3. Outcome variables between the groups.

	MS group	Non-MS group	p-value
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

LOS: Length of Stay, HDU: High Dependency Unit, PICU: Pediatric Intensive Care Unit, ER: Emergency Room.

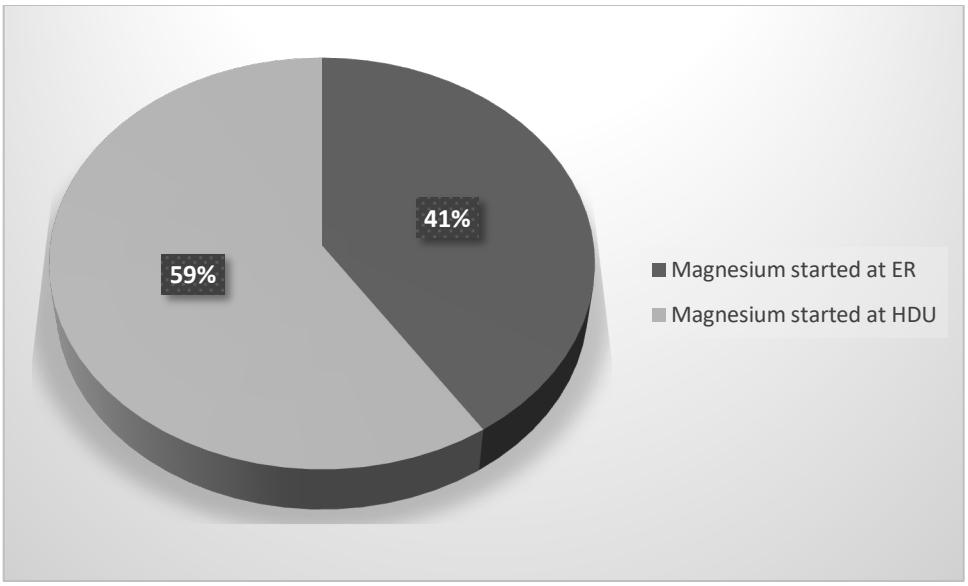

Figure 1. Site of magnesium therapy introduction.

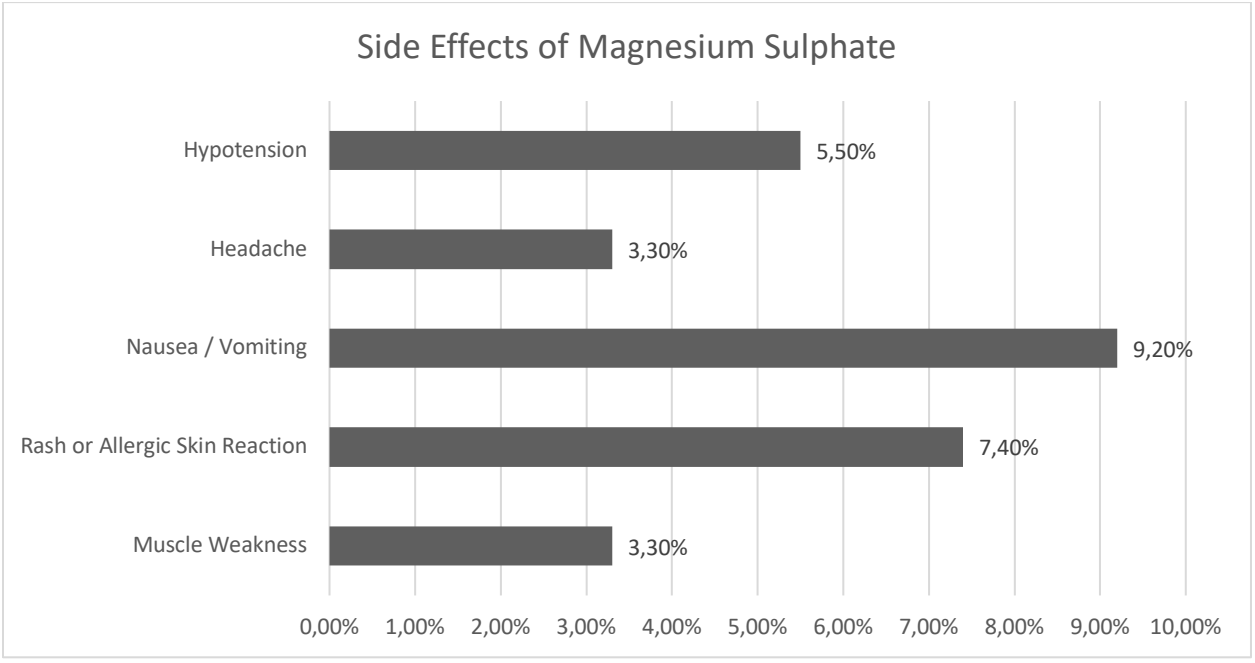

Figure 2. Side effects experienced from IV magnesium sulfate treatment.