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A comparative pilot study of the efficacy and safety of nebulized magnesium sulfate and intravenous magnesium sulfate in children with severe acute asthma

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Abstract

Introduction: Severe asthma attacks are life-threatening, and require serious medical attention. Intravenous $MgSO_4$ is an efficient medication, proven to improve outcomes. To date, most research has focused on administration of nebulized MgSO4 in adults with critical asthma. However, its benefits for treating childhood asthma has been little investigated. This study compared the clinical efficacy and adverse effects of nebulized $MgSO_4$ and intravenous $MgSO_4$ in the treatment of children with severe acute asthma.

Method: A prospective, open-label, randomized, controlled pilot study was conducted in children with severe asthma exacerbation admitted at the Queen Sirikit National Institute of Child Health. Twenty-eight patients were randomized to receive three intermittent doses of nebulized or intravenous MgSO4. The Modified Wood's Clinical Asthma Score was determined prior to, and at 20, 40, 60, 120, 180 and 240 minutes after treatment administration. The length of hospital stay was also recorded.

Results: Fifteen patients received nebulized isotonic $MgSO_4$ and 13 were administered intravenous $MgSO_4$. There were no differences in the baseline characteristics of the two groups, including their initial asthma severity scores (4.87 ± 0.92 vs. 5.0 +0.82; p = 0.69). No statistically significant differences between the two groups were identified at 60 minutes (2.47 ± 0.83 vs. 2.77 ± 0.93; p = 0.37) until 240 minutes. The length of hospital stay for both groups was also similar (4.0 ±1.2 vs. 4.54 ± 2.7; p = 0.51). No adverse effects from $MgSO_4$ administration were observed among the participants.

Conclusions: In this small sample size we demonstrated that nebulized $MgSO_4$ and intravenous $MgSO_4$ are both clinically beneficial and safe for Thai children suffering from severe asthma exacerbation.

Keywords: Asthma; Acute asthma; Nebulized magnesium sulfate; Intravenous magnesium sulfate; Isotonic magnesium sulfate

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Introduction

Severe asthma is generally a major burden to patients and their families, given the frequent hospital admissions and incurred hospital expenses. This inflammatory airway disease continues subclinically with periodic acute exacerbations. Severe acute asthma attacks that are triggered by a stimulus, such as inhaled allergens, irritants, respiratory infection and exercise, are frequently serious and often require close monitoring and intensive emergency treatment. The standard therapies initially performed to relieve bronchial obstruction and reduce inflammation include oxygen, nebulized β2-agonists, anticholinergic agents and systemic corticosteroids, which are usually adequate for many patients. However, a limitation of these therapies is that between 19-50% of patients exhibit only a partial response and require additional treatment.[1] For critically ill patients, a smooth muscle relaxant, such as aminophylline or $MgSO_4$, may be necessary to alleviate bronchospasm. For several decades, aminophylline has been a popular agent for the treatment of serious acute asthma attacks in developing countries. However, due to its narrow therapeutic range, aminophylline is not recommended in the asthma relief

guidelines of western countries, such as that detailed in the Global Initiative for Asthma (GINA) report. Instead, nebulized $MgSO_4$ is recommended as an optional therapy for severe acute asthma exacerbation.[2]

Magnesium is an important intracellular cation, which is not only a basic electrolyte in the human body, but also an essential component of drugs used for the treatment of various diseases, including asthma. The remarkable benefits of magnesium in the treatment of acute asthma were first reported by Haury in 1937.[3] The potential mechanisms underlying the bronchodilation effects of β2-agonists are thought to be varied. For example, magnesium levels have been found to be associated with the movement of smooth muscle. Specifically, low levels of magnesium induce muscle contraction, whereas high levels induce muscle relaxation.[3,4] This relaxation mechanism was supported by a study by Spivy, who investigated the role of $MgCl_2$ in reducing bronchospasm provoked by histamine in animals.[3] Furthermore, $MgSO_4$ is a competitive antagonist for calcium, which is a bronchoconstriction inducer. The mechanisms involve the inhibition of calcium release from the endoplasmic reticulum, causing the bronchial smooth muscles to relax, thereby distending the bronchial tube.[5] Other potential effects of $MgSO_4$ include reducing the levels of acetylcholine and histamine, as well as decreasing the production of adenylyl cyclase and sodium-potassium ATPase enzymes, which enhance the effects of the β2-agonist.[6]

Currently, $MgSO_4$ is available in two forms, intravenous and aerosolized, for the treatment of acute asthma. Magnesium infusion was discovered earlier, and has been used to treat asthma since 1937.[3] Its striking efficacy in the treatment of serious acute asthma patients, both adults and children, has been recognized for over eight decades.[7-10] Shan reported that, combined with β2-agonists and systemic steroids, intravenous $MgSO_4$ improved pulmonary function and reduced hospital admission rates in children.[11] However, magnesium infusion increases blood magnesium levels, and therefore, can cause adverse effects, which has diminished the popularity of intravenous $MgSO_4$. In order to reduce magnesium toxicity, nebulized $MgSO_4$ was developed. Although this regimen has been confirmed to be effective in adults with severe asthma, little research has been conducted on the effects of nebulized $MgSO_4$ in pediatric patients.[12-16] Recently, the Magnesium Trial in Children (MAGNETIC), a large, randomized, placebo -controlled, multicenter trial to evaluate the effects of nebulized $MgSO_4$ in children, reported no statistically significant outcomes in the asthma severity scores of 508 children with severe acute asthma and poor response to conventional therapies, except for those hospitalized within 6 hours of having had asthma symptoms ($p = 0.049$) and those with more severe diseases ($p = 0.03$).[17] Due to the benefits in patients that present early, the GINA guidelines (2015) recommend the use of $MgSO_4$ in children aged over 2 years with very severe illnesses.[2] However, such recommendations are still controversial, and further research is required. Moreover, there is still inadequate information on the use of $MgSO_4$ therapy for the treatment of acute asthma in Thailand. Therefore, the objective of this study was to compare the efficacy and safety of intravenous and nebulized $MgSO_4$ in children affected by severe acute asthma attacks.

Methods

Patients

An open-label, randomized, controlled pilot study was conducted at the Queen Sirikit National Institute of Child Health in Bangkok, Thailand, from March 1 2014 to March 31 2015, following approval of the institute's Ethics Committee. This study was registered in the international clinical trial system (www.clinicaltrials.gov; NCT02112305). The inclusion criteria were inpatient asthmatic children aged between 2 and 15 years old with an asthma score of > 5, indicated as impending respiratory failure by Wood,[18] and children whose pediatrician had decided to used $MgSO_4$ for the treatment of persistent severe asthma. The patients were initially treated with three doses of nebulized salbutamol (0.15 mg/kg/dose) and one dose of nebulized ipratropium bromide/fenoterol (500 μg/dose) in the emergency department, and subsequently treated with intravenous corticosteroid, in addition to several doses of salbutamol or continuous nebulized salbutamol while in the pediatric ward. All patients also received oxygen supplemented with 24-40% FIO_2.

Patients were excluded from the study if they met the following exclusion criteria: (1) history of chronic lung disease, (2) contraindication for $MgSO_4$ due to hepatic or renal disease, (3) allergy to $MgSO_4$, (4) patients that had previously suffered life-threatening conditions, and (5) those whose parent(s) refused participation in the study or who did not sign the informed consent form.

Study Protocol

The 28 patients that required $MgSO_4$ treatment for severe asthma, for which a signed informed consent form was obtained, were randomized into two groups using a computerized base scheme. Each group received a different $MgSO_4$ formulation. The intravenous $MgSO_4$ group was treated with a single dose of $MgSO_4$ infusion (50 mg/kg) for over 20 minutes. The nebulized $MgSO_4$ group received three 2.5 mL doses of isotonic $MgSO_4$ nebulizer (6% solution), each given 20 minutes apart. The 6% solution of isotonic $MgSO_4$ was prepared by diluting 150 mg of the intravenous formula to a concentration of 245 mmol/L, or 337 mosm/L. During the 4-hour experimental period, the standard of care for asthma was provided by the primary physician without any disruptions by the researcher.

The Wood's Clinical Asthma Score, patients' blood pressure, and any adverse effects (including flushing, headache, tremors, nausea, vomiting, hypotension and/or changes in deep tendon reflex) resulting from the two types of therapy were recorded 20, 40, 60, 120 and 240 minutes following initiation of the treatment. The participants were followed up until they were discharged in order to assess the length of hospital stay as a secondary outcome.

Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences version 16 (SPSS, Chicago, IL, USA). An independent t-test was implemented for the continuous variables, and the Fisher's exact test was applied for the categorical variables. The results were considered to be statistically significant at $p < 0.05$.

Results

Twenty-eight children with severe acute asthma were enrolled in the study. All had been treated with frequent aerosolized β2-agonist, anticholinergic drugs, systemic corticosteroids and oxygen supplement by their primary pediatrician (data not shown) prior to $MgSO_4$ treatment. Fifteen children were randomly assigned to receive the nebulized $MgSO_4$, while the remaining 13 children received intravenous $MgSO_4$. The mean age of the nebulized and intravenous MgSO4 groups were 5.4 ± 2.61 and 5.15 ± 3.34 years, respectively. The number of boys was higher in the intravenous $MgSO_4$ group (53.8%) than in the nebulized $MgSO_4$ group (46.7%). All participants were Asian (26 Thai, 1 Cambodian and 1 Filipino). The results are presented in **Table 1**.

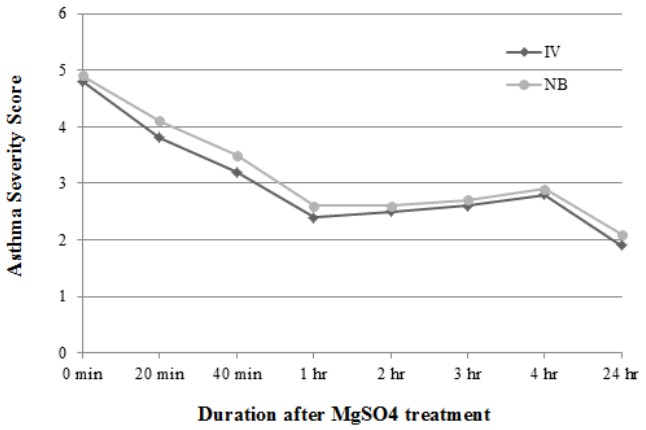

Figure1. Comparison of asthma severity scores over time between the nebulized $MgSO_4$ (NB) and the intravenous $MgSO_4$ (IV) groups

Table 1. Comparison of the baseline characteristics between the two groups of participants

Baseline characteristics	Nebulized $MgSO_4$ (N = 15)	Intravenous $MgSO_4$ (N = 13)
Age (year)	5.4 ± 2.61	5.15 ± 3.34
Gender (male)	7 (46.7%)	7 (53.8%)
Ethnicity (Thai)	14 (93.3%)	12 (92.3%)
Height (cm)	110.8 ± 12.44	109.15 ± 18.75
Weight (kg)	20.6 ± 5.5	17.85 ± 6.41
Heart rate (per min)	144 ± 11.64	145.31 ± 8.9
Respiratory rate (per min)	36.93 ± 4.77	39.08 ± 5.98
Mean BP (mmHg)	75.93 ± 7.44	72.92 ± 6.68
Pulse oximetry (%)	92.8 ± 1.32	92.46 ± 1.81
Breastfeeding	4 (26.7%)	7 (53.8%)
Comorbidity (allergy)	15 (100%)	13 (100%)
Family history of allergic disease	8 (53.3%)	9 (69.2%)
Aeroallergen sensitization	15 (100%)	13 (100%)
Daycare attendance	3 (20%)	3 (23.1%)
Smoking	12 (80%)	7 (53.8%)
Absolute eosinophil count	281.4 ± 229.69	219 ± 369.35
Asthma severity score	4.87 ± 0.92	5.0±0.82

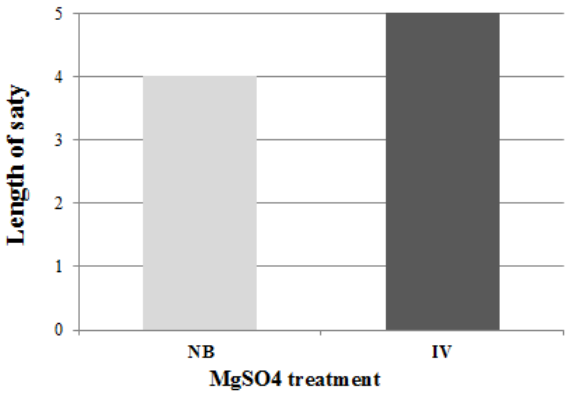

Figure 2. Comparison of the length of hospital stay between the nebulized $MgSO_4$ (NB) and the intravenous $MgSO_4$ (IV) groups

Table 2. Comparison of the characteristics of the participants in the nebulized and the intravenous $MgSO_4$ groups during the study period

Participants' characteristics	Nebulized $MgSO_4$ (N = 15)	Intravenous $MgSO_4$ (N=13)	p value
Heart rate at 60 minutes	130.47 ± 13.67	137.15 ± 10.31	0.161
Respiratory rate at 60 minutes	31.27 ± 3.94	32.92 ± 6.66	0.423
MBP at 60 minutes	75.87 ± 6.09	74.08 ± 5.68	0.431
Pulse oximetry at 60 minutes	99 ± 1	98.23 ± 1.09	0.573
Magnesium level	2.32 ± 0.22	2.59 ± 0.33	0.019*
Adverse reaction	0 %	0 %	NA

Table 3. Comparison of the mean asthma severity scores (ASS) between the nebulized $MgSO_4$ and the intravenous $MgSO_4$ groups

Duration after the MgSO4 treatment	Nebulized $MgSO_4$ (N = 15) ASS (mean + SD)	Intravenous $MgSO_4$ (N = 13) ASS (mean + SD)	p value
Baseline	4.87 ± 0.92	5.00 ± 0.82	0.690
20 minutes	3.80 ± 1.08	4.15 ± 1.07	0.393
40 minutes	3.13 ± 0.83	3.46 ± 1.05	0.365
60 minutes	2.47 ± 0.83	2.77 ± 0.93	0.371
2 hours	2.53 ± 1.13	2.69 ± 0.95	0.692
3 hours	2.60 ± 0.83	2.85 ± 0.99	0.479
4 hours	2.73 ± 0.70	2.92 ± 1.04	0.572
24 hours	1.87 ± 1.06	2.15 ± 0.69	0.411

There were no statistically significant differences between the two groups in terms of their mean age, height, heart rate, respiratory rate, mean blood pressure, breastfeeding during infancy, allergy background, eosinophil count and clinical asthma score, as shown in **Table 1**. Among atopic diseases, allergic rhinitis was the most common allergic condition among the participants. All had aeroallergen sensitization, with house dust mite being the primary cause of allergy (89.2%), followed by American cockroaches (32.1%), cat dander (17.8 %), dog epithelia (14.2%), grass (14.2%) and mold (3.5%). No statistically significant differences were found for environmental exposures between the two groups, including parent smoking, possession of domestic pets or daycare attendance.

With regard to the efficacy and safety of the two types of $MgSO_4$ treatment, no statistically significant differences were identified between the two groups for blood pressure, heart rate, respiratory rate or oxygen saturation 60 minutes after the treatment. However, serum magnesium was higher in the group that received intravenous $MgSO_4$ (2.59 ± 0.33) than in those that received nebulized $MgSO_4$ (2.32 ± 0.22; p = 0.019), as shown in **Table 2**. Deep tendon reflex was also monitored during the study period, with no changes observed in the subjects. Moreover, no patients reported adverse symptoms of $MgSO_4$ toxicity, which include flushing, dizziness, nausea or vomiting.

All patients in both groups showed clinical improvement 60 minutes after $MgSO_4$ administration compared to the baseline assessment, and this continued for 24 hours. In addition, no statistically significant differences in clinical asthma scores were identified in the nebulized and intravenous $MgSO_4$ groups at 60 minutes (2.47 ± 0.83 vs. 2.77 ± 0.93; p = 0.371) or 4 hours (2.73 ± 0.70 vs. 2.92 ± 1.04; p = 0.572) after treatment, as shown in **Table 3** and **Figure 1**.

With regard to the length of hospital stay, the two groups were not statistically different (4.0 ± 1.2 and 4.54 ± 2.7 days for the nebulized and intravenous MgSO4 groups, respectively), as shown in **Figure 2**.

Discussion

Several systematic reviews and meta-analyses have confirmed the efficacy of supplementing conventional therapies (β2-agonist and systemic steroid) with intravenous $MgSO_4$ in patients suffering from severe asthma attacks.[7-11] At the hospital in which this study was undertaken, intravenous $MgSO_4$ is commonly administered to children with status asthmaticus to reduce asthma severity and shorten the length of hospital stay. However, the patients treated with this regimen require frequent venous punctures and tendon reflex assessments to monitor magnesium toxicity. This is not the case for nebulized $MgSO_4$ administration, which has been shown to be effective in children with very severe asthma, provided that treatment begins early, ideally within 6 hours of an attack.[17] The present findings confirm the benefits of combining $MgSO_4$ and conventional bronchodilators for the treatment of asthma exacerbation. Specifically, the bronchodilator $MgSO_4$ seems to take effect as quickly as 60 minutes after administration. In addition, its action was found to last for as long as 4 hours in both nebulized and intravenous forms, a longer bronchial release duration than previously reported in a study by Mahajan.[13] Regarding the length of hospital stay, the results again highlight the efficacy of both nebulized and intravenous $MgSO_4$ therapies.

Although the patients treated with $MgSO_4$ in this study did not experience any adverse events, blood magnesium levels were increased in the group that received intravenous $MgSO_4$ treatment. After the first dose of intravenous $MgSO_4$, the blood magnesium concentration increased significantly compared to from administration of the three doses of nebulized $MgSO_4$. Such a difference is a matter of concern, and therefore, nebulized $MgSO_4$ may be preferable to $MgSO_4$ infusion in asthma patients, particularly those that require a longer hospital stay.

Previous international studies have only focused on the benefits of commercial isotonic $MgSO_4$ solutions, which are not readily available in Thailand.[14-17] Thus, the preparation of nebulized isotonic $MgSO_4$ for use in this study required the assistance of a pharmacist. Not only was this product more economical, but it also proved to be efficacious and safe for the treatment of 15 children with acute asthma attacks. Future studies should evaluate the use of this isotonic solution with a larger sample size to further verify its efficacy and safety.

Despite demonstrating the efficacy and safety of nebulized $MgSO_4$ treatment in comparison with its intravenous counterpart, a limitation of this study was its small sample size. Statistically significant differences between infused and inhaled $MgSO_4$ for the treatment of Thai children with critical asthma attacks may be identified when tested with a larger sample size.

In conclusion, this comparative pilot study found no differences in the efficacy and safety of nebulized and intravenous $MgSO_4$ among Thai children with severe asthma attacks.

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