

Magnesium sulfate vs aminophylline as a second line of treatment in children with severe acute asthma. Randomized clinical trial

Sulfato de magnesio vs aminofilina como segunda línea de manejo en niños con asma aguda severa. Ensayo clínico aleatorizado

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What do we know about the subject matter of this study?

In acute asthma, there are multiple treatment options for patients who fail initial therapy, however, there are still no solid recommendations on which, how, and when to use them.

What does this study contribute to what is already known?

This study reports the efficacy of magnesium sulfate as an effective and safe drug when first-line agents in acute asthma fail and suggests a logical sequence of addition of these second-line agents.

Abstract

Second-line drugs for acute asthma, such as salbutamol, magnesium sulfate, and aminophylline, are generally intravenously administered. **Objective:** To compare the efficacy and safety of using magnesium sulfate or aminophylline in children who did not respond to initial treatment. **Patients and Method:** Randomized clinical trial. Children who did not improve the Modified Pulmonary Index Score (mPSI) receive at random magnesium sulfate (50 mg/kg/single dose) or aminophylline (5 mg/kg/dose followed by continuous infusion at 1 mg/kg/hour for 3 hours). Primary endpoints were changes in mPSI and oxygen saturation; secondary endpoints: hospitalization rate, need for transfer to the intensive care unit, use of a third intervention, and adverse effects. **Results:** 131 patients were studied (66 patients in the aminophylline group and 65 MgSO₄). The mean age was 5 ± 2.3 years, the demographic and clinical parameters did not differ between the groups. In the group that received magnesium sulfate, the mPSI and oxygen saturation changed significantly in favor from 13.1 ± 1.3 to

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4.9 ± 2.5 ($p < 0.001$) and from 3.3 ± 2.5 ; ($p 0.021$), respectively, and their risk of hospital admission (RR 0.68 95% CI [0.56, 0.82]) and of secondary failure (0.16 95% CI 95% [0, 0.38]) decreased. Only one adverse event (tachycardia) was recorded. **Conclusion:** The administration of a single dose of magnesium sulfate proved to be more effective and safe than the use of aminophylline as a second-line drug.

Introduction

Asthma exacerbation is defined as a progressive increase in signs and symptoms as well as deterioration of lung function, significant enough to require a change in treatment, and is largely responsible for frequent emergency room visits and hospitalizations. It may occur in patients previously diagnosed with asthma or, less frequently, be the initial manifestation of the disease¹⁻³.

When treating an asthma exacerbation, the goals of treatment are to reverse airflow obstruction, reduce inflammation, and prevent future relapses. According to good clinical evidence, generally recommended initial treatment strategies consist of inhaled β_2 -agonists, ipratropium bromide, systemic corticosteroids, and controlled oxygen supplementation^{1,2,4}.

Most of the children who present exacerbations classified as mild to moderate concerning their severity respond to drugs considered as first-line, while there is a proportion of children who present greater severity requiring much more intensive treatments⁵.

In patients with severe exacerbations, who do not respond or respond partially to initial treatment, other alternatives have been suggested, commonly considered intravenous (IV), consisting of the administration of β_2 -agonist (salbutamol), magnesium sulfate (MgSO₄), or aminophylline. However, among these treatment options, it is not entirely clear which is the most effective^{6,7}. These broad selection options, along with the variations that exist in the health care practice for this group of patients, further complicate decision making⁸. In adult patients with severe exacerbations, the use of IV MgSO₄ is useful and safe⁹, however, this same conclusion is not entirely shared for its use in children, although it is considered that it could be useful¹⁰.

A recent study on preferences regarding the use of these agents found that most respondents preferred to use IV salbutamol, 28% preferred IV MgSO₄, and 15% preferred to use aminophylline¹¹. In British guidelines, the use of MgSO₄ is recommended as a first treatment option for children with more severe and potentially life-threatening asthma who do not respond to first-line medications⁴.

The objective of this study is to compare the effica-

cy and safety of using magnesium sulfate as a second-line treatment alternative or IV aminophylline in children with acute asthma who do not respond to initial treatment in the emergency room.

Patients and Method

Randomized clinical trial conducted in the pediatric emergency room of the *Hospital Antonio Patricio De Alcalá* in Sucre, Venezuela, between April 2017 and August 2018. Patients ≥ 2 years old and ≤ 12 years old who consulted due to asthma exacerbation were included.

Asthmatic individuals were considered as those patients with the medical diagnosis of asthma or those who had experienced more than three exacerbations and had improved with the use of bronchodilators, treated in an emergency room or at the outpatient level of any health center. Children with chronic respiratory, heart, kidney, immunologic, or hematologic diseases or if they had been hospitalized due to asthma in the last 4 weeks or received IV MgSO₄ in the last 2 weeks were excluded.

All patients were treated according to existing clinical protocols applied by our institution^{1,2,4}. In the initial phase, patients with acute asthma were treated with nebulized salbutamol and systemic corticosteroids. Salbutamol (Salbutamol®, Medifarm, Venezuela, 1ml/5mg) calculated at 0.15 mg/kg dose, administered by a jet nebulizer powered by oxygen 6 l/min. The maximum volume of the nebulized solutions was 3cc completed with normal saline (0.9%). Subsequently, a nebulization was administered every 20 minutes for the next hour.

The systemic IV corticosteroid used was hydrocortisone (Fridalit®, 100mg vials, GynoPharm, Venezuela) calculated in all cases at a 5mg/kg dose.

The severity of the exacerbation was assessed using the modified Pulmonary Index Score (mPIS) which has six evaluation parameters: heart rate, respiratory rate, accessory muscle use, presence of wheezing, the ratio between inspiration and expiration, and oxygen saturation while breathing room air. Each parameter had a score between 0 to 3 depending on the severity. The total score was from 0 to 18 points as the maxi-

mum value. It was considered a mild episode if the score was ≤ 6 points, moderate between 6 and ≤ 11 points, and severe ≥ 12 points¹². This parameter was always assessed by a single investigator.

Changes in mPIS were assessed one hour after; patients who did not achieve a decrease of at least 3 points on the baseline score or those who experienced a worsening of the baseline score were randomized to evaluate second-line therapeutic strategies.

The patients were divided into two groups. Group 1 consisted of patients that received a single dose of IV magnesium sulfate® (MgSO₄) (Alfa, 12%) at 50mg/kg/dose diluted to 30cc of 5% dextrose solution and administered within 30 minutes, and Group 2 consisted of patients that received aminophylline® (Biotech, Venezuela, 240mg/10ml) initially calculated at 5mg/kg dose, diluted with 5% dextrose solution until completing 20cc, and administered IV within 30 minutes, followed by a continuous infusion calculated at 1mg/kg/h for 3 hours.

Randomization was performed using a sequence of numbers generated in Excel, forming blocks of 4 patients for each treatment strategy. A person not involved in patient selection generated the random numbers. Both the patients and the person in charge of the statistical analysis were unaware of the treatment strategy applied.

The mPIS was evaluated at 30, 60, 90, 120, 150, and 180 minutes. If after this time there was no significant improvement in the mPIS (≥ 9 points), the intravenous strategies used were exchanged, extending the evaluation of this subgroup 4 more hours. This subgroup was considered as secondary failure to second-line agents. The primary outcomes showed changes in mPIS and oxygen saturation (SpO₂) at the end of 180 minutes, and the secondary ones showed hospitalization rate, need for intensive care unit (ICU) admission, need to add another drug at the end of 180 minutes, and adverse effects.

For the statistical analysis, we considered a 95% confidence level (type 1 error of 0.05) and 80% statistical power (type 2 error of 0.20). The sample size was estimated between 52 to 60 patients for each group in order to evaluate whether MgSO₄ could reduce the relative risk of hospital admission by 25%, assuming a hospital admission rate of 90% in children treated with aminophylline.

Discrete variables were analyzed using the Chi-square test, and the continuous ones with Student's t-test or Mann Whitney test and Fisher's test. A $p < 0.05$ level was considered statistically significant. Statistical analyses were performed using the Statgraphic Plus 10.0 software.

The study was evaluated and approved by the Postgraduate Study Commission of the *Hospital Antonio*

Patricio De Alcalá, which recognized the ethical aspects following the Declaration of Helsinki and retrospectively registered in the Cuban Public Registry of Clinical Trials (00000324 on 09-07-20). Written informed consent was obtained from all patients by their guardians or caregivers.

Results

During the study period, 1510 patients with asthma exacerbation were evaluated in the emergency room, however, only 131 patients were considered for the study due to no significant improvement in mPIS. After randomization, 65 patients remained in the MgSO₄ group and 66 in the aminophylline one (figure 1).

After randomization, there were no differences in demographic or clinical characteristics at study entry (table 1).

Primary objectives. The primary outcome variables, ratio lung index score at 180 minutes/lung index score at hour 0 and change in room air oxygen saturation (Δ SpO₂) calculated at 3 hours from randomization and initiation of MgSO₄ or aminophylline (table 2).

In the general population, there were significant changes in mPIS as well as SpO₂ between baseline and at 180 minutes of intervention. However, these changes were more significant in children in the MgSO₄ group than in those who received aminophylline. After 3 hours of MgSO₄ or aminophylline infusion, the mPIS score decreased from 13.1 ± 1.3 (SD) to 4.9 ± 2.5 . The differences between means and their percentage variations were equally highly significant [$(-62.7\% \pm 16.3; p < 0.001)$ (12.9 ± 1.2 to 8.6 ± 2.8 ; $-33.9\% \pm 19.4; p < 0.001$)]. Improved mPIS was associated with a greater increase in SpO₂ [3.3 ± 2.5 vs. 2.1 ± 3.4 ; mean difference and 95%CI 1.2 (0.2; 2.3); $p 0.021$] in response to magnesium sulfate than to aminophylline. Figure 2 shows the variations of these primary outcomes as a function of evaluation time.

The efficacy of MgSO₄ in reducing mPIS and SpO₂ in children with severe acute asthma was superior to that of aminophylline at different control points during the 3 hours. Table 3 shows the secondary outcome variables of the secondary objectives.

105 hospital admissions with an mPIS score of 7.7 ± 2.8 were recorded. This group included 42 (64.6%) of 65 children treated with MgSO₄ and 63 (95.5%) of 66 children treated with aminophylline. The relative risk of admission in children with severe acute asthma treated with MgSO₄ was 0.68 95%CI [0.56, 0.82]; $p < 0.001$. 5 (7.7%) of 65 children treated with magnesium sulfate and 32 (48.5%) of 66 treated with aminophylline presented secondary failure, defined as persistence of severe acute asthma with mPIS ≥ 9 points after

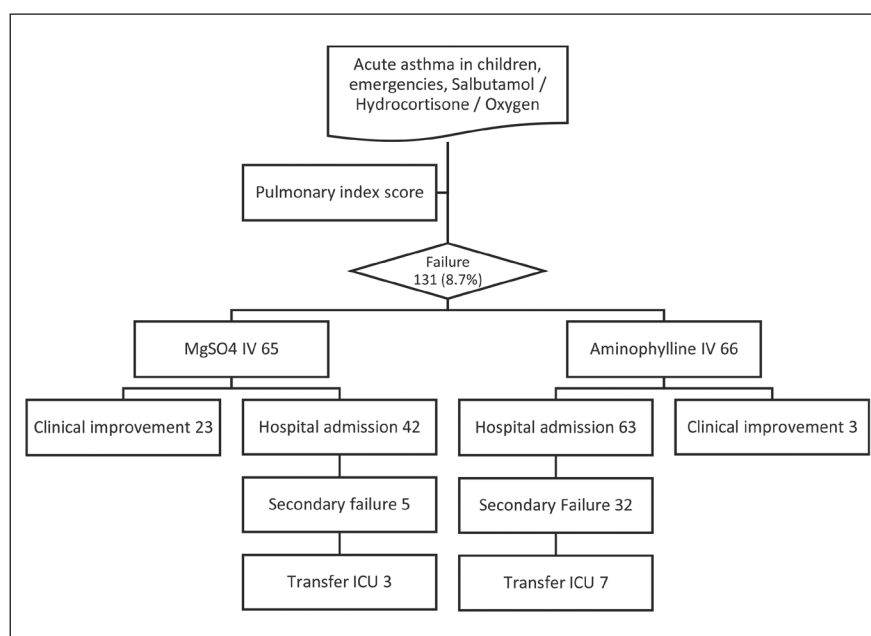


Figure 1. Flow chart for the selection and treatment of patients.

Table 1. Magnesium sulfate versus aminophylline in treatment of severe acute asthma failing salbutamol/hydrocortisone, subgroup comparison after randomization

Variables	Total	Therapeutic intervention		95% Confidence interval	P
		MgSO ₄	Aminophylline		
n	131	65	66		
Sexo masculino, n (%)	73 (55.7)	37 (56.9)	36 (54.5)	1.04 (0.8; 1.4)	0.784 [#]
Mediana edad en años	5 (4;7)	5 (4; 6.5)	5.5 (4; 7)		0.261 [#]
Índice pulmonar, media y DE	13.0 ± 1.3	13.1 ± 1.3	12.9 ± 1.2	0.2 (-0.3; 0.6)	0.410 [†]
Saturación de oxígeno, media y DE	94 ± 2	94 ± 1.3	93 ± 2.6	1.0 (0.1; 1.5)	0.028 [†]

*Chi cuadrado. [#]U de Mann Whitney, prueba no paramétrica para grupos independientes. [†]Student para grupos independientes.

*Tiempo transcurrido desde el inicio de los síntomas en domicilio hasta iniciar la atención médica.

Table 2. Efficacy of magnesium sulfate versus aminophylline in the treatment of severe acute asthma, primary outcome variables

Secondary therapy	Baseline clinical status		Clinical status at 3 hours		Primary outcome variables	
	PIS ₀	SpO ₂ ₀	PIS ₁₈₀ [†]	SpO ₂ ₁₈₀	PIS ₁₈₀ /PIS ₀ [†]	SpO ₂ ₁₈₀ -SpO ₂ ₀
Magnesium sulphate (n 65)	13.1 ± 1.3	93.9 ± 1.3	4.9 ± 2.5	97.2 ± 2.9	0.37 ± 0.16 ^b	3.3 ± 2.5 [#]
Aminophylline (n 66)	12.9 ± 1.2	93.1 ± 2.6	8.6 ± 2.8	95.2 ± 3.8	0.66 ± 0.19 ^b	2.1 ± 3.4 [#]
Difference of means (95 CI)	0.2 (-0.26; 0.62)	0.8 (0.1; 1.5)	-3.7 (-4.6; 2.8)	2.0 (0.8; 3.2)	-0.29 (-0.35; -0.23)	1.2 (0.2; 2.3)
P	0.410	0.028	0.001	0.001	0.001	0.021

[†]PIS₁₈₀ / PIS₀, Ratio between the PIS score at 180 minutes and the PIS score measured at hour 0. [#]P < 0.001, non-independent samples t-test for contrast against baseline values. ^bStudent's t test independent samples for the contrast between MgSO₄ and Aminophylline.

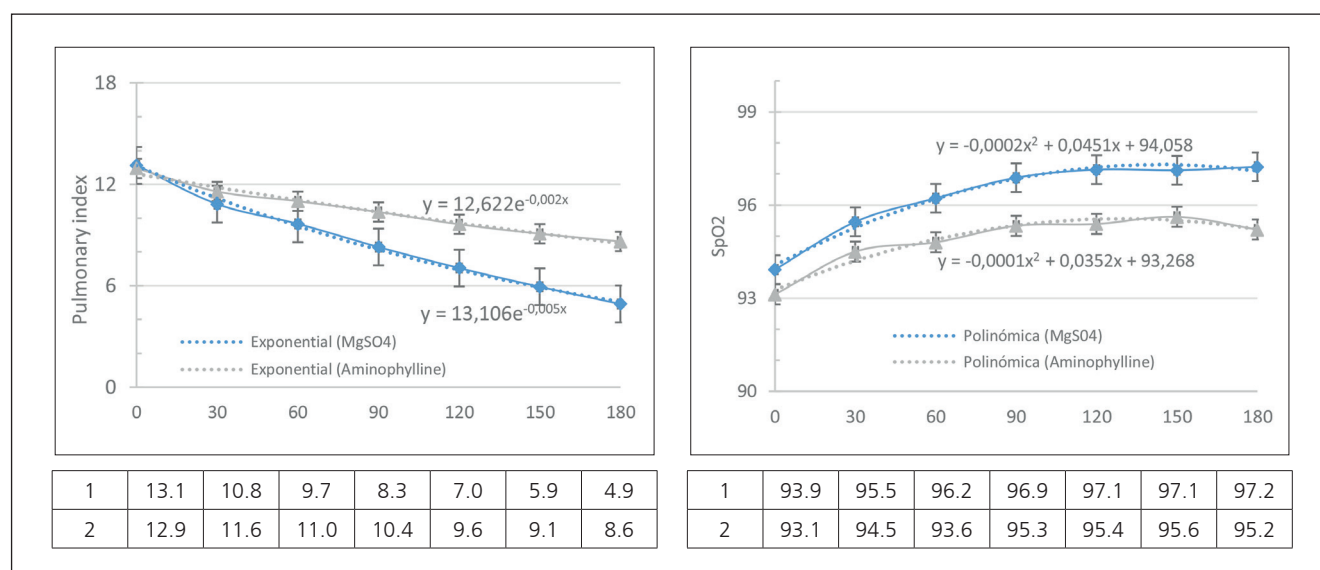


Figure 2. Pulmonary index (A), oxygen saturation, SpO2, (B) in children with severe acute asthma, mean and standard error according to therapeutic group and time in minutes.

Table 3. Secondary outcome variables: Hospital admission, therapeutic failure, and admission to the ICU.

Secondary outcome	Total	MgSO ₄	Aminophyl-line	RR (IC95) [†]	P
Hospital admission					
Yes	105 (80.2)	42 (64.6)	63 (95.5)		
Not	26 (19.8)	23 (35.4)	3 (4.5)	0.68 (0.56; 0.82)	0.001
Secondary failure					
Yes	37 (28.2)	5 (7.7)	32 (48.5)		
Not	94 (71.8)	60 (92.3)	34 (51.5)	0.16 (0.07; 0.38)	0.001
Transfer to ICU					
Yes	10 (7.6)	3 (4.6)	7 (10.6)		
Not	121 (92.4)	62 (95.4)	59 (89.4)	0.44 (0.12; 1.61)	0.324

Admisión hospitalaria, niños con asma aguda grave, índice pulmonar a 3 h ≥ 4 puntos con una razón $PIS_{180}/PIS_0 > 30$; *falla secundaria*, niños con índice pulmonar ≥ 9 puntos luego de 3 horas de tratamiento con sulfato de magnesio o aminofilina; *admisión a UCI*, niños con asma aguda grave, $SO_2 < 90$. Los datos representan frecuencia absoluta (porcentaje). [†]RR (IC95), Riesgo relativo (intervalo de confianza 95%).

3 hours of treatment with MgSO₄ or aminophylline, RR 0.16 95%CI [0.07, 0.38], $p < 0.001$.

Ten children (7.63 %) required admission to the ICU; only 3 patients in the MgSO₄ group vs. 7 in the aminophylline group ($p = 0.3360$). Only one adverse event (tachycardia) was recorded in the aminophylline group, which was observed 90 minutes after the start of the infusion without clinical impact and without the need to discontinue its administration.

Discussion

This open-label randomized study demonstrates the efficacy of using MgSO₄ in children with acute

asthma who did not respond to first-line medications considered standard of care therapy. When comparing mild to moderate severity cases with more severe cases, care practices vary significantly which could be conditioned by the existing conflicts between the different publications to make suggestions in these cases¹³.

In the United Kingdom, they suggest that aminophylline should be reserved for the most severe cases that have not responded to the maximum dose of corticosteroids and bronchodilators, while for the use of MgSO₄ and despite it is considered a safe drug, its efficacy in the pediatric age group has not been established¹⁴.

Singhi et al compared the usefulness of adding ter-

butaline, MgSO₄, or aminophylline in those patients who had a poor response to standard therapy, observing that the MgSO₄ group had a better response with much more marked changes over time than when the other two strategies were used¹⁵. Our results are the same as those reported by Singhi, where they showed that not only the modification of severity is achieved in a shorter time but also a much higher proportion of patients.

A 2006 systematic review, based on 5 studies, evaluated the usefulness of using intravenous MgSO₄ compared with placebo when the first-line strategy was not enough to relieve the exacerbation, finding that its administration was able to reduce hospital admission by 68% (OR 0.32, 95%CI [0.14-0.74])¹⁶. Much more recently, it was found that the group using MgSO₄ had significantly greater improvement in both pulmonary function (SMD 1.94; 95%CI 0.80, 3.08; $p = 0.0008$) and in the reduction of the number of hospitalizations, which were reduced by 45% (RR 0.55; 95%CI 0.31-0.95; $p = 0.03$)¹⁷.

The hospitalization rate in our study was high and was to be expected if we consider that these were refractory patients with a much higher severity that could not be modified with the first-line intervention. It is noteworthy that the hospitalization rate in the group that received MgSO₄ was significantly lower. Admissions to ICU were relatively low (< 10%), which is in line with the report of several studies¹⁸⁻²⁰.

In a randomized controlled study in children with acute asthma, Torres et al. evaluated the efficacy of the addition of MgSO₄ to standard therapy to prevent the use of mechanical ventilation. When compared with standard therapy, only 5% of those who received magnesium required ventilatory support vs. 33% in the standard therapy group ($p = 0.001$), concluding that its use during the first hour of hospitalization significantly reduced the percentage of children requiring ventilatory support²¹.

Our results share this observation since, in addition to the decrease in the hospitalization rate, patients who used MgSO₄ also improved oxygenation (related to SpO₂) significantly both in time variation and the percentage of patients who achieved SpO₂ correction.

A prospective observational multicenter study demonstrates a high variability in the treatment of children with more severe exacerbations concerning the selection of these second-line agents, where 52% used only one, 32% used a combination of two, and 16% used a combination of all three. One important reason for considering intravenous administration was related to low SpO₂ at the time of initial evaluation²².

The latter study indicates that there is no evidence for an optimal approach and currently none of the

widely used guidelines offer guidance for practice in terms of combinations and sequences of administration of these agents. The order commonly found for these agents was IV salbutamol first, then MgSO₄, and finally aminophylline²².

In the last part of our study, we analyzed the evolution of patients who after 180 minutes were unable to modify their mPIS and needed another therapeutic option. This result is in line with the findings of Morris et al since we observed that patients who had initially used aminophylline had a much greater need to use MgSO₄ compared with those who initially received MgSO₄ and then aminophylline. Both the severity regarding changes in mPIS and the percentage of children who improved were much higher when MgSO₄ was added, confirming the combination and sequence described²².

The use of MgSO₄ is safe with minor and infrequent adverse events reported²³. In the meta-analysis by Cheuk et al. when comparing its use with placebo, no adverse events were identified, concluding that its use is not only beneficial in reducing the risk of hospitalization but also that it is a safe drug to use in emergency rooms²⁴.

The lack of a placebo could not be considered a limitation of the study, since in this group of patients with severe disease it would be unethical to use it. Perhaps the greatest limitation could be that it was not multicenter, which could increase the sample size; however, we consider that the size was sufficient to make the suggestions in the population studied.

In conclusion, the administration of a single intravenous dose of MgSO₄ after the first hour in patients with acute asthma who do not respond to initial therapy proved that it significantly improves mPIS and SpO₂ with a significant decrease in hospital admission and is therefore considered much more effective and safer than the use of aminophylline.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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