The effect of nebulized magnesium sulfate on asthma attacks in the children

Nebulize magnezyum sülfatın çocuklarda astım atakları üzerine etkisi

Abstract

Aim: This study aimed to determine the effect of adding nebulized magnesium sulfate to standard treatment in children with moderate to severe acute asthma attacks.

Methods: Pediatric patients admitted to the emergency department with moderate to severe asthma attacks were included in the study. The patients were divided into two groups. Group S received standard treatment, while Group M received nebulized magnesium sulfate in addition to standard therapy.

Results: A total of 129 patients were included in the study, 86 (66.7%) were male, and the median (minimum-maximum) age was 4 (2-8) years. When groups were compared, oxygen saturation at hour 1 was higher (p=0.024), and the PRAM (preschool respiratory assessment measure) scores at the 4th hour were lower (p=0.008) in the group that received magnesium sulfate. The groups had no differences regarding any of the other parameters at the 1st and 4th hours (p>0.05).

Conclusion: Adding nebulized magnesium sulfate to standard treatment in children with asthma attacks improves oxygen saturation faster and positively affects PRAM score at hour 4.

Keywords: Adrenergic beta-2 agonists; asthma; asthmatic crisis; child; inhalers; magnesium sulfate

Öz

Amaç: Bu çalışmanın amacı orta ila şiddetli akut astım atakları olan çocuklarda standart tedaviye nebülize magnezyum sülfat eklenmesinin etkisini belirlemektir.

Yöntem: Acil servise orta ve şiddetli astım atağı ile başvuran pediatrik hastalar çalışmaya dâhil edildi. Hastalar iki gruba ayrıldı. Grup S standart tedavi alırken, Grup M standart tedaviye ek olarak nebulize magnezyum sülfat aldı.

Bulgular: Çalışmaya toplam 129 hasta dâhil edildi, 86'sı (%66,7) erkekti ve ortanca yaş (minimum-maksimum) 4(2-8) idi. Gruplar karşılaştırıldığında magnezyum sülfat verilen grupta 1. saat oksijen satürasyonu daha yüksek (p=0,024), 4. saat PRAM skoru (PRAM: Okul öncesi solunum değerlendirme ölçüsü) daha düşüktü (p=0,008). Diğer parametrelerde gruplar arasında 1. ve 4. saatte fark yoktu (p>0,05).

Sonuç: Astım atağı olan çocuklarda standart tedaviye nebülize magnezyum sülfat eklenmesi oksijen satürasyonunu daha hızlı iyileştirmekte ve 4. saatteki PRAM skorunu olumlu yönde etkilemektedir.

Anahtar Sözcükler: Adrenerjk beta-2 agonistler; astım; astım krizi; çocuk; inhalerler; magnezyum sülfat

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INTRODUCTION

Asthma is a common chronic airway disease in children and is generally a significant burden to patients and their parents. This chronic and inflammatory airway disease proceeds subclinically with periodic acute attacks. Many stimuli, including inhaled allergens, irritants, respiratory infections, and exercise, may trigger severe asthma attacks (1). A severe asthma attack is characterized by progressive symptoms such as shortness of breath, coughing, wheezing, chest tightness, and decreased lung function. Severe asthma attacks are commonly life-threatening and frequently serious situations. It commonly seeks care for close monitoring and intensive emergency treatment.

The main feature of an asthma attack is an obstruction of airflow. The primary goal of treatment advised a stepwise approach by the guidelines is to fix the obstruction of airflow to prevent hypoxemia by oxygen and recurrence (2). The initial steps of asthma treatment include oxygen, short-acting beta 2-agonists, nebulized anticholinergic agents, and corticosteroids in the emergency departments. However, beta 2-agonists act within minutes, whereas corticosteroids require hours. Methylxanthines, such as theophylline, are not advised due to inadequate efficacy, narrow therapeutic index, and frequent side effects (3). Ipratropium bromide, aminophylline or theophylline, intravenous (IV) or inhaled magnesium sulfate, helium, and high-dose inhaled corticosteroids can be used in patients not responding to initial treatment (4).

Some guidelines suggest that inhaled magnesium sulfate may benefit lung function when added to inhaled beta 2-agonists and ipratropium bromide (3). The advantages of using nebulized magnesium sulfate are rapid effect and low incidence of side effects. On the other hand, the disadvantages include reduced medication dosage compared to the IV form and the need for increased respiratory effort to improve drug efficacy (5). The bronchodilator effect of IV magnesium sulfate has been confirmed in several studies, but there is limited evidence about the effectiveness of its nebulized form (6, 7). There are few studies on pediatric patients, and the effects of nebulized magnesium sulfate in this age group are also controversial. The guidelines for pediatric patients suggest that intravenous magnesium sulfate is safe. Still, the results of nebulized magnesium sulfate in pediatric patients are controversial and are not discussed in children.

Nebulized magnesium sulfate may have different effects in pediatric patients. This study aimed to determine the effect of adding nebulized magnesium sulfate to standard treatment in children with moderate to severe acute asthma attacks and to compare various treatment-related characteristics to patients receiving only standard treatment.

METHODS

Study protocol

The Clinical Research Ethics Committee of Inonu University approved this study (date: 18.02.2020, decision no: 2020/418). The study's aim and procedures were explained to children or their parents, and written informed consent forms for participation in the study were obtained. This clinical study was designed by the Consolidated Standards of Reporting Trials (8).

Eligibility criteria

This study included 129 patients, aged between 2 and 8 years, who had moderate to severe acute asthma attacks and were admitted to the pediatric emergency department of a university hospital. We excluded patients with a history of hepatic, renal failure, chronic lung (other than asthma) and heart disease, cystic fibrosis, immunodeficiency, foreign body aspiration, and those with an allergy to magnesium sulfate or salbutamol, failure to get written informed consent for participation in this study. A short, standardized questionnaire was utilized in all patients to identify and record demographic data, complaints before and during treatment, asthma severity, and control level, accompanying diseases, emergency treatment, and vital signs.

Study design

A total of 129 patients between 2 and 8 years of age with moderate to severe acute asthma attacks were divided into group magnesium (group M, n=69) and group standardized (group S, n=60) (**Figure 1. Flow diagram**). Group M was treated with one dose of nebulized magnesium sulfate (150 mg/doz) with three doses of nebulized 1.5 mg / 1.5 ml salbutamol and

one dose of methylprednisolone (1 mg/kg) at 15-minute intervals. Group S (n=60) was treated with three doses of nebulized 1.5 mg/1.5 ml salbutamol and one dose of methylprednisolone (1 mg/kg) for asthma attacks. If group M or S did not respond to each treatment, nebulized salbutamol was re-administered on three occasions at 30-minute intervals. Patients with 94% and lower oxygen saturation were given oxygen supplements with a face mask.

Initial management and assessment

First, all pediatric patients received adequate oxygen via a face mask and a peripherally inserted intravenous line. A trained pediatric nurse in the emergency department performed a standard physical examination. A standardized physical examination was recorded, including measurements of oxygen saturation, and respiratory resistance, as well as vital signs (heart rate, noninvasive blood pressure, and respiratory rate), and identified signs of airway obstruction.

Outcome Measures

Demographic data, including age, sex, and race, were obtained. The consciousness, respiratory rate (per minute), peak heart rate (per minute), participation of accessory respiratory muscles, respiratory state, lung auscultation findings, oxygen saturation, and PRAM (preschool respiratory assessment measure) scores of the patients were recorded at the time of admission, on the 1st and 4th hours of treatment (**Table 1**). The PRAM score was used in this study's clinical evaluation of patients. The 12-point PRAM is a tool for assessing the severity of acute asthma exacerbations in children aged 3 to 6 years. This score has five categories: O_2 saturation (0-1-2), suprasternal retractions (0-2), scalene muscle contraction (0-2), air entry (0-1-2-3), and wheezing (0-1-2-3). This score shows the severity of airway obstruction (mild: <5, moderate: ≥5) and points out a clinically meaningful improvement (change from baseline ≥3) (9).

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 software (SPSS Inc. Chicago, IL, USA). The normality of continuous variable distribution was evaluated using the Kolmogorov-Smirnov test with Lilliefors correction. Descriptive statistics were presented as frequency and percentage for categorical variables and as median (min–max) for quantitative data. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test. Quantitative variables were compared by using the Mann-Whitney U test. p value of 0.05 or lower was considered as significant.

RESULTS

Of the 129 patients, the median age was 4 (min-max:2-8) years, and 86 (66.7%) were male. Of the 101 patients (78.3%) lived in the urban city center. Among the patients, 76 (58.9) had been previously diagnosed with asthma, and 53 (69.7%) were attending regular follow-ups for their condition. Overall, 53 (41.1%) of the patients had had exposure to cigarette smoke. There was no difference between group M and group S regarding gender, age, concomitant allergic disease, exposure to cigarette smoke, and the number of asthma attacks in the past year (**Table 2**).

A comparison of study groups showed that group M had significantly higher oxygen saturation at hour 1 ($p = 0.024$) and significantly lower total PRAM score at hour 4 ($p = 0.008$) compared to group S. There were no differences between the groups in terms of any other variables in either the 1st or the 4th-hour comparisons ($p > 0.05$) (**Table 3**).

DISCUSSION AND CONCLUSION

Adding nebulized magnesium sulfate to standard treatment in patients with moderate to severe asthma attacks led to faster correction of oxygen saturation, as demonstrated by better 1st-hour saturation values. In addition, patients who received magnesium sulfate treatment had lower PRAM scores at the post-treatment 4th hour.

Magnesium can improve the bronchodilator effect to salbutamol in acute asthma by increasing β receptor affinity or upregulation of the β2 receptor. Magnesium also relieves bronchoconstriction by reducing calcium intake and release in bronchial smooth muscles. It reduces the excitability of the muscular membrane by inhibiting the release of acetylcholine from the cholinergic nerve endings. Furthermore, magnesium con-

Table 1. The Preschool Respiratory Assessment Measure (PRAM) score

	Point
O_2 saturation	
≥95%	0
92-94%	1
<92%	2
Suprasternal retractions	
Absent	0
Present	2
Scalene muscle contraction	
Absent	0
Present	2
Air entry*	
Normal	0
Decreased at the base	1
Decreased at the apex and the base	2
Absent/minimal	3
Wheezing	
Absent	0
Expiratory only	1
Inspiratory (± expiratory)	2
Audible without stethoscope or silent chest (minimal or no air entry)	3

* If asymmetric findings between the right and left lungs, the most severe side is rated.

Table 2. Demographic characteristics of the groups

Variables	Group M* (n:69)	Group S** (n:60)	p value
Gender, male, n (%)	47 (68.1)	39 (65)	0.851
Age, median (min-max), year	4 (2-8)	4 (2-8)	0.665
Number of asthma attack within last year, median (min-max),	3 (1-10)	4 (1-10)	0.158
Living city center, n (%)	51 (73.9)	50 (83.3)	0.280
Diagnosed with asthma before consult to emergency, n (%)	41 (59.4)	35 (58.3)	0.9
Taking regularly controller treatment for asthma, n (%)	28 (68.3)	25 (71.4)	0.963
Exposure to smoking, n (%)	25 (36.2)	28 (46.7)	0.307
Co-exist atopic disease, n (%)	41 (59.4)	40 (66.7)	0.505

Max: Maximum, min: Minimum, n: Number, %: Percent

*Group M: Nebulized magnesium sulfate in addition to asthma attack treatment, **Group S: Standard asthma attack treatment

tributes to reduced histamine release from mast cells and the stimulation of nitrous oxide production and prostacyclin synthesis (10-13).

Previous studies compared salbutamol with nebulized magnesium sulfate to salbutamol-only treatment in asthma attacks. In the study conducted by Nannini et al. with 35 patients, a significant increase in PFR (peak flow rate) value was found within 10 minutes (and also at 20 minutes) in those that were given nebulized salbutamol in an isotonic solution of magnesium sulfate, compared to recipients of salbutamol in saline (14). In another study, Mahajan et al. added a dose of nebulized magnesium sulfate to salbutamol in treating asthma in children and found that it was beneficial in clinical improvement. However, they did not examine the response to magnesium sulfate and salbutamol at repeated doses (after the single dose) in the later stages of the asthma attack (15). In the study conducted by

Table 3. Comparison of study variables between groups.

Variable	Group M* (n:69)	Group S** (n:60)	p value
Restlessness, n (%)			
Baseline	14 (20.3)	16 (26.7)	0.518
First hour of treatment	5 (7.2)	6 (10)	0.808
Fourth hour of treatment	6 (8.7)	-	NC
Tachypnea, n (%)			
Baseline	59 (85.5)	53 (88.3)	0.832
First hour of treatment	60 (87)	54 (90)	0.793
Fourth hour of treatment	54 (78.3)	53 (88.3)	0.200
Tachycardia, n (%)			
Baseline	59 (85.5)	58 (96.7)	0.061
First hour of treatment	62 (89.9)	55 (91.7)	0.961
Fourth hour of treatment	63 (91.3)	55 (91.7)	1.0
Wheezing, n (%)			
Baseline	9 (13)	15 (25)	0.13
First hour of treatment	1 (1.5)	5 (8.3)	0.098
Fourth hour of treatment	2 (2.9)	3 (5)	0.665
Use of accessory respiratory muscles, n (%)			
Baseline	43 (62.3)	47 (78.3)	0.075
First hour of treatment	46 (66.7)	29 (48.3)	0.054
Fourth hour of treatment	51 (73.9)	39 (65)	0.364
O_2 saturation, median (min-max)			
Baseline	93 (85-94)	93 (86-94)	0.892
First hour of treatment	93 (89-96)	93 (87-96)	**0.024**
Fourth hour of treatment	94 (87-97)	94 (86-97)	0.393
PRAM score, median (min-max)			
Baseline	4 (2-11)	4 (2-10)	0.282
First hour of treatment	3 (2-11)	4 (2-10)	0.061
Fourth hour of treatment	1 (0-9)	2 (0-9)	**0.008**

Max: Maximum, min: Minimum, n: Number, %: Percent
*Group M: Nebulized magnesium sulfate in addition to asthma attack treatment, **Group S: Standard asthma attack treatment

Aggarwal et al. with 100 patients, 50 patients received magnesium sulfate combined with salbutamol, while the remaining 50 received salbutamol treatment only. The patient's heart rate, blood pressure, and PEFR (peak expiratory flow rate) were measured at baseline and on the 15th, 60th, 75th, and 120th minute. In addition, the patient's serum magnesium and blood gas values at baseline and 120th minutes were measured in both groups. PaO_2 values in blood gas were higher at the 120th minute in both groups, and their results did not demonstrate a significant difference between the groups (16). In our study, oxygen saturation values at the 1st hour of the treatment were significantly higher in the patients who received magnesium sulfate in addition to salbutamol than those who received only salbutamol.

In acute asthma attacks of the pediatric population, lung function tests, such as peak expiratory flow rate or spirometry, are generally used to evaluate the severity of asthma attacks (17). However, it is almost impossible to assess these lung function tests in the preschool age group (due to poor coordination) and in 35-50% of school-age children (due to disease severity and unfamiliarity with the technique) (18, 19). One-quarter of children with asthma, representing more than half of preschool children and patients receiving acute asthma treatment, cannot perform the standard lung function tests under emergency conditions (20). Finding alternative ways to apply clinical asthma guidelines and evaluating disease severity and treatment response in children aged 2–17 years is essential. The clinical scores can be used as simple and inexpensive tools to assess asthma severity for children in different age groups. In an independent study conducted by Birken et al., the PRAM (Preschool Respiratory Assessment Mea-

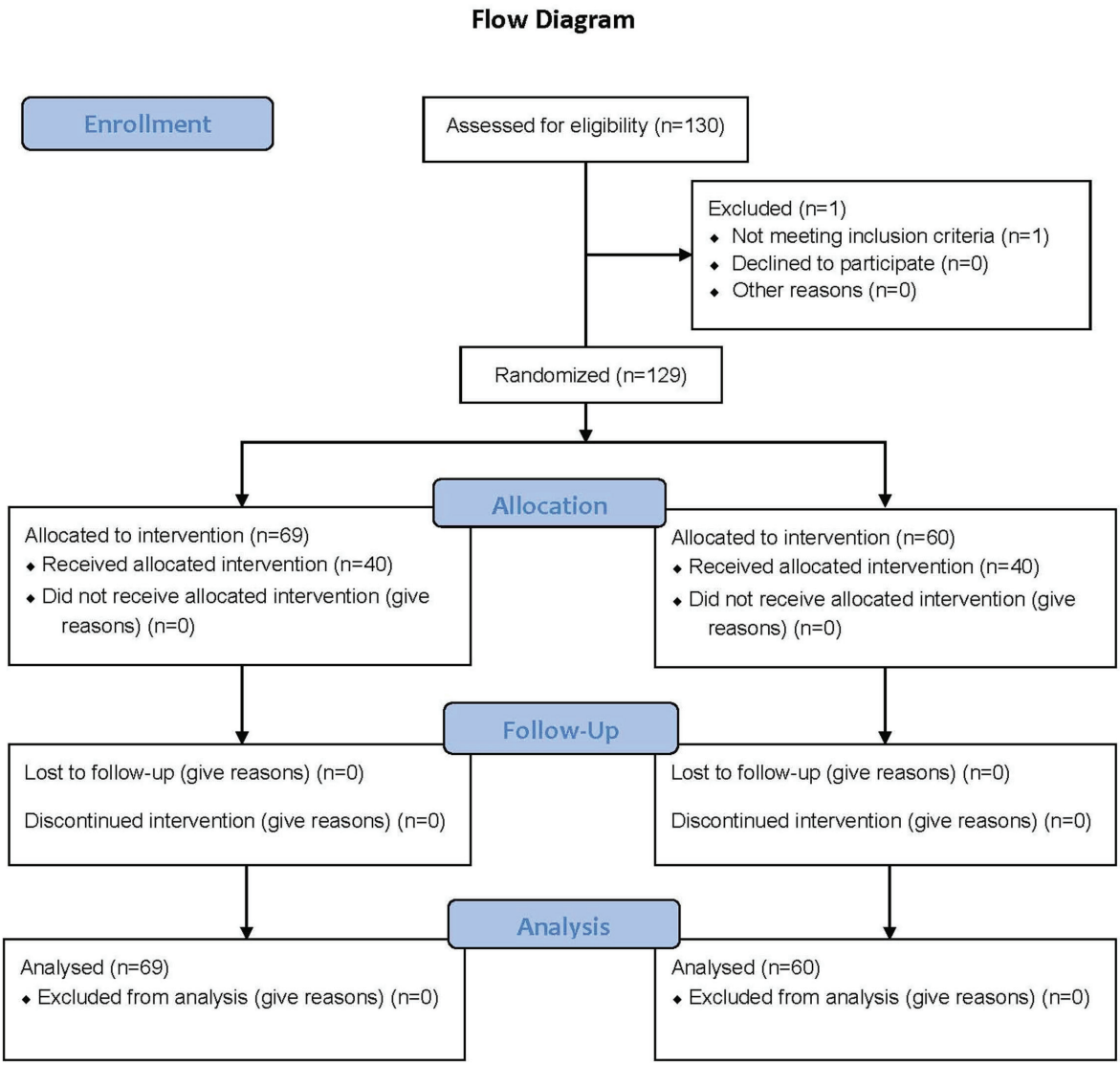

Figure 1. Flow diagram

sure) score was developed and validated in preschool children as one of the two measures of asthma attack severity that demonstrated reliable assessment characteristics in this age group. The PRAM score proved reliable for respiratory resistance in children between 3 - 6 years and was sensitive and distinctive to changes (9, 21). In our study, we evaluated children with an asthma attack who were aged between 2-8 years. The age group of children in this study was unsuitable for measuring lung function tests; thus, the PRAM score was used along with other metrics for assessing patients. The PRAM scores of patients were calculated and recorded at baseline and on the 1st and 4th hours of treatment. The PRAM score of the patients receiving salbutamol with magnesium sulfate was significantly lower than the PRAM score of the patients receiving salbutamol only at the 4th hour of treatment.

The limited number of patients, the conduct of the study in a single center, and not performing double-blind randomization (even though they were randomized to groups) are among the limitations of this study. Studies involving more patients and multicenter designs are needed to confirm our findings and generalize results.

This study shows that adding nebulized magnesium sulfate to standard asthma treatment improves

oxygen saturation faster and positively affects the PRAM score in children with asthma attacks. Therefore, nebulized magnesium sulfate can be used in addition to the standard asthma treatment in pediatric patients with moderate to severe asthma attacks.

Conflict-of-interest and financial disclosure

The authors declare that they have no conflict of interest to disclose. The authors also declare that they did not receive any financial support for the study.

REFERENCES

1. Daengsuwan T, Watanatham S. A comparative pilot study of the efficacy and safety of nebulized magnesium sulfate and intravenous magnesium sulfate in children with severe acute asthma. Asian Pac J Allergy Immunol. 2017;35(2):108-12.
2. Mohammed S, Goodacre S. Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J. 2007;24(12):823-30.
3. Knightly R, Milan SJ, Hughes R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database Syst Rev. 2017;11(11):CD003898.
4. GIF Asthma. Global strategy for asthma management and prevention. Global Initiative for Asthma; 2015. Access date: 08.10.2022. Available from: https://ginasthma.org/wp-content/uploads/2016/01/GINA_Report_2015_Aug11-1.pdf.
5. Goodacre S, Cohen J, Bradburn M, et al. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma (3Mg trial): a double-blind, randomised controlled trial. Lancet Respir Med. 2013;1(4):293-300.
6. Singh AK, Gaur S, Kumar R. A randomized controlled trial of intravenous magnesium sulphate as an adjunct to standard therapy in acute severe asthma. Iran J. Allergy. Asthma Immunol. 2008;7(4):221-9.
7. Kew KM, Kirtchuk L, Michell CI. Intravenous magnesium sulfate for treating adults with acute asthma in the emergency department. Cochrane Database Syst Rev. 2014;(5):CD010909.
8. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. Int J Surg 2011;9:672–7.
9. Chalut DS, Ducharme FM, Davis GM. The Preschool Respiratory Assessment Measure (PRAM): a responsive index of acute asthma severity. J Pediatr. 2000;137(6):762-8.
10. Classen H; Jacob R; Schimatschek H. Interactions of Magnesium with Direct and Indirect Acting Sympathomimetic Amines. Magnesium. 1987;9:80-7.
11. Middleton E Jr. Antiasthmatic drug therapy and calcium ions: review of pathogenesis and role of calcium. J Pharm Sci. 1980;69(2):243-51.
12. Hill J, Britton J. Dose-response relationship and time-course of the effect of inhaled magnesium sulphate on airflow in normal and asthmatic subjects. Br J Clin Pharmacol. 1995;40(6):539-44.
13. Iseri LT, French JH. Magnesium: nature's physiologic calcium blocker. Am Heart J. 1984;108(1):188-93.
14. Nannini LJ Jr, Pendino JC, Corna RA, Mannarino S, Quispe R. Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. Am J Med. 2000;108(3):193-7.
15. Mahajan P, Haritos D, Rosenberg N, Thomas R. Comparison of nebulized magnesium sulfate plus albuterol to nebulized albuterol plus saline in children with acute exacerbations of mild to moderate asthma. J Emerg Med. 2004;27(1):21-5.
16. Aggarwal P, Sharad S, Handa R, Dwiwedi SN, Irshad M. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. Emerg Med J. 2006;23(5):358-62.
17. National Institutes of Health. Global strategy for asthma management and prevention [updated 2005]. Access date: 25.10. 2022. Available from: www.ginasthma.org.
18. Ducharme FM, Davis GM. Measurement of respiratory resistance in the emergency department: feasibility in young children with acute asthma. Chest. 1997;111(6):1519-25.
19. Gorelick MH, Stevens MW, Schultz TR, Scribano PV. Performance of a novel clinical score, the Pediatric Asthma Severity Score (PASS), in the evaluation of acute asthma. Acad Emerg Med. 2004;11(1):10-8.
20. Canny GJ, Reisman J, Healy R, et al. Acute asthma: observations regarding the management of a pediatric emergency room. Pediatrics. 1989;83(4):507-12.
21. Birken CS, Parkin PC, Macarthur C. Asthma severity scores for preschoolers displayed weaknesses in reliability, validity, and responsiveness. J Clin Epidemiol. 2004;57(11):1177-81.