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ORIGINAL ARTICLE

The efficacy of nebulized salbutamol, magnesium sulfate, and salbutamol/magnesium sulfate combination in moderate bronchiolitis

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Abstract The aim of this paper is to compare the effect of nebulized magnesium sulfate to nebulized salbutamol and salbutamol/magnesium sulfate on successful discharge from the emergency department. A total of 56 infants were included in this double-blinded, prospective study. Infants were grouped according to the nebulized treatment they received: group 1—salbutamol/normal saline, group 2—magnesium sulfate and normal saline, and group 3—salbutamol plus magnesium sulfate. Heart beat, bronchiolitis, clinical severity scores (CSS), and oxygen saturation of the patients were determined before and after nebulization (0, 1, 4 h). The patients were monitored for adverse reactions. Post-treatment mean CSS results were significantly lower than pre-treatment scores in all groups at 4 h with no significant difference within groups. CSS scores were lower in the salbutamol/magnesium sulfate group when compared with the magnesium sulfate and salbutamol groups (3.4 (2.4–4.3), 4.7 (3.8–5.7), 4.0 (3.2–4.3)). CSS were significantly lower than those from the magnesium sulfate group. *Conclusion*: Nebulized magnesium sulfate plus salbutamol may have additive effects for improving the short-term CSS.

Keywords Magnesium sulfate · Salbutamol · Bronchiolitis

Abbreviations
CSS Clinical severity scores
SaO_2 Oxygen saturation

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Introduction

Bronchiolitis is a disorder of the lower respiratory tract that occurs most commonly in young children and is caused by infection with seasonal viruses, such as respiratory syncytial virus (RSV). Bronchiolitis is the leading cause of infant hospitalization in the world [16]. The role of bronchodilators in the treatment of bronchiolitis has been the subject of many studies. In general, no single treatment modality has proven effective in controlling the disease.

Magnesium is an important cofactor in many enzymatic reactions and is linked to cellular homeostasis [10]. Studies demonstrated that magnesium inhibits the contraction of smooth muscle, acetylcholine release, and histamine release. Thus, both intravenous and nebulized magnesium sulfate has

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become a treatment option in acute asthma in adults and children [1, 2, 6, 11–13]. The effect of magnesium has not been fully studied in acute bronchiolitis in children (PubMed).

The aim of our study was to determine short-term effects of nebulized salbutamol, magnesium sulfate, and salbutamol/magnesium sulfate measured by clinical severity scores (CSS) in infants with acute moderate bronchiolitis.

Material and methods

This double-blinded, prospective clinical trial was conducted between October 2012 and March 2013 in the short-stay unit of the Pediatric Emergency Department of Erciyes University hospital. Erciyes University Children Hospital is a 200-bedded tertiary hospital in Central Anatolia, Kayseri, Turkey. This hospital is a referral center serving a population of approximately 3 million along with the surrounding cities. The outpatient administration number is approximately 175,000 per year.

Inclusion criteria were as follows: age of 1–24 months, a history of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation, first wheezing episode, and a clinical severity score (CSS) of 4–8 on admission. Viral respiratory infection was diagnosed on clinical grounds. The CSS was defined based on four parameters including respiratory rate, degree of wheezing, degree of accessory muscle use, and general condition, as described previously by Wang et al. [15]. A single point was given to patients with a respiratory rate of 31–45 breaths/min, wheezing at terminal expiration using a stethoscope, intercostal retraction, and normal general condition. Two points were given to patients with a respiratory rate of 46–60 breaths/min, wheezing during the entire expiration or audible on expiration without stethoscope, tracheosternal retractions, and stable general conditions. Three points were given to patients with a respiratory rate of >60 breaths/min, inspiratory and expiratory wheezing without stethoscope and severe retraction with nasal flaring and a general condition of irritability, lethargy, and poor appetite [15].

Exclusion criteria were as follows: infants with CSS <4 or >8, oxygen saturation (SaO_2) <86 % in room air, chronic cardiopulmonary or neurological disease, premature birth, birth weight <2,500 g, history of recurrent wheezing episodes, history of atophy, proven immune deficiency, age <1 month or >2 years, proven or suspected acute bacterial infection, previous treatment with bronchodilators or corticosteroids, the presence of symptoms >7 days, proven asthma in parents and siblings, and consolidation or atelectasis on a chest roentgenogram. The primary physicians (MAO, TE, DE, FT, TK, and MAG) who treat the patients treated the consequent patients with the study drugs ordinarily without knowing the given drugs. Other authors (MK, HP) evaluated the CCS and outcome of the patients at the end of the study. Signed informed consent was obtained from the parents of each infant and the study was approved by the Ethics Committee of Erciyes University.

The investigator examined the children and assigned the CSS. Children meeting the inclusion criteria were invited to participate in the study. Data were collected using standardized forms to document history and physical exam. Each child's age, gender, hospitalization, CSS, respiratory rate, SaO_2 in room air (determined by pulse oximetry), and heart rate were recorded (at 0, 60, 240 min of the study). Chest x-rays were performed. All eligible patients were randomly assigned to one of the three groups: group 1 (n=18) received inhalation of salbutamol (Ventolin, GlaxoSmithKline, Middlesex, UK), 0.15 mg/kg, diluted to 4 ml with 0.9 % saline solution; group 2 (n=19) inhaled magnesium sulfate 150 mg, diluted to 4 ml with 0.9 % saline solution; group 3 (n=19) received inhalation of salbutamol 0.15 mg/kg plus inhaled magnesium sulfate 150 mg, diluted to 4 ml with 0.9 % saline solution; the procedure was performed on two occasions at 30-min intervals. The patients were monitored for hypotension, arrhythmias, and loss of deep tendon reflexes before and after each dose was administered. The patients are discharged if CSS <4, SaO2 >92 % in room air for 4 h, and no feeding difficulty. All statistical analysis was performed by using the SPSS (Chicago, IL) version 11.0 statistical package. The normality of data distribution was assessed by the Shapiro-Wilk and Kolmogorov-Smirnov tests. Kruskal-Wallis and Mann-Whitney U tests were used for comparing values between groups. The chi-square test was used for comparing the distributions between the groups. For repeated measures in the same group, Wilcoxon analyses were used. Findings of P<0.05 were taken to indicate significant differences.

Results

During the period of \study, 216 patients were admitted in our emergency department because of bronchiolitis. One hundred thirty-one children were excluded (the CSS of 22 children were higher than 8; 13 were evaluated as mild (CSS <4); 7 children have additional cardiopulmonary disease; 11 children have neurological disorders; 23 children have premature birth history; 17 have experienced recurrent wheezing; 20 children have a history of previous treatment with bronchodilators or corticosteroids; 11 children have a familial history of asthma; and 7 children have consolidation or atelectasis on a chest roentgenogram). Eighty-five of these children were included. Furthermore, 28 parents did not approve the study protocol. One patient in the magnesium sulfate group was subsequently withdrawn because of deteriorated clinical status. Fifty-six patients were enrolled in the study. The three groups did not have statistical differences with respect to gender, age, and baseline CSS and heart rates. The baseline characteristics of the three groups are shown in Table 1. Clinical scores at 1 and

Table 1 General baseline characteristics of the study groups

	Salbutamol (n=18)	Magnesium sulfate (n=19)	Salbutamol/magnesium sulfate (n=19)	P value
Age months Median (min–max)	7.5 (3–19)	8 (4–22)	8 (3–21)	NS
Gender (m/f)	12/6	12/7	13/6	NS
CSS mean (95 % CI)	5.9 (5.4–6.4)	6.1 (5.6–6.5)	6.3 (5.7–6.8)	NS
Heart rate mean (95 % CI)	149.4 (136.9–161.8)	147.8 (139.4–156.1)	156.7 (149.2–165.2)	NS

CSS clinical severity score [15], *NS* not significant, *95% CI* 95 % confidence interval

4 h were better in all groups when compared with baseline scores (P<0.05). CSS at 4 h in the salbutamol, magnesium sulfate, and salbutamol/magnesium sulfate groups were 3.4 (2.4–4.3), 4.7 (3.8–5.7), and 4.0 (3.2–4.3), respectively. Although CSS were lower in the salbutamol/magnesium sulfate group, compared to the salbutamol and magnesium sulfate groups, there were only significant differences between the magnesium sulfate and salbutamol/magnesium sulfate groups (Table 2). Heart rates at 4 h were significantly lower in the magnesium sulfate and salbutamol/magnesium sulfate groups when compared with baseline values. There were no significant differences in the salbutamol group. Although heart rates at 4 h were lower in the magnesium sulfate and salbutamol/magnesium sulfate groups, there were no significant differences when compared with the salbutamol group (Table 2). In addition, the children treated with salbutamol/magnesium sulfate have been hospitalized less than the other groups but this difference was not found to be significant (Table 2).

All patients were monitored for hypotension, arrhythmias, and loss of deep tendon reflexes and we did not observe any side effects.

Discussion

Although bronchodilator therapy is commonly used the treatment of bronchiolitis; the evidence of its usage is not very strong, and its efficacy is not universally accepted. A Cochrane review of 28 trials comparing bronchodilator use with a placebo for bronchiolitis included data from 1,912 infants. The authors concluded that bronchodilators do not improve oxygen saturation, do not reduce hospital admission after outpatient treatment, do not shorten the duration of hospitalization, and do not reduce the time to resolution of illness at home. Only small improvements in clinical scores were observed [5]. Therefore, the present study aimed to determine the effectiveness of magnesium sulfate with salbutamol or alone in the treatment of acute bronchiolitis. To the best of our knowledge, this is the first study (PubMed) to use nebulized magnesium sulfate with salbutamol or alone in infants with bronchiolitis. Although there was no significant difference between the salbutamol and magnesium sulfate plus salbutamol groups, the magnesium sulfate plus salbutamol group showed improved CSS at 4 h and lesser hospitalization time when compared to the salbutamol and magnesium sulfate groups (Table 2). We believe that our preliminary findings are important. In many studies, the beneficial effects of the bronchodilator therapies may be due to the study populations [5]. These studies included wheezy infants and these patients might have had infantile asthma. In this study, patients with atophy and recurrent wheezing were excluded because these symptoms are predictive for infantile asthma.

Table 2 Baseline, 1 and 4 h clinical scores and heart rates

	Salbutamol (n=18)	Magnesium sulfate (n=19)	Salbutamol/magnesium sulfate (n=19)
CSS 0-h mean (95 % CI)	5.9 (5.4–6.4)	6.1 (5.6–6.5)	6.3 (5.7–6.8)
CSS 1-h mean (95 % CI)	4.7^{+} (3.8–5.6)	5.1^{+} (4.3–5.8)	4.3^{+} (3.4–5.2)
CSS 4-h mean (95 % CI)	$4.0^{+\wedge}$ (3.2–4.3)	$4.7^{+\wedge}$ (3.8–5.7)	$3.4^{*+\wedge}$ (2.4–4.3)
Heart rate 0-h mean (95 % CI)	149.4 (136.9–161.8)	147.8 (139.4–156.1)	156.7 (149.2–165.2)
Heart rate 1-h mean (95 % CI)	153.5 (144.5–162.5)	147.3 (138.9–155.7)	149.1 (141.2–156.9)
Heart rate 4-h mean (95 % CI)	149.4 (138.9–160.0)	$138.2^{+\wedge}$ (131.3–145.1)	$138.4^{+\wedge}$ (129.6–147.1)
Hospitalization hours mean (95 % CI)	24 (23.4–76.9)	24 (25.8–47.4)	20 (15.3–39.0)

CSS clinical severity score, *95% CI* 95 % confidence interval

*p<0.05 when compared with magnesium sulfate group

$^{+}$$p$<0.05 when compared with baseline values

$^{\wedge}$$p$<0.05 when compared with 1-h values

The contraction and dilation of smooth muscles of the bronchi are a result of phosphorylation and dephosphorylating of the myofibrillar proteins conducted by specific enzymes and regulated by intracellular calcium concentration. The phosphorylation and dephosphorylation reactions are carried out by two enzymes: myosin kinase and myosin phosphatase. Myosin kinase phosphorylates myosin chains and depends on magnesium. Myosin phosphatase phosphatases the light chains of myosin and depends on calcium. In bronchial smooth muscle, magnesium decreases intracellular calcium by blocking its entry and its release from the endoplasmic reticulum and by activating sodium–calcium pumps [4, 7, 10]. Magnesium makes competition with calcium at certain binding sites on troponin-C and myosin. Therefore, magnesium has direct effects to myosin kinase and indirect effects to myosin phosphatase which leads to reduction of muscle tension development [4, 7]. Interestingly magnesium may decrease bronchoconstriction due to pilocarpine and histamine, or increase FEV1 in histamine-, methacholine-, and bethanechol-induced bronchoconstriction. In cholinergic motor nerve terminals, magnesium depresses muscle fiber excitability by inhibiting acetylcholine release. Magnesium stimulates nitric oxide and prostacyclin synthesis [3, 14]. These properties have additional bronchodilatation effects on bronchial smooth muscles. Magnesium also stabilizes T cells and inhibits mast cell degranulation, leading to a reduction in inflammatory mediators. Recent studies suggest that it has anti-inflammatory effects and mitigates lung injury [8, 9]. These properties have beneficial effects with salbutamol in infants with bronchiolitis in terms of their short-time clinical scores.

No adverse reaction was observed in the three groups. Also, the hypotension, arrhythmias, and loss of deep tendon reflexes noted in the literature during intravenous magnesium sulfate administration [2, 4–8] were not observed in our study. Heart rates were decreased in the magnesium sulfate and magnesium sulfate/salbutamol groups at 1 and 4 h of the study and did not change in the salbutamol group. The 4-h heart rates in the magnesium sulfate and magnesium sulfate/salbutamol groups were significantly lower when compared with baseline values. However, in the three groups, the 4-h heart rates were tachycardiac. Our preliminary results also indicated that two doses of nebulized magnesium sulfate was not associated with any side effect in the short-term follow-up of children under 2 years of age, a finding which is reported for the first time in the English medical literature. The limitations of our study are as follows: the number of children in the study group was limited; no placebo group was included because we did not find it ethical not to treat patients with moderate bronchiolitis. We excluded children with severe bronchiolitis because of ethical considerations. A power analysis was not done. Unfortunately, this is a limitation of our study. We administered only two doses of magnesium sulfate and magnesium sulfate/salbutamol because there are not enough data in the literature about the dosage, duration, and adverse reactions of nebulized magnesium sulfate in this age group. In conclusion, nebulized magnesium sulfate plus salbutamol treatment may have a beneficial effect in infants with bronchiolitis in emergency departments. Further studies are needed to provide more data on this subject.

Conflict of interest None of the authors have conflict of interest.

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