Is Magnesium Sulfate Treatment Really Effective in Moderate to Severe Bronchiolitis?

Abstract

Objectives: The aim of our study is to examine the efficacy and safety of intravenous magnesium sulfate in moderate-severe acute bronchiolitis.

Working hypothesis: Intravenous magnesium sulfate treatment may be effective in the treatment of patients with bronchiolitis .

Study design: Retrospective, single-center cohort study

Methodology: We conducted a study in 150 infants presenting with moderate to severe acute bronchiolitis. A total of 150 infants aged 1 month to 2 years who presented with acute bronchiolitis to our pediatric emergency department between January 2018 and March 2019 were admitted into the study. The demographic characteristics, clinical score, and management of the patients were examined.

Results: A total of 150 infants were analyzed: 62 in the magnesium sulfate group (Group I) and 88 in the supportive care group (Group II). Baseline clinical characteristics were similar in both groups. Length of hospitalization was significantly shorter in Group II. Clinical severity scores were also lower significantly earlier in Group I (p=0.031, p=0.008, respectively at first and fourth hour).

Conclusions: Intravenous magnesium treatment in moderateto severe acute bronchiolitis does not appear to conferany significant decrease in clinical severity scores when compared to only supportive care.

Keywords: Bronchiolitis; Infant; Magnesium sulfate

INTRODUCTION

Acute respiratory distress in infants is one of the major presenting symptoms in emergency room visits[1]. Acute bronchiolitis is a clinical diagnosis that is the most common cause of hospitalization in infancy; it includes signs and symptoms such as fever, nasal discharge and wheeze, cough, and labored breathing with wide spread crackles on auscultation[2]. There is no established, specific therapy for acute bronchiolitis, while the first line treatment is supportive care. Current guidelines recommend hydration, feeding, humidified oxygen, and nasalsuction[3]. However, these treatments may be insufficient in moderate and severe bronchiolitis.

Bronchodilators and corticosteroids are widely used but not routinely recommended as they are not effective in multiple randomized-controlled trials for the treatment [4-9]. Therefore there is an increasing need to find effective treatments to improve respiratory distress in acute bronchiolitis. Recently, intravenous magnesium sulfate is thought to be an option in treatment due to its reliability, availability and low cost [10].

Magnesium sulfate acts as a calcium antagonist in membrane channels and intracellular space. Magnesium creates a competitive antagonist effect against calcium uptake by bronchial smooth muscle cells, leading to bronchodilation [11-13].

The aim of this study was to compare to what extent intravenous magnesium sulfate infusion and supportive care compared to supportive care alone affect bronchiolitis severity in the early period in patients treated with these two methods. We also examined length of stay and the need for intensive care of the patients.

MATERIALS AND METHODS

Study Protocol

In this retrospective, single-center cohort study, intravenous magnesium sulfate therapy with standard SC was compared to supportive care therapy alone SC. The study was conducted between January 2018 and March 2019 in the Pediatric Emergency Department of the Dr. Sami Ulus Maternity and Children's Hospital, University of Health Sciences, which is a tertiary pediatric hospital in Ankara, Turkey. Emergency department physicians evaluate approximately 150,000 children annually and hospitalize approximately 4,000 patients.

Patients aged 1 month to 24 months were identified from electronic medical records based on a bronchiolitis diagnosis. Acute bronchiolitis was diagnosed clinically in the presence of acute onset shortness of breath, cough, wheezing, tachypnea, and retraction after upper respiratory tract infection [14].

Medical records were reviewed for demographic data including sex and age, requirement for pediatric intensive care unit (PICU) admission, duration of hospital stay, and the use of high-flow nasal cannula (HFNC) oxygen therapy. Bronchiolitis severity was assessed by clinical severity score, which was defined by Wang et al. [15] as seen in Table 1. The Wang severity score was based on respiratory rate, wheezing, signs of retraction, and the patient's general condition and was calculated from the data recorded in the medical files. A score of 4 points and above was evaluated as moderate, 9 points and above as severe bronchiolitis. Patients with mild bronchiolitis (Wang severity score <4), neuromuscular or cardiac disorders, chronic lung disease, previous episodes of wheezing, immunocompromised children, gestational age <37 weeks andcases of incomplete data were excluded. The chart of the study is shown in Figure1.

The decision to use intravenous magnesium sulfate therapy was determined by the physician's opinion. Also, the administration of drugs such as antibiotics, oral and inhaled steroids, various bronchodilators, and oxygen treatment modalities as well as follow-up laboratory tests was at the discretion of the attending physician.

Study measurements and outcomes

Patients who received (Group I) and didn't receive (Group II) magnesium sulfate treatment were compared. Wang severity scores of the patients were recorded before magnesium sulfate therapy in Group I, before supportive care in Group II, and at the 1st, 4th, 8th, 12th and 24th hours of follow-up in both groups. The study was reviewed and approved by the local ethics committee.

Statistical Analysis

Data are expressed as mean and standard deviations (SD) for quantitative variables or numbers and percentages for categorical variables. Continuous data were compared using the Student's t test. Categorical data were examined using the Pearson chi-squared test or the Fisher exact probability test. Statistical significance was considered as $p<0.05$. Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) 20.

RESULTS

One hundred and fifty patients with moderate-to-severe bronchiolitis between January 2018 and March 2019 were enrolled. Of the patients, 62 (41%) (Group I) had received intravenous magnesium sulfate (25 mg/kg/dose) in addition to supportive care and 88 (59%) (Group II) had supportive care alone. The mean (SD) age of the 150 participants was 8.59 (SD±5.15) (range 1-23) months. The average age was 9.16 months and 8.19 monthsfor Group I and Group II patients respectively. The age difference between the groups was not statistically significant (p=0.249). Male incidence was significantly higher in Group I (p=0.015).

There was no significant difference in terms of Wang severity scores on admission between the groups. The decline in Wang severity scores in the first and fourth hour after intravenous magnesium sulfate therapy differed significantly between the groups after the start of therapy (p=0.031, p=0.008). Mean Wang severity scores on the 8th, 12th, and 24th hours were similar in the patient groups for both arms (p>0.05). Respiratory rates in both arms were above the tachypnea limit for age. The mean respiratory rates of the patients before treatment were 57 breaths per minute in Group I and 61 breaths per minute in Group II. A decrease in the respiratory rate at the first, 4th, 8th, 12th and 24th hours of the treatment was determined relativeto the pre-treatment respiratory rates in both groups (Figure 2). Wang severity scores decreased in both groups over time (Figure 3).

With regard to the length of hospital stay, the two groups were statistically different (5.7±2and 4.7±1.6 days for both groups, respectively (p<0.05). The Wang severity score and length of hospital stay of the patients are listed in Table 2.

In Group I 40% of the patients and in Group II 9% of the patients required HFNC oxygen therapy. The use of HFNC was significantly higher in the Group I (p<0.05).

Two patients from Group I were admitted to the PICU, one was followed for two days and the other for eight days. One patient in Group II required intensive care for 2 days and the groups were similar in terms of need for intensive care ($p=0.473$). No patient had symptoms of magnesium sulfate toxicity, including flushing, dizziness, nausea, or vomiting.

DISCUSSION

This retrospective clinical trial in children with moderate to severe bronchiolitis comparing intravenous magnesium sulfate plus supportive care with supportive care alone showed no beneficial effects other than transient clinical improvement.

Wang severity scores decreased during follow-up both in Group I and Group II. While a significant change was detected in the Wang severity score in the first 4 hours of treatment, there was no difference between the groups in the subsequent follow-up. In another clinical trial that investigated the effectiveness of nebulized magnesium sulfate, the magnesium sulfate plus salbutamol group showed improved Wang severity scores at the 4th hour when compared to the salbutamol alone and magnesium sulfate alone groups [16]. A study enrolling children with asthma attacks also supported the early and transient effect of intravenous magnesium sulfate therapy as the effect of the drug occurred in the first hour and continued up to 4 hours [17]. Two randomized, double-blind, placebo-controlled trials showed that magnesium sulfate treatment was not superior to placebo in patients with acute bronchiolitis [1,18].

Nebulized magnesium sulfate has also been tested in bronchiolitis. Administration of nebulized magnesium sulfate and nebulized epinephrine versus nebulized epinephrine alone was found more beneficial in reducing the respiratory score and in relieving symptoms [12]. However, to our knowledge, no study in the literature has compared the intravenous and inhaler forms of magnesium sulfate treatment in patients with bronchiolitis.

It is well known that patients with acute asthma exacerbation who do not respond to first-line therapy can be effectively treated with intravenous magnesium sulfate. Magnesium sulfate can relax smooth muscle and therefore compete with calcium in calcium-mediated smooth muscle binding sites, providing bronchodilation [19]. Although its clinical presentation

resembles asthma, the failure to benefit from magnesium sulfate therapy in acute bronchiolitis may be due to the increased mucus secretion from the peribronchial mononuclear infiltration in pathogenesis in addition to bronchoconstriction, and the presence of obstructions in the lumen due to respiratory epithelial necrosis [20,21].

The dose of intravenous magnesium sulfate for bronchodilation used in trials ranges from 25 to 100 mg/kg/dose (maximum 2 g) [18,22]. The onset of action and the elimination time of intravenous magnesium sulfate treatment is short [23]. Intravenous magnesium sulfate therapy was reported to be well tolerated with only minor side effects reported, such as epigastric or facial warmth, flushing, pain and numbness at infusion site, dry mouth, malaise, and it may have significant effects such as hypotension, cardiac arrhythmias, and respiratory depression [13]. However, arrhythmias, loss of reflexes and muscle weakness, and respiratory depression may develop if total serum magnesium levels exceed 12.0 mg/dL. Reaching this level is only possible with a dose of more than 150 mg/kg [22]. No adverse effects were observed in Group I in this study. This may be due to the daily dose not exceeding 100 mg/kg/day.

A difference was found in the length of hospital stay, which may be due to underlying etiology of patients belonging to the magnesium sulfate group. In previous studies, it was concluded that no significant difference was observed with regard to hospital stay when intravenous magnesium sulfate treatment was used in children with bronchiolitis [1,18].

There was a significant difference between the two groups in terms of the addition of HFNC oxygen therapy. Physicians' concerns about the clinical course of patients may have led to the combined use of both magnesium sulfate and HFNC oxygen therapy in Group I.

Approximately 2-5% of patients with acute bronchiolitis are hospitalized and 3%-11% of these develop the need for intensive care [24]. In the present study we found that 2% were admitted to the PICU. None of the patients required mechanical ventilator support. This may

be related with the exclusion of patients with cardiological, neuromuscular, or immunological conditions, chronic lung disease and a history of prematurity.

There are some limitations of this study. First of all, it was a retrospectively designed and single-center study. The limited number of cases may not reflect the benefits of magnesium sulfate treatment. Moreover, both groups of patients received HFNC treatment at the physician's decision. This may have affected the clinical follow-up. However, the longer duration of hospitalization in the HFNC group and the similar improvement in Wang severity scores were remarkable findings.

These findings reflect physicians' practice at one point of time, but application constantly changes, and our setting was mainly the practice of pediatric physicians. More studies are needed to evaluate the effectiveness of intravenous magnesium sulfate in patients with bronchiolitis.

CONCLUSION

In our study, in moderate to severe bronchiolitis, intravenous magnesium sulfate infusion did not contribute positively to the course of the disease, except for a transient clinical improvement in the early period, and did not shorten the duration of hospitalization.

REFERENCES

1. Pruikkonen H, Tapiainen T, Kallio M, Dunder T, Pokka T, Uhari M, Renko M. Intravenous magnesium sulfate for acute wheezing in young children: a randomised double-blind trial. Eur Respir J 2018;51(2):1701579.

2. Everard ML, Hind D, Ugonna K, Freeman J, Bradburn M, Dixon S, Maguire C, Cantrill H, Alexander J, Lenney W, et al. Saline in acute bronchiolitis RCT and economic evaluation: hypertonic saline in acute bronchiolitis-randomised controlled trial and systematic review. Health Technol Assess 2015;19(66):1-130.

3. Baraldi E, Lanari M, Manzoni P, Rossi GA, Vandini S, Rimini A, Romagnoli C, Colonna P, Biondi A, Biban P, et al. Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. Ital J Pediatr 2014; 40(1): 1-13.

4. Gadomski AM, Brower M. Bronchodilators for bronchiolitis. Cochrane Database Syst Rev 2010;12:CD001266.

5. Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, Klassen TP, Patel H, Fernandes RM. Epinephrine for bronchiolitis. Cochrane Database Syst Rev 2011; 6:CD003123.

6. Blom DJM, Ermers M, Bont L, Van Woensel JBM, Van Aalderen WMC. Inhaled corticosteroids during acute bronchiolitis in the prevention of post bronchiolitic wheezing. Cochrane Database Syst Rev 2007;24(1):CD004881.

7. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, Johnson DW, Klassen TP, Hartling L. Glucocorticoids for acute viral bronchiolitis in infants and young children. Cochrane Database Syst Rev 2010; 6:CD004878.

8. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, Ruddy RM, Malik B, Nelson KA, Bregstein JS, et al. Bronchiolitis study group of the pediatric emergency care applied research network (pecarn). A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. N Engl J Med 2007;357(4):331–339.

9. Oakley E, Brys T, Borland M, Neutze J, Phillips N, Krieser D, Dalziel SR, Davidson A, Donath S, Jachno K, et al. Medication use in infants admitted with bronchiolitis. Emerg Med Australas 2018;30(3):389-397.

10. Liu X, Yu T, Rower JE, Campbell SC, Sherwin CMT, Johnson MD. Optimizing the use of intravenous magnesium sulfate for acute asthma treatment in children. Pediatr Pulmonol 2016;51(12):1414–1421.

11. McLean RM. Magnesium and its therapeutic uses: A review. Am J Med 1994;96:63–76.

12. Modaresi MR, Faghihinia J, Kelishadi R, Reisi M, Mirlohi S, Pajhang F, Sadeghian M. Nebulized Magnesium Sulfate in Acute Bronchiolitis: A Randomized Controlled Trial. Indian J Pediatr 2015;82(9):794-8.

13. Cheuk DK, Chau TC, Lee SL. A meta-analysis on intravenous magnesium sulphate for treating acute asthma. Arch Dis Child 2005;90(1):74-77.

14. Midulla F, Scagnolari C, Bonci E, Pierangeli A, Antonelli G, DeAngelis D, Berardi R, Moretti C. Respiratory syncytial virus, human boca virüs and rhino virüs bronchiolitis in infants. Arch Dis Child 2010;95:35-41.

15 Wang EEL, Milner RA, Navas L, Maj H. Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. Am Rev Respir Dis 1992;145(1):106–109.

16. Kose M, Ozturk MA, Poyrazoğlu H, Elmas T, Ekinci D, Tubas F, Kurt T, Göktaş MA. The efficacy of nebulized salbutamol, magnesium sulfate, and salbutamol/magnesium sulfate combination in moderate bronchiolitis. Eur J Pediatr 2014;173:1157–1160.

17. 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):108-112.

18. Alansari K, Sayyed R, Davidson BL, Al Jawala S, Ghadier M. IV Magnesium Sulfate for Bronchiolitis: A Randomized Trial. Chest 2017 ;152(1):113-119.

19. Griffiths B, Kew KM. Intravenous magnesium sulfate for treating children with acute asthma in the emergency department. Cochrane Database Syst Rev 2016;29;4(4):CD011050.

20.Visscher DW, Myers JL. Bronchiolitis. Proc Am Thorac Soc 2006;3(1):41-47.

21.Mims JW. Asthma: definitions and pathophysiology. Int Forum Allergy Rhinol 2015;5 (1):2-6.

22. Scarfone RJ, Loiselle JM, Joffe MD, Mull CC, Stiller S, Thompson K, Gracely EJ. A randomized trial of magnesium in the emergency department treatment of children with asthma. Ann Emerg Med 2000;36:572–578.

23. Sinert R, Spektor M, Gorlin A, Doty C, Rubin A, Altura BT, Altura BM. Ionized magnesium levels and the ratio of ionized calcium to magnesium in asthma patients before and after treatment with magnesium. Scand J Clin Lab Invest 2005; 65:659–670.

24. Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Arch. Dis. Childh 2003;88(12):1065–1069.