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Original Research Article

Magnesium sulphate nebulization in acute bronchiolitis in infants: a randomized controlled trial

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ABSTRACT

Background: Acute bronchiolitis is a disorder of the lower respiratory tract that occurs mostly in between 1 month to 24 months. There are limited numbers of studies on magnesium sulphate nebulization in acute bronchiolitis. There is a desperate need for a standard treatment which can reduce the morbidity and mortality in acute bronchiolitis. The goal was to study the efficacy of magnesium sulphate nebulization in infants with acute bronchiolitis.
Methods: It was a prospective open labelled randomized controlled study. Children in age group of 2-12 months admitted with clinical diagnosis of acute bronchiolitis in paediatric emergency ward, GMSH-16, Chandigarh. Study group patients were treated with 40 mg/kg magnesium sulphate nebulization diluted with 2-3 ml normal saline in addition to supportive treatment as oxygen and IV fluids, three doses of medication were given at 1 hour interval and it was not repeated after three doses. Control group patients were treated with oxygen therapy, IV fluids, symptomatic treatment for fever and supportive care.
Results: Respiratory distress assessment instrument score and length of hospital stay was significantly lesser in study group as compared to control group. SpO2 was significantly more in study group as compared to control group.
Conclusions: Magnesium sulphate nebulization is effective in improving respiratory distress and oxygen saturation, it also reduces duration of hospital stay in infants with mild to moderate bronchiolitis.

Keywords: Magnesium sulphate, Nebulization, Bronchiolitis

INTRODUCTION

Acute bronchiolitis is a disorder of the lower respiratory tract that occurs mostly in between 1 month to 24 months.[1] It occurs in winter and spring season. The mortality rate is as significant as 0.5-1.5% in hospitalized patients, increasing for patients with underlying cardiac or pulmonary disease.[2] Respiratory *Syncytial virus* (RSV) is main causative organism in around 50% cases of bronchiolitis, other causative organisms are *Parainfuenza virus, Adenovirus and Influenza virus*. It is more common in those who have not been breastfed and in those who live in crowded and unhygienic conditions.[3] Acute bronchiolitis is characterized by bronchiolar obstruction with edema, mucous and cellular debris. Infants initially develop upper respiratory tract infection with sneezing, rhinorrhea and fever (101-102°F). Gradually respiratory distress increases with wheezy cough, dyspnea, irritability and tachypnea. Diagnosis of acute bronchiolitis is mainly clinical, but chest radiograph can be used which shows hyperinflated lungs with patchy atelectasis.[3]

The standard of treatment remains supportive care which includes ensuring adequate oxygen therapy, fluid intake and feeding of infant.[4,5] Meta-analysis of data on most used therapies for acute bronchiolitis have failed to prove any effect on clinical outcome in comparison to placebo.[6-9] Current clinical practice guidelines do not recommend the routine use of any medication but still use of these

therapies for treatment of acute bronchiolitis remains better option.[10]

Recently some of investigators have reported the use of nebulized magnesium sulphate that has benefited many of infants with bronchiolitis.[11,12] Magnesium inhibits the contraction of smooth muscles, acetylcholine release and histamine release.[12] Thus both intravenous and nebulised $MgSO_4$ have become treatment options in asthma. Nebulizer route is a preferred route as compared to intravenous route due to rapid onset of action and lesser side effects. As there are many similarities in clinical symptoms and pathophysiology of bronchiolitis and acute asthma attack, it is suggested that $MgSO_4$ can be used as a new therapy for bronchiolitis.[11]

Objectives

The primary objective of the study was the improvement in RDAI score.

The secondary objective of the study was the improvement in SpO2 and the improvement of the duration of hospital stay.

METHODS

It was a prospective randomised controlled, open labelled study including 104 patients diagnosed as acute bronchiolitis. Study was conducted in paediatric emergency ward, Government multispeciality hospital, Chandigarh from February 2017 to March 2018.

Inclusion criteria

Children in age group of 2-12 months admitted with acute bronchiolitis as per American academy of pediatrics 2014 guidelines were included in the study.[13]

Exclusion criteria

Very sick patients with shock, seizures, tachycardia (heart rate >200/min) and respiratory failure, presence of congenital heart disease or congenital malformation, diagnosis of SAM, pneumonia or pleural effusion, foreign body ingestion, history of prematurity or mechanical ventilation in newborn period, history of nebulization of any drug in past, family history of bronchial asthma, past history of wheeze were excluded from the study.

Methodology

Patients were attended in the emergency room. Detailed history and physical examination of each patient was done which included presenting symptoms like fever, cough, rhinorrhea, noisy breathing, difficulty in feeding and breathing, vitals including heart rate, respiratory rate, CRT, BP and oxygen saturation, sensorium, RDAI score.[14]

After satisfying inclusion and exclusion criteria, written informed consent was taken from attendant of the patient and he was free to withdraw from study any time. Patients were randomly allocated to one of the 2 groups by using random number table generated on computer by statistician. Group allocation was concealed in opaque envelopes. After enrolment, an envelope was opened and patient was assigned to that group by resident doctor.

Study group patients were treated with 40 mg/kg magnesium sulphate nebulization diluted with 2-3 ml normal saline; here normal saline was used as diluent. Three doses of medication were given at 1 hour interval in study group patients and it was not repeated after three doses. Nebulizer was given over 10-15 minutes. Magnesium sulphate is available as 50% intravenous solution having 500 mg/ml of magnesium sulphate in it. In addition study group patients received routine treatment as in control group. Control group patients were treated with oxygen therapy by nasal prongs if SpO2 was less than 92%, IV fluids and symptomatic treatment for fever.

If condition of patient deteriorated in the form of increasing respiratory rate, RDAI score and decrease in oxygen saturation, the patient was to be treated as per standard protocol as nasal CPAP. Patients were examined by investigator at study entry and every day. Monitoring parameters for improvement or worsening of the condition were measured as RR, SpO2, RDAI score, HR and BP and were recorded at admission, then after initial 3 nebulizations followed by 6 hourly interval on day 1 and then at 12 hourly intervals till discharge. Viral studies of patients were not done in our patients.

Discharge criteria were feeding well orally, absence of tachypnea (RR <50 per min.), RDAI score less than 5, oxygen saturation more than 92% in room air. The defined guidelines of central ethical committee for biomedical research on human subject by ICMR and guidelines as per Helsinki declaration was strictly adhered to in the present study. The ethical committee of institute approved this study. This trial was registered at clinical trial registry of India, New Delhi vide no. CTRI/2017/02/007919. Flowchart of case enrollment, group allocation and follow up is shown in Figure 1.

Sample size justification and statistical analysis

Sample size was estimated based on study by Modaresi et al sample size in each group using RDAI difference of 1 with standard deviation of 1.5 was estimated to be 47 subjects per group at a power of 90% and confidence interval of 95%.[11] It was decided to include extra subjects for possible drop outs, so finally we decided to include 52 subjects in each group. Sample size estimation was done by using trial size package in R software (version 3.2.3).

Statistical tool (software) used to analyze the data was SPSS 20.

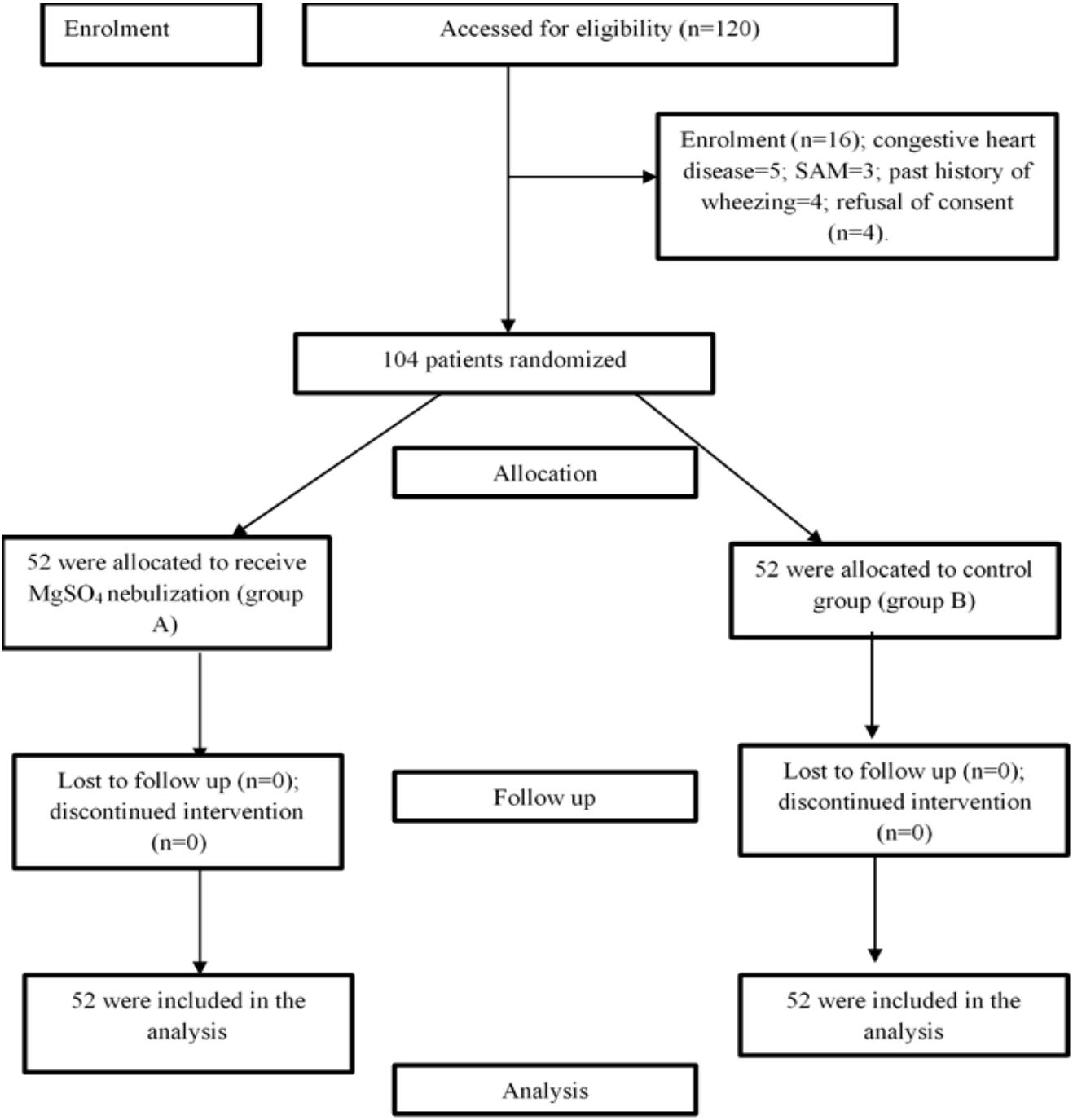

Figure 1: Participants in the study.

RESULTS

During study period total 120 patients with acute bronchiolitis were assessed for the eligibility. Out of which 12 cases were excluded (5 children had congenital heart disese, 3 children had diagnosis of SAM, 4 children had past history of wheeze). Parents of 4 patients refused to participate in the study.

A total of 104 infants aged between 2-12 months fulfilling the clinical criteria of acute bronchiolitis were enrolled in the study. The mean (SD) age in study group and control group was 5.23 (2.7) and 4.85 (2.59) months, respectively. There were 69.2% boys and 30.8% girls in study group. In control group, there were 75% boys and 25% girls. Mean baseline RDAI in study and control groups was 9.15±2.5 and 9.77±2.15, respectively. Mean baseline respiratory rate in study and control groups was 51.77±8.54 and 54.75±8.97 per minute, respectively. Mean baseline oxygen saturation in study and control group was 92.37±1.98 and 92.10±2.07, respectively. Baseline clinical signs and symptoms were comparable between two groups (Table 1).

Table 1: Baseline parameters of patients.

Parameters	Groups		P value
	Group A (n=52)	Group B (n=52)	
Age (in months)	5.23±2.66	4.85±2.59	0.413
Sex			
Male	36 (69.2%)	39 (75%)	0.512
Female	16 (30.8%)	13 (25%)	
RR (per min)	51.77±8.5	54.75±8.9	0.086
RDAI score	9.15±2.5	9.77±2.1	0.181
SpO_2 (%)	92.37±1.9	92.10±2.0	0.5
HR (per min)	127.7±8.7	128±8.5	0.484

Table 2: Comparison of RDAI score with time.

Time (in hours)	RDAI score				P value
	Group A (n=52)		Group B (n=52)		
	Mean	SD	Mean	SD	
0	9.15	2.5	9.77	2.15	0.181
3	7.98	2.62	9.46	2.18	0.0002
6	7.88	2.69	9.04	2.36	0.0022
12	7.42	2.76	8.62	2.35	0.020
24	6.27	2.66	7.50	2.50	0.018

Table 3: Comparison of SpO2 with time between 2 groups.

Time (in hours)	Oxygen saturation (%)				P value
	Group A (n=52)		Group B (n=52)		
	Mean	SD	Mean	SD	
0	92.37	1.98	92.10	2.07	0.500
3	93.90	1.76	92.63	1.66	0.0001
6	94.15	1.54	93.10	1.43	0.0001
12	94.46	1.45	93.92	1.53	0.068
24	95.73	1.51	94.85	1.30	0.002

Number of cases with baseline RDAI score <10 in study group and control group was 31and 22, respectively. Number of cases with baseline RDAI score ≥10 in study group and control group was 21 and 30, respectively. RDAI score was significantly lesser in study group as compared to control group at 3 hours, 6 hours, 12 hours and 24 hours ($p<0.05$) (Table 2). In cases with baseline RDAI score <10, the mean±SD RDAI score was significantly lesser in study group ($MgSO_4$) as compared to control group from 3 hours to 24 hours ($p<0.05$), but there was no significant difference in RDAI score mean (SD) between two groups with base line RDAI score ≥10, from 3 hours to 24 hours ($p>0.05$).

There was no significant difference in SpO2 between two groups at admission ($p=0.5$) and at 12 hours ($p=0.068$). There was significant difference in SpO2 between two groups at 3 hours, 6 hours and 24 hours ($p<0.05$), SpO2 being significantly more in study group as compared to control group (Table 3). In cases with baseline RDAI score <10, oxygen saturation was significantly more in study group as compared to control group at 3 hours, 6 hours and 24 hours ($p<0.05$), but there was no significant difference in SpO2 between two groups of cases with baseline RDAI score ≥10, when compared at 3 hours, 6 hours, 12 hours and 24 hours ($p>0.05$). Mean duration of oxygen therapy was comparable between 2 groups.

There was no significant difference between two groups in relation to duration of hospital stay ($p=0.067$). Duration of hospital stay was significantly lesser in study group as compared to control group in cases with baseline RDAI score <10 ($p=0.029$). There was no significant difference between two groups in relation to duration of hospital stay ($p=0.078$) in cases with baseline RDAI score ≥10. There was no dropout of patient and all patients recovered (Figure 1). There was no deterioration in signs and symptoms in any patient in either group.

DISCUSSION

We studied the efficacy of magnesium sulphate nebulization in acute bronchiolitis in children aged 2-12 months. In our study, magnesium sulphate nebulization

led to better improvement in RDAI score, oxygen saturation as compared to control group. We had 49% of patients with baseline RDAI of >10, on subgroup analysis in these patients, there was no significant difference of RDAI and oxygen saturation between magnesium sulphate study group and control group.

Study by Modaresi et al also showed beneficial effect of $MgSO_4$ nebulization in infants with bronchiolitis.[11] They used adrenalin and $MgSO_4$ (40 mg/kg/dose) nebulization in study group and only adrenalin in control group, nebulization was used 4 hourly after initial 3 doses at 20 minute intervals where as we used only 3 initial doses at 1 hour interval. NICE and AAP guidelines do not recommend adrenalin nebulization in bronchiolitis.[13,15]

Kose et al12 also used $MgSO_4$ nebulization in a RCT involving 3 groups; group 1 (n=18) received inhalation of salbutamol, 0.15 mg/kg, diluted to 4 ml with 0.9% saline solution; group 2 (n=19) inhaled $MgSO_4$ 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 $MgSO_4$ 150 mg, diluted to 4 ml with 0.9% saline solution; the procedure was performed on two occasions at 30 min interval. Improvement in clinical severity score was significantly more in salbutamol plus $MgSO_4$ group as compared to $MgSO_4$ group. In our study, mean duration of hospital stay was significantly lesser in study group as compared to control group in mild to moderate illness and not in severe cases. In a study by Modaresi et al mean (SD) length of hospital stay in $MgSO_4$ plus adrenaline nebulization group was 84.3 (9.7) hours and in adrenaline nebulization group was 84.7 (10.1) hours ($p=0.9$).[11]

There were no adverse effects of $MgSO_4$ like nausea vomiting, apnea, arrhythmia, hypotension, loss of deep tendon reflexes observed in our study and in studies done by Kose et al and Powell et al.[12,16]

Strength of our study was good sample size and its randomized controlled trial design, resulting in good match for signs and symptoms. There was no dropout and withdrawal of patients during the study.

Limitation of our study is that we had no facility for viral studies of our patients. Other studies have not graded the severity of acute bronchiolitis, while in our study only about 50% of patients had baseline RDAI score more than 10 (severe distress), this being the limitation of our study. So a larger study is needed to see effect of $MgSO_4$ nebulization in severe bronchiolitis. $MgSO_4$ nebulization is effective in improving respiratory distress and oxygen saturation in acute bronchiolitis in infants with mild to moderate bronchiolitis with baseline RDAI of <10. $MgSO_4$ nebulization reduces duration of hospital stay in mild to moderate bronchiolitis, $MgSO_4$ nebulization is safe in infants with acute bronchiolitis.

CONCLUSION

The conclusion of my study is that magnesium sulphate nebulization can be used in infant with acute bronchiolitis. There were no adverse effects of $MgSO_4$ like nausea vomiting, apnea, arrhythmia, hypotension, loss of deep tendon reflexes observed in our study. Magnesium sulphate nebulization is effective in improving respiratory distress (RDAI score) and oxygen saturation in acute bronchiolitis. In cases with baseline RDAI score <10, the mean±SD RDAI score was significantly lesser in study group ($MgSO_4$) as compared to control group from 3 hours to 24 hours ($p<0.05$). Duration of hospital stay was significantly lesser in study group as compared to control group in cases with baseline RDAI score <10 ($p=0.029$.

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