

## Normal Saline vs. Hypertonic Saline Nebulization for Acute Bronchiolitis: A Randomized Clinical Trial

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### Abstract

#### Background

We aimed to compare the efficacy of nebulized hypertonic (3%, 5% and 7%) saline with normal saline in hospitalized infants with acute bronchiolitis.

#### Materials and Methods

In this triple-blinded randomized clinical trial, 120 children with moderate to severe bronchiolitis randomly assigned into four groups to receive nebulized normal saline (group A), saline 3% (group B), saline 5% (group C), and saline 7% (group D). The length of hospital stay (LOS) as primary outcome and the use of oxygen, temperature, oxygen saturation (SPO<sub>2</sub>), pulse rate (PR), respiratory rate (RR), and bronchiolitis severity score were measured in the beginning of the study and during hospitalization.

#### Results

The mean age of patients was  $5 \pm 0.423$  months and 79 of them (65%) were male. The length of hospital stay (LOS), and use of oxygen supplementation was not different between group A and B ( $P=0.36$ ), but significantly lower than group C and D ( $P<0.001$ ). Vital signs, improvement in severity score and oxygen saturation were similar between groups.

#### Conclusion

Our study demonstrated that nebulization with 3% hypertonic saline and 0.9% saline can significantly reduce hospitalization rate compared nebulization with 5% and 7% hypertonic saline.

**Key Words:** Bronchiolitis, Children, Length of stay, **Saline solution.**

\*Please cite this article as: Reisi M, Afkande N, Golmakani H, Khademian M. Normal Saline vs. Hypertonic Saline Nebulization for Acute Bronchiolitis: A Randomized Clinical Trial. Int J Pediatr 2018; 6(11): 8507-16. DOI: **10.22038/ijp.2018.31026.2739**

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Received date Feb:11, 2018; Accepted date: Jun.12, 2018

## 1- INTRODUCTION

Acute bronchiolitis mainly caused by respiratory syncytial virus (RSV), is the most common lower respiratory infection and the leading cause of hospitalization in children younger than 2 years (1). Acute bronchiolitis is usually self-limited, however, this disorder may be associated with several severe complications, such as secondary bacterial infection, apnea, nasal flaring, grunting, and intercostal, supracostal, and subcostal retractions (2). Supportive care, with supplemental oxygen to correct hypoxia, minimal handling to minimize the risk of exhaustion and the provision of fluids, remains the mainstay of management. Although mortality rate of bronchiolitis has been reduced from 20% in the 1940s to less than 1%, but it has still remains a major cause for infant morbidity and mortality. The median duration of admission is 3 days, considerably higher than for other acute pediatric admissions (median 1 day). The course of the illness or length of hospital stay has not been impacted by treatments including oral and inhaled steroids, antiviral agents and a variety of bronchodilators (3).

Multiple studies evaluate the efficacy of nebulized hypertonic saline (HS) 3% in acute bronchiolitis and some of them have suggested that nebulized hypertonic saline (HS) may influence the course of the illness and decrease the duration of hospitalization (16-20). The American Academy of Pediatrics (AAP) recommends the use of nebulized hypertonic saline 3% for infants hospitalized with bronchiolitis (21). Most clinical trials evaluate the role of nebulized hypertonic saline (HS) 3% in bronchiolitis but few studies evaluate higher concentration of hypertonic saline (5%,7%) in bronchiolitis (5, 22, 23). There is no comparative study on more than two types of HS in bronchiolitis. So this triple controlled-trial study was conducted to

compare the effect of nebulized 3%, 5% and 7% hypertonic saline with normal saline on the course of the illness, bronchiolitis respiratory assessment score and length of hospital stay in bronchiolitis.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

We conducted a triple-blinded, randomized, controlled trial to compare the efficacy of hypertonic saline (3%, 5% and 7%) versus 0.9% (normal) saline for the treatment of acute viral bronchiolitis. The study performed at department of pediatrics, Imam Hossein hospital, Isfahan University of Medical Sciences for duration of 14 months between September 2014 and March 2016. The study was approved by local ethics committee of Isfahan University of Medical Sciences. On behalf of each child, at least one legal caregiver signed a written informed consent form before study start.

### 2-2. Methods

In this project one hour after initial assessment, with a computer-generated list of random numbers, children were divided randomly in four groups. All the vials containing normal saline and different concentration of hypertonic saline were labeled with four different codes. None of the parents of the patients (patients are infants), health care providers, and physicians evaluating bronchiolitis severity score before and after intervention. Data collectors and outcome assessors did not know the density of the each vial. Patients treated with 4 mL of the study nebulization mixed with 1mL of epinephrine (1/1000) on enrollment and every four hours until discharge (15, 16). Drugs were delivered by pressurized oxygen through a face mask with the flowmeter set at 4 L/min. Additional treatment (e.g. supplementary oxygen and hydration) were administered if needed. Patients could be discharged when feeding

well without respiratory distress and oxygen saturation could be maintained at or above 90% with air room. However, social factors such as consensus and availability of family members determined the actual time of discharge.

### **2-3. Measuring tools**

Length of hospital stay (LOS) was defined as the hours from the first study inhalation until discharge from the hospital, as recorded in the medical record for each patient. Bronchiolitis severity score, the use of oxygen, temperature, oxygen saturation (SPO<sub>2</sub>), pulse rate (PR), respiratory rate (RR) were recorded immediately at admission, 1 hour, 5 hours, 12 hours and 24 hours after that. The bronchiolitis severity score was evaluated using Wang Respiratory Score which reliability and validity have been confirmed previously (12). This score was the sum of points allotted, from 0 (indicating normal findings) to 3 (indicating severe illness), for each of the following: respiratory rate, wheezing, retractions and general condition.

### **2-4. Statistical Analysis**

We used SPSS 21.0 statistical packages (SPSS Inc., Chicago, Illinois) for statistically analysis. P-value of 0.01 was considered as the level of significance. We calculated mean  $\pm$  standard deviation with percentages for to provide 90% to show a mean severity score improvement of 10% for the 5%, 3 relevant variables; Chi-2 test was used for categorical variables and one-way analysis of variance with post hoc Bonferroni correction was used for continuous variables. We calculated sample size required % and 7% saline group versus the 0.9% saline group, assuming a standard deviation of about 1 for each mean severity score. Then, we estimate that each sample group should be up to 30. We intended to definitively compare the 7%, 5% and 3% saline groups. Patients enrolled with outcome

data at 24 hours properly were included in the analysis.

### **2-5. Inclusion and exclusion criteria**

Hospitalized children aged 1–24 months with moderate to severe bronchiolitis were eligible for the study inclusion criteria consisted of acute onset of respiratory distress, first episode of wheezing, chest radiography compatible with bronchiolitis and bronchiolitis severity score of at least 5. Exclusion criteria included: family history of asthma, history of atopy, history of wheezing, previous use of glucocorticoids or bronchodilators, history of prematurity (gestational age < 34 weeks), loss of consciousness, history of chronic heart, pulmonary, neurologic, oncologic or immunologic disease.

### **2-6. Intervention**

All the vials containing normal saline and different concentration of hypertonic saline were labeled with 4 different codes. Then through a computer-generated list of random numbers, children were divided randomly in 4 groups. Patients treated with 4mL of the study nebulization mixed with 1mL of epinephrine (1/1000) on enrollment and every 4 hours until discharge. Drugs were delivered by pressurized oxygen through a face mask with the flow meter set at 4 L/min. Additional treatment (e.g. supplementary oxygen and hydration) were administered if needed.

### **2-7. Ethical consideration**

This study was approved by local ethics committee of Isfahan University of Medical Sciences Ethics committee ID-number: IR.MUI.REC.1394.3.242 and has been registered by the Iranian Registry for Clinical Trials with this code: IRCT20141201020175N3.

## **3- RESULTS**

During the study period, 197 patients with bronchiolitis were admitted in the

emergency department. Seventeen children did not meet inclusion criteria; they were evaluated as mild respiratory distress assessment instrument [RDAI] < 5. Forty two children were excluded (12 children had previously used bronchodilators, 6 children had premature birth, 13 children had family history of asthma and 11 children had chronic cardiopulmonary disease). Thus, one hundred thirty eight children were included. Furthermore, 11 parents did not confirm the consent form or did not cooperate properly. Thus, one hundred twenty seven patients were enrolled in the study. Seven children were subsequently withdrawn because of deteriorating clinical status. Finally 120 previously healthy infants hospitalized with acute bronchiolitis enrolled in the study. **Table.1** shows the baseline characteristics of participants in the studied groups. Age, gender, heart rate, respiratory rate and temperature were not significantly difference between study groups ( $P>0.05$ ).

**Figures 1 and 2** present mean of bronchiolitis severity score and oxygen saturation in patients with bronchiolitis in different therapeutic approaches at admission time and 1, 5, 12 and 24 hour (s) after admission. ANOVA test with repeated observations showed that in all four groups, the mean of bronchiolitis severity score decreased significantly over time ( $P < 0.001$ ), but one way ANOVA showed that the mean of bronchiolitis severity score at baseline ( $P = 0.83$ ), one hour after treatment ( $P = 0.73$ ), five hours after treatment ( $P = 0.48$ ), 12 hours after treatment ( $P = 0.22$ ), and 24 hours after treatment ( $P = 0.06$ ) did not differ significantly between the four groups (**Figure.1**). ANOVA test with repeated observations showed that the mean percentage of oxygen saturation in the normal saline ( $P = 0.009$ ), hypertonic saline (% 3) ( $P < 0.001$ ), hypertonic saline 5% ( $P < 0.001$ ), and hypertonic saline 7%

( $P < 0.001$ ) has increased significantly over time. One-way ANOVA showed that there was no significant difference in mean oxygen saturation of oxygen at admission time between the four groups ( $P = 0.96$ ), but one hour after treatment ( $P < 0.001$ ), five hours after treatment ( $P < 0.001$ ), 12 hours after treatment ( $P = 0.001$ ), and 24 hours after treatment ( $P = 0.003$ ), there was a significant difference between the four groups. The LSD post hoc test showed that the mean percent oxygen saturation of arterial blood one hour after treatment in hypertonic saline 5% and 7% groups were significantly higher than the hypertonic saline 3% group ( $P < 0.01$ ).

Five hours after treatment mean percent oxygen saturation in the hypertonic saline 5% and 7% groups were significantly higher than the hypertonic saline 3% and normal saline groups ( $P \leq 0.01$ ). Twelve hours after treatment, the mean oxygen saturation percentage of oxygen in the hypertonic saline group 5% and 7% were significantly higher than the hypertonic saline 3% ( $P < 0.05$ ) and normal saline groups ( $P < 0.05$ ); 24 hours after treatment, the mean oxygen saturation percentage in the hypertonic saline 5% and 7% groups were significantly higher than the hypertonic saline 3% ( $P < 0.05$ ), and normal saline groups ( $P < 0.05$ ) (**Figure.2**).

Mean (SD) of length of stay (LOS) and duration of oxygen supplementation use in patients with bronchiolitis and different therapeutic approaches are presented in **Table.2**. One-way ANOVA showed that the mean LOS ( $P < 0.001$ ) and duration of oxygen supplementation use ( $P = 0.001$ ) between the four groups were different significantly. Mean duration of oxygen supplementation use in the hypertonic saline 3% group did not have a significant difference with the hypertonic saline 5% ( $P = 0.10$ ), but significantly less than the hypertonic saline 7% ( $P = 0.001$ ). Pair wise comparison indicated that mean (SD) of LOS was significantly lower in normal

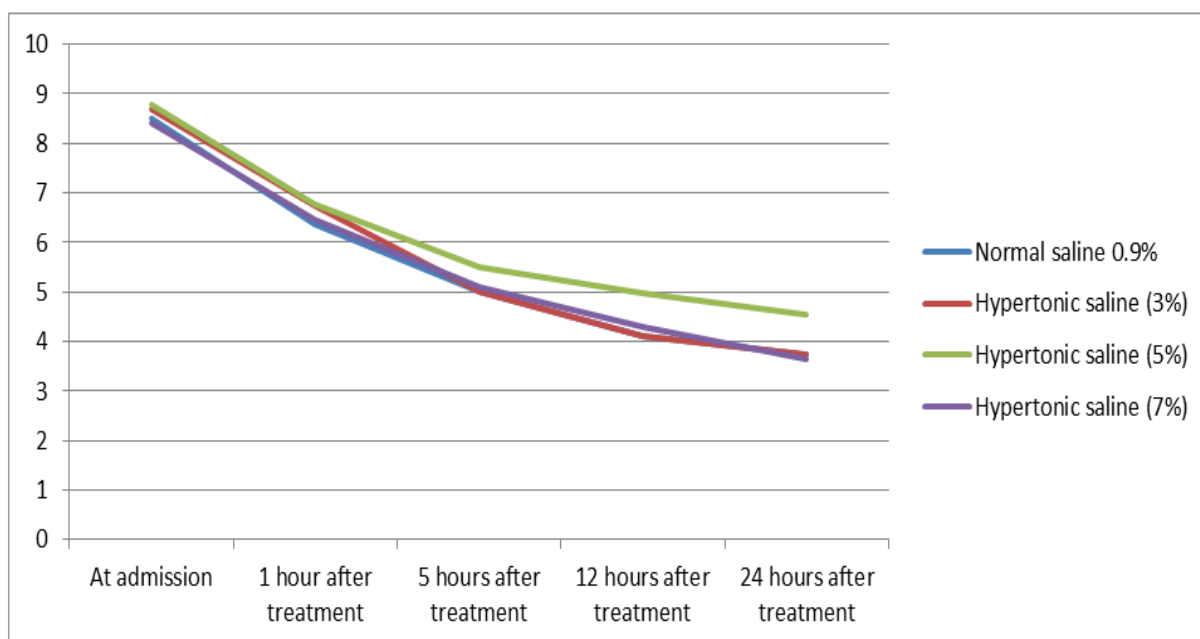
saline group than hypertonic saline 5% ( $P<0.001$ ) and hypertonic saline 7% groups ( $P<0.001$ ). Also, mean (SD) of LOS was significantly higher in hypertonic saline 7% group than hypertonic saline 3% group ( $P=0.007$ ), and hypertonic saline 5% than hypertonic saline 3% group ( $P=0.005$ ). Pair wise comparison indicated that mean (SD) duration of oxygen supplementation use was significantly

higher in hypertonic saline 7% group than normal saline ( $P<0.001$ ). Also, mean (SD) duration of oxygen supplementation use was significantly higher in hypertonic saline 7% group than hypertonic saline 3% groups ( $P=0.001$ ). Length of stay (LOS), and use of oxygen supplementation was not different between children treated with normal saline and those treated with hypertonic saline 3% ( $P=0.36$ ).

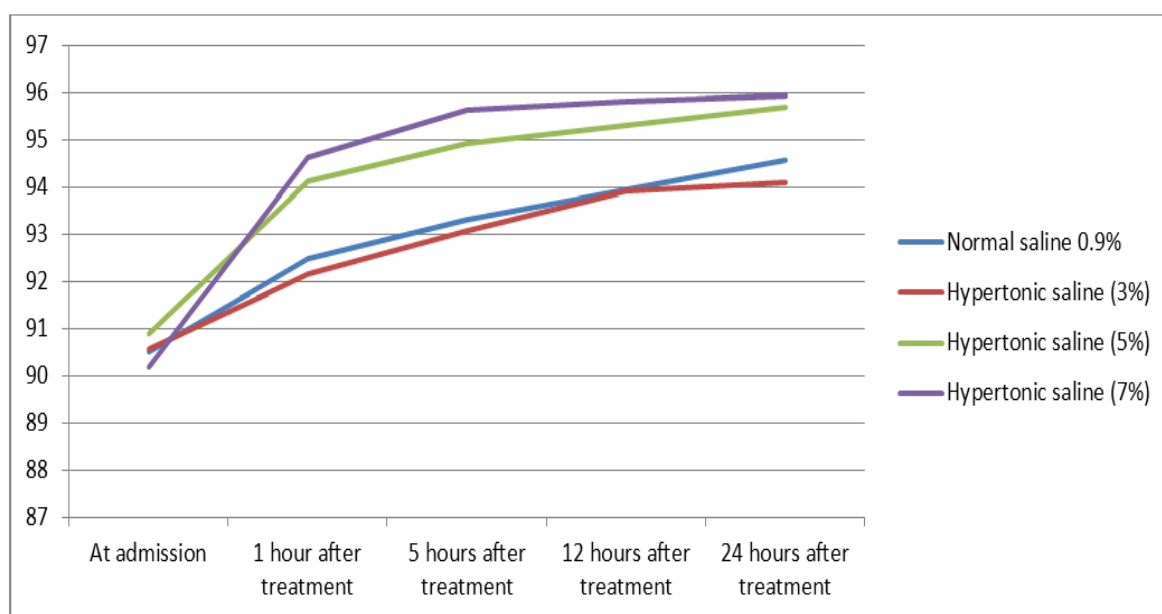
**Table-1:** Baseline characteristics of children with acute bronchiolitis

Variables	Normal saline 0.9%	Hypertonic saline 3%	Hypertonic saline 5%	Hypertonic saline 7%	P- value
Age (months)	4.7(4.6)	5.7(5.2)	5.3(4.8)	4.3(3.4)	0.65
Gender(male/female), number	22/8	18/12	20/10	19/11	0.73
Heart rate (per minute)	102(5)	106(6)	105(5)	109(7)	0.79
Respiratory rate (per minute)	66(4)	63(6)	68(5)	65(4)	0.84
Temperature (per minute)	37.8(0.4)	38(0.3)	37.8(0.4)	38.1(0.3)	0.89

The values are presented as mean (standard deviation).



**Fig.1:** Bronchiolitis severity score in patients with bronchiolitis with different therapeutic approaches at admission time and 1, 5, 12 and 24 hours after admission.



**Fig.2:** Oxygen saturation in patients with bronchiolitis with different therapeutic approaches at admission time and 1,5,12 and 24 hours after admission.

**Table-2:** Mean (SD) of length of stay (LOS) and duration of oxygen supplementation use in patients with bronchiolitis and different therapeutic approaches

Variables	Normal saline 0.9%	Hypertonic saline 3%	Hypertonic saline 5%	Hypertonic saline 7%	P-value
LOS (hour)	30.8 (19.1)	35.2 (14.2)	49 (17.7)	48.4 (2.1)	<0.001
Duration of oxygen supplementation use	2.2 (6.2)	3.2 (5.3)	8.4 (13.2)	14.2 (18.9)	<0.001

LOS: length of stay.

#### 4- DISCUSSION

In this study we evaluated the effectiveness of nebulization with different concentration of hypertonic saline as well as normal saline in the treatment and outcome of acute bronchiolitis using variables such as LOS, duration of oxygen supplementation use, bronchiolitis severity score and oxygen saturation. Our results indicated that nebulization with hypertonic saline (3%, 5%, 7%) had not significant superiority to 0.9% saline to reduce duration of hospitalization, duration of oxygen supplementation use and bronchiolitis severity score. Given that acute bronchiolitis is one of the most frequent causes of hospitalization in infancy, several studies as well as review

papers have been investigated the outcomes of different therapeutic approaches of the diseases in infants mainly regarding to the effectiveness of hypertonic saline than normal saline (24-27). The results of available data are controversial and non-conclusive due to the heterogeneity in reviewed papers and trials. Two Cochrane database systematic reviews in 2008 and 2013 reported that it is suggested that nebulized 3% saline could have appropriate impact on LOS and improvement of clinical severity score in affected infants (28, 29). But some recent studies conducted in this field reported that the above mentioned finding are hampered due to high heterogeneity of reported trials and also publication of more recent studies

in this topic. Results of a systematic review and meta-analysis by Maguire et al. in 2015 indicated that reviewing of fifteen trials demonstrated reduced mean LOS and Clinical Severity Score (CSS) after using hypertonic saline solution. But the results had considerable heterogeneity. They concluded that they could not provide an evidence-base for using hypertonic saline for acute bronchiolitis because of the high levels of heterogeneity (30). In another study in UK, Everard et al. have demonstrated that hypertonic saline 3% was not a cost-effective treatment for acute bronchiolitis and also it had not significant clinical benefit on LOS (31).

Conversely, another meta-analysis published in 2014 demonstrated that nebulized hypertonic saline therapy not only reduces the duration of hospitalization for acute bronchiolitis in infants, but also is beneficial in decreasing the rate of admission (11). A recent review study in 2016, by Baron et al. reviewed all clinical trials used American Academy of Pediatrics (AAP 2014) guidelines on the management of bronchiolitis by using hypertonic saline. They reviewed 22 clinical with 2,682 infants. They concluded that hypertonic saline could reduce LOS when it used more than 72 hours. They also suggested that it could reduce the emergency admission rate (32).

In a prospective, double-blinded randomized clinical trial, Köse et al. compare the efficacy of salbutamol/hypertonic saline 7% and 3% to 0.9% saline/salbutamol in the treatment of acute bronchiolitis. Their evaluated outcomes were LOS and CSS. Their findings indicated that hypertonic saline 7% and 3% could not reduce the LOS and improve the CSS of infants with acute bronchiolitis (33). In another study in The Netherlands, Teunissen and colleagues compared the impact of hypertonic saline 3% and 6% with normal saline in hospitalized children with acute

bronchiolitis. They demonstrated that though saline 3% and 6% are safe but they had not any advantages than normal saline regarding LOS, duration of supplemental oxygen use or tube feeding (34). In this study we compared hypertonic saline 3%, 5% and 7% with normal saline by evaluation of four outcomes including LOS, bronchiolitis severity score, oxygen saturation and duration of oxygen supplementation use. Our study demonstrated that nebulization with hypertonic saline 3% and normal saline can significantly reduce LOS compared nebulization with 5% and 7% hypertonic saline. It seems that using hypertonic saline 7%, 5% had not improving effect on LOS than hypertonic saline 3% and normal saline and also there was no significant difference between hypertonic saline 3% and normal saline.

Our findings were similar to the results of Ojha et al. which revealed that nebulization with hypertonic saline 3% compared with normal saline did not have any significant impact on reduction of hospital stay (6). In our study duration of oxygen supplementation use was not different between hypertonic saline 3% and 5% and normal saline groups, but it was significantly higher in hypertonic saline 7%. It is suggested that hypertonic saline could not reduce the duration of oxygen supplementation use in comparison with normal saline. Our results were similar to the findings of Ojha et al. They indicated that nebulization with 3% hypertonic saline compared with 0.9% saline did not have any significant impact on reduction of duration of oxygen supplementation use (6).

In this study oxygen saturation increased significantly at admission time and 1, 5, 12 and 24 hours after admission in all studied groups. Between group analysis indicated that there was significant difference between hypertonic saline 7% and 5% with hypertonic saline 3% and normal saline. It

seems that all therapeutic approaches could significantly increase oxygen saturation during 24 hours after admission but hypertonic saline 7% and 5% had more favorable effect in this field. In current study, though the mean of bronchiolitis severity score decreased significantly over time in the four studied groups, but there was no significant difference between groups and hypertonic saline had not superior effect than normal saline. Our results were similar to that reported by Ojha and colleagues. They revealed that nebulization with hypertonic saline 3% did not prove superiority to 0.9% saline for improving the bronchiolitis severity score in patients with viral bronchiolitis (6).

In the study of Khalid Al-Ansar, nebulization with 5% hypertonic saline had superior to 0.9% saline for improving the bronchiolitis severity score in patients with viral bronchiolitis in the early treatment setting, and possibly superior to 3% saline as well (5). Our findings indicated that hypertonic saline 5% and 7% had not favorable effect on the treatment of acute bronchiolitis regarding LOS, duration of oxygen supplementation use and bronchiolitis severity score than normal saline except for oxygen saturation. Given that the LOS, duration of oxygen supplementation uses and bronchiolitis severity score are more important factors in the management of acute bronchiolitis, it is suggested that hypertonic saline 5% and 7% have not any preference to normal saline in this field.

In addition considering that there was not any significant difference between hypertonic saline 3% and normal saline, it is also suggested that hypertonic saline with different concentrations have not any advantages than normal saline in the treatment of acute bronchiolitis. The main limitation of this study was small sample size of patients. In addition considering the effectiveness of nebulized epinephrine in hypertonic saline in the management of

acute bronchiolitis in infants, it would be more favorable to compare the combination therapy of nebulized epinephrine with different concentrations of hypertonic saline solutions. The strength of current study was that we compare the outcome of using different concentrations of hypertonic saline with each other and with normal saline; there was not any similar studies which evaluate all of them in one study.

## 5- CONCLUSION

The findings of this study indicated that hypertonic saline 5% and 7% had not any preference to normal saline on the treatment of acute bronchiolitis regarding LOS; duration of oxygen supplementation use and bronchiolitis severity score and the efficacy of hypertonic saline and normal saline in mentioned factors were similar.

**6- CONFLICT OF INTEREST:** None.

## 7- ACKNOWLEDGMENT

We would like to show our gratitude to Dr. Silva Hovespian for sharing her pearls of wisdom with us during process of the results and cooperation in our research.

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