Original Research Article

A study of response to inhaled short acting Beta 2 stimulant in recurrent wheezers less than 2 years of age

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Abstract

Background: In young children, wheezing, either transient or persistent, can be severe and cause a low quality of life existence with frequent use of health care system and economic costs. **Aim and objective:** To know the response of salbutamol in recurrent wheezers less than 2 years of age. **Methodology:** This double blinded randomized control trial was conducted from July 2015-septebetamber 2017, Study included 100 children upto 2 years of age. After taking written consent, relevant history was taken; general and systemic examination was done and all relevant anthropometric variables were recorded, baseline vitals (heart rate, respiratory rate, oxygen saturation and RDAI score) were taken. Nebulization was given to patients as per computer generated randomization solution (either salbutamol or placebo) at 6 hours interval. Vitals were again recorded after 1 hour, after 24 hours of nebulization and at discharge. Data was analysed with appropriate statistical tests. **Results:** Heart rate was significantly more (P=0.05) after 1 hour in group I (salbutamol). Respiratory rate was not significantly changed in both groups. SpO2 was statistically more significant (0.009) after 24 hours in group II(NS). RDAI score was significantly less (0.019) after 1 hour in group II (NS). Hospital stay was significantly more (0.002) in group II (NS).

Key Word: Beta 2 stimulant.

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INTRODUCTION

Wheezing is a common problem around the world. Wheezing during early life represents a common disorder characterized by airways obstruction. Wheezing is a multi-factorial manifestation, typically related to bronchiolitis or asthma, however different less regular conditions might be consider in case of atypical presentation. Recurrent wheezing have a significant morbidity and it's evaluated that 33% of school-age children manifest the symptom during the first 5 years of life. Structural deformities, aspiration syndrome, foreign body inhalation, gastro esophageal reflux, fistulas and swallowing disorders related to neurologic or muscular dysfunction can present as recurrent wheeze. Recurrent infections of the lower respiratory tract can present as recurrent wheezing and host defense abnormalities may be considered as differential diagnosis of wheezing. Cystic fibrosis, bronchopulmonary dysplasia, obliterans bronchiolitis, interstitial lung disease and paradoxical vocal cord dysfunction are different causes to recognize. [1] Acute lower respiratory infections are the most widely recognized reason for morbidity and possibly preventable cause of mortality in infants.[2] Infancy is a basic time for the post-natal lung growth and development. Repeated lower respiratory tract infection in young children increases the likelihood of chronic pulmonary disorders in later life. [3] Globally, bronchiolitis is the commonest type of intense lower respiratory tract infection during initial 2 years of life.[2,4] Respiratory

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Syncytial Virus (RSV) is most regular viral infection causing bronchiolitis. The viral infection happens in upper respiratory tract and spreads to lower respiratory tract in few days, resulting in inflammation of bronchiolar epithelium, peribronchiolar infiltrating of white blood cells, mostly mononuclear cells and edema of submucosa and adventitia. Different treatment modalities have been attempted with frequently disappointing outcomes. Meta analysis[5,6] information on most utilized treatments include supportive care, satisfactory oxygenation, nebulization with bronchodilators, epinephrine, glucocorticoids, normal saline and hypertonic (3%Nacl). Antibiotics have no role unless there is coexisting bacterial infection and are in fact counter-productive otherwise.[5] Inhalation therapy with nebulizer is important modality of management of different respiratory and other illness in pediatric practice. Medications given by inhalation route are absorbed through lung surface and have systemic and local effects.[7] Respiratory Distress Assessment Index Score (RDAI) is utilized to characterize the seriousness of bronchiolitis on clinical grounds. [8] Patients of Bronchiolitis can worsen quickly without any warning signs, hence the nebulization therapy should be started as soon as the clinical diagnosis is made for better prognosis and outcome of the patient. Also these solutions have none to rare minor side effects, so it is safe to begin an early nebulization treatment. Many studies demonstrate that children over the age of 20 months with recurrent wheezing attacks respond to salbutamol in a similar manner to their older asthmatic counter parts. Studies were however unable to show any improvement in lung function or clinical state in the wheezy children between ages of 7 – 18 months of age.[9] Preliminary information recommends that beta adrenoceptors are present and functional in airway preparations of infant mammals. Data on human infant bronchi isn't yet available. [10] There have been various studies researching the effectiveness of beta 2 agonists for treating wheeze in infants as they are believed to be the best medications in the treatment of variable airways obstruction in adults and children. Beta2 agonists remain the most regularly recommended prescriptions for treating wheeze in infancy by respiratory pediatricians and general pediatricians alike. However the evidence from the literature does not necessarily support this practice. [11] From the evidence available single doses of nebulized bronchodilators for acute attacks of wheeze have not been appeared to be essentially superior to placebo, neither for chronic wheeze, nor for multiple dose treatment of acute attacks is adequate information available. Still beta2 agonists are utilized frequently as bronchodilators for children under the age of two years with recurrent wheezing. [10]

This study is designed to know the effectiveness of beta2 stimulants in recurrent wheezers under 2 years of age to get clarity from the above controversies.

MATERIAL AND METHODS

Present study was a Prospective, double blinded, randomized control trial. It was conducted at Dr. D. Y. Patil Medical College and Research Center, Pimpri in the Department of Pediatrics during July 2015 to September 2017. Study population was children with clinical diagnosis of recurrent wheeze.

Inclusion criteria: 1. Children from birth – 24 months of age with clinical diagnosis of recurrent wheeze. 2. Children with 2 or more than 2 episodes of wheeze.

Exclusion criteria: 1.Children who have already received bronchodilator treatment within 8 hours of being accessed. 2. Patients with Underlying congenital heart disease and lung abnormalities. 3. Parents who refused to give consent for study. 4.Patients requiring ICU (PICU and NICU) admission.

Study was approved by ethical committee of the institute. A valid written consent was taken from parents after explaining study to them. In this study, total 100 patients were enrolled. Sample size was got by using the below formula Alfa = 0.01, Beta = 0.02 , Power = 0.80 and Number of treatment groups = 2 (salbutamol and placebo) Children were divided into 2 treatment groups by using randomization technique as said below Study Group I - Salbutamol nebulization with the pressure driven nebulizer. Control Group II- Normal saline (NS) nebulization with pressure driven nebulizer.The randomization sequence was computer generated. The allocation sequence was concealed at all times throughout the study. The computer generation and allocation were performed by the statistician, external to the study team. Upon enrollment, an infant was assigned to the next number on the appropriate stratified list. Each unique number was assigned to one of the two groups. Two different solutions were prepared, one with Normal Saline + Salbutamol, 15 ml of normal saline was removed from 100ml NS bottle and 15 ml of salbutamol solution was added to it in an aseptic manner. Second solution was having only normal saline. The solutions were labeled as A and B without knowledge of observer and 2 cc of each solution was used to nebulize patients randomly and same solution was used for particular patient during observation period. Observer was blinded about the solution used in. patients. Nebulization is continued for every 6 hour interval. The following parameters recorded were Heart rate, Respiratory rate, Oxygen Saturation (SpO2) and Respiratory distress assessment index score (RDAI). Parameters were recorded before enrolment as a baseline, one hour after nebulization and at the end of 24 hours (after

4 nebulizations). Patients were followed up for Heart rate, Respiratory rate, SpO2 and RDAI score at the time of discharge. Data was analyzed by using SPSS software version 17. Comparison of age, heart rate, respiratory rate and oxygen saturation between study group (I) and control group (II) was done by using T- test. Man Witne (MW) test was used for comparing RDAI scores between study group and control group.

RESULTS

In group I mean age was 12.32(±6.93), in group II mean age was 11.86(±6.60). T test was applied as test of significance and showed t value as 0.34 and p value as 0.74, which was not statistically significant. . In group I 32 patients were males, 18 patients were females. In group II 31 patients were males and 19 patients were females. Both the groups were comparable with respect to age and sex. In group I 44 patients were having fever, 36 patients were having cough, 46 patients were having cold and 13 patients were having feeding difficulty. In group II 43 patients were having fever, 39 patients were having cough, 49 patients were having cold and 14 patients were having feeding difficulty. Z test was applied as test of significance and z values as 0.30 for fever, 0.69 for cough, 1.39 for cold, 0.23 for feeding difficulty and P values as 0.77 for fever, 0.49 for cough, 0.36 for cold, 0.82 for feeding difficulty. The above values were not statistically significant. (table 1) In group I mean length was 74.66(±8.63), mean weight was 9.43(±2.11), mean head circumference was 45.14(±2.41). In group II mean length was 73.74(±8.82), mean weight was 9.10(±1.99), mean head circumference was 44.86(±2.66). T test was applied as test of significance and showed t values as 0.53 for length, 0.80 for weight, 0.58 for head circumference and P values as 0.60 for length, 0.42 for weight, 0.58 for head circumference. Which was not significant. Table 2 shows comparison of heart rate between group I and group II at baseline, 1 hour, 24 hours and at discharge. In group I mean heart rate per minute at baseline was 144.66(±15.25), after 1 hour was 149.86(±16.93), after 24 hours was 139.24(±15.58) and at the time of discharge was 129.20(±10.31). In group II mean heart rate at baseline was 140.72(±13.63), after 1 hour was 138.42(±15.03), after 24 hours was 133.70(±13.61) and at the time of discharge was 126.88(±9.60). T test was applied as test of significance and t values were 1.36 at baseline, 3.57 after 1 hour, 1.89 after 24 hours and 1.16 at the time of discharge. P values were 0.18 at baseline, 0.05 after 1 hour, 0.061 after 24 hours and 0.25 at the time of discharge. Heart rate was significantly more in study group (I) than control group (II) after 1 hour of nebulization (P=0.05). Table 3 shows comparison of respiratory rate between group I and group II at baseline, 1 hour, 24 hours and at discharge. In group I mean respiratory rate per minute at baseline was 55.16(±9.52), after 1 hour was 54.28(±9.63), after 24 hours was 50.68(±9.63) and at the time of discharge was 42.0(±5.46). In group II mean respiratory rate at baseline was 52.64(±9.86), after 1 hour was 51.08(±10.02), after 24 hours was 47.44(±9.04) and at the time of discharge was 40.12(±4.20). T test was applied as test of significance and showed t values as 1.30 at baseline, 1.63 after 1 hour, 1.73 after 24 hours, 1.93 at discharge and P values were 0.20 at baseline, 0.11 after 1 hour, 0.086 after 24 hours and 0.057 at discharge. The above values of Respiratory rate were statistically not significant. Fig 1 shows comparison of SpO_2 between group I and group II at baseline, 1 hour, 24 hours and at discharge. In group I mean SpO_2 (%) at baseline was 95.26(±3.46), after 1 hour was 95.60(±3.33), after 24 hours was 96.20(±3.28) and at the time of discharge was 98.10(±0.81). In group II mean SpO_2 (%) at baseline was 96.38(±2.93), after 1 hour was 96.60(±2.67), after 24 hours was 97.68(±2.10) and at the time of discharge was 98.32(±0.65). T test was applied as test of significance and showed t values as 1.74 at baseline, 1.65 after 1 hour, 2.68 after 24 hours, 1.49 at discharge and P values as 0.084 at baseline, 0.11 after 1 hour, 0.009 after 24 hours and 0.14 at discharge. SpO_2 was significantly more in control group (II) than study group (I) after 24 hours of nebulization ($P<0.05$). Percentage (%) change of SpO_2 was more from baseline to discharge in study group than control group. Fig 2 shows comparison of RDAI score between group I and group II at baseline, 1 hour, 24 hours and at discharge. In group I mean RDAI score at baseline was 5.96(±2.17), after 1 hour was 5.88(±2.21), after 24 hours was 4.96(±2.09) and at the time of discharge was 3.44(±1.56). In group II mean RDAI score at baseline was 5.16(±2.14), after 1 hour was 4.80(±1.91), after 24 hours was 4.36(±1.75) and at the time of discharge was 3.08(±1.29). Man-Witne test was applied as test of significance and showed z values as 1.75 at baseline, 2.34 after 1 hour, 1.29 after 24 hours, 0.93 at discharge and P values as 0.079 at baseline, 0.019 after 1 hour, 0.20 after 24 hours and 0.35 at discharge. RDAI score was significantly less in control group (II) than study group (I) after 1 hour of nebulization ($P<0.05$). Percentage (%) change of RDAI score was more from baseline to discharge in study group (I) than in control group (II). Table 4 shows comparison of hospital stay between study group (I) and placebo group (II). Mean stay in study group (I) was 8.58 (±1.20) and in placebo group (II) was 9.34 (±1.14). T test was applied as test of significance and showed t value as 3.26 and P value as 0.002. The above result shows significantly increased hospital stay in control group (II) than in study group (I).

Table 1: Chief complaints wise distribution of children in group I and group II

Chief complaints	Group I (n=50)	Group II (n=50)	Z Value	P Value
Fever	44 (88)	43 (86)	0.30	0.77
Cough	36 (72)	39 (78)	0.69	0.49
Cold	46 (92)	49 (98)	1.39	0.36
Feeding difficulty	13 (26)	14 (28)	0.23	0.82

Table 2: Comparison of heart rate at baseline, 1hrs, 24hrs, discharge between group I and group II

Heart rate/min at	Group I (n=50)		Group II (n=50)		t Value	P Value
	Mean	SD	Mean	SD		
Baseline	144.66	15.258	140.72	13.635	1.36	0.18
1hrs	145.86	16.934	138.42	15.032	3.57	0.05
24hrs	139.24	15.582	133.70	13.619	1.89	0.061
Discharge	129.20	10.317	126.88	9.606	1.16	0.25

Table 3: Comparison of respiratory rate at baseline, 1hrs, 24hrs, discharge between group I and group II

Respiratory rate/min at	Group I (n=50)		Group II (n=50)		t Value	P Value
	Mean	SD	Mean	SD		
Baseline	55.16	9.528	52.64	9.868	1.30	0.20
1hrs	54.28	9.630	51.08	10.022	1.63	0.11
24hrs	50.68	9.635	47.44	9.044	1.73	0.086
Discharge	42.00	5.466	40.12	4.207	1.93	0.057

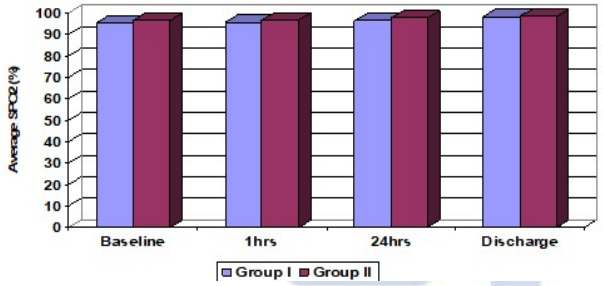

Figure 1

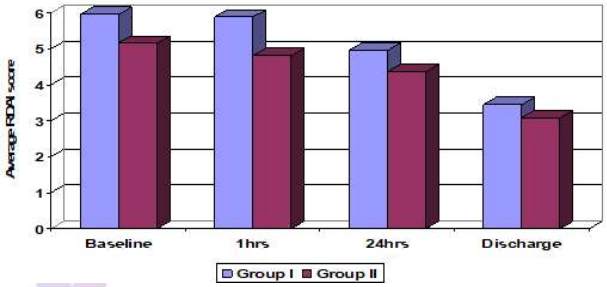

Figure 2

Figure 1: Bar diagram showing comparison of SPO2 at baseline, 1hrs, 24hrs, discharge between group I and group II; **Figure 2:** Bar diagram showing comparison of RDAI score at baseline, 1hrs, 24hrs, discharge between group I and group II

Table 4: Comparison of hospital stay between group I and group II

Hospital	Group I (n=50)		Group II (n=50)		t Value	P Value
	Mean	SD	Mean	SD		
Stay (days)	8.58	1.20	9.34	1.14	3.26	0.002

DISCUSSION

In this study out of total 100 patients between birth to 24 months, heart rate was significantly less in group II (NS) (p=0.05) than in group I (salbutamol) after 1 hour of nebulization. In the study conducted by Madhusmita som *et al.*. [12] Mean Heart rate increased from 152.26 per minute to 160.59 per minute (p<0.001). In the study conducted by Lenney W. *et al.*.[9] Mean initial pulse rate was increased from 116 per minute to 140 per minute after 5 minutes of salbutamol nebulization. In this study out of total 100 patients between birth to 24 months, respiratory rate was not significant. In the study conducted by Chavasse R *et al.*.[13] Respiratory rate was found to fall significantly following nebulized salbutamol during an acute exacerbation of wheeze. In the study conducted by Bentur L *et al.* (1992)[14] was performed entirely in the emergency department during an acute exacerbation of wheeze. 28 participants were assessed following either 0.3mg/kg salbutamol nebulized in two divided doses over 1 hour or placebo. The participants showed an improvement (fall) in respiratory rate of 7.7 breaths per minute following salbutamol compared to 2.6 breaths per minute following placebo a difference of -5.1 breaths per minute, 95% CI -9.45 to-0.75. In the study conducted by Madhusmita som *et al.* [12] Mean respiratory rate decreased from 73.65 per minute to 60.48 per minute. In our study SpO2 was significantly more in group II (NS) than in group I (salbutamol) (P=0.009) after 24 hours of nebulization with salbutamol. In the study conducted by Elaine EL Wang *et*

al.[15] The poorer response with salbutamol was also significant when compared with the control (F=4-81, p=0.03). In the study conducted by Bentur L *et al.* (1992).[14]There was an improvement in oxygen saturation of 1.3% after salbutamol compared to a deterioration of -0.3% following placebo (difference 1.6, 95% CI 0.33 to 2.87). In the study conducted by Madhusmita som *et al.* [12] The oxygen saturation measured by pulse oxymeter in the salbutamol group was increased from 91.13 to 93.87 (p<0.001). In present study we found, RDAI score was significantly less in group II (NS) (P=0.019) than in group I (salbutamol) after 1 hour of nebulization. In the study conducted by Madhusmita som *et al.*, [12] The RDAI score fell from 13.19 to 7.24 (P<0.001).). In the study conducted by Gadomski AM *et al.*, [16] In 7 inpatient and 8 outpatient studies, average clinical score decreased slightly with bronchodilators (standardized mean difference (SMD) -0.37, 95% CI -0.62 to -0.13, n=1006). In the study conducted by Chavasse R *et al.*.[13] There was an improvement in symptom score (which assessed wheeze and accessory muscle use) of 2.9 points following salbutamol versus 0.4 points following placebo (difference -2.5, 95% CI -3.88 to -1.12). In the study conducted by Elaine EL Wang *et al.*. [15] No significant difference was observed for either agent (salbutamol or ipratropium bromide) or the combination on clinical score compared with placebo. In fact, the mean clinical score improved the most in the placebo recipients. In this study out of 100 patients between birth to 24 months, hospital stay was significantly more in group II (NS) (P=0.002) than in group I (salbutamol). In the study conducted by Gadomski AM *et al.*, [16] Inpatient bronchodilator treatment did not reduce the duration of hospitalization (MD 0.06, 95% CI –0.27 to 0.39, n=349). In the study conducted by Elaine EL Wang *et al.*, [15] No significant difference was observed for either agent (salbutamol or ipratropium bromide) or the combination on hospitalization compared with placebo. Although data from studies spanning more than 20 years show that β2 adrenoceptor agonists do not produce a clinically significant improvement in lung function in wheezy infants, [17] it is now becoming clear that this finding cannot be explained by the absence of β2receptors.[18] The airways of wheezy infants differ from those of normal subjects in several ways; there is evidence to suggest that they are smaller than those of age matched non-wheezy controls [19] and that they are more likely to show fixed airway obstruction. [20] The effect of salbutamol is not significant, even though β2 receptors are present in children less than 2 years because of immaturity of the β2 receptors in smooth muscles of bronchial wall. The effect of normal saline is significant as obstruction is a result of mucosal edema and excessive mucus production secondary to an inflammatory process.

CONCLUSION

Normal saline should be preferred over salbutamol for recurrent wheeze in less than 2 years of age.

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