

BRONCHIOLITIS;

Role of oral salbutamol administration for providing symptomatic relief in children.

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ABSTRACT.. Objectives: To determine the efficacy of oral salbutamol administration for symptomatic relief in children less than two years of age with acute mild bronchiolitis. **Study Design:** Interventional study. **Place and duration of study:** Outpatient department of Department of Pediatrics, independent university hospital, Faisalabad, Pakistan, from October 2010 to March 2011. **Methodology:** 160 children less than two years of age diagnosed clinically as acute mild bronchiolitis with comparable baseline parameters (age, weight, duration of present illness) were included in the study. They were randomly placed in two groups, Salbutamol Group (SG) (n=80) Placebo Group (PG) (n=80) and were followed daily for first 3 days, then on day 5 and day 7 in outpatient department. Oral salbutamol was administered (0.1 mg/kg/dose) three times daily for 7 days or till complete resolution of illness, whichever came earlier. Time for resolution of illness (ROI) was primary outcome variable whereas time for resolution of cough, coryza, breathlessness, wheeze, achievement of normal feeding and sleep patterns and salbutamol adverse effects were secondary outcome variables. **Results:** Mean duration of resolution of illness (ROI) was similar in both groups. (6.1 ± 0.75) days in the salbutamol group and (6.0 ± 0.80) days in placebo group ($p=0.53$). There was no significant resolution time difference of secondary outcome variables between the two study groups. Cough (SG 4.1 ± 0.70 , PG 4.1 ± 0.68 , $P=0.68$) Coryza (SG 4.3 ± 0.59 , PG 4.2 ± 0.62 , $P=0.14$) Wheeze and Breathlessness (SG 3.8 ± 0.60 , PG 3.8 ± 0.63 , $p=0.24$) Sleep (SG 4.5 ± 0.40 , PG 4.4 ± 0.55 , $p=0.19$) Feeding (SG 4.3 ± 0.59 , PG 4.2 ± 0.62 , $P=0.14$). Salbutamol adverse effects (tremors, irritability) were observed in 13 (16.25%) children in salbutamol group. **Conclusions:** Oral salbutamol administration is not superior to placebo in providing symptomatic relief in children with acute mild bronchiolitis.

Key words: Salbutamol, children, bronchiolitis.

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INTRODUCTION

Bronchiolitis is an acute, infectious and inflammatory disease of the upper and lower respiratory tract that occurs in all age groups but primarily affects infants and children younger than two years of age¹⁻⁶.

On the basis of physical findings and pulse oximetry, Bronchiolitis is categorized into mild, moderate and severe forms. This categorization of disease has therapeutic and prognostic significance. Majority of the cases of acute Bronchiolitis are of mild severity which is characterized by a playful and feeding well child, respiratory rate ≤ 60 breath/min, heart rate ≤ 200 beats/min, no or minimal respiratory distress and hemoglobin oxygen saturation $\geq 95\%$ in room air^{7,8,9}.

Respiratory syncytial virus is the etiological agent in 50 to 90% cases of acute Bronchiolitis¹⁰. As no specific curative treatment is available at present for

the viral etiology, therapy is primarily directed towards symptomatic relief and maintenance of adequate hydration and oxygenation of the child¹¹.

Although Bronchiolitis is generally a mild, self limiting disease^{12,13} requiring supportive outpatient treatment in most of the cases but parents and clinicians always look for a drug which provides symptomatic relief, reduces the physical and mental agony of children and their parents, reduces hospital revisits, retards the progression of severity of disease and decreases the admission rate^{14,15,16,23}. Bronchodilators (inhaled and oral) are commonly prescribed for the symptomatic treatment of acute Bronchiolitis^{17,18}. Most studies available so far used bronchodilators in nebulised form and in emergency settings²¹. Few regional and international studies are available on the use of oral salbutamol in the treatment of acute Bronchiolitis^{19,20}. We planned and conducted this study to assess the

efficacy of oral salbutamol administration for providing symptomatic relief in the treatment of acute mild Bronchiolitis in infants and children less than two years of age.

METHODS

This interventional study was a randomized, placebo controlled trial. It was conducted by the Department of Pediatrics at the outpatient department (OPD) of Independent University Hospital which is a tertiary care teaching hospital attached with Independent Medical College Faisalabad, Pakistan. Duration of study was six months from October 2010 to March 2011. During this time period, seven thousands and two hundred patients were seen in OPD. Out of these, two hundred and seventy two children less than two years of age were diagnosed with acute Bronchiolitis. Two hundred consecutive children younger than two years of age fulfilling the clinical diagnostic criteria of acute mild Bronchiolitis were included in the study.

Diagnosis of Bronchiolitis was made clinically. Any child less than two years of age with first episode of wheezing along with mild upper respiratory tract flu like symptoms (cough, coryza and mild fever) breathlessness of variable severity, diffuse bilateral rhonchi on chest auscultation and a suggestive radiograph, was diagnosed as a case of acute Bronchiolitis. Acute mild Bronchiolitis was defined by a playful and feeding well child, respiratory rate ≤ 60 breath/min, heart rate ≤ 200 beats/min, no or minimal respiratory distress and hemoglobin oxygen saturation $\geq 95\%$ in room air.

Children with moderate to severe acute Bronchiolitis at presentation, children whose disease progressed to moderate or severe acute Bronchiolitis during the study, any pre or coexisting cardiopulmonary disease, severe malnutrition, family or personal history of atopy or bronchial asthma, sick, lethargic and poorly feeding septic children, children who were already on bronchodilators during the current illness and children

whose parents did not comply with the study protocol during the course of study were excluded from the study.

Protocol of study was fully explained to the parents or caregivers of children included in the study in simple and plain language. An informed consent was obtained in each case. Clearance from the institutional ethical committee was obtained.

Children included in the study were randomized in two groups placing 100 children in each group. A child either received oral salbutamol in a dose of 0.1 mg/kg/dose three times daily or placebo provided from the hospital pharmacy, for a maximum of 07 days or till the resolution of illness whichever came first. Other supportive treatment measures included on demand continuation of food and fluids, paracetamol as antipyretic, sodium chloride 0.9% nasal drops, humidification of room air and steam inhalation. Danger signs of worsening disease severity were explained to parents. Children were followed up in OPD daily for first three days and then on 5th and 7th day of interventional trial. At each follow up visit, therapeutic compliance, resolution of illness (ROI), presence and severity of Bronchiolitis symptoms including cough, coryza, wheeze, breathlessness, feeding and sleeping pattern of the child and presence of any adverse effects of salbutamol including irritability, tremors and vomiting were asked, observed and noted in a proforma.

Time to resolution of illness (ROI) defined as the time from enrolment in study to the time the child returned to his or her baseline health status, was the primary outcome variable and was compared between the two groups. Adverse effects of salbutamol and Bronchiolitis symptoms noted during each follow up visit (cough, coryza, breathlessness, wheeze, time to achieve normal sleeping pattern and time to achieve normal feeding pattern) were taken as the secondary outcome variables. Age, sex, present weight and

duration of present illness were recorded in each case as baseline data.

Data was analyzed using the computer program IBM SPSS Statistics version 19. Chi square test was used for qualitative data and paired student's t- test was used for quantitative data. P value ≤ 0.05 was considered significant.

RESULTS

Enrolment, exclusion and final distribution of children in both study groups are shown in Table-I.

Baseline parameters (Table II, fig.1 and fig.2) including age, sex, present weight and duration of present illness were comparable in both groups. Predominance of male sex, Salbutamol Group 48/80 (60%) Placebo Group 44/80 (55%) was present in both groups.

Study groups	Total no. of children at the start of study (n=200)	Children excluded based on increasing disease severity	Children excluded based on non-compliance	Total no. Of children by the end of study (n=160)
Salbutamol group (SG)	n=100	n=08	n=12	n=80
Placebo group (PG)	n=100	n=09	n=11	n=80

Table-I. Enrolment and final distribution of children in Salbutamol and Placebo groups

Parameter	Salbutamol Group (n=80) Mean \pm SD	Placebo Group (n=80) Mean \pm SD	Mean Difference	(95% CI)	P-value
Age (month)	7.6 \pm 4.7	8.0 \pm 4.9	-0.42	(-1.3,0.4)	0.34
Weight (Kg)	7.2 \pm 1.8	7.5 \pm 1.7	-0.36	(-0.74,0.01)	0.06
Duration of present illness days	3.7 \pm 1.04	3.8 \pm 1.07	-0.13	(-0.47,0.20)	0.43

Table-II. Baseline Parameters in the Salbutamol Group (SG) Vs Placebo Group (PG)

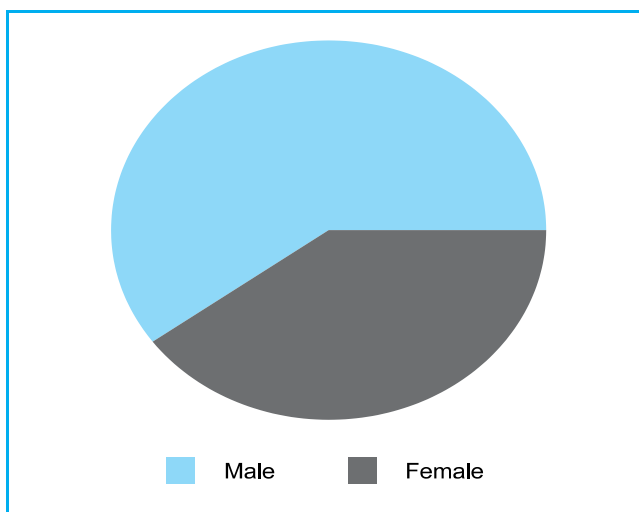


Fig-1. Distribution of males (m) and females (f) in salbutamol group m= 48 (60%) f= 32 (40%)

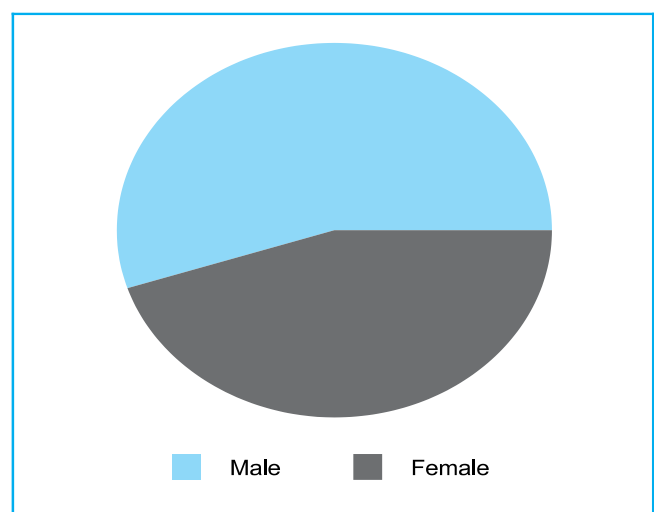


Fig 2: Distribution of males (m) and females (f) in placebo group m= 44(55%) f=36 (45%)

Significant results regarding symptomatic improvement and resolution of illness (ROI) were available on day 3 of daily OPD follow up in both groups. Breathlessness and wheeze were first to improve. In salbutamol group (SG), breathlessness and wheeze improved in 64/80 (80%) children whereas in placebo group (PG), breathlessness and wheeze improved in 62/80 (78%) children. Improvement in cough and coryza was observed in 56/80 (70%) children in SG and 54/80 (68%) children in PG. Sleep and feeding patterns improved in 51/80 (64%) children in SG and 53/80 (66%) children in PG. Resolution of illness (ROI) was observed in 36/80 (45%) children in SG and 34/80 (43%) children in PG. Tremors and irritability were observed in 13 (16.25%) children from salbutamol group.

Resolution of illness was complete in both study groups by day 7 (Table III). Median value of ROI for salbutamol group was 6.1 days as compared to 6.0 days for placebo group ($p=0.53$).

DISCUSSION

As there is no significant difference in overall resolution of illness (ROI), our primary outcome measure in both salbutamol and placebo groups, we conclude that oral salbutamol administration is not superior to placebo for symptomatic relief and overall

resolution of illness in children with acute mild bronchiolitis.

The results of our study are consistent with a double blind randomized placebo controlled trial conducted in India by Gupta et al¹⁹ who also studied children diagnosed as acute mild bronchiolitis based on clinical criteria. Duration of Resolution of illness in our study (median 6 days) was not significantly different from their study (median 5 days) although their study was double blinded, included children less than one year of

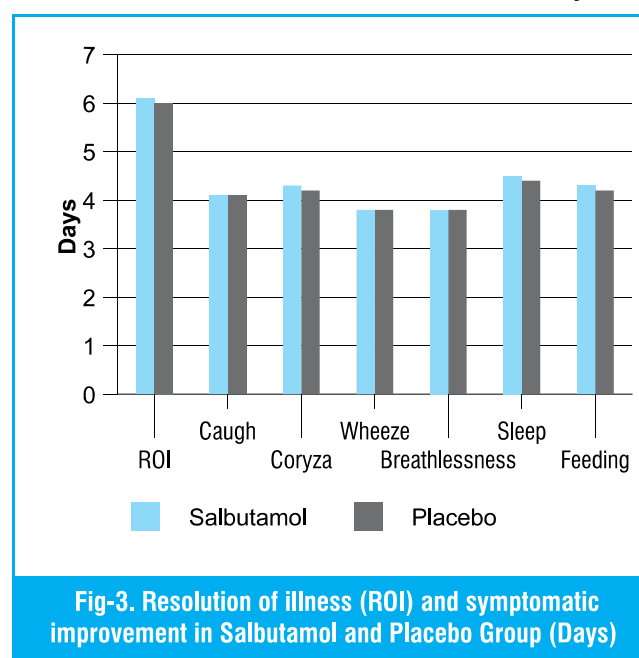


Fig-3. Resolution of illness (ROI) and symptomatic improvement in Salbutamol and Placebo Group (Days)

Parameter	Salbutamol Mean \pm SD	Placebo Mean \pm SD	Mean Difference	(95% CI)	P-value
Resolution of illness (days)	6.1 \pm 0.75	6.0 \pm 0.80	0.08	(-0.18,0.36)	0.53
Cough (days)	4.1 \pm 0.70	4.1 \pm 0.68	-0.05	(-0.29,0.19)	0.68
Coryza (days)	4.3 \pm 0.59	4.2 \pm 0.62	0.13	(-0.04,0.31)	0.14
Wheeze (days)	3.8 \pm 0.60	3.8 \pm 0.63	0.07	(-0.11,0.27)	0.24
Breathlessness (days)	3.8 \pm 0.60	3.8 \pm 0.63	0.07	(-0.11,0.27)	0.24
Normal sleep (days)	4.5 \pm 0.40	4.4 \pm 0.55	0.09	(-0.05,0.25)	0.19
Normal feeding (days)	4.3 \pm 0.59	4.2 \pm 0.62	0.13	(-0.04,0.31)	0.14

Table-III. Resolution of Illness (ROI) and Symptomatic improvement in Salbutamol and Placebo group

age and a longer follow up time (14 days) was followed.

Another study, a randomized controlled trial conducted in Canada by Patel et al²⁰ showed comparable results as ours with median ROI being 8 days which is longer than median ROI of 6 days in our subjects. This difference of 2 days in overall ROI may be due to multiple factors. Unlike our study, their study also included children with moderate form of acute bronchiolitis; diagnosis of bronchiolitis was confirmed by laboratory studies with Respiratory Syncytial Virus (RSV) being the major pathogen involved and a study population with different ethnic and genetic background.

A double blind placebo controlled interventional trial conducted by Gadososki et al^{21,22} using oral and nebulized salbutamol in children with bronchiolitis, also did not find any significant role of salbutamol for providing symptomatic relief. The major limitations of their study were short follow up time, 30 and 60 minutes for outcome assessment (symptomatic relief) following administration of oral salbutamol and no consideration of overall resolution of illness. Salbutamol does not achieve significant serum levels within one hour of its oral administration. We followed our patients daily for first 3 days and then at 5th and 7th day of intervention which provided us with a longer follow up time for observation of both study groups for symptomatic relief and overall resolution of illness.

The major limitation of our study was the lack of etiologic diagnosis. The diagnosis of acute mild bronchiolitis was made on clinical and laboratory assessments. Randomizations of study groups help minimize the effects of this anomaly.

CONCLUSIONS

On the basis of our results regarding symptomatic relief and resolution of illness in both salbutamol and placebo groups and comparison with other similar

studies, we conclude that oral salbutamol administration is not superior to placebo in providing symptomatic relief and earlier resolution of illness in children with acute mild bronchiolitis.

We recommend that oral salbutamol should not be prescribed routinely to children with acute mild bronchiolitis as it has no significant role in providing symptomatic relief and earlier resolution of illness. Adverse effects of salbutamol may further complicate symptoms of acute bronchiolitis.

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