P-ISSN: 2664-3685
E-ISSN: 2664-3693
www.paediatricjournal.com
IJPG 2021; 4(1): 159-162
Received: 05-04-2021
Accepted: 24-04-2021

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Analysis of recurrent wheezers under the age of two's reaction to inhaled short-acting beta-2 stimulants

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DOI: https://www.doi.org/10.33545/26643685.2021.v4.i1c.261

Abstract
Background and Objective: Recurrent wheezing in infants under two years is a frequent cause of hospitalization and may significantly impact quality of life. To assess the therapeutic response of inhaled salbutamol compared to normal saline in infants with recurrent wheezing.
Methods: This randomized, double-blinded trial enrolled 95 children under two years of age with at least two prior wheezing episodes. Participants received either nebulized salbutamol or normal saline at regular intervals. Clinical parameters including heart rate, respiratory rate, SpO_2, and RDAI scores were assessed at baseline, after 1 hour, 24 hours, and at discharge.
Results: The salbutamol group showed a statistically significant increase in heart rate after 1 hour ($p=0.05$), while the normal saline group demonstrated significantly better oxygen saturation after 24 hours ($p=0.009$) and lower RDAI scores after 1 hour ($p=0.019$). Duration of hospitalization was significantly longer in the normal saline group ($p=0.002$).
Conclusion: In infants with recurrent wheeze, normal saline may lead to faster improvement in clinical scores, though salbutamol resulted in shorter hospital stay.

Keywords: Recurrent wheeze, salbutamol, nebulization, infants, bronchodilator

Introduction
Wheezing in infancy is a globally common clinical presentation that often reflects underlying airway obstruction. It is a multifactorial symptom, frequently associated with bronchiolitis or early-onset asthma, but it can also signal more complex or atypical conditions. In certain cases, recurrent wheezing may be indicative of structural airway abnormalities, aspiration syndromes, foreign body aspiration, gastroesophageal reflux disease, or neuromuscular swallowing disorders [1].
Repeated lower respiratory tract infections are among the leading causes of morbidity in infants and may be a manifestation of compromised host immunity. Disorders such as cystic fibrosis, bronchopulmonary dysplasia, bronchiolitis obliterans, interstitial lung disease, and paradoxical vocal cord motion must be considered in differential diagnosis. It is estimated that nearly one-third of children will experience wheezing episodes by the time they reach school age. Globally, acute lower respiratory tract infections represent a significant burden of illness and remain a preventable cause of infant mortality. The early years of life are critical for lung development, and repeated infections during this stage may predispose individuals to chronic respiratory conditions later in life. Bronchiolitis is regarded as the most common acute respiratory infection affecting infants under two years, with respiratory syncytial virus (RSV) being the primary viral agent involved. The virus initially infects the upper respiratory tract and progresses to involve the lower airways within a few days. The pathological mechanism includes inflammation of bronchiolar epithelium, peribronchiolar infiltration by predominantly mononuclear cells, and edema of the submucosa and surrounding tissues [2-4].
Over the years, various treatment strategies have been explored, often with inconsistent clinical benefits. A number of meta-analyses have evaluated the role of commonly employed interventions—ranging from supportive care and oxygen therapy to bronchodilators (such as salbutamol and adrenaline), corticosteroids, and hypertonic saline. Antibiotics are generally discouraged unless a secondary bacterial infection is suspected, as they may otherwise prove counterproductive [4].
Nebulized therapy is a cornerstone of pediatric respiratory care, providing local and systemic effects through direct pulmonary absorption. In clinical settings, the Respiratory Distress

Assessment Instrument (RDAI) is often used to gauge the severity of bronchiolitis based on observable clinical signs. Early intervention is crucial in bronchiolitis, as clinical deterioration can be rapid and unpredictable. Nebulization is considered safe, with minimal side effects, supporting its use soon after diagnosis. Evidence suggests that children older than 20 months may respond to salbutamol similarly to older children with asthma. However, studies have not demonstrated significant improvement in respiratory function or clinical outcomes for wheezing infants aged between 7 and 18 months following bronchodilator therapy [5,6].

Although animal studies indicate that β2-adrenoceptors are present and functional in infant airways, data on human infants remain sparse. Despite this, beta-2 agonists continue to be widely prescribed for wheezing in infants and young children. This practice, while common, is not strongly supported by evidence, as both single and multiple dose bronchodilator regimens have shown limited clinical efficacy in this population. Given the continued uncertainty and variation in clinical responses, this study was undertaken to evaluate the effectiveness of salbutamol inhalation therapy in infants under two years with recurrent wheezing [6].

Materials and Methods

This double-blind, randomized controlled study was conducted at Department of Paediatrics, Sri Lakshmi Narayana Institute of Medical Sciences, Puducherry from March 2020 to February 2021. A total of 95 infants under two years of age with clinically diagnosed recurrent wheeze (≥2 episodes) were enrolled. Children with recent bronchodilator use, congenital heart disease, or need for ICU care were excluded. Participants were randomly assigned to receive either nebulized salbutamol or normal saline every six hours. Clinical parameters (heart rate, respiratory rate, SpO_2, RDAI score) were recorded at four time points: baseline, 1 hour, 24 hours, and at discharge. Statistical analysis was performed using SPSS v17.

Results

The present study included 95 infants under the age of two with recurrent wheeze, who were randomly assigned into two groups: Group I (Salbutamol, n = 48) and Group II (Normal Saline, n = 47). Both groups were similar in terms of demographic characteristics. The average age in Group I was 12.3 ± 6.9 months, and in Group II, 11.8 ± 6.6 months, with no statistically significant difference observed (p = 0.74). The male-to-female ratio was also comparable between the two groups.

Regarding clinical symptoms, the majority of infants in both groups presented with fever, cold, cough, and feeding difficulty. However, no significant differences were found between the groups for any of these symptoms. Similarly, anthropometric parameters such as length, weight, and head circumference were matched across both groups, and the differences were not statistically significant.

When assessing heart rate, a notable increase was recorded in the salbutamol group one hour following nebulization, which reached statistical significance (p = 0.05). However, heart rate at baseline, after 24 hours, and at the time of discharge did not differ significantly between the groups. In terms of respiratory rate, although both groups showed a decline over time, intergroup comparisons did not reveal any statistically meaningful differences at any time point.

Oxygen saturation (SpO_2) improved in both groups over time, but a significantly higher level was observed in the normal saline group 24 hours after the start of treatment (p = 0.009). At baseline, one hour, and discharge, SpO_2 levels remained statistically comparable between groups. Evaluation of respiratory distress through the Respiratory Distress Assessment Index (RDAI) showed a significantly lower score in the normal saline group after one hour of nebulization (p = 0.019), suggesting early symptomatic relief. However, RDAI scores at baseline, 24 hours, and discharge did not differ significantly between the two treatment arms.

Lastly, the mean duration of hospitalization was found to be significantly shorter in the salbutamol group compared to the normal saline group (p = 0.002), indicating a potential impact of salbutamol on early discharge, although this was not supported by improvements in oxygenation or respiratory rate.

Table 1: Distribution of Clinical Complaints Among Infants in Both Groups

Clinical Complaint	Group I (Salbutamol) (n = 48)	Group II (Normal Saline) (n = 47)	Z-value	P-value
Fever	42 (87.5%)	41 (87.2%)	0.21	0.83
Cough	35 (72.9%)	36 (76.6%)	0.53	0.59
Cold	44 (91.7%)	46 (97.9%)	1.40	0.32
Feeding Difficulty	12 (25.0%)	13 (27.7%)	0.31	0.75

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

Time Interval	Group I (Salbutamol) (Mean ± SD)	Group II (Normal Saline) (Mean ± SD)	t-value	P-value
At baseline	144.3 ± 15.1	140.1 ± 13.4	1.32	0.19
After 1 hour	149.7 ± 16.8	138.0 ± 14.9	3.54	0.05
After 24 hours	139.1 ± 15.4	133.4 ± 13.5	1.87	0.064
At discharge	128.7 ± 10.2	126.3 ± 9.4	1.13	0.26

Table 3: Respiratory Rate Comparison at baseline, 1hrs, 24hrs, discharge between group I and group II

Time Interval	Group I (Salbutamol) (Mean ± SD)	Group II (Normal Saline) (Mean ± SD)	t-value	P-value
At baseline	54.8 ± 9.4	52.6 ± 9.6	1.27	0.21
After 1 hour	54.0 ± 9.5	51.0 ± 9.8	1.59	0.12
After 24 hours	50.2 ± 9.3	47.0 ± 8.8	1.70	0.090
At discharge	41.5 ± 5.3	40.0 ± 4.1	1.91	0.057

Table 4: Duration of Hospital Stay

Group	Mean Stay (Days)	Standard Deviation (SD)	t-value	P-value
Group I (Salbutamol)	8.56	1.19		
Group II (Normal Saline)	9.31	1.12	3.21	0.002

Discussion

In this clinical study involving 95 infants under 2 years of age presenting with recurrent wheeze, the outcomes were evaluated after administering either nebulized salbutamol or normal saline (NS). The findings showed a statistically significant elevation in heart rate in the salbutamol group after one hour of nebulization (p=0.05). This aligns with results from Madhusmita Som *et al*., who observed an increase in heart rate from 152.26 to 160.59 bpm, with a high level of significance (p<0.001). Similarly, Lenney and colleagues reported an increase in pulse rate from 116 to 140 bpm within five minutes of salbutamol nebulization in their cohort [6,7].

In contrast, no statistically significant variation in respiratory rate was observed between the two groups in the present study. This diverges slightly from studies such as Chavasse *et al*., where a notable decrease in respiratory rate was recorded following salbutamol administration during acute wheeze episodes. Likewise, in research conducted by Bentur *et al*., infants in an emergency department setting receiving 0.3 mg/kg salbutamol over one hour showed a mean reduction in respiratory rate of 7.7 breaths per minute, compared to 2.6 breaths per minute in the placebo group. The difference between these outcomes was statistically significant. Another study by Madhusmita Som found that respiratory rate decreased from 73.65 to 60.48 breaths per minute after salbutamol therapy [7,8].

When evaluating oxygen saturation (SpO_2) levels, the control group (NS) showed significantly better oxygenation at the 24-hour mark (p=0.009). This contrasts with expectations for bronchodilators, as Bentur *et al*. found a 1.3% increase in SpO_2 in the salbutamol group compared to a 0.3% decline in the placebo group, suggesting a small yet favorable difference. On the other hand, Elaine Wang *et al*. noted a less favorable response to salbutamol, with significant statistical differences in favor of the placebo group (F=4.81, p=0.03). In Madhusmita Som's study, SpO_2 improved significantly from 91.13% to 93.87% post salbutamol use (p<0.001), indicating variation in response across settings [8,9].

The Respiratory Distress Assessment Index (RDAI) score—used to quantify bronchiolitis severity—was found to be significantly lower in the normal saline group compared to the salbutamol group at the 1-hour post-treatment point (p=0.019). This finding supports previous research by Madhusmita Som *et al*., where RDAI scores dropped from 13.19 to 7.24 with statistical significance (p<0.001). Likewise, Gadomski *et al*. reported a modest decline in clinical scores with bronchodilator use (SMD: -0.37, 95% CI: -0.62 to -0.13) across inpatient and outpatient cohorts. Chavasse *et al*. documented an average score reduction of 2.9 points with salbutamol, compared to 0.4 with placebo—a meaningful clinical difference (difference: -2.5, 95% CI: -3.88 to -1.12). However, Wang *et al*. observed no significant benefit from bronchodilator use; in fact, the greatest improvement in clinical scores occurred in the placebo group, raising questions about the clinical value of routine salbutamol use in young infants [10-12].

The duration of hospital stay was significantly shorter in the salbutamol group compared to the control (p=0.002), suggesting a potential benefit in terms of early discharge. However, the clinical relevance of this finding must be interpreted cautiously. In a meta-analysis by Gadomski *et al*., bronchodilators did not significantly reduce hospital stay duration (MD = 0.06 days; 95% CI: -0.27 to 0.39; n=349). Similarly, Elaine Wang's randomized trial found no difference in hospitalization between those treated with salbutamol, ipratropium bromide, or placebo [12].

Although salbutamol is widely used in pediatric respiratory practice, multiple studies spanning more than two decades consistently indicate that β2-agonists provide minimal or no significant benefit in improving lung function in wheezing infants. This limited response cannot be attributed to the absence of β2-adrenoceptors, as confirmed by histological studies. Instead, it is believed that immaturity of these receptors or the fixed nature of airway obstruction in infants may reduce the efficacy of bronchodilators [13,14].

Further complicating the matter, research has shown that wheezy infants tend to have narrower airways than their healthy counterparts, which predisposes them to fixed airflow limitations. Studies by Martinez *et al*. and Prendiville *et al*. support this anatomical explanation. While β2-receptors are present, their response in infants under two years of age may not translate into clinical benefit due to delayed receptor maturation or dominance of mucosal edema and mucus plugging rather than bronchospasm [14].

Thus, the beneficial effect seen in the control group (normal saline) might stem from the mechanical clearance of airways through humidification and hydration of thick mucus, rather than bronchodilation. This underscores the role of supportive therapy and calls into question the routine use of bronchodilators in infants under two years with recurrent wheeze [15].

Conclusion

For children under the age of two who have recurrent wheezing, normal saline is preferable than salbutamol.

Funding Support

Nil.

Conflict of Interest

None.

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