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Original Article

Levosalbutamol via Metered-Dose Inhaler with Spacer Versus Nebulizer for Acute Exacerbation of Bronchial Asthma in Children – A Randomized Controlled Trial

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Abstract

Introduction: Acute paediatric asthma can pose an emergency challenge requiring medical preparedness. Hence, it is prudent to identify the best drug-delivery option for managing acute asthma exacerbations. The objective of the study was to compare the effectiveness of metered dose inhaler with spacer (MDI-S) versus nebulizer (NEB) in delivering levosalbutamol for acute exacerbation of asthma in children.

Methods: This randomized clinical trial enrolled 58 children aged five to 15 years with mild-moderate asthma and randomly divided them into two treatment groups – Group MDI-S (N = 29) and Group NEB (N = 29). Pulmonary Index Score (PIS) along with signs and symptoms of asthma were compared between the groups before and one hour after levosalbutamol treatment. Chi square test was used to compare continuous variables and the level of significancewas set at $P < 0.05$.

Results: The two groups showed no significant differences in median age, age of wheezing onset, prior hospitalizations, and PIS before treatment ($p > 0.05$). Even one hour after treatment, they did not differ significantly in PIS and hospital admissions ($P > 0.05$). All children showed improvement in their asthmatic status after the therapy and none showed any worsening of their condition.

Conclusions: Metered dose inhaler with spacer is an effective and efficient alternate to the routinely used nebulizer for managing acute asthmatic episodes in children.

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Introduction

Asthma is a growing public health problem with a significant global impact, especially in children.[1,2] It is a heterogeneous disease characterized by chronic inflammation of airways presenting with respiratory symptoms like wheezing, shortness of breath, tightness of chest and cough with varying intensity, together with variable limitation of expiratory airflow.[3] With a national prevalence of 17.23 million (2.05%), India accounts for 13.09% of the global burden of asthma, contributing to 13.2 thousand deaths.[3,4] A focused study in India found that nearly 30% of children were suffering

from asthma in a specific Indian population cohort.[1] This increasing prevalence can be attributed to urbanization, air pollution and environmental / tobacco smoke.[1,2,5] By 2025, asthma is expected to affect another 100 million people worldwide.[6]

Childhood asthma may impair airway development and pose lung function deficits that may track into adulthood with / without further progressive loss.[3] Therefore, early diagnosis and management are of utmost importance, along with identification of triggers, facilitating lifestyle changes and medical preparedness.[3,7] Current guidelines recommend short-acting bronchodilators (β-2 agonists like levosalbutamol) to reverse airflow obstruction in case of acute asthmatic exacerbations.[7] In this modern era of advanced medicine, sophisticated techniques are used to deliver these bronchodilators such as metered dose inhaler (MDI) and nebulizer (NEB).[7]

While nebulization may be preferred in young patients or those unable to coordinate inhalation, MDI-spacer (MDI-S) technique may be just as effective, or even better, in routine or supervised clinical scenarios for delivering aerosolized medication.[7] Considering that these are often employed on an emergency basis, it is prudent to identify the best drug-delivery option for managing acute asthma episodes.

Hence, the present study aimed to compare the effectiveness of MDI-S versus NEB in delivering levosalbutamol for acute exacerbation of asthma in children aged five to 15 years.

Methods

This open-labeled, prospective, randomized, non-inferiority, clinical trial was conducted at a tertiary care hospital from August 2019 to March 2020, seven months duration in Tamil Nadu, India. The research was initiated after obtaining ethical clearance from the Institutional Review Board (Project No.18 / 348) and registered under the Clinical Trials Registry India (CTRI) with CRTI number CTRI/2020/03/023829. Based on a previous study by Deerojanawong et al, comparing clinical scores of two groups with standard deviation of 1.4, power 90%, alpha error 5%, inferior margin of 1 and attrition rate of 10%, the required sample size was determined to be 29 children per group.[8] After obtaining informed consent from their parents / guardians, we included 58 children aged between five to 15 years, presenting to the emergency and outpatient department of the paediatric wing with acute exacerbation of mild to moderate asthma indicated by a Pulmonary Index Score (PIS) of 0 - 11, as per GINA Guidelines 2018 updates.[9,10] The study excluded children with severe asthma and those < five and > 15 years.

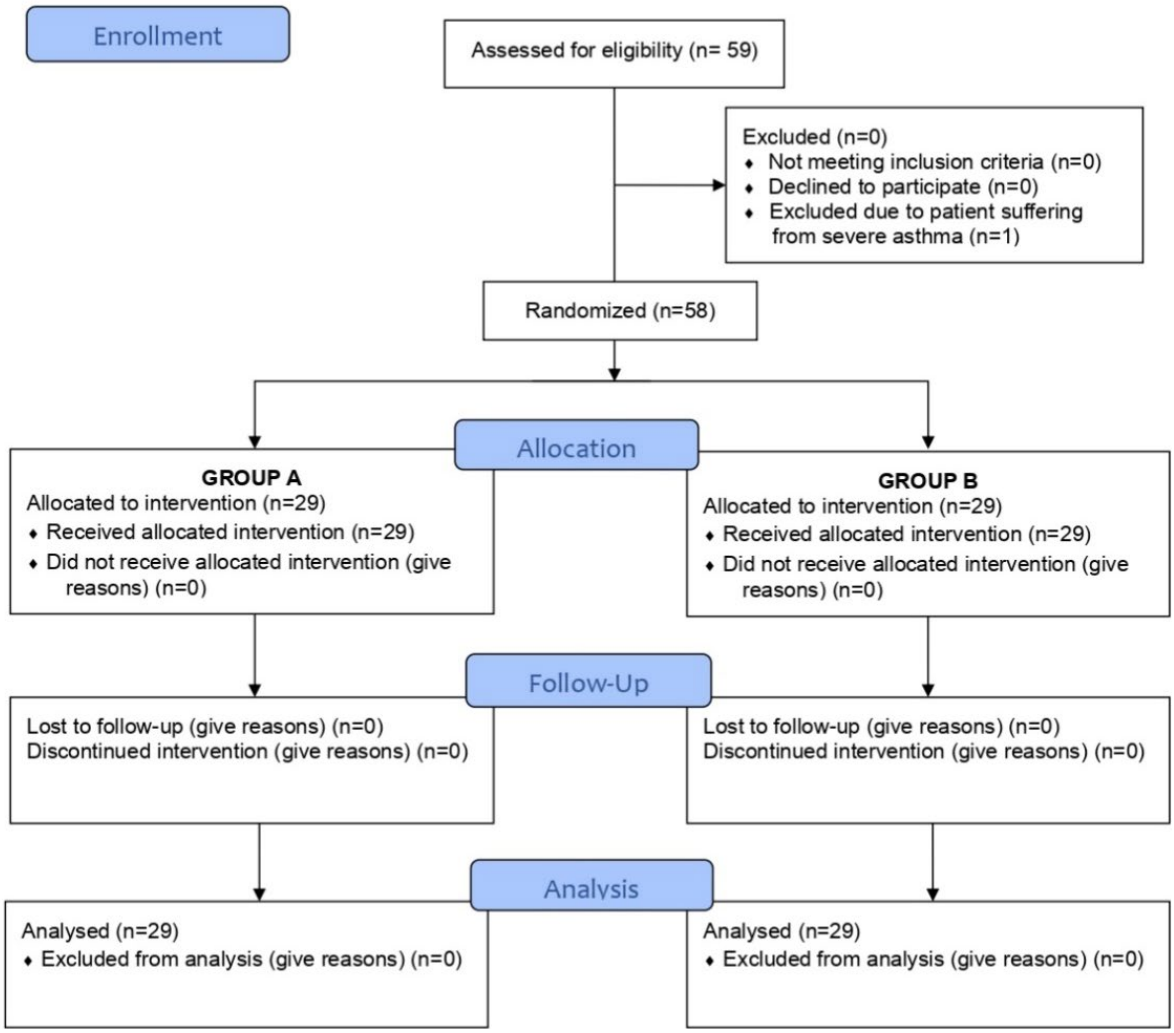
A validated PIS evaluation was done prior to the initiation of treatment as per protocol and after one hour post treatment. The parameters of PIS (Table-1) include respiratory rate (RR), presence of wheezing, inspiratory and expiratory ratio, retractions, and oxygen saturation.

Table 1: Pulmonary Index Score[8]

Score	Respiratory rate (per min)	Presence of wheezing	Inspiration: Expiration ratio	Retractions	Oxygen saturation
0	< 30	None	2:1	None	99 - 100%
1	31 – 45	End expiration	1:1	Intercostal or subcostal	96 - 98 %
2	46 - 60	Entire expiration	1:2	Intercostal and subcostal	93 - 95 %
3	> 60	Entire inspiration and expiration	1:3	Intercostal, subcostal, and cervical	< 93 %

RR was determined by observation of the thoracic movement over a full minute. After collection of baseline demographic data from all eligible children, they were randomized by variable block method. Randomization details were kept concealed in an opaque, sequentially numbered, sealed envelope. After the recruitment, principal investigator opened the envelope and accordingly assigned the participants to either Group-A (MDI-S) or Group B (NEB) as mentioned in the envelope. (Figure 1). The MDI-S group received Levosalbutamol (Levolin Inhaler 50 mcg / puff - Tran spacer VM spacer) two to four puffs every 20 minutes for three doses as needed. Following each puff, the children took five tom six breaths from the spacer device held in place. The NEB group received Levosalbutamol 2.5 mL aerosol solution (0.075 mg / kg, minimum 1.25 mg Levolinrespule 2.5 mL) with 2.5 mL normal saline solution. Aerosols were generated by jet nebulizer (PHILIPS Respironics Innospire Essence) via facemask for 10 – 15 minutes every 20 minutes for three doses as needed. All participants were reassessed with PIS after one hour post-treatment to evaluate the clinical improvement. One hour post treatment, all patients showed improvement in each groups. But while comparing two groups post treatment, it was not statistically significant.

Figure : Study Flow Chart



Results

This study enrolled 58 children with a median age of nine (6 ± 12) years in the MDI-S group and eight (5 ± 10) years in the NEB group ($P = 0.420$). The median age at the time of first wheezing attack was five years in the both the groups ($P > 0.05$).

Table 2: Comparison of demographic characters of the two groups

Parameters		Group-A (MDI-S) (N = 29)	Group-B (NEB) (N = 29)	p-value
Gender (%)	Male	55.2	62.1	0.594
	Female	44.8	37.9	
Median age (years)		9 (6 ± 12)	8 (5 ± 10)	0.420
Median age of first wheezing attack (years)		5 (4.5 ± 9)	5 (3.5 ± 8.5)	0.596
Previous hospitalizations (%)	No admission	69	69	0.650
	1 admission	27.6	20.7	
	2 admissions	3.4	6.9	
	3 - 4 admissions	0	0	
	≥ 5 admissions	0	3.4	
History of ICU admissions (%)	No admission	96.6	96.6	1.000
	1 admission	3.4	3.4	
Asthma medications (%)	No medications	17.2	31	0.689
	β2 Agonist (Inhaler/ Nebulization - intermittent/oral)	79.2	65.4	
	Steroid inhaler	3.4	3.4	

Table-2 presents an inter-group comparison of the demographic characters. The groups did not differ significantly in the age of wheezing onset, prior hospitalizations, and PIS ($P > 0.05$).

Table 3: Pre-treatment observations before levosalbutamol

Parameters		Group-A (MDI-S) (N = 29)	Group-B (NEB) (N = 29)	p-value
Respiratory rate (%)	< 30	31	20.7	0.661
	31 - 45	55.2	62.1	
	46 - 60	13.8	17.2	
Wheezing (%)	None	0	0	0.030
	End expiration	75.9	48.3	
	Entire expiration	24.1	51.7	
Inspiratory : Expiratory (%)	2:1	10.3	10.3	0.572
	1:1	48.3	34.5	
	1:2	34.5	51.7	
	1:3	6.9	3.4	
Accessory muscle use (%)	No	34.5	6.9	0.010
	iYes	65.5	93.1	
Oxygen saturation (%)	99 - 100	0	0	0.379
	96 - 98	20.7	31	
	93 - 95	72.4	55.2	
	≤ 93	6.9	13.8	
Pulmonary Index Score	Mild	69	55.2	0.279
	Moderate	31	44.8	

Table-4: Post-treatment observations with levosalbutamol

Parameters		Group-A (MDI-S) (N = 29)	Group-B (NEB) (N = 29)	p-value
Respiratory rate (%)	< 30	75.9	79.3	0.753
	31 - 45	7	20.7	
	46 - 60	0	0	
Wheezing (%)	None	37.9	34.5	0.962
	End expiration	55.2	58.6	
	Entire expiration	6.9	6.9	
Inspiratory: Expiratory (%)	2:1	41.4	41.4	0.889
	1:1	48.3	51.7	
	1:2	10.3	6.9	
	1:3	0	0	
Accessory muscle use (%)	No	72.4	75.9	0.764
	Yes	8	7	
Oxygen saturation (%)	99 - 100	17.2	24.1	0.316
	96 - 98	75.9	62.1	
	93 - 95	3.4	13.8	
	≤ 93	3.4	0	
Pulmonary Index Score	Mild	96.6	93.1	0.553
	Moderate	3.4	6.9	

Tables 3 and 4 consolidate the pre- and post-treatment observations with levosalbutamol. No significant pre-treatment differences were noted between the groups. However, one hour after treatment, PIS showed significant clinical improvement in both the groups but no significant post-treatment differences between the groups (P > 0.05) (Table 5). One child in the NEB group was admitted in paediatric intensive care unit (PICU), but none in MDI – S group (Table 5). Four children in each group were admitted in the paediatric general ward one hour after treatment and no children worsened following treatment in either groups (P > 0.05). All other children were discharged as outpatients (Table-5).

Table 5: Secondary outcome

Parameters	Group-A (MDI-S) (N = 29)	Group-B (NEB) (N= 29)	P-value
Mean Pulmonary Index Score	6.2 ± 1.6	6.8 ± 2.1	0.18
No of children admitted in PICU after stabilization	0	1	0.6
No of children admitted in ward	4	4	
No of children discharged as outpatient	25	24	

Discussion

Acute paediatric asthma can pose an emergency challenge requiring medical preparedness. Hence, it is prudent to identify

This study excluded children with severe asthma because they need be hospitalized for immediate care, making them unamenable to outpatient study. To evaluate the severity of acute asthma exacerbations, PIS was employed as it is simple and easy to apply over children.[9] Levosalbutamol was utilized because its aerosolized therapy has lesser side effects affecting heart rate and serum potassium levels than salbutamol, besides having broncho-protective and anti-edematous properties along with bronchodilator effect. Moreover, it also inhibits the activation of eosinophils and mast cells.[11,12]

Historically, NEBs have been routinely employed to deliver medications to children where other modalities have failed and allow large doses of drug to be delivered. However, they come with high costs, reduced portability, slower drug delivery, and electricity-dependent function. On the other hand, MDIs come with lower costs and provide easy portability, faster delivery, elimination of need for coordination with inhalation,

and finer aerosolized vapors so that children cannot smell and taste the medications.[13]

The results of the present study are reflected also in those of a systematic review by Roncada et al that found no significant differences between the two inhalation techniques for any of the four outcomes analyzed: heart rate, RR, O_2 saturation and asthma score.[7] However, Barkiya et al demonstrated that the salbutamol administration through MDI-S had similar efficacy and fewer side effects (like tachycardia) than NEB delivery in the treatment of acute asthmatic exacerbation in 60 children aged between five to15 years.[12]

In line with the present study, Deerojanawong et al demonstrated that salbutamol and placebo administered by MDI-S and mask did not differ significantly from NEB in asthma symptoms improvement in children.[8] Similarly, Snider et al demonstrated that MDI-S showed similar efficacy as breath-actuated NEB in 890 children aged two to 17 years with acute exacerbation of mild to moderate asthma.[14] However, a meta-analysis by Payares-Salamanca et al showed a significantly greater PIS reduction and a significantly smaller heart rate increase with albuterol delivered through MDI-S than through NEB ($P < 0.05$).[15]

Considering that the present study found similar improvements with both MDI-S and NEB, it resonates with the sentiments of Nambiar et al who studied parental perceptions about the use of MDI vs NEB in children with acute asthma exacerbation and stressed that parental education is necessary for progressing into a new era of MDI therapy that will make asthma management more affordable and accessible.[16]

However, this research is a single-center study with a limited sample size and limited variables covered. Further multi-center large-scale studies are encouraged to explore these therapies on a wider platform for generalization and implementation of the results of our study.

Conclusions

The administration of levosalbutamol through MDI-S with mask and nebulizer are equally efficacious and non-inferior to each other in attaining symptomatic relief in children with mild to moderate acute exacerbation of paediatric asthma. Metered dose inhaler with spacer is an effective and efficient alternate to the routinely used nebulizer for managing acute asthmatic episodes in children.

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