ORIGINAL ARTICLE

Comparing Treatment Effectiveness and Costs for Bronchospasm in Hospitalized Children: Salbutamol Inhaler with Spacer vs. Nebulizer – A Retrospective Study

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ABSTRACT

Introduction: The study, conducted at Sultan Ahmad Shah Medical Centre, aimed to compare outcomes in bronchospasm-treated children using metered-dose inhalers (MDIs) with spacers versus nebulizers. The primary focus was on assessing the length of stay (LOS) and treatment costs associated with each modality. The hypothesis anticipated no significant differences between the MDI and nebulizer groups. **Materials and methods:** This retrospective cohort study, spanning from January to December 2022, involved 128 children aged between two and 12 years old. The nebulizer group data covered the period from June 2019 to March 2020, while the MDI group data spanned from March 2020 to December 2021. Patient selection utilized universal sampling, and data were extracted from patient notes. The methodology included the use of a structured pro-forma for data collection, evaluating variables such as LOS, treatment costs, cumulative salbutamol dose, heart rate, and clinical parameters. **Results:** The results revealed no significant difference in LOS between the two groups. However, the MDI group demonstrated lower costs compared to the nebulizer group (RM10,486.00 vs. RM12,273.00 each treatment per hospital stayed). While differences in cumulative salbutamol dose were observed, no significant distinctions were noted in other clinical parameters. **Conclusion:** The study concluded that MDI with a spacer showed similar ward stay durations but with lower costs compared to nebulizers. This underscores the economic and practical benefits of using MDI, including a reduced risk of disease transmission and decreased nursing workloads. *Malaysian Journal of Medicine and Health Sciences* (2024) 20(SUPP3): 73-79. doi:10.47836/mjmhs20.s3.11

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INTRODUCTION

During the 2003 severe acute respiratory syndrome (SARS) outbreak, healthcare workers (HCWs) constituted a substantial proportion, ranging from 20% to 40% of the infected population (1-2). As the global spread of the Covid-19 epidemic unfolded, ensuring the health and safety of healthcare workers became a paramount concern, prompting modifications in healthcare practices to minimize the risk of exposure (3).

Nebulizer therapy is a conventional approach in acute respiratory care, valued for its ability to deliver medication directly to target tissues, bypassing systemic circulation. This method minimizes systemic side effects and allows for higher medication doses. However, the generation of aerosols during nebulizer therapy poses a potential risk of infection transmission to HCWs. The produced aerosols, containing particles smaller than 10 µm, disperse widely and can linger in the environment for extended periods, thereby increasing the risk of disease dissemination, particularly in enclosed spaces (4-7).

Salbutamol delivered through inhalation is a routine practice in paediatric wards for treating acute respiratory illnesses, a common cause of admissions. Salbutamol is effective in relieving airway bronchospasm, a frequent feature in lower respiratory tract infections caused by viruses (8). Nebulizers are commonly utilized for administering inhaled salbutamol due to their perceived convenience, cost-effectiveness, and simultaneous oxygen delivery. Their extensive use is notable in cases of acute bronchiolitis, where nebulized fluids aid in mobilizing secretions and enhancing recovery

(9). However, with the advent of Covid-19, metered-dose inhalers (MDIs) are considered a safer alternative. Despite this perception, more information is required to compare the efficacy of nebulizers and MDIs in managing bronchospasm across various aetiologies, including asthma.

Cost-effectiveness is a pivotal consideration in clinical decision-making, particularly when multiple treatment options offer comparable effectiveness or efficacy (10). Accessible information on treatment costs is indispensable for clinicians to make informed choices, contributing to health economic benefits by selecting the most cost-effective treatment for patients.

This study aims to assess whether changes in B2 agonist method of delivery will give impact on outcomes such as clinical responses, length of stay (LOS) and treatment costs. We hypothesize that there will be no different in the efficacy and side effect of B2 agonist treatment and LOS, but with significant reduction in treatment cost when the drug is delivered using MDI with spacer compared to nebulizers.

MATERIALS AND METHODS

2.1 Study Design

This retrospective cohort study was conducted over one year, from January 2022 to December 2022, at Sultan Ahmad Shah Medical Centre in Kuantan, Malaysia. The focus of the study was on children aged two to twelve years who were admitted to the general paediatric ward between June 2019 and December 2021 for bronchospasm. Universal sampling was employed, encompassing all eligible children within the specified timeframe.

2.2 Group Allocation:

The patient admission registry from June 2019 to December 2021 was scrutinized for this study, and historical notes were retrieved. Patients were classified into two groups: the nebulizer group and the MDI group. The nebulizer group included eligible patients admitted for bronchospasm between June 2019 and March 2020, who received regular Salbutamol via nebulizer. The MDI group comprised patients admitted between March 2020 and December 2021, receiving regular Salbutamol via MDI with a spacer, with or without rescue nebulized Salbutamol.

2.3 Data Collection:

Demographic and clinical information was meticulously collected from historical patient notes using a structured research pro-forma. The pro-forma comprised three sections: socio-medico-demographic background, treatment received, and clinical/non-clinical outcomes. Patient identification was conducted using personal registration numbers to ensure confidentiality. Patients with at least 50% completed data were randomly selected from both groups to form the final cohort.

The outcomes of interest included the length of hospital stay (LOS) and treatment costs between patients receiving nebulized Salbutamol and those treated with MDI. The side effects of Salbutamol were observed by comparing heart rates between the two groups. Other variables included the cumulative dose of Salbutamol, adjunct treatments, non-invasive ventilation (NIV), and the severity of respiratory illness. Severity was scored according to the assessment of the paediatric doctors on admission to the ward. Paediatric Respiratory Severity Score (PRESS) scores were calculated to determine the overall severity of each group (11).

2.4 Sample Size Calculation:

The sample size was calculated using PS Power software. A previous study indicated a within-group standard deviation of 1 day for the duration of stays in the nebulized Salbutamol group (12). Detecting a difference of 0.5 days between the groups, with α of 0.05 and a type-II error of 80%, required a sample size of 128.

2.5 Data Analysis:

Descriptive statistics summarized socio-demographic characteristics. Numerical data were presented as mean (SD) or median (IQR), and categorical data as frequency (percentage). Independent T-test or Mann-Whitney test compared continuous outcomes, and Chi-Squared or Fisher-Exact test compared categorical outcomes between the two groups.

2.6 Cost-Effectiveness Analysis:

A comprehensive cost-effectiveness analysis was conducted using the collected data. This analysis included the identification of both variable costs (related to consumables and medications) and fixed costs (such as ward charges and human resources per hour). An average-based costing approach was employed to determine the cost-effectiveness ratio between the two groups. Each variable was assessed for its cost per unit (1 unit hour) in terms of the actual cost in Ringgit Malaysia. Costs associated with entry to the emergency department, the utilization of human resources (including nurses and medical assistants), ward charges, and consumables and medications were determined using average-based costing and standardized to the 1-unit hour. The collected data were then leveraged to calculate the average length of stay, involving division of the total number of hours by the total number of patients in each group and further division by 24.

2.7 Ethical Approval:

Ethical approval was obtained from the International Islamic University Malaysia Research Ethics Committee (IREC) with ID number IREC2021-118. All forms were anonymized, and no personal identification was documented on any research materials. Respondents were identified using research IDs known only to the

research team.

RESULTS

A total of 128 patients were included in the study, with 57 (22 female and 35 male) children in the nebulizer group and 71 children (25 female and 46 male) in the MDI group. The mean age was 36.4 (SD 29.5) months in the nebulizer group and 37.2 (SD 39.7) months in the MDI group. Children in the MDI group exhibited a significantly longer duration of symptoms before admission compared to those in the nebulizer group, although their duration of shortness of breath (SOB) was similar. However, there were no significant differences in the causes of respiratory illness between the two groups. Table I provides a comprehensive overview of the cohort's characteristics.

Table I: The Characteristics of Each Group

Characteristic	Mean ± SD / Frequency (%)		p-value
	Nebulizer, (n = 57)	MDI[a], (n = 71)	
Age (months)	36.4 (29.5)	37.2 (39.7)	.885 [b]
Sex			
Male	35 (61.4)	46 (64.8)	.693 [c]
Female	22 (38.6)	25 (35.2)	
Diagnosis			
LRTI	35 (61.4)	46 (64.8)	.780 [c]
Wheezing induced by others	7 (12.3)	10 (14.1)	
Asthma	15 (26.9)	15 (21.1)	
Duration of symptoms prior to admission (days)	3.3 (3.45)	3.8 (3.16)	**.031** [b]
Prior beta agonist used before admission			
No	49 (86.0)	54 (76.0)	.160 [c]
Yes	8 (14.0)	17 (24.0)	
Pulse rate			
Normal	3 (5.3)	2 (2.8)	.728 [c]
Mild tachycardia	41 (71.9)	56 (78.9)	
Severe tachycardia	13 (22.8)	13 (18.3)	
Underlying respiratory illness			
No	41 (73.2)	50 (70.4)	.729
Yes	15 (26.8)	21 (29.6)	

[a] 43 of 71 (60.6%) patients received rescue nebulisation in the MDI group
[b] chi square
[c] Mann-Whitney U

Kruskal-Wallis H tests were conducted to compare symptom severity between patients treated with nebulized salbutamol and metered-dose inhaler (MDI) with a spacer. The analysis covered breathlessness, ability to talk, wheezing, respiratory rate, chest indrawing, oxygen saturation, and interrupted feeding. Results showed no significant differences in most symptoms, except for chest indrawing, ability to talk, and interrupted feeding. While nebulized patients exhibited more variability in severity levels, the overall severity assessed by the PRESS score demonstrated no significant differences between the nebulized and MDI groups. The severity of respiratory distress is summarised and compared in Table II.

Table II: Parameters for severity of respiratory distress

Parameters	Frequency, n (%)		P value [a]
	Nebuliser N=57	MDI N=71	
Breathlessness level			
None	2 (1.8)	0 (0)	.263
Mild	37 (66.1)	55 (77.5)	
Moderate	18 (32.1)	16 (22.5)	
Ability to talk			
Form sentences	1 (1.7)	0 (0)	.052
Talk in phrases	43 (75.5)	63 (88.7)	
Talk in words/ unable to talk	13 (22.8)	8 (11.3)	
Wheezing level			
No audible	30 (52.6)	46 (64.8)	.223
Audible	27 (47.4)	25 (35.2)	
Respiratory rate level			
Not tachypnoeic	42 (73.7)	56 (78.9)	.369
Tachypnoeic	15 (26.3)	15 (21.1)	
Used of accessory muscles			
No	15 (26.3)	36 (50.7)	**.006**
Yes	42 (73.7)	35 (49.3)	
Oxygen saturation			
No desaturation	53 (93.0)	69 (97.2)	.465
Desaturation	4 (7.0)	2 (2.8)	
Feeding			
Uninterrupted	25 (43.9)	44 (70.0)	**0.041**
Interrupted	32 (56.1)	27 (33.0)	
PRESS SCORE			
Mild	21 (36.8)	40 (56.3)	0.086
Moderate	28 (49.1)	25 (35.2)	
severe	8 (14.1)	6 (8.5)	

[a] Chi-squared test

The modalities of treatments received by both groups were compared and presented in Table III. As anticipated, children in the nebulizer group received a higher dose of salbutamol and underwent more physiotherapy. Additionally, they were more likely to be administered anti-muscarinic drugs, initiated on antibiotics, receiving intravenous fluids, and commenced on Montelukast. Notably, there were no discernible differences between the groups concerning the use of oral steroids, oxygen requirements, or the use of preventive medications before admission.

Table III: Modalities of treatment received by patients in both groups

Treatment modality	Mean (SD) / Frequency (%)		p-value
	Nebulizer	MDI[a]	
Antibiotic			
No	15 (26.3)	31 (43.7)	.049
Yes	42 (73.7)	40 (56.3)	
Steroid			
No	28 (49.1)	25 (35.2)	.093
Yes	29 (50.9)	46 (64.8)	
Intravenous drip			
No	24 (42.1)	43 (62.3)	.030
Yes	33 (57.9)	26 (37.7)	
Supplement oxygen (nasal prong)			
No	1 (1.8)	1 (1.6)	.914
Yes	56 (98.2)	63 (98.4)	
Supplement oxygen (HFN-C[a])			
No	55 (96.5)	64 (100.0)	.124
Yes	2 (3.5)	0 (0)	
Supplement oxygen (CPAP[b])			
No	56 (98.2)	64 (100.0)	.279
Yes	1 (1.8)	0 (0)	
Chest physiotherapy			
No	26 (45.6)	59 (83.1)	<.001
Yes	31 (54.4)	12 (16.9)	
Nebulised Antimuscarinic			
No	9 (15.8)	61 (85.9)	<.001
Yes	48 (84.2)	10 (14.1)	

[a]HFNC: high-flow nasal cannula, [b]CPAP: continuous positive airway pressure

Table IV presents the comparison of outcomes between the two groups. An independent sample t-test was conducted to assess differences in the length of stay between patients treated with nebulized salbutamol and those receiving a metered-dose inhaler (MDI) with a spacer. The analysis indicated no significant differences in the length of stay between the two groups [t (98.502) = -1.29, p > 0.05]. Patients receiving nebulized salbutamol reported a nearly identical length of stay compared to those receiving MDI, with a mean difference of -6.13 and standard error (SE) of 4.59. The non-significant p-value reinforces the conclusion that there is no substantial difference in the length of stay between the nebulized and MDI groups.

Table IV: Comparison of outcomes between both groups

Outcomes	Mean (SD)		Mean difference (95% CI)	P value [a]
	Nebuliser	MDI		
Length of Stay (hours)	48.4 (30.2)	42.2 (21.2)	6.2 (-2.8, 15.2)	.200

CONTINUE

Table IV: Comparison of outcomes between both groups (CONT.)

Outcomes	Mean (SD)		Mean difference (95% CI)	P value [a]
	Nebuliser	MDI		
Cumulative dose of salbutamol received (microgram)	46250 (61700)	12400 (25200)	33850 (17935.3, 49764.6)	**<.001**
Highest Heart Rate (bpm)	148.7 (16.8)	145.7 (16.3)	3.0 (-2.8, 8.8)	.328

[a] Independent t-test

A Mann-Whitney U test was employed to assess differences in the cumulative dose of salbutamol and the highest heart rate between patients treated with nebulized salbutamol and those using a metered-dose inhaler (MDI) with a spacer. Results showed significant differences in the cumulative dose of salbutamol [U(126) = 2527.5, p < 0.05], with nebulized patients receiving a significantly higher dose. However, no significant differences were observed in the highest heart rate between the two groups. The mean rank of the cumulative dose of salbutamol was significantly higher in nebulizer patients compared to MDI patients.

Cost effectiveness.

The MDI group exhibited a coefficient of 1.65, while the nebulizer group showed a coefficient of 2.1. With the coefficients obtained and the groups merged, the costs per 1 unit hour were then multiplied with the respective coefficients. The final average costs obtained for MDI group was RM 10,486.00 while nebulize group was RM 12,273.00. Using the values, the cost effectiveness ratio was calculated and was 0.85.

This showed that the treatment average-based cost for group MDI is 15% more cost effective in comparison to nebulizer, with actual monetary difference to be RM 1,787.00 average per patient. This can be calculated further to determine the total monetary cost for the service provider over 1 fiscal year where the total will be available. In summary, the treatment using MDI is more cost-effective than using nebulization alone. Healthcare providers may utilize the results in reducing total overall costs for both hospital and patients.

DISCUSSION

During the Covid-19 pandemic, MDI with spacer was utilised to deliver inhaled Salbutamol for the needful patients and the dosage were 4 to 6 puff for less than 6 years old and 6 to 12 puffs for those more than 6 years old (100 µg per puff). Prior to the covid pandemic, nebulise Salbutamol was the mainstay method. This primarily owing to the in-charge ward doctors were more comfortable with the nebuliser and parents required to buy the spacer or valve holding chamber (VHC). Whilst for the nebuliser, all the cost were bear by the hospital. Consequently, many parents'

reluctance to buy the spacer or VHC. This created two groups of cohorts that utilised different mechanism to delivered B2- agonist though at different period.

The study showed that, in these 2 years old or more children, there was no significant difference in LOS in the ward between wheezing children who predominantly used MDI and spacer with rescue nebuliser compared to those who mainly used nebuliser (t = - 1.29, p = 0.02) albeit at lower cost (RM10,486.00 vs RM12,273.00). In a random clinical trial (RCT) in 60 children less than 5 years old with moderate acute exacerbation bronchial asthma, no difference in duration of stayed in the ward between children used MDI against children with nebuliser (13). Another retrospective study in older asthmatic children aged between 3 to 12 years old also has similar outcome (14). Unfortunately, there were not many studies that scrutinized the LOS as the outcome and the data mainly in asthmatic children though bronchospasm could be manifested in any lower respiratory tract infections in children (15). This may because of brief duration of admission in these children and that merely of a few days (in this study, both group mean is around 2 days with SD also around 1-2 days). The actual difference between the groups was of a few hours. Though it was statistically significant, it may not be clinically relevant or have much impact in everyday life. Regardless, the study objective is to demonstrate equivalent, and the conclusion is using MDI with spacer in treatment of bronchospasm was not inferior compared to nebuliser alone in respect of LOS in the ward. Metered-dose inhaler has a shorter preparatory and delivery time than nebuliser when were to be given to the patients thus benefited the nursing staff (16). Deerojanawong et al has demonstrated there were no significant differences in lung function test in children less than 5-year-old who are wheezing either they inhaled 2 puffs of salbutamol or 0.15 mg/kg nebulised salbutamol. For this group of children, the researchers calculated pulmonary function parameters derived from flow volume loops (volume to peak tidal expiratory flow over total expiratory volume, V(PTEF)/V(E); time to peak tidal expiratory flow over total expiratory time, T(PTEF)/T(E); and ratio of tidal expiratory flow at 25% remaining expiration to peak expiratory flow, 25/PF), compliance (Crs), and resistance (Rrs) of the respiratory system (17).

Alhaider et al. showed cost reduction in medications for both B2 agonist (30 %) and inhaled steroid (87%) when delivered with MDI rather nebuliser in admitted wheezing children (16). Usage of MDI for treatment of bronchospasm ensue lower in cost in emergency department (18-19). In Colombia, MDI for acute asthma broadly result in lowering the average medical cost per patient (USD 96.68 vs. USD121.41). Additionally, the difference could be more considerable when considering the probability of being admitted is lower in MDI patients (0.8900 vs 0.9219) (20). Anyhow, the study was based on analysis of decision-analysis model to estimate cost effectiveness rather real cost calculation. The study excluded children below than 2 years old of age as many of these children suffered acute bronchiolitis. The effect of acute bronchiolitis to B2-agonist were capricious though it alluded to not responding (21). Hence, the final analysis could be biased if one of the groups has more under 2 years old children. The nebuliser group has more variables to indicate it may contain higher number of severe cases (using accessory muscle, interrupted feeding). This was an expected phenomenon amid the lock down, there were decreased admission to the ward with less severe cases (22). However, after analysing the PRESS score, the overall severity between the groups were no differences. The nebuliser group significantly utilised chest physio, started on montelukast, antimuscarinic medication, and longer period of illness before admitted. This was linked to pre-Covid-19 disease management wherein little fear in the HCW regarding disease transmission as during Covid-19 period. Parents also tend to wait a few days before brought their children to the hospital during pre-Covid-19 unlike during pandemic whereby parents would immediately seek treatment once symptoms emerged. The nebuliser children were as expected inhaled significantly higher dose of Salbutamol and have higher heart rate though it was no significant differences. In one previous study, the nebuliser group has significant higher heart rate than children with MDI-spacer (17). The study included small children aged less than 2 years whereas our study excludes them. Small children have been shown could have mark increased in heart rate when exposed to B2-agonist (21). A meta-analysis indicated nebuliser albuterol has slightly higher risk of increased in heart rate (MD −6.47; 95% CI, −11.69 to −1.25; I2 = 0%; p = .02), but no difference in nausea, palpitations, and tremor (23). The same meta-analysis which included 15 studies (n = 2057) concluded there was no significant differences in terms of hospital admission (relative risk, 0.89; 95%, CI, 0.55-1.46; I2 = 32%; p = 0.65) between the two albuterol delivery methods. Sixty-one percent of the MDI group received rescue therapy with nebuliser, and it was dictated by clinical decision. This notably because of clinical deterioration at the early stages of the disease and most of these children were given for a few times only thus will not influence the outcome. This was with the viewed of inadequate data on MDI usage during severe wheezing episodes especially in small children. These children have very poor tidal volume, therefore there was a possibility of inadequate medication delivered during this critical period if MDI was utilised. These children also needed to be served with oxygen continually.

Additional aspects when using MDI-spacer that the user must be aware included the importance of proper sealed between the spacer and the mouth, decrease deposition of medication in airway in fighting and crying child, optimising medication dose by given one dose at a time and an effective spacer

or VHC that made of anti-electrostatic material (24). The study is a retrospective study with data collected from the case note. The incomplete data especially due to incomplete documentation were not included in the study thus excluded some patients. In assessment of the severity, clinical sign such as severity of breathlessness are dependent on the admission doctor's assessment and could be quite subjective.

CONCLUSION

This retrospective study has showed that using MDI with spacer to deliver salbutamol has similar duration in ward stayed with those utilised nebulisers alone but at lower cost. The other possible benefits included aiding reduced transmission of airborne diseases and reducing nursing workloads. Thus, the regular used of MDI in the ward should be encouraged and should become a mainstay.

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