Original Article

Factors Associated with the Use of Continuous Nebulization with Beta$_2$ Agonist in Wheezing Children at Faculty of Medicine Vajira Hospital

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Objective: To identify factors associated with the use of β_2 agonist continuous nebulization in children treated for wheezing.

Materials and Methods: This was a case-control study of children aged 1 to 15 years admitted with wheezing to a general pediatric ward of Faculty of Medicine Vajira Hospital between January 2014 and November 2016. Data of wheezing children were collected from in-patient charts. Characteristic features of who had continuous nebulization (case) were compared to those who had intermittent nebulization (control).

Results: One hundred children (25 cases, 75 controls) were included in the present study. Oxygen saturation <95% on admission and systemic corticosteroids use were independent risk factors for continuous nebulization with odds ratio [OR] of 5.26 (95% CI: 1.86 to 14.83, $p = 0.002$) and 20.00 (95% CI: 1.92 to 99.98, $p = 0.012$) respectively. Subgroup analysis of participants in recurrent wheezing children (n = 43), only oxygen saturations <95% was an independent risk factor for continuous nebulization with OR of 24.66 (95% CI: 3.70 to 164.62, $p = 0.002$).

Conclusion: Oxygen saturations <95% on admission and systemic corticosteroid use were independent risk factors for continuous β_2 agonist nebulization in wheezing children.

Keywords: β_2 agonist continuous nebulization, Wheezing, Risk factors

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Dyspnea is an emergency condition in children that requires immediate medical treatment. The main cause of dyspnea is lower airway obstruction which can be triggered by a number of factors. The signs and symptoms are breathing with a whistling or rattling sound in the chest, known as wheezing.

Many factors are known to contribute to wheezing in childhood. Common pathologic factors are respiratory tract infection and allergens. Infectious agents may differ in each age group. In children younger than 1 year old, respiratory syncytial virus [RSV] infection has been identified as a significant cause of wheezing[1]. In children aged 1 to 3 years, rhinovirus is more common pathogen[1]. In children older than 1 year, respiratory infection or frequent exposure to allergens or other stimulants, such as, cigarette smoke are prominent factors[1]. One study found that 58% of pediatric patients with wheezing symptoms had a family member who was a cigarette smoker[2].

Respiratory viral infection, allergy, and wheezing can cause anatomical changes of respiratory structures and increase the risk of developing asthma in the future[3]. Wheezing can be found in children who suffer from coughing and dyspnea; 24% to 35% of them had chance of being diagnosed with asthma[4].

There were many factors which were associated with the severity of wheezing as well as their respond to treatment. Recognition of these factors are important if that the caregiver can increase awareness so that appropriate treatment can be initiated earlier, reduce the need for ventilator support and to decrease the progression to respiratory failure, or even death.

Previous studies focused more on the

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influencing factors for wheezing or severity of asthma. These features were overweight, history of allergic rhinitis, history of cigarette smoke exposure, an unsanitary household environment, history of inhaled β_2 agonists >4 times within 3 months, duration of symptoms before treatment, and presence of hypoxemia[5-9].

Treatment for wheezing generally depends on its severity. Treatment includes β_2 agonist bronchodilator which can be administered by nebulizer inhalation, or intravenous in severe cases. The nebulizer is generally given by intermittent administration. In children who have severe symptoms or those who have only partial response to the intermittent nebulizer, continuous β_2 agonist would be used[10]. Continuous nebulization significantly improved clinical asthma score and decreased admissions in pediatric asthma patients in the emergency department[11]. One study by Papo et al compared intermittent vs. continuous nebulization among children with impending respiratory failure due to status asthmaticus[12]. The children in the continuous nebulization group had symptoms improved faster, shorter hospital stay, and no different side effects compared to those receiving intermittent treatment[12].

All pediatrician, in our hospitals, in general pediatric ward, generally used β_2 agonist for the patients with wheezing. However, the nebulizer may be administered either intermittent or continuous depending on symptoms, severity, and upon discretion of the pediatrician in charge. Pediatric pulmonologist would in service in difficult cases upon consultation.

Objective

We aimed to identify the factors associated with the use for β_2 agonist continuous nebulization in children admitted with wheezing to our pediatric ward.

Materials and Methods

The present study was approved by the Ethics Committee of the institution. We conducted a case-control study among children who were admitted to the general pediatric ward of the Department of Pediatrics, Faculty of Medicine Vajira Hospital between January 1, 2014 and November 30, 2016. Children were included if they met the following criteria: aged 1 to 15 years, presented with wheezing, and responded to a β_2 agonist nebulization, did not have an underlying disease that might cause wheezing (e.g., heart disease, chronic lung disease, subglottic stenosis), and had data available data.

The children were divided into cases or control (1: 3). Cases were children who received continuous β_2 agonist nebulization treatment whereas controls were children who received β_2 agonist intermittent nebulization treatment. Cases were matched to control by age within 1 year.

Data collection and definitions

Data collected were: demographic data of the patients and related history (gender, obesity, history of allergic rhinitis, history of recurrent wheezing, history of asthma with its severity as well as their family history of asthma), environmental factors (cigarette smoke exposure, RSV infection, and season), pre-hospital prophylaxis or treatment (before and during the current episode), season during admission, oxygen saturations, and presence of any lung infection.

Obesity was assessed by a percentage of reference body weight relative to height (weight-for-height) >140. Overweight was assessed as a percentage of reference body weight relative to height of 120 to 140. Wheezing was breathing difficulty with a whistling sound detected by physical examination by a physician. Recurrent wheezing was defined as an experience of at least one previous episode of wheezing without receiving a diagnosis of asthma. Family history of asthma was defined with their father or mother had history of asthma. Asthma symptom control was categorized as well-controlled, partly controlled, and uncontrolled asthma according to the Global Initiative for Asthma criteria for 2015[13]. Pre-hospital treatment included no treatment, β_2 agonist treatment by either nebulization or metered dose inhaler [MDI], antibiotics or other treatments.

Statistical analysis

Data were analysed by SPSS statistical analysis for Windows version 22.0 (IBM Corp, Armonk, NY). Descriptive data were presented as median and interquartile range or number and percentage. Features associated with the type of β_2 agonist nebulization (intermittent vs. continuous) were determined by univariate analysis. Significant factors from univariate analysis were entered for multivariate analysis by multiple logistic regression, and were presented with odds ratios [ORs] and 95% confidence intervals [CIs]. *p*-value <0.05 was considered as statistical significant.

We also performed subgroup analyses among the wheezing patients with recurrent wheezing, asthma and first wheezing.

Results

Demographic data of cases and controls

During the study period, 100 children met all inclusion criteria. Approximately 66% were males, 25% were obese, 22% had history of allergic rhinitis, 28% had asthma, and only 20% had family history of asthma. Recurrent wheezing was present in 43%. Asthma was diagnosed in 28%: 9% were well-controlled, 16% partly controlled, and 3% poorly-controlled. Pre-hospital prophylactic inhaled corticosteroids or montelukast resulting in complete symptom control were identified in 29% of the patients with recurrent wheezing. Cigarette smoke exposure was recorded in 32%. Nearly half of the wheezing (47%) occurred in rainy season.

Upon hospital admission, 37% of the patients had oxygen saturation <95% on admission, 21% had RSV infection, and 56% had pneumonia. Approximately 55% were treated with β_2 agonists by nebulization or MDI before hospitalization.

Analyses of factors between cases and controls of all patients

The mean ages of 25 cases was 3 years old (IQR, 2 to 5 years) and of 75 controls was 3 years old (IQR, 2 to 4 years). By univariate analysis, we found 3 factors were significantly associated with the use of continuous nebulizer. The ORs were 3.50 (95% CI: 1.09 to 11.22, p = 0.040) for male sex, 16.67 for systemic steroid (95% CI: 2.27 to 100.00, p = 0.006) and 6.07 (95% CI: 2.25 to 16.34, p<0.001) for oxygen saturation <95% on admission. By multivariate analysis, significant factors of continuous nebulizer were systemic steroid use with OR of 20.00 (95% CI: 1.92 to 99.98, p = 0.012) and oxygen saturation <95% on admission with OR of 5.26 (95% CI: 1.86 to 14.83, p = 0.002) whereas male gender was only nearly significant with OR of 3.33 (95% CI: 0.92 to 12.02, p = 0.067). There were no statistically significant difference of other factors between cases and controls (Table 1).

Analyses of factors between cases and controls among patients with recurrent wheezing

Among 43 wheezing children with recurrent wheezing, there was a statistically significant association between rainy season and oxygen saturations <95% on admission and cases (use of continuous nebulization): OR 10.29 (95% CI: 1.74 to 60.90, p = 0.010) for rainy season and 35.50 (95% CI: 4.92 to 201.56, p-value = 0.002) for oxygen saturation <95% on admission (Table 2). Only oxygen saturation <95% remained significant by multivariable analysis, with OR of 24.66 (95% CI, 3.70 to 164.62, p = 0.002).

Analyses of factors between cases and controls among patients with asthma

For the association of pattern of nebulizer used in 28 wheezing children with asthma, There were no statistically significant difference of all factors between cases and controls.

Analyses of factors between cases and controls among patients without previous wheezing

For the association of pattern of nebulizer used in 29 children presented with first wheezing. There were no statistically significant difference of all factors between cases and controls (data not shown).

Discussion

We analyzed data from 100 children with wheezing, aged 1 to 15 years, who were hospitalized to a general pediatric ward to identify factors associated with the need for β_2 agonist continuous nebulization.

We found oxygen saturations <95% on admission and systemic corticosteroids use were independently associated with β_2 agonist continuous nebulization in wheezing children. Previous studies evaluated the risk factors of wheezing or asthma without focusing on the pattern of nebulization. One study by Belessis et al[7] reported the use of intermittent nebulization of β_2 agonist as the initial treatment. In non-responders, the treatment was changed to continuous nebulization and subsequent intensive care admission if failed continuous nebulization. Their study found one among several factors associated with the continuous nebulization and ICU admission was oxygen saturation on present ≤91% which was similar to the present study.

Receiving corticosteroids treatment was significantly associated with cases (β_2 agonist continuous nebulization in wheezing child) in our study. This finding was different from other previous studies which rarely used systemic corticosteroids for preschool children with general episodes of wheezing not diagnostic of asthma[14-17]. Generally, systemic corticosteroids using was reserved to the more severe illness[18,19], so systemic corticosteroids in wheezing children might represent severe symptoms of the patients and the need of β_2 agonist continuous nebulization as found in the present study.

Regarding the history of asthma symptom control, we found no association between the asthma symptom control (good or poor) with β_2 agonist

Table 1. Characteristic features with their odds ratio between the wheezing patients who had continuous (case, n = 25) or intermittent b2 agonist nebulizer (control, n = 75)

General characteristics/ factors	Cases (n = 25)	Controls (n = 75)	Univariate		Multivariate	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Median age, year (Q1-Q3)	3 (2 to 5)	3 (2 to 4)	NA	NA	NA	NA
Gender: male	21	45	3.50 (1.09 to 11.22)	0.040	3.33 (0.92 to 12.02)	0.067
Overweight and obesity	3	22	0.33 (0.09 to 3.36)	0.605	NA	NA
Family history of asthma	3	17	2.15 (0.57 to 8.06)	0.257	NA	NA
History of allergic rhinitis	5	17	0.85 (0.28 to 2.61)	0.780	NA	NA
Prophylactic medication:						
Inhaled corticosteroid	6	17	0.93 (0.32 to 2.69)	0.891	NA	NA
Montelukast	2	5	0.82 (0.15 to 4.52)	0.821	NA	NA
Hx of wheezing/ asthma:						
None	4	25	1.00	NA	NA	NA
Recurrent wheezing	13	30	2.71 (0.78 to 9.36)	0.115	NA	NA
Well-controlled asthma	2	7	1.79 (0.27 to 11.86)	0.548	NA	NA
Partly controlled asthma	4	12	12.50 (0.91 to 172.08)	0.353	NA	NA
Uncontrolled asthma	2	1	2.08 (0.44 to 9.79)	0.059	NA	NA
β_2 agonist treatment before hospitalization	14	41	0.99 (0.40 to 2.48)	0.989	NA	NA
Systemic corticosteroids use	24	43	16.67 (2.27 to 100.00)	0.006	20.00 (1.92 to 99.98)	0.012
Smoking exposure	8	24	1.00 (0.38 to 2.64)	1.000	NA	NA
Seasons:						
Winter	6	29	1.00	NA	NA	NA
Summer	4	14	1.38 (0.33 to 5.70)	0.655	NA	NA
Rainy	15	32	2.27 (0.78 to 6.62)	0.135	NA	NA
Oxygen saturation <95% on admission	14	13	6.07 (2.25 to 16.34)	<0.001	5.26 (1.86 to 14.83)	0.002
RSV infection	4	17	0.71 (0.43 to 4.05)	NA	NA	NA
Pneumonia	16	40	1.50 (0.72 to 5.30)	0.550	NA	NA
Antibiotics use	16	30	NA	0.182	NA	NA

CI = confidence interval, NA = not applicable, OR = odds ratio

continuous nebulization. This result was consistent with the report of Belessis et al[7] in children that history of asthma control was not associated with the severity of current asthma attack or the use of continuous nebulization and ICU admission.

Although other studies reported the association of RSV infection, obesity, season, history of smoking exposure, family history of asthma, familial allergic rhinitis, and pneumonia and wheezing or asthma, the present study could not demonstrate such associations. This might be due to small number of patients in the present study.

Regarding the wheezing children with recurrent wheezing, we found only oxygen saturations <95% on admission was associated with β_2 agonist continuous nebulization which was consistent with previous report[7].

The present study had some limitations aside from the small number of patients. Not all inciting factors were analyzed i.e. other viruses such as rhinovirus that affected patients aged 1 to 3 years suffered wheezing. Our wheezing patients might actually be ultimately diagnosed as asthma, the overlapping of diagnosis may actually represent the spectrum of symptoms and illnesses and the diagnosis of wheezing in our patients might be an underestimation.

Conclusion

Oxygen saturation <95% on admission and systemic corticosteroids using were risk factors for β agonist continuous nebulization in wheezing children. We also found that oxygen saturations <95% on admission was risk factor for β_2 agonist continuous nebulization in cases presenting with recurrent (non-

Table 2. Analysis of factors associated with the use of continuous β_2 agonist nebulization in patient with recurrent wheezing who had continuous (case, n = 13) or intermittent β2 agonist nebulizer (control, n = 30) (n = 43)

Factors	Cases (n = 13)	Controls (n = 30)	Univariate		Multivariate	
			OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Gender: male	10	19	1.93 (0.44 to 8.55)	0.387	NA	NA
Overweight and obesity	2	10	0.36 (0.07 to 1.97)	0.240	NA	NA
Family history of asthma	0	5	NA	0.301	NA	NA
History of allergic rhinitis	3	6	1.20 (0.25 to 5.77)	0.820	NA	NA
Prophylactic medication:						
Inhaled corticosteroid use	0	1	NA	1.000	NA	NA
Montelukast use	0	0	NA	1.000	NA	NA
Treatment before hospitalization: β_2 agonist	5	18	0.42 (0.11 to 1.58)	0.199	NA	NA
Systemic corticosteroids use	12	20	1.38 (0.28 to 4.55)	0.78	NA	NA
Smoking exposure	7	11	2.01 (0.54 to 7.54)	0.298	NA	NA
Seasons:						
Winter	2	18	1.00	NA	NA	NA
Summer	3	5	5.40 (0.70 to 41.75)	0.106	NA	NA
Rainy	8	7	10.29 (1.74 to 60.90)	0.010	3.01 (0.51 to 17.86)	0.225
Oxygen saturation <95% on admission	9	2	35.50 (4.92 to 201.56)	<0.001	24.66 (3.70 to 164.62)	0.002
RSV infection	2	2	2.55 (0.32 to 20.38)	0.379	NA	NA
Pneumonia	10	15	3.33 (0.77 to 14.58)	0.110	NA	NA
Antibiotics use	10	12	NA	0.75	NA	NA

CI = confidence interval, NA = not applicable, OR = odds ratio

asthma) wheezing. Further study in larger cohorts is required.

What is already known on this topic?

Continuous nebulization significantly improved clinical asthma score faster and decreased admissions in pediatric asthma patients in the emergency department than those receiving intermittent treatment.

What this study adds?

Factors associated with the use of continuous nebulization in wheezing children were oxygen saturation <95% on admission and systemic corticosteroids use. These features in wheezing children should raise an awareness of disease severity and prompted the clinicians to consider the use of β_2 agonist continuous nebulization earlier in their treatment.

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Potential conflicts of interest

The authors declare no conflict of interest.

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