Sys Rev Pharm 2020;11(9):905-912
A multifaceted review journal in the field of pharmacy

Evaluation the Effect of Pulmicort Inhalation on Children with Acute Asthma Attack

Ahmad Bahrami [1], Shabahang Jafarnejad [2], Hamidreza khoshnezhad Ebrahimi [2], Seyedeh Mahsa Mahmoudinezhad Dezfouli[2], Rozhin Pahlevani [3*]

[1] Research center of Pediatric Infectious Diseases, Institute of immunology and Infectious Diseases, Ali Asghar Hospital Iran University of Medical Sciences (IUMS), Tehran, Iran
[2] Department of Emergency Medicine, School of Medicine, Iran University of Medical Sciences (IUMS), Ali Asghar Children Hospital, Tehran, Iran
[3]Pediatrician, Iran University of Medical Sciences (IUMS), Ali Asghar Children Hospital, Tehran, Iran

Corresponding Author: Rozhin Pahlevani, Pediatrician, Iran University of Medical Sciences (IUMS), Ali Asghar Children Hospital, Tehran, Iran
Email: Pahlevan.r@iums.ac.ir

ABSTRACT

Background: Asthma is one of the most common chronic diseases in childhood, and acute asthma is the most common emergency and one of the main reasons for hospitalization in children. One in 20 people suffers from asthma around the world.
Objectives: The present study has evaluated the effect of inhaled corticosteroids (Pulmicort), on the symptoms of asthma and hospitalization duration in children with acute asthma attack.
Methods: This study is a randomized clinical trial study had done as a pilot form with a control group (generally 80 children were studied) and is organized as a double blinded. All children have asthma disease and at the first of the study their asthma scores were determined. Then patients are divided into two groups (case and control). Ventolin and hydrocortisone are given to children in both groups. Also, the case group received nebulized budesonide (Pulmicort) and the control received nebulized normal saline (as a placebo).
Results: The mean age among participants is 6.6± 2.8 years old. The difference of sex and age between case and control is not significant. Asthma severity and rate of respiratory between two groups at the first of study were not different too, and both groups were in moderate to severe asthma attack. The differences of wheeze, cough, and distress scores between two groups are significant at 6h, 12h, 24h, and 48h. So that in terms of improving the score of wheezing, cough and respiratory distress in the case group compared to the control group in the mentioned hours are quite significant (P value: <0.001).The difference of hospitalization time between case and control are significant too (P value <0.001), In a way we saw its duration shortened in a case group.
Conclusion: The study showed that budesonide makes the procedure of the treatment faster and it reduces the duration of the hospitalization. The results showed that the effect of budesonide on patient's symptoms was positively considerable. In this study no side effect of inhaled corticosteroid was observed during hospitalization. Therefore, it can be a good choice used for the treatment of acute asthma besides the standard guideline of acute asthma treatment.

Keywords: Asthma, pediatric asthma, Budesonide, Pulmicort, Corticosteroid

Correspondence:
Rozhin Pahlevani
Pediatrician, Iran University of Medical Sciences (IUMS), Ali Asghar Children Hospital, Tehran, Iran.
Email: Pahlevan.r@iums.ac.ir

BACKGROUND

Asthma is one of the most common chronic diseases in childhood, and acute asthma is the most common emergency and one of the main reasons for hospitalization in children. One in 20 people suffers from asthma around the world. Asthma causes significant deaths in about 14% of boys and 10% of girls in childhood (1, 2). About 7 to 23 percent of patients are usually hospitalized with moderate to severe asthma symptoms (3). Asthma is a chronic disease characterized by inflammation of the airways, severe bronchial sensitivity, and airway reconstruction(4). Patients with asthma often experience symptoms such as cough, wheezing, sleep disturbances, and respiratory problems (5). These symptoms can interfere with normal daily activities. One of the important goals of asthma management is to prevent it from getting worse. Proper management of asthma in the form of outpatient treatment can help people attend school and work, as well as reduce the risk of developing asthma. The goal of asthma treatment in children is to achieve asthma control by optimizing lung function, reducing daily and nocturnal symptoms, reducing the limitations of daily activities, and the need for sedative treatment (6). Corticosteroids are very effective in reducing airway inflammation and are widely used in asthma management. Corticosteroids almost effect on all inflammatory mechanisms, including cytokine modulation, production of cytokine (cytokine receptor), inhibition of eicosanoid synthesis, inhibition of eosinophil accumulation, basophil, and other leukocytes in lung tissue, and decreased vascular permeability (7). Systemic corticosteroids include both oral and non-oral steroids that are used for severe asthma attacks. The use of oral drugs has certain disadvantages in childhood. Non-edible use of these drugs is painful and time-consuming in childhood. On the other hand, children may vomit or not take oral steroids, which can significantly delay treatment (8).

Objectives: Clinical trial researches have shown the effectiveness of inhaled corticosteroids in controlling acute asthma versus placebo (9-12). But there are little researches to show that inhaled corticosteroids (Pulmicort), can improve the symptoms of acute asthma

attack in children comparison to other first line asthma drugs and make hospitalization duration shorter. We try to design a pilot study and show how inhaled budesonide (pulmicort) can affect acute asthma symptoms and hospitalization duration in pediatric. regular Cochran's study of inhaled corticosteroids for acute asthma has suggested further studies about this particular issue (9).

METHODS

Study design: This study is a randomized clinical trial study (pilot form) with a control group and is organized as a double blinded. The allocation Concealment was in a randomized block method (4, 6, 8, 10, 12 blocks in each group). The present study was performed on children at Ali Asghar children hospital (Tehran, Iran) in 2020 and the sampling method was performed by accident.

Inclusion criteria: The participants' age range is between 2 and 12 years old and all of them diagnosed as acute asthma attack. None of them have other chronic and specific comorbid diseases.

Exclusion criteria: If the child has a severe acute asthma disease or needs other medical procedures or has a heart problem disease was excluded from the study. Lack of willingness to participate in the study, patients with chronic lung disease other than asthma, and children who have received specific steroid medications over the past 7 days are also were excluded from the study.

Drug Dose:

All children have asthma disease and at the first of the study their asthma scores were determined. All patients with acute asthma attacks are treated through standard asthma treatments which including oxygen and beta-2 agonists and systemic corticosteroids. Then patients are divided into two groups (case and control). The case group received nebulizer budesonide (Pulmicort) and the control received 3 cc of normal saline instead of that (placebo). The dosage of Ventolin is 0.05 mL (2.5 mg) to 0.1 mL (5 mg) (0.03 mL (0.15 mg) × body weight (kg)). The dosage of intravenous hydrocortisone is 40 mg/kg/day. The dosage of inhaled Pulmicort was 0.25 mg every 6 hours and up to 4 mg/day. If the patient's condition worsens, he/she will be transferred to the intensive care unit and will be excluded from the study. Monitoring the patient's condition will be in 6, 12, 24, and 48 hours later after consumption the nebulizing drugs. The patient's clinical score is determined based on their cough (Without/ mild/ moderate/severe), distress (without/ mild/ moderate/severe), and wheeze scores (score 3-0), No symptom (score 0), symptom at the end of exhalation (score 1), symptom at exhalation (score 2), symptom at inhalation and exhalation (score 3). All children were under consideration from the time of hospitalization until discharge from the hospital with cardiopulmonary monitoring and by checking vital sign and their symptoms.

Description of the blinding method: The sealed envelope about the choice of medicine or placebo is in the hands of the nurse of the triage or ward and is randomly assigned to the patients. The patients and the doctor are not aware of the medicine or placebo. The nurse is merely informed of the medicine and placebo. The drug or placebo in the syringe used in a nebulizer by the nurse of triage.

Statistical analysis: Statistical package for social sciences (SPSS v.21, IBM Inc., Chicago, IL, USA) software was used for analyzing the data. Descriptive statistics are used to measure demographic characteristics. Fisher's chi-square and accurate statistical tests will be used to compare groups at the beginning of the study. Wilcoxon will be used to check for changes in asthma scores.

Ethical issue: The study was approved by Iran University of Medical Sciences and written consent was obtained from parents of children. The ethical code is IR.IUMS.FMD.REC.1399.145 and also the IRCT code is IRCT20190106042260N2.

RESULTS

The results show the effect of Pulmicort in case and control groups among children with asthma who referred to Ali Asghar children hospital (Tehran, Iran) in 2020. The mean age among participants is 6.6± 2.8 years old. The difference of sex and age between case and control is not significant (sex P value= 0.799, age P value= 1.000). The difference in asthma severity and rate of respiratory (RR) between case and control group at the first of the study is not different too (RR P value= 0.302 and asthma severity= 0.333), and both of groups were in moderate to severe asthma attack.

The hospitalization time was between 1 to 4 days. About 72.5 % (n=29), 25 % (n=10), and 2.5 % (n=1) of case group were hospitalized for 1, 2, and 3 days, respectively. Also, 7 % (n=3), 42.5 % (n=19), 32.5 % (n=13), and 12.5 % (5) of the control group were hospitalized for 1, 2, 3, and 4 days. So, the difference of hospitalization time between case and control are significant (P value <0.001).

The description of wheeze, cough, and distress scores are shown in tables 2, 3, and 4. The differences of wheeze, cough, and distress scores between two groups were significant at 6h, 12h, 24h, and 48h. So that over time (in 48h after hospitalization) in the case group we saw the complete disappearance of the symptoms of cough and shortness of breath and wheezing, but in the control group the symptoms remained still mild. The progress of cough, wheeze, and distress scores at all steps and in each group are showed in table 5 and 6.

DISCUSSION

The present study has evaluated the effect of pulmicort inhalation on children with acute asthma attack. Based on a study, the prevalence of asthma among Middle Eastern children is 7.53 %(13). Also, another study in Gorgan (Iran), suggested that 7% of children had asthma. The study concluded that the rate of asthma in the Middle east is lower than in developed countries (14). In the United States, in 2010, 1.800.000 people have been referred to the emergency department for asthma problems (Centers for Disease Control, 2014). Patients with asthma often experience symptoms such as cough, wheezing, sleep disturbances, and respiratory problems (5).

Inhaled corticosteroids (ICs) are the fundamental treatment of asthma in adults and children. They are the most effective anti-inflammatory drugs for the treatment of recurrent asthma. Since their introduction in the early 1970s, no other effective drug has been found to treat asthma. Treatment with ICs reduces asthma mortality. Also, research has shown that ICs treatment reduces symptoms, improves lung function, and reduces the severity of asthma (15, 16). Cs treatment reduces the burden of asthma, reduces the number of night awakenings due to respiratory symptoms in children, and this is valuable for children, especially help them to attend the school, sports, and other social activities (17). In most countries, the use of ICs would be recommended for the treatment of persistent asthma. Due to the effectiveness of ICs in moderate to low doses, the risks of side effects are reduced (18). Studies of different populations have shown that one in three children has wheezing at least once before reaching the third year of life, and by the age of 6,

this number has increased by 50 percent (19, 20). Common guidelines recommend that patients with moderate or severe asthma, every 15 to 20 minutes in the first hour, receive three doses of antagonist-β medications inhaled or nebulized with ipratropium bromide (21, 22). Corticosteroids, which are given immediately after admission to the emergency department, reduce admission rate especially in patients with severe asthma (23). The primary treatment for asthma exacerbations is the repeated use of beta-2 agonists and systemic corticosteroids. The treatment for asthma attacks depends on its severity. Beta-2 agonists are initially used alone, and corticosteroids are added if they do not respond quickly and steadily (18). In the United States, when asthma symptoms worsen in a patient, National Heart, Lung, and Blood Instructions (NHLBI) guidelines recommend using a short-acting beta-2 agonist (SABA) without considering current asthma medications (18). Instead, the Global Asthma Guide (GINA) recommends increasing the combined dose of budesonide/formoterol (Symbicort Turbuhaler) (24). Surprisingly, experimental studies have shown that high-dose of Pulmicort (budesonide) can reduce the peak of severity and quickly improve clinical and hospital discharge (25, 26). The side effects of β2-agonists are palpitations, tremor, headache, tachyphylaxis, and metabolic effects (27). Increased risk of cardiovascular death, ischemic heart disease and cardiac failure are side effects of nebulized and oral β_2-agonists (27). One-term use of high-dose inhaled corticosteroid therapy has potential to cause systemic side effects such as impaired growth in children, skin thinning and bruising, cataracts, decreased bone mineral density, and Hypothalamic–pituitary–adrenal-axis suppression (28). It is considerable that none of these side effects were observed in among our patients who received pulmicort inhalation.

In the present study, Ventolin and hydrocortisone are given to children in both groups a standard treatment of asthma attack. Also, the case group received nebulized budesonide (Pulmicort) and the control received 3 cc of normal saline (as a placebo). Patients' symptoms were categorized in 4 groups (without symptoms, symptoms at inhalation and inspiration, symptoms at the end of expiration, and symptoms at the expiration). The results showed that the first wheeze score of case and control group was not different significantly and both of them have mild to moderate asthma symptoms ; however, the symptoms of wheezing after 6 hours at inspiration and expiration in case and control were zero and 45%. Generally, after 12 hours 60% of case group had no symptom of wheezing, while 97.5% of control group had symptoms of wheezing. Also, the first cough score of case and control group was not different significantly. But after 6 hours there was no severe cough in case group whereas 65% of control group had severe cough scores. Finally, after 48 hours no symptoms of cough were observed in case group while 10% of control group were in this condition. It is considered that after 12 hours 97.5% of case group showed no symptoms of distresses while 92.5% of control group had mild distress. After 24 hours all of the patients in case group were out of distress comparison to 87.5% of control groups at the same time. Almost all symptoms in each group (wheezing, coughing, and distress) had significant difference between different steps first time, 6, 12, 24, and 48 hours later.

There are other studies about the effect of budesonide on severe and mild to moderate asthma and some of them compare the effect of this medication to others. An article in 2017 reviewed the scientific evidence of budesonide usage and formoterol for treatment, improvement, and alleviation of severe asthma attacks in outpatients referred to the emergency room. The targets were over 12 years old and were known to have asthma. Most of the articles in this review supported the beneficial effects of budesonide and formoterol in continuing treatment and relieving severe asthma attacks. However, four articles of this review found that the use of budesonide and formoterol at the time of severe asthma attacks did not differ significantly from placebo. Therefore, the use of budesonide and formoterol can be useful in controlling and relieving asthma attacks (29). Another study in 2016 compared the clinical effects of beclomethasone dipropionate and budesonide in the treatment of children with mild persistent asthma. In this study, two randomized, controlled and case children aged 7-15 years were examined. From 85 patients with mild persistent asthma, 42 received budesonide and others received beclomethasone dipropionate at a dose of 400 micrograms per day. Measurement results included changes in FEV1, symptom scores, and side effects. Significant improvement in FEV1 was observed in the budesonide group compared with the beclomethasone dipropionate group at the end of two months of treatment. But in terms of scores, the symptoms and side effects of the two groups did not differ significantly (30). A study in 2010 evaluated patients who were at the age of 5 to 18 years and were randomly assigned to the study. Inhaled Budesonide (200 micrograms/puff) or fluticasone propionate (250 micrograms/puff) was treated for 3 months and two puffs daily. There were two groups: the budesonide group and the fluticasone propionate group. After 3 months, the peak of expiratory flow improved in both groups. In the first month in the Budesonide group, the peak expiratory flow improved more than in the fluticasone propionate group, although the difference was not significant. At the end of the study, the researchers concluded that the improvement in lung function in the budesonide group was faster than in the fluticasone group (31).In 2020 a systemic review and meta-analysis involving 25 studies and 2733 patients show that high doses of ICS, in addition to SCS, reduce the risk of hospital admission in Emergency department for treatment of moderate-to-severe asthma exacerbations(32).

CONCLUSION

The study showed that budesonide makes the procedure of the treatment faster and it reduces the duration of the hospitalization. The results show that the effect of budesonide on patient's symptoms was positively considerable in acute asthma attack. In this study no side effect of inhaled corticosteroid (Pulmicort) was observed. It is recommended to be used along with other routine acute asthma attack treatments. It is suggested that more studies with large sample size and also using other Para-clinic exams such as spirometry done, to obtain more results, and evaluate the long-term side effects of budesonide used in children acute asthma attack.

ACKNOWLEDGEMENT

The authors would like to thank Ali asghar clinical research development center for editorial/search/assistance.

REFERENCES

1. Eder W, Ege MJ, von Mutius E. The asthma epidemic. New England Journal of Medicine. 2006;355(21):2226-35.
2. Subbarao P, Mandhane PJ, Sears MR. Asthma: epidemiology, etiology and risk factors. Cmaj. 2009;181(9):E181-E90.
3. Rabe K, Vermeire P, Soriano J, Maier W. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. European Respiratory Journal. 2000;16(5):802-7.
4. Shabahang Jafarnejad ea. Clinical guidelines on pediatric asthma exacerbation in emergency department, a narrative review. European journal of translational myology. 2010;30(1):8682.
5. Bergeron C, Tulic MK, Hamid Q. Airway remodelling in asthma: from benchside to clinical practice. Canadian respiratory journal. 2010;17(4):e85-e93.
6. Reddel HK, Levy ML. The GINA asthma strategy report: what's new for primary care? NPJ primary care respiratory medicine. 2015;25(1):1-4.
7. Schleimer RP. Glucocorticoids. Their mechanisms of action and use in allergic diseases. Allergy, Principles and Practice, 5th edn. 1998;638.
8. Scarfone RJ, Loiselle JM, Wiley II JF, Decker JM, Henretig FM, Joffe MD. Nebulized dexamethasone versus oral prednisone in the emergency treatment of asthmatic children. Annals of emergency medicine. 1995;26(4):480-6.
9. Edmonds ML, Milan SJ, Camargo Jr CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database of Systematic Reviews. 2012(12).
10. Rodrigo GJ. Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation. Chest. 2006;130(5):1301-11.
11. Guttman A, Afilalo M, Colacone A, Kreisman H, Dankoff J, Group AES. The effects of combined intravenous and inhaled steroids (beclomethasone dipropionate) for the emergency treatment of acute asthma. Academic emergency medicine. 1997;4(2):100-6.
12. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. Academic emergency medicine. 1998;5(3):209-13.
13. Mirzaei M, Karimi M, Beheshti S, Mohammadi M. Prevalence of asthma among Middle Eastern children: A systematic review. Medical journal of the Islamic Republic of Iran. 2017;31:9.
14. Bazazi H, Gharagozlou M, Kassai M, Zahmatkesh H, Parsikia A. The prevalence of asthma and allergic disorders among school children in Gorgan. 2007.
15. Adams NP, Bestall JC, Jones P. Budesonide versus placebo for chronic asthma in children and adults. Cochrane Database of Systematic Reviews. 1999(4).
16. Adams NP, Bestall JC, Malouf R, Lasserson TJ, Jones P. Beclomethasone versus placebo for chronic asthma. Cochrane Database of Systematic Reviews. 2005(1).
17. Steenhuis TJ, Landstra AM, Verberne AA, van Aalderen WM. When Asthma Interrupts Sleep in Children. BioDrugs. 1999;12(6):431-8.
18. National AE, Prevention P. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. The Journal of allergy and clinical immunology. 2007;120(5 Suppl):S94.
19. Hess J, De Jongste J. Epidemiological aspects of paediatric asthma. Clinical & Experimental Allergy. 2004;34(5):680-5.
20. Jew GW. Challenges and healthcare quality improvement strategies for asthma care for preschool children: Boston University; 2016.
21. Camargo Jr CA, Spooner C, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database of Systematic Reviews. 2003(4).
22. Vermeire P, Rabe K, Soriano J, Maier W. Asthma control and differences in management practices across seven European countries. Respiratory medicine. 2002;96(3):142-9.
23. Rowe BH, Spooner C, Ducharme F, Bretzlaff J, Bota G. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews. 2001(1).
24. Health NIo. Global Initiative for Asthma. Global strategy for asthma management and prevention. NHLBI/WHO work shop report. 1995.
25. Nuhoglu Y, Atas E, Nuhoglu C, Iscan M, Ozcay S. Acute effect of nebulized budesonide in asthmatic children. JOURNAL OF INVESTIGATIONAL ALLERGOLOGY AND CLINICAL IMMUNOLOGY. 2005;15(3):197.
26. Sano F, Cortez GK, Solé D, Naspitz CK. Inhaled budesonide for the treatment of acute wheezing and dyspnea in children up to 24 months old receiving intravenous hydrocortisone. Journal of allergy and clinical immunology. 2000;105(4):699-703.
27. Abramson MJ, Walters J, Walters EH. Adverse effects of β-agonists. American Journal of Respiratory Medicine. 2003;2(4):287-97.
28. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respiratory medicine. 2006;100(8):1307-17.
29. Walek S, McDonald A, Wolff R. An Investigation Into the Evidence Behind Budesonide/Formoterol (Symbicort®) Usage in the Outpatient Setting as Reliever Medication for Asthma. 2017.
30. Singh A, Nandan D, Dewan V, Sankar J. Comparison of clinical effects of beclomethasone dipropionate & budesonide in treatment of children with mild persistent asthma: A double-blind, randomized, controlled study. The Indian journal of medical research. 2016;144(2):250.
31. Kuo L-Y, Hung C-H, Tseng H-I, Wu J-R, Jong Y-J, Chu Y-T. Effects of budesonide and fluticasone propionate in pediatric asthma patients. Pediatrics & Neonatology. 2010;51(1):31-6.
32. Kearns N, Maijers I, Harper J, Beasley R, Weatherall M. Inhaled Corticosteroids in Acute Asthma: A Systemic Review and Meta-Analysis. The Journal of Allergy and Clinical Immunology: In Practice. 2020;8(2):605-17.e6.

Table 1. characteristics of case and control groups (descriptions show by number, percent in a group)

	Group 1 (case)		Group 2 (control)	
Sex	Male	29 (72.5%)	Male	30 (75%)
	Female	11 (27.5%)	Female	10 (25%)
Age	2 years old	4 (10%)	2 years old	2 (5%)
	3 years old	4 (10%)	3 years old	4 (10%)
	4 years old	4 (10%)	4 years old	4 (10%)
	5 years old	4 (10%)	5 years old	6 (15%)
	6 years old	4 (10%)	6 years old	4 (10%)
	7 years old	4 (10%)	7 years old	4 (10%)
	8 years old	4 (10%)	8 years old	4 (10%)
	9 years old	4 (10%)	9 years old	4 (10%)
	10 years old	4 (10%)	10 years old	4 (10%)
	11 years old	3(7.5 %)	11 years old	3(7.5 %)
	12 years old	1 (2.5%)	12 years old	1 (2.5%)
Asthma Severity	Moderate	7 (17.5%)	Moderate	4 (10 %)
	Severe	33 (82.5%)	Severe	36 (90%)
Respiratory Rate	50-60	12 (30%)	50-60	8 (20%)
	Upper 60	28 (70%)	Upper 60	32 (80%)

Table 2. Proportion of wheeze score among case and control group in four steps (descriptions show by number (percent in a group)

	Group 1			Group 2			P value
Wheeze Score	First time	Without	0	First time	Without	0	0.55
		End of Exp	0		End of Exp	0	
		Ins and Exp	32 (80%)		Ins and Exp	34 (85%)	
		Exp	8 (20%)		Exp	6 (15%)	
	6h later	Without	0	6h later	Without	0	<0.001
		End of Exp	30 (75%)		End of Exp	0	
		Ins and Exp	0		Ins and Exp	18 (45%)	
		Exp	10 (25%)		Exp	22 (55%)	
	12h later	Without	24 (60%)	12h later	Without	1 (2.5%)	<0.001
		End of Exp	16 (40%)		End of Exp	21 (52.5%)	
		Ins and Exp	0		Ins and Exp	0	
		Exp	0		Exp	18 (45%)	
	24h later	Without	36 (90%)	24h later	Without	0	<0.001
		End of Exp	4 (10%)		End of Exp	35 (87.5%)	
		Ins and Exp	0		Ins and Exp	0	
		Exp	0		Exp	5 (12.5%)	
	48h later	Without	38 (95%)	48h later	Without	7 (17.5%)	<0.001
		End of Exp	2 (5%)		End of Exp	29 (72.5%)	
		Ins and Exp	0		Ins and Exp		
		Exp	0		Exp	4 (10%)	
1- Exp= Expiratory 2- Ins= Inspiratory							

Table 3. Proportion of cough score among case and control group in four steps (descriptions show by number (percent in a group)

	Group 1			Group 2			P value
Cough Score	First time	Without	0	First time	Without	0	1.000
		Mild	0		Mild	0	
		Moderate	6 (15%)		Moderate	6 (15%)	
		Severe	34 (85%)		Severe	34 (85%)	
	6h later	Without	0	6h later	Without	0	<0.001
		Mild	30 (75%)		Mild	0	
		Moderate	10 (25%)		Moderate	14 (35%)	
		Severe	0		Severe	26 (65%)	
	12h later	Without	0	12h later	Without	0	<0.001
		Mild	36 (90%)		Mild	20 (10%)	
		Moderate	4 (10%)		Moderate	30 (75%)	
		Severe	0		Severe	6 (15%)	
	24h later	Without	15 (37.5%)	24h later	Without	0	<0.001
		Mild	25 (62.5%)		Mild	5 (12.5%)	
		Moderate	0		Moderate	35 (87.5%)	
		Severe	0		Severe	0	
	48h later	Without	40 (100%)	48h later	Without	4 (10%)	<0.001
		Mild	0		Mild	21 (52.5%)	
		Moderate	0		Moderate	15 (18.8%)	
		Severe	0		Severe	0	

Table 4. Proportion of distress score among case and control group in four steps (descriptions show by number (percent in a group)

	Group 1 (case)			Group 2 (control)			P value
Distress Score	First time	Without	0	First time	Without	0	0.390
		Mild	0		Mild	0	
		Moderate	9 (22.5%)		Moderate	6 (15%)	
		Severe	31 (77.5%)		Severe	34 (85%)	
	6h later	Without	0	6h later	Without	0	<0.001
		Mild	35 (87.5%)		Mild	2 (5%)	
		Moderate	5 (12.5%)		Moderate	38 (95%)	
		Severe	0		Severe	0	
	12h later	Without	39 (97.5%)	12h later	Without	3 (7.5%)	<0.001
		Mild	1 (2.5%)		Mild	37 (92.5%)	
		Moderate	0		Moderate	0	
		Severe	0		Severe	0	
	24h later	Without	40 (100%)	24h later	Without	35 (87.5%)	0.021
		Mild	0		Mild	5 (12.5%)	
		Moderate	0		Moderate	0	
		Severe	0		Severe	0	
	48h later	Without	40 (100%)	48h later	Without	35 (87.5%)	0.021
		Mild	0		Mild	5 (12.5%)	
		Moderate	0		Moderate	0	
		Severe	0		Severe	0	

Table 5. comparison of Wheeze, Cough, and distress scores of cases (group 1) between four steps (Wilcoxon test was performed)

Criteria group 1	P value	Z
wheeze 6h[1] – wheezing 1*	<0.001	-5.631
wheeze 12h - wheeze 6h	<0.001	-5.058
wheeze 24h - wheeze 12h	0.002	-4.707
wheeze 48h - wheeze 24h	<0.001	-3.162
cough 6h – cough 1	0.031	-5.706
cough 12h – cough 6h	<0.001	-2.449
cough 24h – cough 12h	<0.001	-3.945
cough 48h - --cough 24h	<0.001	-6.726
distress 6h – distress 1	<0.001	-5.734
distress 12h -distress 6h	0.317	-6.070
distress 24h - distress 12h	1.000	-1.000
distress 48h - distress 24h	1.000	.000
1*:at the first, before consuming a drug		

Table 6. comparison of Wheeze, Cough, and distress scores of controls (group 2) between four steps (Wilcoxon test was performed)

Criteria group 2	P value	Z
wheeze 6h[1] - wheezing 1*	<0.001	-4.000
wheeze 12h - wheeze 6h	<0.001	-6.252
wheeze 24h - wheeze 12h	0.001	-3.207
wheeze 48h - wheeze 24h	0.005	-2.828
cough 6h – cough 1	0.033	-2.138
cough 12h - cough 6h	<0.001	-4.707

cough 24h - cough 12h	**0.020**	**-2.333**
cough 48h - cough 24h	**<0.001**	**-4.523**
distress 6h – distress 1	**<0.001**	**-6.000**
distress 12h - distress 6h	**<0.001**	**-6.252**
distress 24h - distress 12h	**<0.001**	**-5.657**
distress 48h - distress 24h	**1.000**	**.000**
1*: at the first, before consuming a drug		