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Evaluation Of The Effectiveness Of Montelukast In Children With Recurrent Obstructive Bronchitis

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Abstract- Background: The objective of the study was to evaluate the effectiveness of montelukast sodium in the treatment and prevention of recurrent obstructive bronchitis in children.

Methods: 80 children aged 1 to 7 years with recurrent obstructive bronchitis were enrolled and randomly divided into 2 groups. Group I (control) included 40 patients who received standard therapy. Group II (main) included 40 patients who received oral montelukast sodium. The effectiveness of the therapy was evaluated by cough relief, sputum separation, RDAI scale, and modified bronchophonography indicator.

Results: Patients who received montelukast had significantly accelerated elimination of cyanosis (by 0.7 days; P<0.05), cough relief (by 0.9 days; P<0.05), disappearance of respiratory failure (by 0.7 days; P<0.05) in comparison with the control group. Positive dynamics of indicator E:I index was observed on average starting from 3 days (P<0.05) until the last day of inpatient treatment (P<0.01) in patients of the main group in comparison with the control group. The anti-relapse effect of montelukast sodium, detected during follow-up of patients for 12 months after discharge, was established, so the frequency of repeated episodes of the disease was 33-59% less frequent in patients of the main group (P<0.01; P<0.001).

Conclusion: Using of montelukast sodium in recurrent obstructive bronchitis in children contributes to significant progress in the dynamics of the disease, leads to a significant decrease in the severity of bronchial obstruction according to the E: I index. The use of the drug causes a decrease in repeated relapses of the disease within 12 months.

Keywords: montelukast sodium, prevention, relapses, obstructive bronchitis, children.

1. INTRODUCTION

Respiratory diseases are a socially significant and most common group of diseases among the child population, occupying a leading place in the structure of the overall incidence of children [3]. The leading role among bronchopulmonary diseases, along with pneumonia and bronchiolitis, belongs to acute bronchitis in children.due to its high prevalence, obstructive nature and recurrent course, early disability and the risk of death, it is a serious problem [5].

Bronchoobstructive syndrome is most common in children with acute obstructive bronchitis and bronchiolitis, but in recent years, the proportion of patients with recurrent obstructive bronchitis has increased [6, 11]. Recurrent obstructive bronchitis is a pathological condition with repeated episodes of bronchial obstruction against the background of acute respiratory infections, which most often occurs in young children, i.e. the period of life in which there

are morphological features of the bronchial tree and increased reactivity of the bronchi to various environmental factors [1].

Over the past 20 years, the relevance of chronicling bronchopulmonary processes has increased significantly, especially among children [10], which is due to the impact of various premorbid and adverse environmental factors, and an increase in the number of frequently ill children. Special attention is paid to recurrent episodes of obstructive bronchitis. Recent studies have revealed a variety of pathogenetic mechanisms involved in the development of bronchoobstructive syndrome in children [16]. Anti-inflammatory drugs are of great importance in the pathogenetic treatment of recurrent bronchial obstructive syndrome in children [14, 19]. Numerous studies and observations show the need for targeted search for infectious agents in chronic or recurrent bronchitis, primarily herpes viruses, followed by appropriate treatment [2]. The most widely used leukotriene receptor antagonist is montelukast sodium, which reduces the symptoms of bronchial asthma and allergic rhinitis in children, provides a bronchoprotective effect, anti-inflammatory effect, and prevents airway remodeling [4]. There are a limited number of studies that indicate the need for phenotyping of respiratory diseases accompanied by bronchial obstructive syndrome for the development of corrective therapy, control of the course, outcome, and prevention of relapses of the disease [12]. There are several studies devoted to investigation of effectiveness of montelukast sodium in bronchial asthma in children [7], but, unfortunately, there are only a few studies examining the effectiveness of antagonists of leukotriene receptors in patients with recurrent obstructive bronchitis in children, what was the relevance of the present work.

2. MATERIALS AND METHODS

We examined children aged 1 to 7 years with recurrent obstructive bronchitis who were treated in the emergency Pediatrics and pediatric intensive care units of the SFRNCEMP. The criteria for hospitalization and recruitment to the study group were as follows: rdai score≥6 points, E:I index score >1.40, ineffective treatment at home for ≥48 hours, adverse background and concomitant diseases. The design was consistent with a randomized controlled clinical trial.

The criteria for exclusion from the observation groups were chronic or congenital diseases of the Central nervous, cardiovascular, and bronchopulmonary systems. A total of 82 patients with recurrent obstructive bronchitis who met the inclusion criteria were included in the study, but 2 patients were excluded during the examination due to the detection of congenital diseases of the vital systems. As a result, 80 patients participated in the study.

Patients were randomly divided into 2 groups. Group I (control) included 40 patients who received standard therapy. Group II included 40 patients who received oral montelukast sodium. The therapeutic dosage of the drug was 0.2 mg / kg / day, the daily dose was prescribed once a day for the entire duration of the disease. As a prevention of repeated episodes of bronchial obstructive syndrome, the drug was prescribed at a dose of 0.1 mg / kg / day, the duration of anti-relapse therapy was 30 days.

Along with clinical and laboratory-instrumental methods of research, the following methods were used: the respiratory disorders scale-RDAI, the saturation method-SpO2, and modified bronchophonography using the E:I index method, which made it possible to objectively assess the severity of bronchial obstruction.

The effectiveness of the antileukotriene drug was evaluated based on objective signs of cough and sputum. Assessment of the severity of cough in patients was evaluated by a point system: 0 points - no cough, 1 point-a single cough, 2 points-cough is moderate and 3 points-frequent,

painful cough, and sputum discharge was evaluated as follows: 0 points - no sputum, 1 point - it departs easily, 2 points - it departs hard and 3 points – viscous inseparable sputum.
Additional criteria for the effectiveness of therapy were the duration of oxygen therapy and the duration of hospitalization. The child's condition, along with the clinical examination, was evaluated daily before and 60 minutes after inhalation according to the studied parameters.
Management of patients was carried out in accordance with the specifics of the Emergency medical service, diagnostic and treatment standards (recommended deadlines for inpatient treatment of bronchopulmonary diseases were observed). The discharge criteria were: satisfactory condition, SpO2.

Ethical Consideration
The study was approved by the Medical Ethics Committee of the Ministry of Health of the Republic of Uzbekistan in accordance with the Declaration of Helsinki. Both informed and written consents were obtained from the parents or from appropriate relatives or guardians of the patients and healthy individuals of the control group. The trial is registered at the US National Institutes of Health (ClinicalTrials.gov ID NCT04613180. 03.11.2020).

3. RESULTS

The main indicators of patients of the compared groups at admission to the hospital were analyzed and compared. The analysis showed that the patients selected in the main and control groups were comparable in terms of gender, age, and address indicators (table 1). also, patients in both groups compared had parity in the number of attacks of bronchial obstruction over the past 12 months and in the severity of bronchial obstruction at admission.

Table 1. Baseline characteristics of patients with recurrent obstructive bronchitis on admission to the hospital (M±m)

Characteristics	Group I (n=40)	Group II (n=40)	P-value
Gender			
Male n (%±m)	24 (60±7,8)	22 (55±7,9)	>0,5
Female n (%±m)	16 (40±7,8)	18 (45±7,9)	>0,5
Age			
1-3 years n (%±m)	17 (42,5±7,8)	15 (37,5±7,7)	>0,5
4-5 years n (%±m)	16 (40,0±7,8)	20 (50±7,9)	>0,5
>5 years n (%±m)	7 (17,5±6,0)	5 (12,5±5,2)	>0,5
Average (%±m)	3,2±0,3	3,1±0,3	>0,5

Residence address			
Urban n (%±m)	17 (42,5±7,8)	19 (47,5±7,9)	>0,5
Rural n (%±m)	23 (57,5±7,8)	21 (52,5±7,9)	>0,5
Degree of bronchial obstruction at admission			
I degree of bronchial obstruction n (%±m)	14 (35±7,5)	15 (37,5±7,7)	>0,5
II degree of bronchial obstruction n (%±m)	21 (52,5±7,9)	22 (55±7,9)	>0,5
III degree of bronchial obstruction n (%±m)	5 (12,5±5,2)	3 (7,5±4,2)	>0,5
Number of bronchial obstruction episodes during last 12 months			
<3 n (%±m)	3 (7,5±4,2)	2 (5±3,5)	>0,5
3-5 n (%±m)	31 (77,5±6,6)	29 (72,5±7,1)	>0,5
>5 n (%±m)	6 (15±5,7)	9 (22,5±6,6)	>0,5
Average (M±m)	4,3±0,3	4,5±0,3	>0,5
Disease duration			
Up to 1 year n (%±m)	3 (7,5±4,2)	2 (5±3,5)	>0,5
1-2 years n (%±m)	14 (35±7,5)	17 (42,5±7,8)	>0,5
>2 years n (%±m)	23 (57,5±7,8)	21 (52,5±7,9)	>0,5
Average duration (M±m)	1,8±0,2	1,7±0,2	>0,5

Note: P-value –significance of differences between group I and group II indicators

We conducted a comparative analysis of the main clinical indicators of patients (table 2). During the comparison of clinical data on admission, no significant differences were found both in clinical criteria (cough and sputum in points, the intensity of wheezing, the degree of participation of auxiliary muscles in the act of breathing), and in the main instrumental and functional indicators of bronchial obstruction (saturation, rdai score, E:I index). It was noted that the indicators shown in table 2 indicate both the need for hospitalization and emergency medical and diagnostic measures, and the same severity of the patient's condition at

admission. The revealed relative equality of severity of key clinical manifestations of recurrent obstructive bronchitis in both study groups emphasized the high objectivity of the selection of patients and the study as a whole.

Table 2. Clinical characteristics of the examined patients upon admission to the hospital (M±m)

№	Clinical characteristics	Group I (n=40)	Group II (n=40)	P-value
1.	Saturation	93,8±0,8	94,2±0,7	>0,5
2.	RDAI scale	8,5±0,5	8,3±0,6	>0,5
3.	E:I index	1,6±0,1	1,6±0,1	>0,5
4.	Cough (in points)	1,7±0,1	1,6±0,1	>0,5
5.	Sputum (in points)	1,5±0,1	1,6±0,1	>0,5
6.	Wheezing during inhalation (points)	1,2±0,1	1,3±0,1	>0,5
7.	Wheezing during exhalation (points)	1,5±0,1	1,4±0,1	>0,5
8.	Number of involved lung fields (points)	1,7±0,1	1,6±0,1	>0,5
9.	Retractions of subclavian spaces (points)	1,5±0,1	1,6±0,1	>0,5
10.	Intercostal space retractions (points)	1,6±0,1	1,5±0,1	>0,5
11.	Retractions of subcostal spaces (points)	1,4±0,1	1,3±0,1	>0,5

Note: P-value –significance of differences between group I and group II indicators

When comparing the indicators of the clinical course of the disease in patients of group I and II, it was noted that in General, clinical symptoms were resolved faster in patients who received oral montelukast sodium in addition to standard therapy (table 3). Thus, the General condition significantly improved faster by an average of 1.1 days (P<0.01), cyanosis of the skin and mucous membranes disappeared 0.7 days faster in patients of group II compared to group I (P<0.05). Cough was stopped significantly longer in patients with recurrent obstructive bronchitis who received standard therapy without montelukast sodium compared to patients in group I for an average of 0.9 days (P<0.05). In our study, the relief of respiratory failure with standard therapy in patients occurred on average 0.7 days slower than in group II (P<0.05).

Physical changes in the lungs, when compared, did not show any significant significant differences (P>0.5), only on average 0.3 days faster normalized in patients receiving oral montelukast sodium in comparison with standard therapy. In the end, the use of the drug led to a significant reduction in the duration of inpatient treatment, since group I patients were in the clinic for an average of 1.1 bed days longer compared to group II patients (P<0.01).

Table 3. Dynamics of normalization of clinical symptoms (M±m)

№	Symptome	Time of disappearance (in days)		P-value
		Group I (n=40)	Group II (n=40)	
1.	**Normalization of the state**	5,7±0,3	4,6±0,3	<0,01
2.	Elimination of cyanosis	4,3±0,2	3,6±0,2	<0,05
3.	**Relief of cough**	6,1±0,4	5,2±0,4	<0,05
4.	Respiratory failure	4,3±0,3	3,6±0,3	<0,05
5.	Physical changes in the lungs	5,8±0,2	5,5±0,3	>0,5
6.	**Tachypnea**	3,8±0,2	5,1±0,3	<0,001

7.	The duration of hospital stay	5,1±0,3	6,2±0,3	<0,01

Note: P-value –significance of differences between group I and group II indicators

To objectively evaluate the effectiveness of oral administration of montelukast sodium, we studied the dynamics of the e index:I index by modified bronchophonography (table 4). The study showed that patients who received the proposed drug orally had a faster normalization of the ratio of exhalation to inhalation duration in comparison with patients who were on standard therapy. A significant difference in the ratio of exhalation to inspiration began to be observed on average starting from 3 days of treatment until the end of observation.

Table 4. Dynamics of indicator E:I index (M±m)

Groups	Day 1	Day 2	Day 3	Day 4	Day 6
Group I	1,64±0,10	1,58±0,06	1,48±0,05	1,42±0,03	1,29±0,03
Group II	1,63±0,10	1,52±0,07	1,34±0,06*	1,21±0,04**	1,08±0,02**

Note: P-value –significance of differences between group I and group II indicators

To determine the effectiveness of montelukast sodium in the prevention and prevention of recurrent bronchial obstruction, we conducted a comparative follow-up of patients for 12 months after discharge from the hospital. The study showed (table 4) that there was a significant reduction in the frequency of development of relapses in the group of patients treated with montelukast sodium in a dose of 0.1 mg/kg/day after discharge from the hospital, so for the first 3 months there was a reduction in the frequency of relapses by 30% on average (P<0.01), between 4 and 6 months, the decline lasted on average 33% (P<0.001). Observation of patients in the period from 7 to 9 months after discharge from the hospital showed a further decrease in the frequency of relapses of the disease by an average of 59% (P<0.001) in patients receiving montelukast sodium in comparison with the control group, from 10 to 12 months – a decrease of 55% in patients of group II.

Table 5. Comparative analysis of the frequency of relapses after treatment

The period of second follow-up examination after discharge from the hospital	Relapse frequency		P-value
	Group I	Group II	
First 3 months	0,76±0,08	0,58±0,04	<0,01
4-6 months	1,72±0,11	1,29±0,07	<0,001
7-9 months	2,95±0,15	1,85±0,12	<0,001
10-12 months	3,46±0,17	2,22±0,08	<0,001

Note: P-value –significance of differences between group I and group II indicators

4. DISCUSSION

According to the results of our study, there was a significant clinical effectiveness of oral administration of montelukast sodium in patients with recurrent obstructive bronchitis in comparison with patients who received standard therapy (table 3), which in our opinion is associated with the effect of the drug on all parts of the inflammatory response. The results of our study are quite consistent with a number of international randomized clinical trials. Thus,

the study Hussein HR, Gupta A (2017) analyzed the effect of a 12-week course of montelukast sodium on the parameters of external respiration, indicators of bronchial reactivity, and markers of eosinophilic inflammation in children with atopic and non-atopic asthma and a repeated episode of bronchitis combined with allergic rhinitis [9]. The study included 69 children aged 3 to 16 years. The results of the study showed that montelukast sodium significantly reduces the Hyper-airiness of the lung tissue, eliminates obstructive ventilation defects, restores the sensitivity of the bronchial receptor apparatus, and controls the activity of eosinophilic inflammation. In children with non-atopic asthma, the positive effect on the studied parameters was maximal, including complete restoration of ventilated volumes. In a study by Visitsunthorn N. et al. (2011) a randomized clinical trial of antileukotriene drugs was conducted, which showed their high effectiveness in the treatment of hyperreactivity and allergic bronchial inflammation in children with bronchial asthma [17]. Our objective assessment of the indicators of external respiratory function (modified bronchophonography using the E:I index method) showed (table. 4) that the use of montelukast sodium leads to a significant reduction in the long expiratory phase on average from the 3rd day of treatment in children with recurrent obstructive bronchitis in comparison with patients receiving standard therapy. The identified positive effect of the drug is also confirmed in a number of studies, so in the work of Hoshino M. (2019) obtained data indicating the comparative effectiveness of montelukast sodium in comparison with inhaled bronchodilators (atrovent) [8].

In our study, we noted the high effectiveness of low dosages of montelukast sodium (0.1 mg / kg / day) in preventing relapses of the disease (table. 5) on average by 30-59% during the first 12 months after discharge from the hospital ($P<0.01$; $P<0.001$), which was apparently associated with high anti-inflammatory activity of the drug, leading to a decrease in hyperreactivity of small-caliber bronchi in children. Our data on the high anti-relapse activity of the leukotrietriene receptor antagonist is also consistent with global data. Similar results were obtained in the study of Massingham K., Fox S., and Smaldone A. who studied the comparative effectiveness of basic therapy with montelukast and inhaled glucocorticosteroid fluticasone in prolonged forms of bronchoobstructive syndrome in children, which also showed the advantage of leukotriene receptor antagonists in preventing relapses of the disease [13].

There are also numerous studies on the effects of montelukast. Thus, the study by Wang X. et al. (2019) summarizes current data on the role of leukotrienes in the pathogenesis of allergic diseases of the respiratory tract, in particular bronchial asthma in children [18]. In the article Zhang YF defined the role of antileukotriene drugs, noted the prospects and key indications for the use of montelukast in the treatment of bronchial asthma and allergic rhinitis in children [20]. The Peng WS study presents data on the significance of infection in the formation of bronchoobstructive syndrome in children [15]. Special attention is paid to recurrent episodes of obstructive bronchitis. Numerous studies and observations show the need for a targeted search for infectious agents in chronic or recurrent bronchitis, primarily herpes viruses, followed by appropriate treatment. Leukotriene receptor antagonists (montelukast) have a fairly active anti-inflammatory effect, which is often necessary for bronchitis.

The analysis of multicenter studies has shown that a number of authors who conducted a study of the effectiveness of oral use of montelukast sodium in the treatment and prevention of frequent cases of bronchial obstructive syndrome in children agree on the importance of a leukotriene receptor antagonist in patients with recurrent bronchial obstruction.

5. CONCLUSION

The study of the course of recurrent obstructive bronchitis in children showed that there is certainly a large contribution of endogenous and exogenous risk factors in the formation of the recurrent course of the disease. To determine the criteria for adequate pharmacotherapy, its schemes and methods, it is necessary to influence the main markers of allergic inflammation in the lower respiratory tract, which are an urgent task, the solution of which will optimize the control of repeated episodes of the disease and improve the quality of life of patients.

The analysis of the latest global studies devoted to the analysis of the effectiveness of the use of montelukast sodium in the treatment and prevention of children with recurrent forms of bronchial obstructive syndrome and bronchial asthma showed in some cases good results, indicating a certain positive effect of the drug. The revealed effectiveness of oral administration of montelukast sodium in preventing repeated episodes of recurrent obstructive bronchitis in our study is apparently due to the pronounced anti-inflammatory, anti-allergic properties of this group of drugs, which certainly contributes to a decrease in the reactivity of the bronchi, bronchioles and the respiratory tract as a whole, which ultimately reduces the overall incidence among this category of patients.

Thus, oral use of montelukast sodium in recurrent obstructive bronchitis in children contributes to significant progress in the dynamics of the disease, leads to a significant decrease in the severity of bronchial obstruction according to the E: I index. The use of the drug causes a decrease in repeated relapses of the disease within 12 months, which allows us to conclude that there is a certain advantage of montelukast sodium as a preventive tool for preventing the development of chronization of bronchoobstructive syndrome and further transformation of the disease into bronchial asthma.

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