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EFFICACY OF MONTELUKAST ADDED TO INHALED BUDESONIDE IN COMPARISON OF INHALED BUDESONIDEON CONTROL OF MILD TO MODERATE ASTHMA IN CHILDREN

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ABSTRACT

Background: While Guideline recommends daily treatment of corticosteroids to control asthma symptoms, Montelukast, a leukotriene receptor antagonist, is effective in treating asthma symptoms. **Objective:** To test the hypothesis that combined administration of multiple doses of inhaled Budesonide and oral montelukast provides additional benefit compared with Budesonide alone in children patients with mild and moderate severity of persistent asthma. **Methods**: An open Randomized trails study included 120 patients presenting to the clinic at Tishreen University Hospital over one year from March 2020 to March 2021. The patients were randomized to two equal groups: inhaled Budesonide only (group A) and inhaled Budesonide with oral montelukast (group B) by inhalation chamber over 12 weeks. All clinical variables by fill out a questionnaire, pulmonary functions (PEF, FEV1) were recorded at the baseline, 6, and 12 weeks. **Results:** The results showed that adding Montelukast to inhaled Budesonide improves the FEV1, PEF values, and quality of life (decrease the use of beta 2 agonists, the frequency of asthma symptoms, the night symptoms, and the defines activate with a significant difference. **Conclusion:** This study suggests that there is a therapeutic benefit of adding Montelukast to inhaled Budesonide in the treatment of patients with mild and moderate severity of persistent asthma

KEYWORDS: Montelukast, inhaled Budesonide, persistent asthma, mildand moderate severity.

INTRODUCTION

Asthma is one of the most common chronic childhood conditions in the world Health Organization (WHO) study, asthma affects more than 300 million people worldwide. 6.1 million of them are under 18 years.[1] Asthma increased annually, it is estimated that asthma patients will receive to 400million people in 2025.[2] Inhaled Budesonide (IB) is the first, most effective treatment in persistent asthma of all degrees and ages.[3] IB inhabits the excessive inflammatory response, reduce the number of inflammatory cells in the airways. Besides, it counteracts the structural changes caused by asthma (Remodeling process).[4] The cysteinyl leukotriene (LCT4, D4, E4) are important inflammatory mediators in many pathophysiological changes in the lungs including airway, hyper- irritation, increased secretion, reduced ciliary activity, and enhanced eosinophilia into the respiratory tract.[5] Anti Cys LTs as Montelukast has an important role in managing asthma by the act on a point in the inflammatory chain.[6] Some studies have shown that the use of inhaled steroids leads to significant side effects such as a decrease in growth velocity during the first year of treatment, inhibition of hypothalamic-pituitary-adrenal axis, ophthalmic effects, hoarseness, and oral mycoses.[7]

The aim of the study to evaluate the effectiveness of the sharing between oral Montelukast and inhalation of Budesonide in improving pulmonary functions (FEV1, PEF) in children with mild and moderate severity of persistent asthma.

MATERIAL AND METHODS

The current study was reviewed and approved by the

ethical committee of Tishreen University Hospital. Informed consent wasobtained from the patient's parents.

✓ **Eligibility criteria**

An open randomized label trial study included children aged 6-15 years with mild and moderate severity of persistent asthma diagnosed depending on GINA 2020 and NHBI guidelines (frequently of symptoms, impact on quality of Life, FEV1 over 60%, reversibility test after bronchodilator more than 13%) who referred to the pediatric clinic at Tishreen University Hospital over one year from March 2020 to March 2021. Inclusion criteria included cardiac malformations, chronic pulmonary disease, past treatment with corticosteroid or other asthma therapy over one month before, and presence of any sense of the drug component.

✓ **Initial management and assessment**

On arrival in the Pediatric Clinic, a detailed history was taken and clinical examination, length, and weight were performed to rule out any associated illness. Any medications received by the patient within 1 month of their visit were noted. Questionnaire (from 0 worse to 20 normal) was filled out by the parents to assess the asthma score and its effect of life quality during the previous 4 weeks.

The degree of spam (PEF, FEV1) was accessed by spirometer which recorded as the best of the three readings using a Vitalograph model 6000 Alpha. The same instrument was used throughout the study. After 20 minutes of bronchodilator (salbutamol) inhalation, the reversibility test was done to evaluate the severity.

✓ **Randomization and medications**

After enrolment patients were randomly allocated to one of the two study groups. We used random number tables for the randomization. The medications were constituted in both groups as follows.

Group A: received inhaled Budesonide (200 mcg every 12 hours) by inhalation chamber over 12 weeks.

Group B: received inhaled Budesonide (200 mcg every 12 hours) by inhalation chamber in combination with oral chewable Montelukast 5mg over 12 weeks.

✓ **Assessment of response**

All clinical variables by fill out a questionnaire, pulmonary functions (PEF, FEV1) were recorded at 6, 12 weeks. The patient was advised to use salbutamol inhalation if the necessary and refereed the hospital if there were severe symptoms. Any side effects noted by the patient or physicians were recorded. The primary objective was to determine whether changes in PEF, FEV1 produced by the two interventions would be significantly different in the two study groups.

✓ **Statistical methods**

All data were analyzed using Statistical Package for social sciences (SPSS version 20). Descriptive statistical parameters (mean and standard deviation, frequencies, and percentage) were calculated for each quantitative variable. Between-group comparisons of qualitative data were done using the Chi-Square test or Fisher's exact test. We used Friedman Test to compare the mean of several related populations and the Mann Whitney test to study the difference between the means of two independent groups. The results were considered significant at the 5% level ($p< 0.05$).

RESULTS

Figure 1 shows the enrolment and allocation of the patients to the two study groups. Of 120 patients with mild and moderate severity of persistent asthma. A total of 120 patients were recruited and randomly allocated to the two study groups, with 60 patients in each group, 5 patients did not complete the study plan and were included as failure to treat (In Intention to treat). The average age of the study patients was 9.6±2.8 years. The groups did not differ significantly as regards their age, sex, weight, and length **(Table 1).**

The baseline FEV1 of the two groups was not significantly different. With treatment, the FEV1 rose significantly within each study group with a percentage improvement of 23.8% in group A compared to 28.3% in group B **(Table 2).**

There was an elevation in PEF values in both groups (a percentage improvement of 25% in group A compared to 36.4% in group B) with significant difference **(Table 3).**

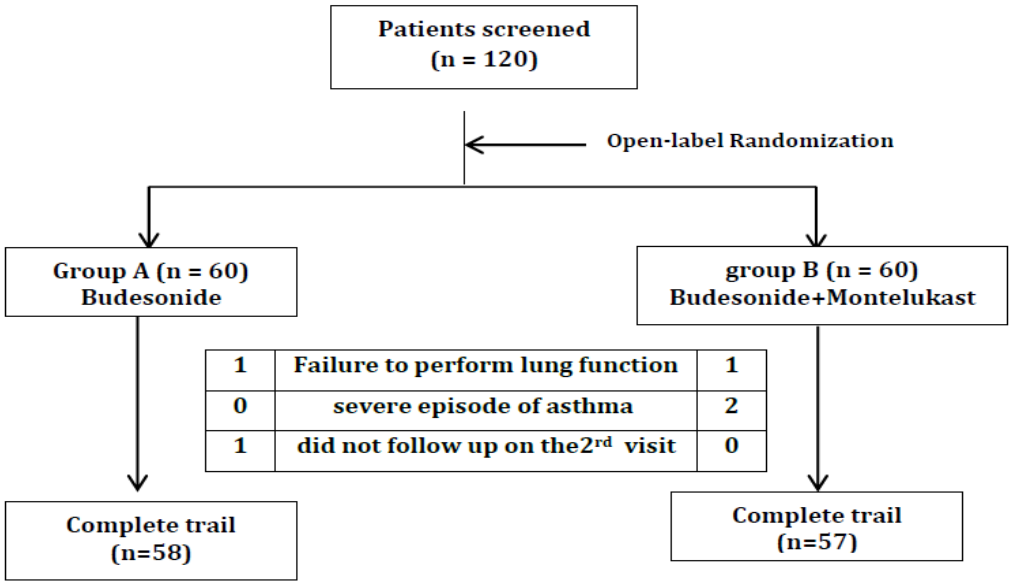


Figure 1: Flow diagram showing enrolment and allocation of patients to the Budesonide alone or Budesonide+Montelukast group.

Table (1): Baseline characteristics of the patients in the two study groups.

		Group A	Group B	p-value
Sex	**Male, n(%)**	31(51.7)	33(55)	0.7
	Female, n(%)	29(48.3)	27(45)	
Age		9.2±2.7	10.1±2.8	0.09
weight		30.6±9.8	34.2±10.6	0.06
length		133.01±15.1	135±21.9	0.5

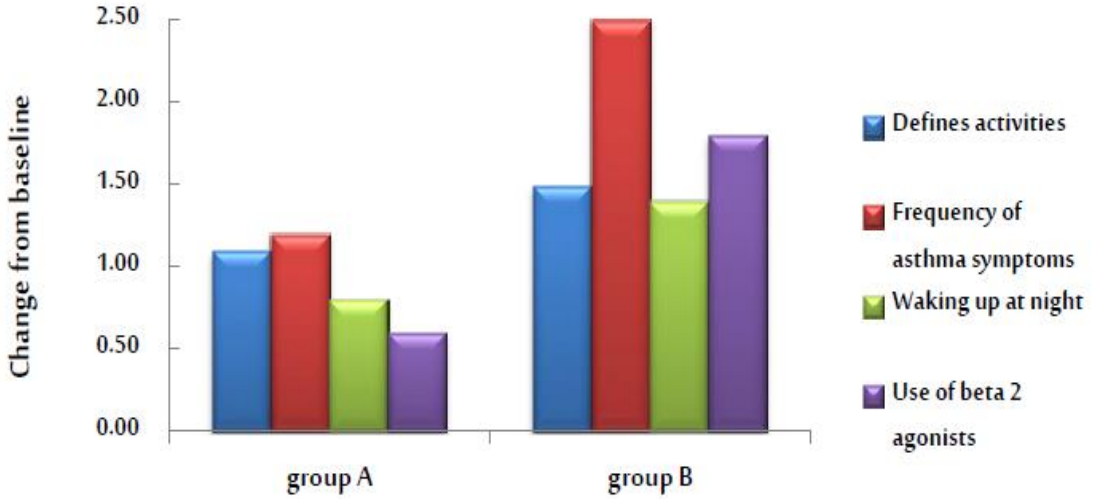
Table (2): comparison of the studied groups according to FEV1.

FEV1	Group A	Group B	p-value
Baseline	72±9.25	74.5±4.25	0.1
1st visit	78.93±12.5	85.4±10.65	0.01
2nd visit	88.91±21	96.15±12.47	0.04
p-value	0.0001	0.0001	

Table (3): comparison of the studied groups according to PEF.

PEF	Group A	Group B	p-value
Baseline	81,06±15.4	86.7±8.3	0.1
1st visit	86.9±19.06	96.8±12.9	0.02
2nd visit	98.3±27.6	112.7±17.5	0.02
p-value	0.0001	0.0001	

The quality of life in group B was better than group A with asignificant difference (p=0.0001) **(Figure 2).** There were no side effects of the use of drugs in the study groups.



DISCUSSION AND CONCLUSION

We conducted the present study to investigate the role of inhaled Budesonide with oral montelukast versus inhaled Budesonide alone in patients with mild and moderate severity of persistent asthma. The study showed that inhaled Budesonide with oral montelukast had a significant beneficial effect on FEV1,PEF, and quality of life compared with inhaled Budesonide in patients with mild andmoderate severity of persistent asthma.

Wang's retrospective study observed that the use of combination Budesonide and Montelukast for asthmatic children aged 4 to 11 years leads to an increase (12.4%) in FEV1 values in addition to a decrease in the frequency of asthma symptoms, the use of beta-2 agonists, and the number of waking times at night compared to using Budesonide inhalation alone, and this is consistent with the results ofthe current study.[8] Stelmach found in his study greater improvement in PEF 25-75% after 4 weeks of treatment in Budesonide and Montelukast which could be explained by the oral Montelukast may reach the inflamed small lower airways, while inhaled drugs hardly reach them.[9]

Yu Zhang observed a higher improvement of FEV1 and PEF values in the combined treatment group (Budesonide and Montelukast) compared to Budesonide alone that is similar to the results of our study. He also observed lower levels of inflammatory factors (TNF a, IL4, IL8, CRP), and higher immune markers (CD4 +, CD3 +, CD8 +, andIgE) levels in the co-group compared to monotherapy.**[10]** Monitoring PEF alone is considered an insufficient indicator for controlling asthma symptoms and in determining treatment in children, as some children lack adequate skills to properly conduct lung function (PEF, FEV1), so monitoring degrees of clinical improvement and controlling asthma symptoms (ACS) in addition to lung functions is more reliable in evaluating the effectiveness of treatment.**[11]** The current study depended on the lung function (PEF, FEV1), degrees of clinical improvement, and follow-up patients to ensure adherence to medication and monitor asthma symptoms control**.**

There are some limitations of this study. Firstly, the study was open- label randomization with its limitation which may increase the selection bias. Secondly, cases of this study were selected from asingle-center, and thus, it may be not generalized to other pediatric populations.

The present study showed that there may be a therapeutic benefit of the addition of Motelukast to Budesonide inhalation in the treatment of mild and moderate severity of persistent asthma.

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