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Effect of Antiasthma Medication on Blood Eosinophil Count and Serum Immunoglobulin E Levels: A Randomized Controlled Study

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Authors' contributions

This work was carried out in collaboration among all authors. Author SAD conceptualized and designed the study, drafted the initial manuscript, coordinated and supervised data collection and approved the final manuscript as submitted. Authors WAW and IA carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted. Authors KMK, MN and SAD designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript and approved the final manuscript as submitted. All authors read and approved the final manuscript.

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ABSTRACT

Background: Asthma is a chronic inflammatory condition of lung airways resulting in episodic airflow obstruction.
Aims: The main objective of this study is to find the effect of antiasthma medication on serum IgE levels and blood eosinophil count.
Study Design: This randomized controlled trial study was performed in children aged 6-15 years of age, with clinically stable and moderate persistent asthma.
Results: The findings of this study indicate both group (Budesonide/formoterol group and budesonide group) patients experienced a significant decrease in serum IgE levels and blood

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eosinophil counts over the study period. However, the difference in two groups was not statistically significant.

Conclusions: Inhaled steroids are effective in controlling systemic inflammation in asthma as evidenced by a decrease in IgE levels and eosinophil counts. However addition of LABA doesn't have any additive effect.

Keywords: Asthma; budesonide; eosinophil; IgE levels; inhaled steroids; LABA.

1. INTRODUCTION

Bronchial asthma (BA) is a chronic inflammatory disease with a marked heterogeneity in etiology, pathophysiology and clinical aspects, leading to the identification of different phenotypes (early onset atopic/allergic, eosinophilic, exercise-induced, obesity and paucigranulocitic [1]. Subsequently, taking into account the molecular mechanisms underlying the pathophysiology of bronchial inflammation, the concept of endotypes has been introduced [2]. BA is often sustained by allergic sensitization, which leads to bronchial hyper-responsiveness and acute bronchoconstriction in response to specific and non-specific triggers. For many years, from a pathogenic perspective, the focus of research has been on the role of T cells in the initiation and perpetuation of inflammation [3,4]. In particular, T helper 2 (Th2) cells have been identified as the cells involved in controlling immunoglobulin E (IgE) production because of their ability to produce interleukin (IL)-4 and IL-13, and influence the functioning of eosinophils through the actions of IL-5 [5].

The biological role of IgE is complex and related to its ability to influence the functioning of several immune and structural cells involved in the pathogenesis of chronic allergic inflammation [6]. The biological pathways that IgE uses to influence cell activity rely on interactions with specific receptors. Two classes of receptors have been identified: high-affinity (FcεRI) receptors and low-affinity CD23 (or FcεRII) receptors. FcεRI receptors are not only expressed by mast cells and basophils but also by dendritic cells (DCs), airway smooth muscle cells (ASMCs), epithelial cells, endothelial cells, and eosinophils [7,8,9,10]. DCs can provide all of the co-stimulatory signals required for activation of T cells, which play a key role in the pathogenesis of BA. DCs are dedicated antigen-presenting cells and are key in the induction of Th2 cell activation in the primary immune response to allergens [11,12]. The ability to present antigens is amplified by IgE bound to FCεRI receptors expressed on the surface of DCs [6]. It has been shown that IgE captures the allergens, facilitating their presentation to memory Th2 lymphocytes [13]. FcεRI–IgE-dependent allergen presentation by DCs may critically lower the atopic individual's threshold to mount allergen-specific T cell responses. In fact, the targeting of allergens to FcεRI via IgE leads to a 1000-fold increase in the activation of T cells in addition to the production of chemokine ligand 28 (CCL28), a chemokine that selectively attracts Th2 lymphocytes [14]. Furthermore, the activation of allergen-specific Th2 cells is associated with an amplification of allergen-specific IgE production in a vicious cycle of the pathogenic mechanisms of allergic asthma [6]. IgE antibodies are also able to negatively modulate the innate function of plasmocytoid DCs. In these cells, the activation of FcεRI receptors blocks, or at least reduces, the intracellular signals involved in type I interferon (IFN) production [15]. The reduction in IFN production correlates with the defect in anti-viral response in allergic asthma patients [16]. Moreover, viral respiratory infections can be the initial cause of asthma, and can result in exacerbations and worsen severity. Research to understand the relationship between IgE and virus infection susceptibility was spurred, in part, by the results of the clinical trial performed using omalizumab in children with asthma [6]. The study found that anti-IgE therapy was able to reduce the exacerbations typically occurring in the spring but mainly in the fall when the children go back to school. It is known that the majority of exacerbations are induced by viral respiratory infections [17].

Increased numbers of eosinophils have been reported in the peripheral blood of patients with eosinophilic disorders such as asthma [6]. Eosinophilic inflammation of the airways characterizes disease severity in subsets of individuals with severe asthma and there is a direct relationship between eosinophil count and the frequency of asthma exacerbations [18,19, 20]. Eosinophil differentiation, activation and survival mainly depend upon the effects of IL-5. This cytokine, produced at the bronchial level by Th2 cells as well as by mast cells and basophils,

circulates through the blood and arrives at the bone marrow where it stimulates eosinophil progenitors, which migrate towards the bronchial walls under the effect of chemokines such as eotaxins (CCL11) [21]. However, other cytokines are also able to directly influence eosinophils. Granulocyte–macrophage colony stimulating factor (GM-CSF) and IL-3 activate and enhance eosinophil functions, such as cytotoxic killing, superoxide production, leukotriene production, and Ig-induced degranulation [22].

In our study, we tried to find the effect of antiasthma medication on serum IgE levels and blood eosinophil count.

2. MATERIALS AND METHODS

2.1 Study Design

This randomized controlled trial study was performed in Department of Paediatrics, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, between March 2016 and February 2018 in children aged 6-15 years of age. Children with clinically stable and moderate persistent asthma and with forced expiratory volume in one second (FEV1) of more than 60% after the bronchodilator had been withheld for 6 hours were included in the study. Children with history of life-threatening asthma and adverse reactions to the medications used in the study were excluded from the study.

2.2 Data Collection

Children with signs and symptoms of asthma and who satisfied the inclusion criteria were selected. History of day time symptoms (use of short acting beta agonists/week), nighttime awakening/month, number of acute exacerbations, was obtained from the patients. The children were divided into 2 groups. Both groups received fixed dose of inhalational steroids (budesonide 400micrograms/day). While as only one group received long-acting beta agonists (formoterol 12 micrograms/day). The Children were free to use short acting beta agonists (albuterol).

The children were assessed at 3, 6 and 9 months for asthma control and for eosinophil count and IgE levels.

2.3 Statistical Analysis

All the continuous variables of the study have been shown in terms of descriptive statistics. To analyse the data, we have applied standard statistical tests like unpaired t- test, chi square test, mcnemar test. The results obtained have been discussed on 5% level of significance i.e $p< 0.05$ considered significant. Moreover, the appropriate statistical charts have been used to represent the data. The statistical software SPSS V-20 has been used for the statistics.

3. RESULTS AND DISCUSSION

Comparison of serumIgE Levels in the two groups: (Tables 2,3,4,5 and Fig. 1).

Comparison of eosinophil count in the two groups: (Tables 6,7,8,9 and Fig. 2).

Asthma is characterized by airway inflammation and hyper responsiveness. Besides local inflammation, asthma is also found to have systemic inflammation [23]. Eosinophils and IgE are considered to play a significant role in allergic immune responses. The reduction of IgE levels and eosinophils counts seems to be an attractive target in the management of allergic diseases like asthma, allergic rhinitis etc. Inhaled steroids inhibit the number of circulating eosinophils in asthma [24]. In the present study, we determined to examine whether the addition of LABA to inhaled steroids causes greater fall in IgE levels and eosinophil counts.

Sixty children who met the inclusion criteria were included. They were randomly divided into two treatment groups. Efficacy variables studied were blood eosinophil count and serum IgE levels in each group at each visit. The mean (±SD) age of the patients in our study was 9.3(±3.1) years in group 1 and 8.9(±2.6) years in group 2. The age distribution in the two groups was statistically insignificant (>0.05).

Table 1. Comparison of age in the two study groups

Variable(age)	Group 1 (steroid+LABA)	Group 2(steroid)
Mean	9.3	8.9
SD	3.1	2.6
95% CI	8.2-10.4	7.9-9.9
P-value	0.807	

Table 2. Serum IgE levels at the start of therapy

Variable (IgE levels)	Group 1	Group 2
Mean	59.7	57.8
SD	24	28
P-value	0.78	

Unpaired t-test

Table 3. Serum IgE levels at 3 months of therapy

Variable (IgE levels)	Group 1	Group 2
Mean	30.2	35.7
SD	17.6	18.3
P-value	0.2	

Unpaired t-test

Table 4. Serum IgE levels at 6 months of therapy

Variable (IgE levels)	Group 1	Group 2
Mean	26	31.6
SD	13	14
P-value	0.12	

Unpaired t-test

Table 5. SerumIgE levels at 9 months of therapy

Variable (IgE levels)	Group 1	Group 2
Mean	23	27.9
SD	10.2	12.2
P-value	0.092	

Unpaired t-test

We studied and compared serum IgE between two groups at the start, 3 months, 6months and 9months of therapy. Both groups experienced a statistically significant decrease inserum IgEover the study period. There was a greater decrease in IgE levels in budesonide/formoterol group when compared to budesonide alone group. However, the difference in the two groups was not statistically significant.

The second parameter we studied and compared was blood eosinophil count between two groups at the start, 3 months, 6months and 9months of therapy. There was a decrease in eosinophil count in both budesonide/formoterol group and budesonide alone group throughout study period. However, the difference in two groups was not statistically significant.

Our results were consistent with the study done by Kamaran O et al. [25]. They randomized the patients into 3 groups. Group 1 used inhaled budesonide, group 2 used inhaled budesonide/ formoterol and group 3 used inhaled budesonide and oral montelukast. They didn't find any statistically significant difference in IgE, total eosinophil, IL-13 and IFN-gamma between the three groups.

Inhaled steroids exhibit their role in asthma by suppressing the inflammatory cascade. Small amounts of steroid are absorbed systemically. This translates into a decrease in IgE and eosinophil counts. However, addition of LABA to inhaled steroids doesn't have any effect on the levels of IgE and eosinophil counts.

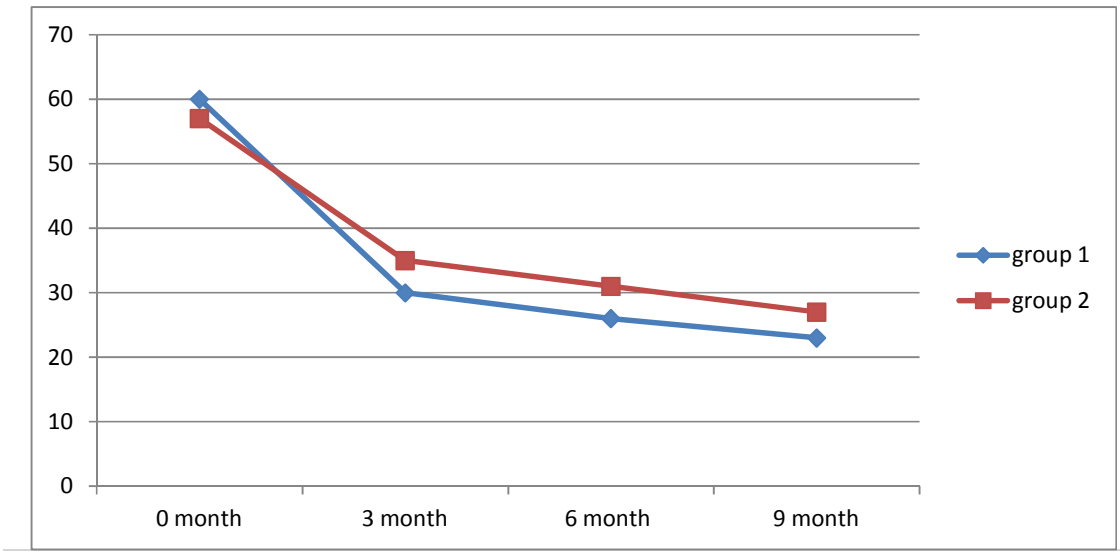

Fig. 1. Comparison of a decrease in IgE levels in the two groups

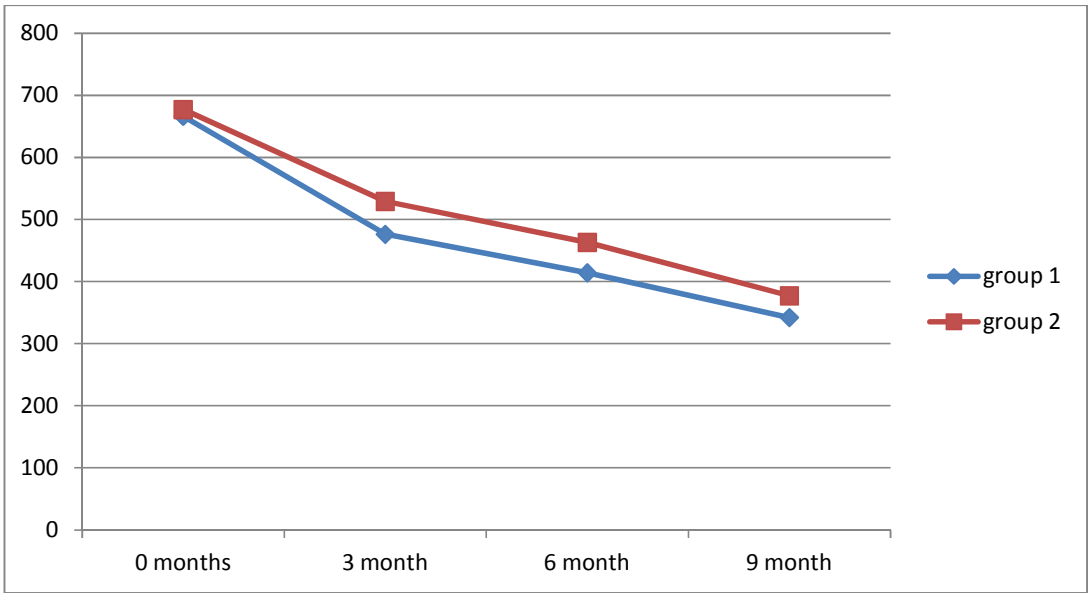

Fig. 2. Comparison of decrease in eosinophil count between the two groups

Table 6. Blood eosinophil count at the start of therapy

Variable (eosinophils)	Group 1	Group 2
Mean (MEDIAN)	666 (695)	677 (630)
SD	184	206
P-value	0.82	

Unpaired t-test

Table 7. Blood eosinophil count at 3 months of therapy

Variable (eosinophils)	Group 1	Group 2
Mean (MEDIAN)	476 (431)	529 (450)
SD	172	206
P-value	0.29	

Unpaired t-test

Table 8. Blood eosinophil count at 6 months of therapy

Variable(eosinophils)	Group 1	Group 2
Mean (MEDIAN)	414 (390)	463 (400)
SD	134	196
P-value	0.26	

Unpaired t-test

Table 9. Blood eosinophil count at 9 months of therapy

Variable(eosinophils)	Group 1	Group 2
Mean (MEDIAN)	342(330)	377(325)
SD	104	143
P-value	0.285	

Unpaired t-test

4. CONCLUSION

Inhaled steroids are effective in controlling systemic inflammation in asthma as evidenced by a decrease in IgE levels and eosinophil counts. However addition of LABA doesn't have any additive effect.

CONSENT

As per international standard or university standard written parents' consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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