

Original Research Article

Comparative study of inhaled steroids versus inhaled steroids plus long acting beta agonists in childhood asthma: a randomized controlled study

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ABSTRACT

Background: Asthma is a chronic inflammatory condition of lung airways resulting in episodic airflow obstruction causing considerable morbidity in paediatric population. The main objective of the study was to find out whether addition of long acting beta agonists to steroids provides better asthma control.

Methods: 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 SABA use in Budesonide/formoterol group patients was significantly less compared to budesonide group patients (1.5 ± 1.1 v/s 2.13 ± 0.9 , p-value 0.01). Both groups experienced decrease in night time symptoms and acute exacerbations however there was no significant difference between the two groups in these variables.

Conclusions: This study showed addition of LABA to inhaled steroids in moderate persistent asthma provided better asthma control and LABA is mainly recommended to be used as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled corticosteroids.

Keywords: Asthma, Budesonide, Inhaled steroids, LABA, SABA

INTRODUCTION

Asthma is a chronic inflammatory condition of lung airways resulting in episodic airflow obstruction.¹ Airway inflammation is associated with airway hyper reactivity or bronchial hyper responsiveness (BHR), which is defined as the inherent tendency of the airways to narrow in response to various stimuli (eg, environmental allergens and irritants).²

Guidelines from the National Asthma Education and Prevention Program, which were updated in 2007, highlight the importance of correctly diagnosing asthma.³ To establish the diagnosis of asthma, the clinician must confirm the following: Episodic symptoms of airflow obstruction are present, Airflow obstruction or symptoms are at least partially reversible and alternative diagnoses

are excluded. Thus, obtaining a good patient history is crucial when diagnosing asthma and excluding other causes.

National and international asthma treatment guidelines have recently focused on control of asthma. They recommend different combinations of controllers for long term treatment of persistent asthma including addition of long-acting beta-2-agonists (LABA) to inhaled corticosteroid (ICS) therapy.^{4,5}

Inhaled corticosteroids (ICS) remain the cornerstone of asthma treatment for children of all ages.^{4,5} They are the most potent and effective anti-inflammatory medication currently available. Corticosteroids block late-phase reaction to allergens, reduce airway hyper responsiveness, and inhibit inflammatory cell migration

and activation.⁶⁻⁸ ICS reduce asthma symptoms, improve quality of life, reduce frequency and severity of exacerbations, and reduce asthma mortality.⁹⁻¹¹

NAEPP EPR 3 recommend combination therapy for the majority of children with moderate to severe persistent asthma.¹² The most popular combinations are the use of ICS in combination with LABA and ICS in combination with leukotriene receptor antagonists (LTRAs). Salmeterol and formoterol are highly selective, third generation LABAs that have been available for use since the early 1990s. Salmeterol and formoterol, however, differ in their pharmacological properties. One important difference is that the onset of action of formoterol is faster than that of salmeterol.^{13,14} A significantly greater improvement in FEV1 was noted within three minutes of dosing with formoterol than salmeterol and continued to have a more pronounced effect for the three hours following dosing. Formoterol produces bronchodilation as fast as the short-acting β_2 -agonist salbutamol.^{15,16}

In this study authors tried to find out whether addition of LABA to inhaled steroids provides better asthma control than when inhaled steroids are used alone in children with moderate persistent asthma.

METHODS

Study Design

This randomized controlled trial study was performed in Department Of Paediatrics, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, between September 2016 and July 2018 in children aged 6-15 years of age.

Inclusion criteria

- 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 study.

Exclusion criteria

- Children with history of life threatening asthma and adverse reactions to the medications used in the study were excluded from study.

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), night time 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. The children recorded their use of albuterol (200 microgram), symptoms of asthma, absence from school and night waking. Spirometry was also done at each visit.

Statistical analysis

All the continuous variables of the study have been shown in terms of descriptive statistics. In order to analyse the data, authors 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 have been used for the statistics.

RESULTS

Sixty children who met the inclusion criteria were included. They were randomly divided into two treatment groups. Efficacy variables studied included day time and nocturnal symptoms, rescue medication (short acting beta-agonist) use per week and number of acute exacerbations. The mean (\pm SD) age of the patients in this study was 9.3 (\pm 3.1) years in group 1 and 8.9 (\pm 2.6) years in group 2. The age distribution in the two groups was statistically insignificant (>0.05) (Table 1).

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	

Comparison of SABA use/week in the two groups

Average use of rescue medications (SABA) per week was studied at 3, 6 and 9 months and compared between the groups as shown in Table 2, 3 and 4. At 3 months, SABA use in Budesonide/formoterol group patients was significantly less compared to budesonide group patients (1.5 ± 1.1 v/s 2.13 ± 0.9 ; p -value 0.016). The advantages of the first group in SABA use over the second were maintained at 6 months (1 ± 0.7 v/s 1.4 ± 0.6 ; p -value 0.014) and at 9 months (0.6 ± 0.6 v/s 1.1 ± 0.75 ; p -value 0.007).

Comparison of night time symptoms in the two groups

Authors studied and compared night time symptoms between two groups at the start, 3months, 6months and 9months of therapy. There were no statistically significant differences in night time symptoms between two groups throughout study period (Table 5, 6, 7 and 8).

However both groups experienced a statistically significant decrease in night time awakening/month over the study period (Table 9 and 10).

Table 2: Number of times SABA used over 1 week on an average at 3 months.

Variable (SABA use)	Group 1	Group 2
Mean (median)	1.5 (1)	2.13 (2)
SD	1.1	0.9
Range	0-4	1-4
p-value	0.0163	

Unpaired t-test

Table 3: Number of times SABA used over 1 week on an average at 6 months.

Variable (SABA use)	Group 1	Group 2
Mean (median)	1.0 (1)	1.4 (1)
SD	0.7	0.6
Range	0-2	1-3
p-value	0.014	

Unpaired t-test

Table 4: Number of times SABA used over 1 week on an average at 9 months.

Variable (SABA use)	Group 1	Group 2
Mean (MEDIAN)	0.6 (1)	1.1 (1)
SD	0.6	0.75
Range	0-2	0-3
p-value	0.0071	

Unpaired t-test

Table 5: Number of patients having night time symptoms at the start of the study.

Night symptoms	Group 1	Group 2	p-Value
Yes (present)	22	21	0.774
No (absent)	8	9	
Total (patients)	30	30	

Table 6: Number of patients having night time symptoms at 3 months of the study.

Night symptoms	Group 1	Group 2	p-Value
Yes	8	10	0.57
No	22	20	
Total	30	30	

Comparison of acute exacerbations in the two groups

There was no statistical difference between the two groups during study period, however Budesonide/formoterol combination appears to be marginally better than budesonide in decreasing acute exacerbations (Table 11 and Figure 1).

Table 7: Number of patients having night time symptoms at Six months of the study.

Night symptoms	Group 1	Group 2	p-Value
Yes	7	10	0.39
No	23	20	
Total	30	30	

Table 8: Number of patients having night time symptoms at Nine months of the study.

Night symptoms	Group 1	Group 2	p-Value
Yes	4	10	0.067
No	26	20	
Total	30	30	

Table 9: Number of patients having night symptoms at 0 and 9 months in group 1.

Night symptoms	0 months	9 months	p-Value
Yes	22	4	<0.0001
No	8	26	
Total	30	30	

Table 10: Number of patients having night symptoms at 0 and 9 months in group 2.

Night symptoms	0 months	9 months	p-Value
Yes	21	10	0.0092
No	9	20	
Total	30	30	

Table 11: Number of patients having acute exacerbations during study period.

Acute exacerbations	Group 1	Group 2	p-Value
Yes	9	13	0.28
No	21	17	
Total	30	30	

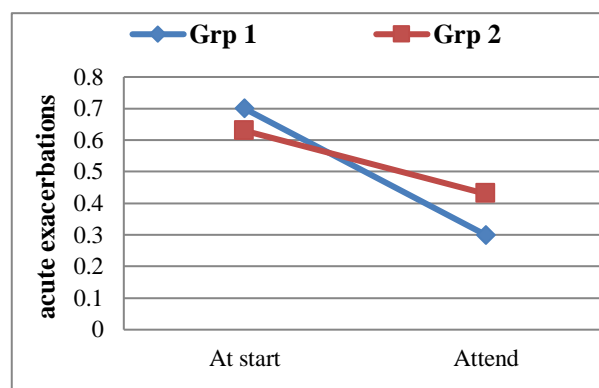


Figure 1: Comparison of acute exacerbations in the two groups.

DISCUSSION

In this study we tried to find out whether addition of LABA to inhaled steroids provides better asthma control than when inhaled steroids are used alone in children with moderate persistent asthma.

Average use of rescue medications (SABA) per week was primary efficacy variable compared between the groups. At 3 months, SABA use in Budesonide/formoterol group patients was significantly less compared to budesonide group patients (1.5 ± 1.1 v/s 2.13 ± 0.9 ; p-value 0.016). The advantages of the first group in SABA use over the second were maintained at 6 months (1 ± 0.7 v/s 1.4 ± 0.6 ; p-value 0.014) and at 9 months (0.6 ± 0.6 v/s 1.1 ± 0.75 ; p-value 0.007). Zetterström O et al.¹⁷ compared Budesonide/formoterol in a single inhaler with budesonide alone, and with concurrent administration of budesonide and formoterol from separate inhalers, in patients with asthma, not controlled with inhaled glucocorticoids alone. Use of rescue medication, total asthma symptom scores and percentage of symptom-free days improved more with both single inhaler and separate inhaler therapy than with budesonide alone, as did asthma control days (approximately 15% more, $p < 0.001$ versus budesonide, both comparisons, with a marked increase in the first week). All treatments were well tolerated and the adverse event profile was similar in all three treatment groups.

Both groups experienced a decrease in night time awakening/ month over the study period. Greater number of patients did not experience night time symptoms in case of budesonide/ formoterol group as compared to budesonide alone group. However, the difference between the two groups was not statistically significant at any time during the study period (p-value > 0.05). Bateman ED et al.¹⁸ concluded from their study that there were numerical improvements in night-time awakenings (7.9% vs 9.6%) in favor of budesonide/formoterol when compared with fluticasone.

Budesonide/formoterol combination appears to be marginally better than budesonide in decreasing acute exacerbations. In budesonide/formoterol group 70% patients didn't experience acute exacerbations in comparison to budesonide group in which 56% patients didn't experience acute exacerbations during the study period. However the difference was not statistically significant ($p = 0.36$). In a study conducted by Pauwels RA et al, patients being treated with glucocorticoids were randomly assigned to one of four treatments given twice daily by means of a dry-powder inhaler (Turbuhaler): 100 microg of budesonide plus placebo, 100 microg of budesonide plus 12 microg of formoterol, 400 microg of budesonide plus placebo, or 400 microg of budesonide plus 12 microg of formoterol.¹⁹ The rates of severe and mild exacerbations were reduced by 26 percent and 40 percent, respectively, when formoterol was added to the lower dose of budesonide. The higher dose of budesonide

alone reduced the rates of severe and mild exacerbations by 49 percent and 37 percent, respectively. Patients treated with formoterol and the higher dose of budesonide had the greatest reductions - 63 percent and 62 percent, respectively. Symptoms of asthma and lung function improved with both formoterol and the higher dose of budesonide, but the improvements with formoterol were greater.

CONCLUSION

To conclude, addition of LABA to inhaled steroids in moderate persistent asthma provided better asthma control in the study population. LABA is mainly recommended to be used as add-on therapy for patients whose asthma is not controlled on low to high doses of inhaled corticosteroids. In this study, addition of LABA to moderate dose of inhaled steroids (budesonide=400microgram/day) resulted in less need for SABA as a rescue medication. So, combination therapy (steroid+LABA) is a better treatment option in children with moderate persistent asthma as compared to steroids alone.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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