COMPARISON OF EFFICACY OF BUDESONIDE/FORMOTEROL VERSES FLUTICASONE/FORMOTEROL IN THE TREATMENT OF BRONCHIAL ASTHMA

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ABSTRACT
Background and Objectives: The present study was designed to compare fixed combination of budesonide plus formoterol, with the fixed combination fluticasone plus formoterol. Main objective was to find out the combination having more efficiency and least adverse reactions. Methods: This was a prospective observational study done for 9 months. Total number of patients participated in this study was 85. Out of this 44 patients were treated with budesonide/formoterol (400/6) and 41 patients were treated with fluticasone/formoterol (250/6). Baseline was measured at the time of admission as Forced expiratory volume in 1st second & Peak expiratory flow rate. Review of patients was done after 10 days. Results & Discussion: A significant improvement of lung functions from baseline was observed in both groups at all time point. Budesonide/formoterol showed more improvement in lung function than fluticasone/formoterol. Budesonide/formoterol showed 2.14L/min increase in peak expiratory flow rate and 1.1% increase in FEV1 than that of fluticasone/formoterol. Also FEV1 in liter had an increase of 0.04L than fluticasone/formoterol. Conclusion: The combination budesonide/formoterol had slightly increased efficacy than fluticasone/formoterol. Tolerability was found to be similar for both combinations. But fluticasone/formoterol is expensive than budesonide/formoterol. Thus the budesonide/formoterol is more economical for the patients. It indirectly improves the patient adherence to the medication. Thus budesonide/formoterol combination was found to be better for an asthma patient in terms of efficacy and cost.

KEYWORDS: Asthma, Budesonide, Formoterol, Fluticasone, Inhaled corticosteroids in asthma.

INTRODUCTION
INHALED CORTICOSTEROIDS (ICS)
This year is the 50th anniversary of the introduction into clinical use of the first modern inhaler for the management of asthma – the pressurized metered-dose inhaler (pMDI). The pMDI was initially used for the administration of the non-selective beta-agonists adrenaline and isoprenaline. However, the epidemic of asthma deaths which occurred in the 1960s led to these drugs being superseded by the selective short-acting beta-agonist salbutamol, and the first inhaled corticosteroid (ICS) beclometasone. At the same time, sodium cromoglycate was introduced, to be administered via the first dry-powder inhaler, the Spinhaler. But owing to its relatively weak anti-inflammatory action its use is now very limited. Over the last 10 years, the long-acting beta-agonists (LABAs) have become an important add-on therapy for the management of asthma, and they are now often used with ICS in a single ICS/LABA combination inhaler.

LONG ACTING BETA 2 AGONIST
The two long-acting β2-agonists, formoterol and salmeterol, provide long-lasting bronchodilation (12 or more hours) when administered as aerosols. Unlike the more water-soluble short acting β2-agonists, the long-acting agents are lipid-soluble, readily partitioning into the outer phospholipid layer of the cell membrane. Salmeterol is more β2-selective than albuterol and more bronchoselective by virtue of its property of remaining in the lung tissue cell membrane, which produces its longer duration. However, both formoterol and salmeterol will produce dose-dependent systemic β2-agonist effects.

INHALED CORTICOSTEROID AND BETA 2 AGONIST COMBINATION
Inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy. For patients with persistent or uncontrolled asthma for whom low-to-medium doses of ICSs are insufficiently effective, there may be reluctance to increase the steroid dose because of concerns about
corticosteroid-related adverse events. Instead, patients may be prescribed a combination of an ICS and a long-acting β2-agonist (LABA). A substantial body of evidence from randomized controlled trials indicates that addition of a LABA to existing ICS therapy is clinically more effective than increasing the dose of ICS monotherapy, even when taking into consideration the heterogeneity observed in patient responses to asthma controller medications. The use of LABAs without concomitant use of an ICS is contraindicated in patients with asthma because LABA monotherapy is less effective than treatment with an ICS and there are concerns regarding its safety.

MATERIAL AND METHOD

Study design
It is a Prospective observational study.

Study duration
Total duration of the study was 9 months.

Study site
The study was conducted at the pulmonary medicine department of a tertiary care teaching hospital.

Ethical approval
Before conducting the study a protocol was prepared for which the permission was obtained from Institutional Ethical Committee (IEC) held on 13th January 2016.

Study population
Sample size for the study was greater than 38 from each treatment group.

Study criteria
The patients who satisfied the inclusion and exclusion criteria were selected randomly.

Inclusion Criteria
- Patient who are willing to participate in the study
- In patients with age greater than or equal to 12 years
- Patients diagnosed with bronchial asthma.
- Patients who are prescribed with budesonide plus formoterol or fluticasone plus formoterol powder inhalation

Exclusion criteria
- Patient using other anti asthmatic drugs
- Pregnancy and lactation

Source of data
Patient Case Records: It included following information:

- Patient Demographics
- Patient history notes
- Drug Treatment charts
- Laboratory investigation report
- Discharge summary

Study materials
- Patient data collection form.
- Informed consent form and patient information sheet

Study procedure

This was a Prospective observational study which was conducted in the pulmonary department of the 500 bed tertiary care teaching hospital. All patients having bronchial asthma using a combination of budesonide + formoterol or fluticasone + formoterol who are willing to participate, after signing informed consent form were included in the study. Selected patients were divided into two groups such as A and B where:
  - A - treated with budesonide + formoterol (400/6) 2 puff BID
  - B – treated with fluticasone + formoterol (250/6) 2 puff BID

Outcome was measured in terms of Peak expiratory flow rate (PEFR), forced expiratory volume at first second (FEV1) at the time of admission and follow up was done after 10 days. FEV1 of patients were measured using spirometer and PEFR by peak flow meter.

Other data includes demographic data such as name, age, gender, location, past medical history, patient history, lab values were collected from patient interview, case note and health professionals.

Statistics
Data collected was analyzed using Statistical Package for Social Science version 16 (SPSS). Descriptive statistics were given as mean and SD for continuous data or as percentage for frequency. Before and after treatment was compared with paired t test. Independent variable t test was given as comparison of mean in two populations.

RESULTS AND DISCUSSION

The proposed work entitled “Comparison of efficacy of budesonide/formoterol versus fluticasone/formoterol in the treatment of bronchial asthma” was a prospective study carried out in 500 bedded tertiary care hospital.

Assessment of prevalence of asthma
Total number of patients admitted in pulmonary department were taken for the assessment of prevalence.

<table>
<thead>
<tr>
<th>Table: Assessment of prevalence of asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category of patients</td>
</tr>
<tr>
<td>Number of patient admitted in pulmonary department</td>
</tr>
<tr>
<td>Number of patient admitted in pulmonary department with asthma</td>
</tr>
</tbody>
</table>
Prevalence of asthma in pulmonary department was found to be 3.31%. When this result was categorized by gender, 2.92% and 3.67% for male and female respectively, and 70.03% of these asthma patients are using either Budesonide+ formoterol or fluticasone + formoterol combination.

According to the study conducted by Aggarwal AN et al, prevalence of asthma ranges between 1.33%- 3.55% in different study centres in India and male prevalence ranges from 1.4%- 3.36% and female prevalence ranges 1.23- 3.76%.

**Gender distribution**

In our study females were more in number than male.

### Table: gender distribution

<table>
<thead>
<tr>
<th>Gender</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32</td>
<td>38%</td>
</tr>
<tr>
<td>Female</td>
<td>53</td>
<td>62%</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td>100%</td>
</tr>
</tbody>
</table>

Total number of patients selected from the pulmonary department was 85. Out of that 62% patients belong to female and 38% belong to male.

Study shows increased percentage of female patients is due to the increased incidence of females in the department. As we discussed earlier, after puberty females have greater chance for asthma according to Demarco R et al.

### Treatment groups

Sample size of our study was 76 patients. Data of 85 patients were used in the study.

### Table: treatment groups

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of patients</th>
<th>Males</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide + Formoterol (A group)</td>
<td>44</td>
<td>43.2%(19)</td>
<td>56.8%(25)</td>
</tr>
<tr>
<td>Fluticasone + Formoterol (B group)</td>
<td>41</td>
<td>31.7%(13)</td>
<td>68.3%(28)</td>
</tr>
</tbody>
</table>

Total patient participated in the study was 85. Out of that 44 patients were enrolled in group A constitute 19 males and 25 females. 41 patients were enrolled in group B constitute 13 male and 28 females. In both groups female patients are in greater number. The study conducted by Aggarwal AN et al. also showed similar result, increased prevalence of asthma in females.

### Age classification

Asthma was most prevalent in age group greater than 59 having 43 patients and it was about 50.6%. And least prevalent in 20 – 29 group contain only one patient that was 1.2%

### Age classification

The increased percentage of patients in age group greater than 59 is due to the decrease in lungs functions on age. This is due to the decline of lungs function after the age of 30. But, age group 10-19 had greater chance of asthma than 20-29. According to Huib AM et al. It was seen that lung function was maximum at the age of 20-35.

### Comparison of efficacy of group a and group b

Comparison of efficacy of Budesonide/formoterol versus Fluticasone/formoterol were done in terms of lung function tests. Two parameters were measured during the
study. They were forced expiratory volume at 1st second and peak expiratory flow rate.

1. Peak expiratory flow rate (pefr)

Table: Peak Expiratory flow Rate (PEFR)

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Base line (L/min)</th>
<th>Review (L/min)</th>
<th>P value</th>
<th>Average increase(L/Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Group A</td>
<td>155.91</td>
<td>45.35</td>
<td>179.55</td>
<td>48.31</td>
</tr>
<tr>
<td>Group B</td>
<td>139.02</td>
<td>48.72</td>
<td>159.76</td>
<td>48.55</td>
</tr>
</tbody>
</table>

P value = 0.085

The average increase in PEF Rate on review after 10 days was found to be 23.63 L/min in group A and 21.46 L/min in group B. That means budesonide + formoterol has 2.17L/min increase in PEF Rate than the other group. From the result it was found that budesonide/ formoterol had greater efficacy than fluticasone/formoterol according to Peak Expiratory Flow Rate.

Our study shows similar results to to Cukier A et al. also showed greater efficacy for budesonide/formoterol than fluticasone/formoterol to improve peak expiratory flow rate.

2. Improvement of forced expiratory volume at first second (fev1) in (l)

Forced expiratory volume at first second is an important lungs function test to assess the efficacy of asthmatic drug.

Table: Improvement of Forced Expiratory Volume at First Second (FEV1) in (L)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Base line (l)</th>
<th>Review (l)</th>
<th>P value</th>
<th>Increase in fev1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEAN</td>
<td>SD</td>
<td>MEAN</td>
<td>SD</td>
</tr>
<tr>
<td>Group A</td>
<td>1.1</td>
<td>0.32</td>
<td>1.29</td>
<td>0.31</td>
</tr>
<tr>
<td>Group B</td>
<td>1.09</td>
<td>0.28</td>
<td>1.24</td>
<td>0.28</td>
</tr>
</tbody>
</table>

P value = 0.155
From this result it was clear that group A (budesonide + formoterol) showed 0.04L increase in improvement of FEV1 than that of group B (fluticasone + formoterol). Group A showed increased efficacy than that of group B. Greater efficacy of budesonide formoterol was due to the faster onset action of budesonide than the fluticasone. A study conducted by Day J et al. also demonstrated the faster onset action for the budesonide than that of fluticasone.

Bodzenta Lukaszyk et al. also showed similar results to our study. Their study also showed increased improvement of FEV1 in patients treated with budesonide + formoterol combination than that of fluticasone +formoterol. Budesonide/formoterol showed 0.043 L greater improvement than the fluticasone/formoterol.

3. Improvement of forced expiratory volume in first second (FEV1) in percentage

Table: Baseline FEV1 and review FEV1 in percentage

<table>
<thead>
<tr>
<th>Treatment groups</th>
<th>Base line FEV1 in %</th>
<th>Review FEV1 in %</th>
<th>P value</th>
<th>Increase in FEV1 in percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Group A</td>
<td>45.38</td>
<td>13.40</td>
<td>54.95</td>
<td>13.12</td>
</tr>
<tr>
<td>Group B</td>
<td>42.70</td>
<td>10.65</td>
<td>51.21</td>
<td>10.97</td>
</tr>
</tbody>
</table>

Figure: Baseline FEV1 and review FEV1 in percentage

From this result it was clear that group A (budesonide + formoterol) showed 1.1% increase in improvement of FEV1 than that of group B (fluticasone + formoterol). Group A showed increased efficacy than that of group B. Greater efficacy of budesonide formoterol was due to the faster onset action of budesonide than the fluticasone. A study conducted by Day J et al. also demonstrated the faster onset action for the budesonide than that of fluticasone.
Bodzenta L et al. also showed similar results to our study. Their study also showed increased improvement of FEV1 in patients treated with budesonide + formoterol combination than that of fluticasone +formoterol. In that study, Budesonide/formoterol showed 0.043 L greater improvement in FEV1 than the fluticasone/formoterol.

CONCLUSION
This study was performed to compare the efficacy of budesonide/formoterol versus fluticasone/formoterol in bronchial asthma. Both medications were the combination of inhaled corticosteroid with long acting beta 2 agonist. Outcome of the study were measured in terms of forced expiratory volume in first second (FEV1), peak expiratory flow rate (PEFR). Tolerability of these combinations were also assessed. Prevalence of asthma was found to be 3.31%. More prevalence was shown by female population. Both combinations showed significant improvement in FEV1 and PEFR from the baseline. But budesonide/formoterol showed more improvement in FEV1 and PEFR than fluticasone/formoterol. Overall adverse drug reactions were found to be similar in magnitude for both treatment group. Thus both combinations had similar tolerability profile. Budesonide/formoterol is more economical for patient than fluticasone/formoterol. There for this combination is necessary to use in asthmatic patients to reduce the economic burden for purchasing the medication.

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Abin Joseph

REFERENCE