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COMPARATIVE STUDY THE EFFICACY OF FORMOTEROL MOMETASONE VIS AVIS FORMOTEROL FLUTICASONE

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ABSTRACT

Bronchial asthma is a widespread disease affecting around 300 million people of all ages globally. Patients from all ethnic backgrounds, suffer from asthma and the burden of this disease to governments, health care systems, families, and patients is increasing worldwide (Masoli *et al.*, 2004)[i].

It is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment (Rai *et al.*, 2007)[ii]. There has been a noticeable increase in the healthcare burden due to asthma globally.

Formoterol a nd salmeterol are two long-acting β2- agonists given by inhalation , with bronchodilating effects lasting for at least 12 h after a single administration. Formoterol has a faster onset of action compared with salmeterol. The aim of this study was to perform a systematic review and meta-analysis on the data published from previous review in order to calculate pooled estimates of effectiveness and safety assessment of formoterol and salmeterol in treatment of patients with asthma.

INTRODUCTION

Bronchial asthma is a widespread disease affecting around 300 million people of all ages globally. Patients from all ethnic backgrounds, suffer from asthma and the burden of this disease to governments, health care systems, families, and patients is increasing worldwide (Masoli *et al.*, 2004)[iii].

It is a chronic inflammatory disorder of the airways associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment (Rai *et al.*, 2007)[iv]. There has been a noticeable increase in the healthcare burden due to asthma globally. The prevalence and mortality from asthma have shown an upward trend during an era when quality medications are easily available for asthma (Alderson, 1987)[v].

Data on prevalence of asthma is now available from several countries. Prevalence varies from region to region depending upon the definition used for diagnosis of asthma (Peat *et al.*, 1992; ECRHS, 1996; Burney *et al.*, 1997; Dubois *et al.*, 1998; Braman, 2006; To *et al.*, 2010)[vi,vii,viii,ix,x,xi]. The prevalence of asthma is reported to range from 1.2 to 6.3% adults in most countries (Aggarwal *et al.*, 2006)[xii]. On the other hand, diagnosed asthma (i.e. asthma ever diagnosed by a clinician) in adults is generally reported as 2.7 to 4.0% in most European countries, 12.0% in England and 7.1% in the US (ECRHS, 1996; Burney *et al.*, 1997; Chhin *et al.*, 1997;)[vii,viii,xiii]. In Australia, the prevalence is rather high (9.5 to 17.9%) (Peat *et al.*, 1992; Peat *et al.*, 1994)[vi,xiv]. Tristan da Cunha is an unique example where more than half the population (56%) is reported to suffer from asthma, supporting a strong genetic link (Zamel *et al.*, 1996)[xv].

There is very limited data on asthma epidemiology from the developing world, including India. However, India is a vast country with immense geographical, economical, racial, religious and socio-political diversity. There are obvious differences in prevalence of disease and approach to management of health problems (Jindal *et al.*, 2005)[xvi]. In a recent multicentric study, prevalence of asthma in India has been reported to be 2.05% (Jindal, 2010)[xvii].

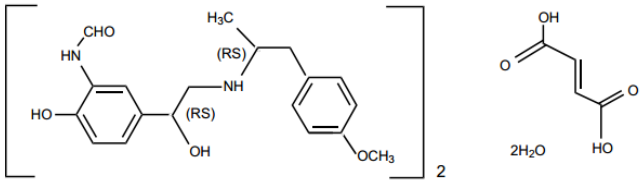
Inhalers are being used for management of asthma for quite some long since the introduction of first pressurized metered-dose inhaler (pMDI) in 1956 using rapidly acting nonselective β-agonists (*i.e.*, isoprenaline and epinephrine) followed by selective short-acting β2-adrenergic agonist (SABA) salbutamol and inhaled corticosteroids and leukotriene modifiers (Crompton 2006)[xviii].

Although the selective long-acting β_2-adrenergic agonist (LABA) salmeterol was introduced as monotherapy in the late 1980s and early 1990s, concerns about the risk of severe asthma attacks associated with SABAs carried over to this class of therapy (Crompton 2006)[xviii]. Moreover, studies demonstrated that monotherapy with a LABA was insufficient to control asthma (Lazarus *et al*. 2001; Lemanske *et al*. 2001)[xix,xx]. Concerns regarding the safety of high-dose ICSs (*e.g.*, rare cases of adrenal suppression) and findings from randomized, controlled trials showing a more effective reduction in symptoms and exacerbations with a reduced ICS dose and a LABA (eg, salmeterol or formoterol) compared with high-dose ICS alone eventually cemented the role of LABA in the therapeutic armamentarium (Crompton 2006)[xviii]. Indeed, contemporary asthma treatment guidelines recommend add-on LABA to ICS therapy for those patients who do not respond optimally to low- to medium-dose ICS (Crompton 2006; GINA, 2007; NAEPP, 2007)[xviii,xxi,xxii].

Formoterol is a long-acting β_2 agonist which has been used for treatment of asthma in monotherapy for quite long. Mometasone furoate and Fluticasone are synthetic glucocorticoids that have shown efficacy in treatment of asthma either alone or in combination with LABA drugs (Tan *et al.*, 2008; McKeage and Keam, 2009)[xxiii,xxiv]. However, there is limited literature available on evaluation of efficacy of Formoterol/Mometasone and Formoterol/Fluticasone combinations in management of bronchial asthma. Hence, the present study is being carried out to evaluate and compare the safety and efficacy of inhaled formoterol/mometasone combination with formoterol/fluticasone in patients of bronchial asthma in order to fill this gap.

The pharmacology of all the trial drugs is being cited below. All the information has been obtained from latest updates of FDA available from drugs.com.

FORMOTEROL FUMARATE



Formoterol fumarate has a molecular weight of 840.9, and its empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. Formoterol fumarate is a white to yellowish crystalline powder, which is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether[xxv].

CLINICAL PHARMACOLOGY

Mechanism of Action

Formoterol fumarate is a long-acting selective beta2-adrenergic receptor agonist (beta2-agonist). Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at beta2-receptors than at β_1-receptors. Although β_2-receptors are the predominant adrenergic receptors in bronchial smooth muscle and β_1-receptors are the predominant receptors in the heart, there are also β_2-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective β_2-agonists may have cardiac effects. The pharmacologic effects of β_2-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells. In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Long-acting beta-2 adrenergic agonists increase the risk of asthma-related death. Use of formoterol for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use formoterol only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication. Once asthma control is achieved or maintained, assess the patient at regular intervals and step down therapy (eg, discontinue formoterol) if possible without loss of asthma control, and maintain patient on a long-term asthma control medication. Do not use formoterol for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Data from controlled clinical trials suggest that long-acting beta-2 adrenergic agonists increase the risk of asthma-related hospitalization in children and adolescents. Consider a fixed-dose combination product containing both an inhaled corticosteroid and a long-acting beta-2 agonist to ensure adherence with both drugs in children and adolescents who asthma who require the addition of a long-acting beta-2 agonist to an inhaled corticosteroid. In cases in which the use of a separate long-term asthma control medication and a long-acting beta-agonist is clinically indicated, appropriate steps must be taken to ensure adherence with both components.

Hypersensitivity reactions, including anaphylaxis, angioedema, bronchospasm, rash, and urticaria, have been observed immediately after administration of formoterol. Formoterol inhalation powder contains trace levels of milk protein, which may produce allergic reaction in patients with severe milk protein allergy.

Use with caution in patients with convulsive disorders or thyrotoxicosis, and in patients unusually responsive to sympathomimetic amines.

Acute worsening of or deteriorating asthma or chronic obstructive pulmonary disease. Use of formoterol in these conditions is not appropriate.

Primary treatment of severe acute asthmatic attacks or status asthmaticus when intensive measures (e.g., oxygen, parenteral bronchodilators, IV corticosteroids) are required.

- Fluticasone in fixed combination with salmeterol: primary treatment of status asthmaticus or other acute episodes of asthma or COPD when intensive measures are required.
- Known hypersensitivity to fluticasone or any ingredient (e.g., milk protein) in the formulation

OBJECTIVES

The present study was carried out to observe the effects of inhaled formoterol/fluticasone against formoterol/mometasone in bronchial asthma. The objectives of the study were as follows:

1. To compare the efficacy of formoterol/mometasone.
2. To study the effect on human body.

MATERIAL AND METHOD

STUDY AREA: Lucknow, the capital of Uttar Pradesh, the most populous state of India having a population of around 40 lacs, providing a true representation of North Indian population.

STUDY CENTRE: Departments of Pharmacology and Pulmonary Medicine, Era's Lucknow Medical College and Hospital, Lucknow.

RESEARCH DESIGN: Prospective cross-over study.

DURATION OF STUDY: Eighteen months starting from January 2012.

STUDY SUBJECTS: All known cases of Bronchial Asthma diagnosed on the basis of spirometry coming to Department of Pulmonary Medicine, ELMC&H, Lucknow.

INCLUSION CRITERIA

1. Newly diagnosed patients of Bronchial Asthma who have consented for inclusion in study and regular follow up.
2. Either gender aged upto 60 years.
3. Providing consent for participation in study.

EXCLUSION CRITERIA

1. Patients who are in Acute Exacerbation of Bronchial Asthma (AEBA).
2. Elderly patients aged above 60 years.
3. Patients with renal, cardiac and liver disease are excluded.

METHOD

All those patients fulfilling the inclusion criteria and not falling in the domain of exclusion criteria were invited to participate in the study. All those consenting to participate in the study were enrolled in the study.

Each patient of the study population was subjected to the detailed history and thorough clinical examination and details was recorded in a proforma.

The following investigations were suggested:

Investigations:

1. Hb
2. TLC/DLC
3. Chest X-Ray

Diagnostic Criteria For Bronchial Asthma (GINA Guidelines, 2010)

Diagnosis of Bronchial Asthma was based on:

- History

- Spirometry

Staging of Bronchial Asthma according to spirometry tests:

a) **Intermittent**:

Symptoms< a week

Brief exacerbations

Nocturnal symptoms not more than twice a month

- FEV_1 or PEF > 80% predicted
- PEF or FEV_1 variability <20%

b) Mild Persistent

Symptoms > a week but < a day

Exacerbations may affect activity and sleep

Nocturnal symptoms> twice a month

- FEV_1 or PEF>80% predicted
- PEF or FEV_1 variability<20-30%

c) **Moderate Persistent Symptoms daily**

Exacerbation may affect activity and sleep

Nocturnal symptoms> a week

Daily use of inhaled short-acting β_2 agonist

- FEV_1 or PEF 60-80%
- PEF or FEV_1 variability>30%

d) **Severe Persistent Symptoms daily Frequent exacerbations**

Frequent nocturnal asthma symptoms Limitation of physical activities

- FEV1 or PEF<60% predicted
- PEF or FEV_1 variability>30%

SPIROMETRY

- Spirometry was done by Medikro Spirostar USB M9479 (Finland) machine as per the American Thoracic Society Criteria.

The following measurements were done

- **FVC (forced vital capacity)**: maximum volume of air that can be exhaled during a forced maneuver.
- **FEV_1 (forced expired volume in one second)**: volume expired in the first second of maximal expiration after a maximal inspiration. This is a measure of how quickly the lungs can be emptied.
- **FEV1/FVC**: FEV1 expressed as a fraction of the FVC, gives a clinically useful index of airflow limitation.
- A normal ratio of FEV_1/FVC is 0.8 for adults 20-39 years old, 0.75 for adults 40-59 years old, 0.7 for adults 60-80 years old; a post-bronchodilator value less than 0.7 indicates airflow limitation and the possibility of COPD.

  FEV_1 is influenced by age, sex, height and ethnicity, and is best considered as a percentage of the predicted normal value. Normal adults without airflow limitation have an FEV_1 > 80% predicted.

INTERVENTION

Group I: A total of 25 patients were first given 200/10 µg mometasone furoate/formoterol (MF/F) administered through metered-dose inhaler (MDI) in patients. Subsequently they were tried for evaluation in Group II using cross-over design.

Group II: A total of 25 patients were first Patients were given 200/10 µg fluticasone/formoterol (FL/F) administered through metered-dose inhaler (MDI) in patients. Subsequently they were tried for evaluation in Group I using cross-over design.

Intervention Protocol: We used a crossover study design wherein half the patients were subjected to trial of Group I protocol for 12 weeks. After 12 weeks these half were subjected to Group II protocol for 12 weeks.

The other half of patients was first subjected to Group II protocol for 12 weeks followed by 12 weeks which was subsequently followed by Group I protocol.

Laying Off Period: A lay-off period of two weeks was given between two intermittent crossovers.

Outcome measures: Pulmonary functions were recorded at baseline and change in pulmonary functions following intervention was recorded.

SAMPLE SIZE CALCULATION

The sample size was calculated at Department of Community Medicine, Era's Lucknow Medical College, Lucknow. The following formula was used to calculate the sample size:

$$n = \frac{(z_\alpha + z_\beta)^2 * (\sigma_1^2 + \sigma_2^2)}{d^2}$$

Where σ_1=9.54 and σ_2=11.74; d=11.74 □ 9.54 = 2.2 (Maspero *et al.*, 2010)**Ошибка! Закладка не определена.**

Type 1 error =5% Type II error =10%

Power of study=90% then sample size comes out to be n=46 + 10% loss to follow up =50 per group

General Examination:

Pulse:

SpO_2:

BP:

Respiratory:

Accessory Muscles of Respiration: Working/Not-Working

Type of Respiration:

Systemic Examination:

Respiratory System Examination:

Investigation:

Blood Sample for

TLC, DLC

PFER:

PFT:

Variable	Ref. Value	Pre test	Post test
FEV_1			
FVC			
FEV_1/FVC			

STATISTICAL ANALYSIS

The data was analyzed using Statistical Package for Social Sciences (SPSS) version 20.0. Values are represented as numbers, percentages and mean and standard deviation. Comparison of change in pulmonary functions following intervention was compared using paired "t"-test. Confidence level of the study was kept at 95%, hence a "p" value less than 0.05 indicated a statistically significant difference

Results

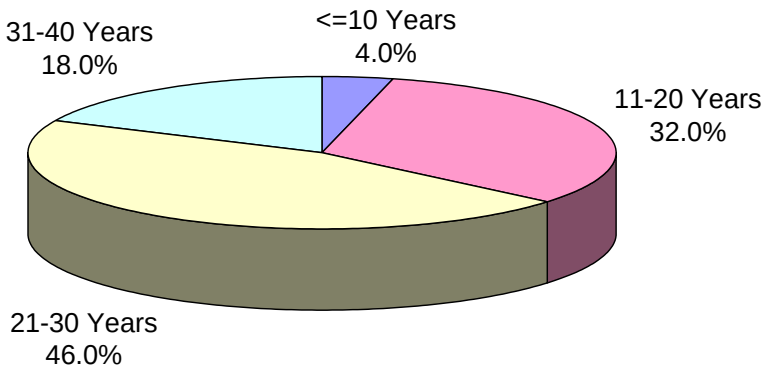
The present study was carried out to observe the effects of inhaled formocresol/fluticasone against formoterol/mometasone in bronchial asthma.

For this purpose, a total of 50 patients of bronchial asthma fulfilling the inclusion criteria and not falling in the domain of exclusion criteria were enrolled in the study.

Table 1 shows age wise distribution of patients:

Table 1: Age wise distribution of Patients

SN	Age Group	No. of Patients	Percentage
1.	≤10 Years	2	4.0
2.	11-20 Years	16	32.0
3.	21-30 Years	23	46.0
4.	31-40 Years	9	18.0
Mean Age±SD (Range) in years		22.38±7.46 (8-38)	

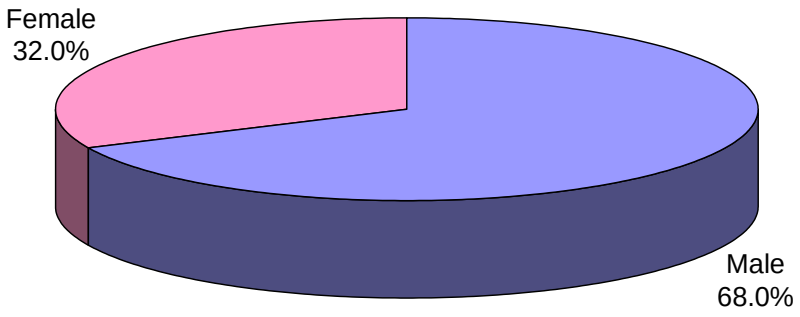


Age of patients ranged from 8 to 38 years. Maximum number of patients (n=23; 46%) were aged 21-30 years followed by those aged 11-20 years (32%). There were only 2 (4%) patients who were ≤10 years of age and 9 (18%) patients aged 31-40 years. Mean age of patients was 22.38±7.46 years.

Table 2 shows gender wise distribution of patients:

Table 2: Distribution of Patients according to gender

SN	Gender	No. of Patients	Percentage
1.	Male	34	68.0
2.	Female	16	32.0z

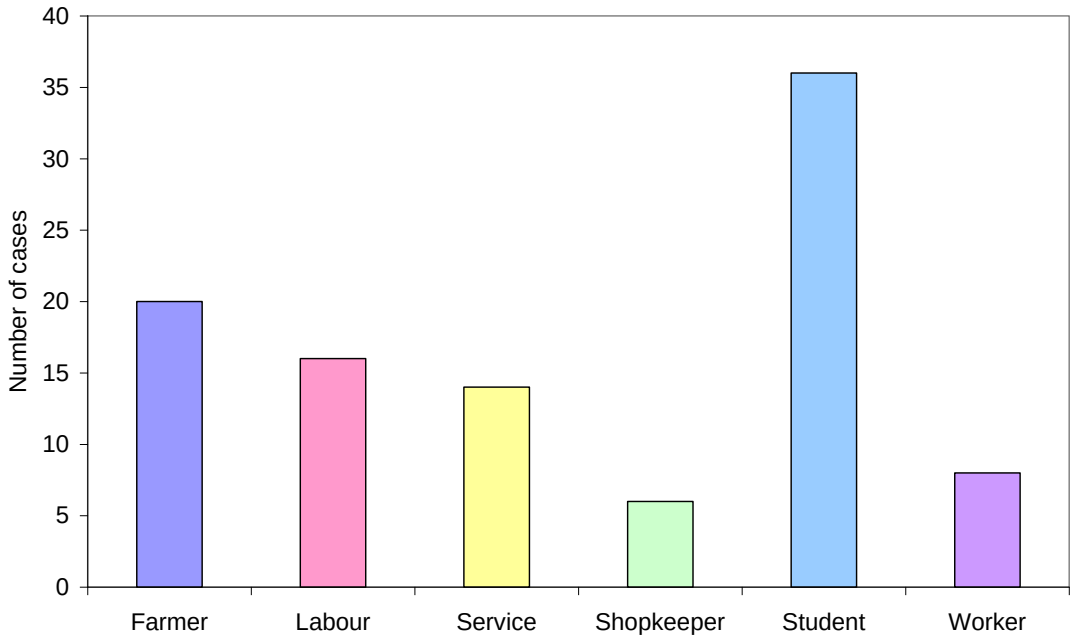


Majority of patients were males (68%). There were 16 (32%) females. Male to female ratio of patients was 2.13:1.

Table 3 shows distribution of patients according to occupation:

Table 3: Distribution of Patients according to occupation

SN	Occupation	No. of Patients	Percentage
1.	Farmer	10	20.0
2.	Labour	8	16.0
3.	Service	7	14.0
4.	Shopkeeper	3	6.0
5.	Student	18	36.0
6.	Worker	4	8.0



Maximum number of patients were students (n=18; 36%) followed by farmers (n=10; 20%), labourers (n=8; 16%), those in service (n=7; 14%), domestic workers (n=4; 8%) and shopkeepers (n=4; 8%).

DISCUSSION

Long-acting β_2 agonists in combination with inhaled glucocorticosteroids are the mainstay of severe persistent asthma treatment (Masoli, 2004)[iii]. The introduction of long acting β_2 agonists has brought a new dimension to symptomatic treatment. The long lasting bronchodilating effect of this new class of medications is especially desirable for children, who have longer night rests and more frequent periods of extensive physical activity than

most adults. Another advantage offered by long acting β_2 agonists is their twice a day application, which results in increased patient compliance (Harold, 1995; Barnes, 1996)[xxvi,xxvii]. Formoterol is a long and rapid acting, selective β_2 agonist with a bronchodilator effect lasting 12 hours (Anderson, 1995)[xxviii]. In adult patients with asthma, it is currently recommended as an alternative to increasing moderate doses of inhaled corticosteroids or as an adjunct to high doses of inhaled corticosteroids (Arvidsson, 1991; GINA, 1995)[xxix,xxx].

Mometasone is a common glucocorticosteroid being used as an adjunct to Formoterol and has shown promising results in the management of bronchial asthma**Ошибка! Закладка не определена.**-**Ошибка! Закладка не определена.**. Fluticasone is another glucocorticosteroid, use of which has recently been started as an adjunct to long acting beta agonist Formoterol and has also shown good response**Ошибка! Закладка не определена.**-**Ошибка! Закладка не определена.**. Despite being same class of drugs, there are few comparative studies comparing the efficacy of Mometasone and Fluticasone as an adjunct to Formoterol and virtually there is gap of knowledge regarding the relative superiority of either of two combinations and hence there is need to fill this gap and to substantiate the current pool of knowledge with newer findings related with safety, efficacy and acceptability in different parts of world.

With this background, the present study was carried out using a three period crossover study. A crossover study has two advantages over a non-crossover longitudinal study. First, the influence of confounding covariates is reduced because each crossover patient serves as his or her own control. In a non-crossover study, even randomized, it is often the case that different treatment-groups are found to be unbalanced on some covariates. In a controlled, randomized crossover designs, such imbalances are implausible (unless covariates were to change systematically during the study). Second, optimal crossover designs are statistically efficient and so require fewer subjects than do non-crossover designs (even other repeated measures designs). Additionally, crossover trials are suitable for the study of short term outcomes in chronic diseases or processes because the disease or process needs to persist long enough for the investigator to expose the subject to each of the experimental treatments and measure the response. Also the treatment must be one that does not permanently alter the disease or process under study (Sibbaid and Roberts, 1998)[xxxi]. From the point of view of present study, bronchial asthma is a chronic disease process which provides ample opportunity to try both the trial drugs in the same patient using a longitudinal design. This type of study design has been used effectively previously by Berger *et al.* (2013)**Ошибка! Закладка не определена.** in a randomized, multicenter, placebo-controlled, single-dose four-period crossover study. Unlike the study of Berger *et al.* (2013) who had three group combinations to compare we had only two group combinations for comparisons hence we needed only a three period study that include baseline, period 1 and period 2.

In present study age of enrolled patients ranged from 8 to 38 years. Maximum number of patients (n=23; 46%) were aged 21-30 years followed by those aged 11-20 years (32%). There were only 2 (4%) patients who were ≤10 years of age and 9 (18%) patients aged 31-40 years. Mean age of patients was 22.38±7.46 years. Asthma attacks all age groups starting from childhood (WHO, 2013)**Ошибка! Закладка не определена.**. There were two reasons for having fewer patients from younger and older age groups first, with respect to younger patients, they are generally dealt in Pediatric facility of our hospital and the present study was carried out in collaboration with Department of Pulmonary Medicine of our institution, thus the fewer number of patients in younger age groups ≤20 years could be because of restricted access. Second, with respect to elderly patients, the inclusion criteria restricted their inclusion as the study subjects. The age profile of patients in present study is similar to that reported by Anuradha *et al.* (2011)[xxxii] who also found majority of their patients to be aged between 21 to 40 years. In a nation wide multicentric study Jindal *et al.* (2010)[xxxiii] reported that below 45 years of age, age group 35-44 years is more commonly affected (45.5%) followed by age group 25-34 years (33.1%) and age group 15-24 years (21.4%) thus showing a progressive trend with increasing age. In present study too, we observed a progressive trend of proportion of bronchial asthma patients with increasing age, however, this trend was broken after 30 years of age. The reason for this was mainly because of voluntary nature of inclusion. In present study patient participation was done consensually and willingness to participate in the study was the major criteria for inclusion. Moreover, being longitudinal in nature, most of the patients aged >30 years who were working did not take part in the study as the study required a minimum of three visits. On the contrary, patients in younger age groups who were generally students and had more opportunity to spare time for repeat hospital visits for the purpose of study voluntarily took part in the study.

CONCLUSION

On the basis of observations made in present study the following conclusions can be drawn:

1. Pre-bronchodilator FEV_1 absolute values ranged from 0.57 to 2.89 with a mean value of 1.49±0.63 while FEV_1 % values ranged from 21 to 91 with a mean value of 47.56±14.73% which changed to range from 0.8 to 3.5 and attain a mean value of 1.89±0.66 in absolute terms and from 26 to 102 with a mean value of 63.98±15.17% in percentage terms, thus showing a difference ranging from 0.14 to 0.8 with a mean value of 0.40±0.19 in absolute terms and from 12 to 87 with a mean value of 25.12±15.02 in percentage terms.

2. After intervention, FEV_1 (Pre) absolute values in Group I (formoterol/ mometasone) ranged from 0.35 to 2.55 with a mean value of 1.35±0.60 and FEV_1 (Pre) % values ranged from 46 to 64 with a mean value of 55.02±5.01 which changed to range from 0.57 to 2.96 with a mean value of 1.68±0.58 for absolute and from

60 to 81 with a mean value of 72.06±5.86 for percentage. Thus showing a change ranging from 0.06 to 0.43 with a mean value of 0.27±0.08 for absolute and from 13 to 27 with a mean value of 17.62±3.76 for percentage.

3. After intervention, FEV_1 (Pre) absolute values in Group II (Formoterol/ Fluticasone) ranged from 0.45 to 2.56 with a mean value of 1.40±0.58 and FEV_1 (Pre) % values ranged from 46 to 65 with a mean value of 54.92±5.01 which changed to range from 0.69 to 3 with a mean value of 1.71±0.57 for absolute and from 61 to 85 with a mean value of 75.48±5.03 for percentage. Thus showing a change ranging from 0.08 to 0.9 with a mean value of 0.34±0.15 for absolute and from 15 to 27 with a mean value of 20.90±2.84 for percentage.

On the basis of observations in present study, the Fluticasone/ Formoterol showed an edge over Mometasone/Formoterol, however, given the limitation of time, further studies with larger sample size and longer duration are recommended to substantiate these findings.

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