

Use of beclomethasone/budesonide and formoterol adjustable dose as single maintenance and rescue therapy in the management of bronchial asthma

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Abstract

Aims: The aim of the following study is to determine the efficacy of single maintenance and rescue therapy (SMART) with adjustable dosing in management of persistent bronchial asthma. **Settings and Design:** It was a follow-up, prospective observational study over a period of 1 year in the pulmonary medicine department of a tertiary hospital. **Subjects and Methods:** Patients with newly diagnosed persistent bronchial asthma were started on a single inhaler containing budesonide/formoterol in a combination of 100 mcg/6 mcg in a dose of 4 puffs twice daily with as needed extra puffs (up to maximum 12 puffs/day) and were monitored for the subjective and objective control of asthma with parameters such as asthma control test score, forced expiratory volume in 1 s and peak expiratory flow rate in total 4 follow-up visits at 1 month, 3 months, 6 months and 1 year with step ping up or stepping down of the therapy according to the level of control of asthma. **Statistical Analysis Used:** The data was statistically analyzed by *t*-test using SPSS 14 software. **Results:** Guideline-defined asthma control could be achieved in 34 of the 40 patients and they could be successfully stepped down. Only 3 out of the 40 patients had acute exacerbations all of which were mild. They were managed by stepping up of the therapy. In another three patients stepping down was not possible due to persistence of partially controlled asthma. There was overall improved compliance on the part of the patients. **Conclusions:** SMART therapy is effective in the treatment of bronchial asthma in our kind of set-up. Only in future, similar studies need to be done with a larger sample size.

Keywords: Asthma control test score, adjustable dosing, forced expiratory volume in 1 s, peak expiratory flow rate, single maintenance and rescue therapy

Bronchial asthma is a chronic inflammatory disorder of airways associated with airway hyper responsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night/in the early morning. ^[1] These episodes are usually associated with widespread, but variable airflow obstruction that is often reversible either spontaneously or with treatment.

Asthma is one of the most common chronic diseases in the world. It is estimated that around 300 million people in the world currently have asthma. ^{[2],[3]} The estimated prevalence ranges from 1% to 18% of the population in different countries. The prevalence of asthma increases as communities adopt modern life-style and urbanization. As the proportion of people living in urban areas increases there is likely to be a marked increase in the number of people with asthma which already accounts for about 250,000 deaths and 1% of DALY's lost world-wide per year. ^[2] As far as India is concerned the estimated burden of asthma is more than 15 million. ^[4] Moreover, like many other non-communicable diseases, asthma prevalence is by the day rising more rapidly now in the developing countries. With such high prevalence comes also the cost spent on the healthcare visits for asthma therefore asthma management and control is of utmost importance.

There is no permanent cure for asthma however the disorder can be controlled. The international guidelines stipulate goals for optimizing asthma treatment such as preventing acute and chronic symptoms, minimizing exacerbations and emergency care and maintaining a normal level of physical activity.

As asthma is an inflammatory disorder the aim of treatment is to decrease inflammation by anti-inflammatory drugs and corticosteroids are the cornerstone for asthma management since they suppress virtually every step of the inflammatory cascade in asthma.

Inhaled route is the best route of corticosteroids therapy as it provides targeted drug delivery, acts faster, small dose is required and is easy to take. However, some patients require high doses of inhaled corticosteroid (ICS) to achieve an acceptable level of asthma control and this may lead to both local side-effects such as oral candidiasis, hoarseness and skin bruising and systemic side-effects, i.e., suppression of the hypothalamic-pituitary adrenal axis, osteoporosis and (in children) growth retardation. For this reason sustained release theophylline and leukotriene modifiers have been combined with ICS as an alternative to an increase in ICS doses alone. An alternative to these additional therapies are long acting β_2 agonists (LABA). Addition of a LABA to maintenance treatment with ICS improves asthma control shown by various studies. ^{[5],[6]}

The following figure highlights synergistic interaction of LABA and ICS [\[Figure 1\]](#):

At present, there are two LABA that are available-salmeterol and formoterol. Both are highly potent and selective β_2 agonists. Both being more lipophilic than short acting beta agonists (SABA), they are long acting. After inhalation both will contact the epithelium and both being lipophilic a proportion will diffuse through the epithelial cell membrane with subsequent release of small amounts that can activate β_2 receptors. ^[7] However, formoterol being more lipophilic of the two a larger proportion of it will diffuse through airway wall to exert a relaxation effect on airway smooth muscle cells; this account for its rapid onset of action (within 1-3 min) when compared with salmeterol (onset in 30 min). Both have actions that can last for 12 h at least. Hence, there can be two approaches of using ICS/LABA: One by using the combination for maintenance and giving

salbutamol, the SABA, for relief from acute exacerbations. The other one is using ICS/LABA combination for both maintenance and relief with additional puffs during acute exacerbations.

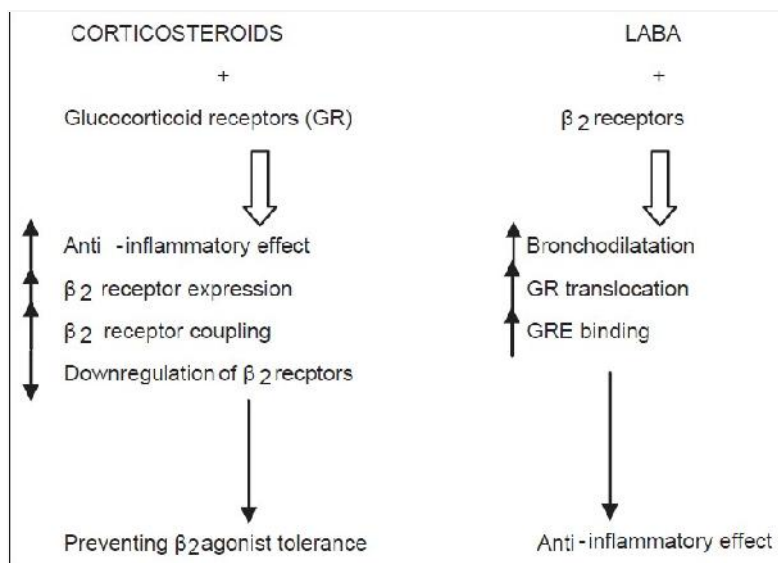


Figure 1: Synergistic interaction between corticosteroids and long acting β_2 agonists

Moreover, it has been shown that asthma being a chronic disease there are treatment failures due to reasons like poor compliance on the part of patient due to inconvenience and cost of therapy, lack of avoidance of triggers, suboptimal inhaler technique and variable response. So, one way to improve patient and provider adherence can be to simplify asthma treatment. This can be addressed by using single maintenance and rescue therapy (SMART), i.e., SMART which will involve the use of beclomethasone/budesonide and formoterol combination in a single inhaler both for maintenance and rescue therapy. Then the symptomatic control of asthma in the patient can be assessed using the Global Initiative for Asthma (GINA) guidelines [\[1\]](#) and the dose can either be stepped up (if control not achieved) or stepped down (if control achieved) i.e., adjustable dosing strategy.

In this the patient can be educated to take extra inhalations (up to 12/day) when he has acute symptoms which will mean that the patient will not have to carry a separate salbutamol inhaler for rescue therapy. This will improve compliance and also control asthma. Furthermore, due to the stepping up/stepping down approach minimum possible dose of ICS can be achieved without compromising with the symptomatic control of asthma.

Now, it therefore becomes imperative to check the efficacy of the approach in actual practice to control persistent asthma.

Hence, we conducted this study with an aim of assessing the effectiveness of SMART with regards to the subjective and objective control of persistent asthma in actual clinical practice.

Subjects and methods



A study to assess the effectiveness of SMART using adjustable dosing in the management of persistent bronchial asthma was conducted in the pulmonary medicine department of our hospital a tertiary care center.

Study description

Duration of study

The study was a follow-up study over a period of 1 year.

Design

It was an observational study.

Methodology

The study was conducted on 40 patients diagnosed as persistent asthma and of age above 12 years of both sexes. The following criteria were then applied:

Inclusion criteria

1. Patient willing to participate in the study
2. Patient willing to follow-up as required
3. Age of the patient > 12 year; both the sexes
4. Patient should be a diagnosed case of persistent bronchial asthma according to the GINA guidelines.

Exclusion criteria

1. Patient not willing to participate in the study
2. Patient not willing to follow-up regularly
3. Patients < 12 years of age
4. Patients of bronchial asthma who are diagnosed as intermittent asthma according to GINA guidelines
5. Patients with any known contraindications for the use of either of the two medications used in the study.

Parameters studied at the initiation of study

A detailed medical history was obtained and a detailed physical examination done of each subject. Baseline investigations carried out included a complete blood count, fasting blood sugar level, blood urea nitrogen, human immunodeficiency virus, serum immunoglobulin E levels and a chest radiograph.

Follow-up

The patients were followed-up over the duration of 1 year from the start of therapy. The nature of visits being:

- Visit 1: At the start of therapy
- Visit 2: At 1st month
- Visit 3: At 3rd month
- Visit 4: At 6th month

- Visit 5: At 1 year.

Details of drug therapy

The subjects then received beclomethasone/budesonide and formoterol 100 mcg/6 mcg in a single inhaler as 4 puffs twice daily; started at the 1st visit. They were then assessed for the level of control of bronchial asthma (according to GINA guidelines) at every visit. Those having their asthma controlled at any visit during follow-up had the dose reduced (step down) to 2 puffs twice daily where as those not having symptomatic control of their asthma were continued on the same dosage until control of symptoms. The patient who had worsening of asthma after step down of therapy at the previous visit were again given the earlier dose of 4 puffs twice daily, i.e., step up. In either of the cases the patients were allowed up to 12 extra puffs through the same inhaler, i.e., using it as SMART. The patients were to report to clinician immediately in case of no relief even after the above treatment. The patients continued to use the same therapy for the entire duration of 1 year.

Assessment at every visit

At every visit a detailed history regarding frequency of day time symptoms, nocturnal symptoms, limitation of daily activity, need for rescue medication, their self-perception of level of control and any acute exacerbation.

Asthma control test (ACT) score was calculated using the above. ^[8] Peak expiratory flow rate (PEFR) was measured with Wrights peak flow meter. Forced expiratory volume in 1 s (FEV1) value obtained from spirometry data.

Results

At the end of study, patients were assessed in terms of above parameters using Microsoft excel software and SPSS software. Statistical analysis was performed with the *t*-test. Then, it was evaluated as the impact on control and management of persistent asthma in terms of these parameters.

Results



The study carried out in pulmonary medicine department of our institute - a tertiary care center included 40 patients of diagnosed persistent bronchial asthma as per GINA guidelines [\[Table 1\]](#), [\[Table 2\]](#) and [\[Table 3\]](#).

Basic features	Details
Mean age of patients	43.8 years
Male/female	20/20
Average baseline ACT score	13.55
Average baseline FEV ₁	54.2%
Average baseline PEFR	254.75
Severity of asthma (%)	Number of patients
Mild (FEV ₁ > 80)	0
Moderate (FEV ₁ – 60-80)	13
Severe (FEV ₁ < 60)	27
Formoterol + budesonide baseline dose	800 mcg/48 mcg
Number of exacerbation of therapy	3

ACT - Asthma control test, FEV₁ - Forced expiratory volume in 1 s, PEFR - Peak expiratory flow rate

Table 1: Baseline characteristics of the study group were as follows

	Mean	SD	Minimum	Maximum
Age (year)	43.13	14.53	17	83
PEFR	254.75	71.07	150	450
FEV ₁ %	54.28	12.56	24.00	79.00

SD - Standard deviation, FEV₁ - Forced expiratory volume in 1 s, PEFR - Peak expiratory flow rate

Table 2: Descriptive statistics for baseline characteristics of the study group were as follows

	N	Percentage
Gender		
Female	20	50.0
Male	20	50.0
Total	40	100.0
Severity of asthma		
Severe	27	67.5
Moderate	13	32.5
Mild	0	0.00
Total	40	100.0

Table 3: Gender and severity of asthma

Age and sex distribution

Out of 40 patients 20 were male and 20 female [\[Figure 2\]](#) and [\[Figure 3\]](#).

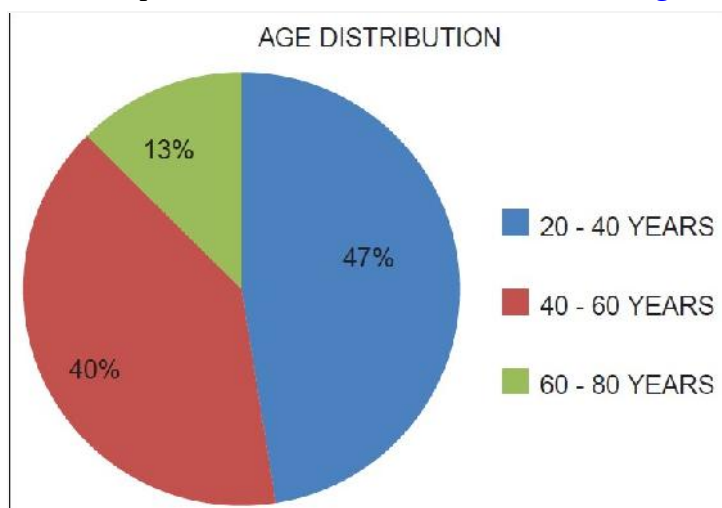


Figure 2: Pie chart showing age distribution among study population

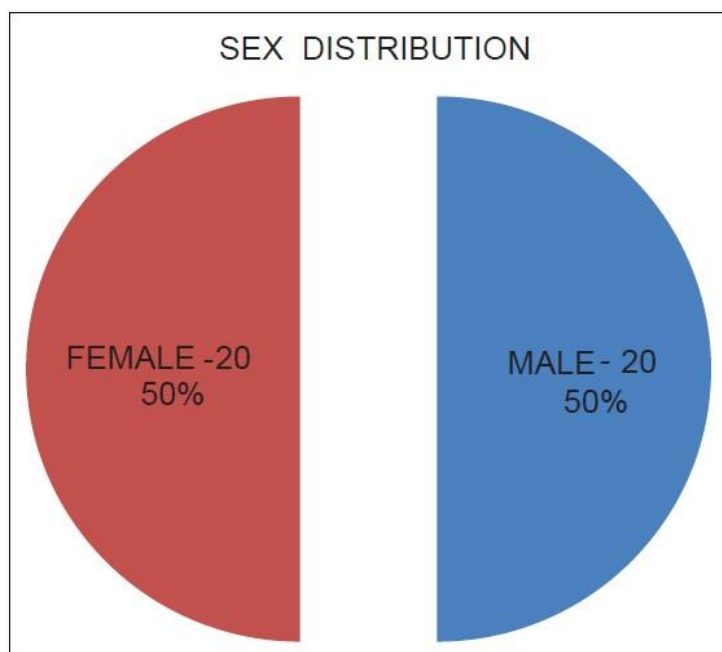


Figure 3: Pie chart showing sex distribution among study population

ACT score

$P < 0.005$ indicates there was a significant improvement in asthma as demonstrated by significant improvement in ACT score [\[Table 4\]](#), [\[Table 5\]](#) and [\[Table 6\]](#) and [\[Figure 4\]](#) and [\[Figure 5\]](#).

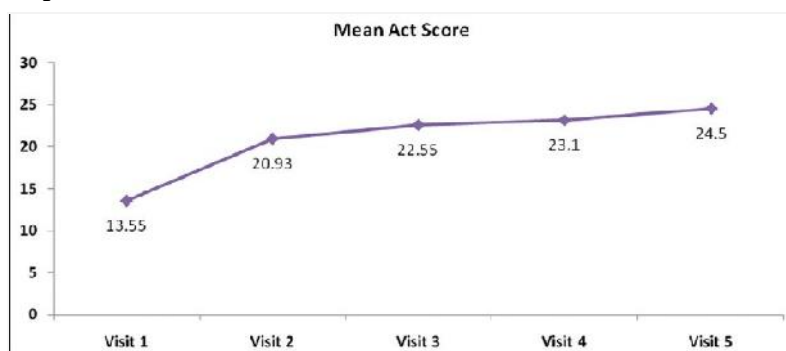


Figure 4: Graph showing improvement in mean asthma control test score during follow-up visits

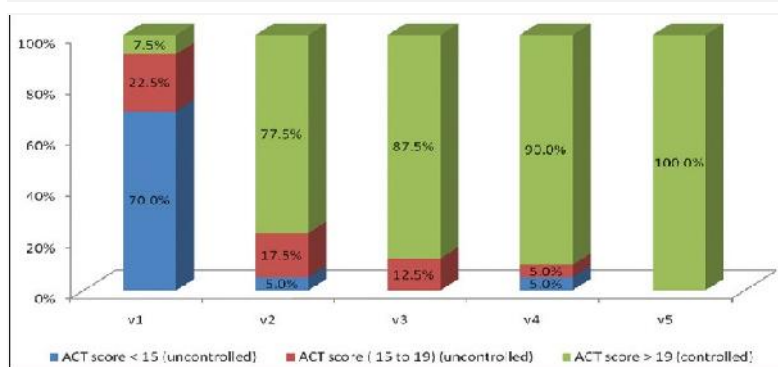


Figure 5: Bar diagram showing improvement in control of asthma by mean asthma control test score during follow-up visits

Parameters	Visit	N	Mean	SD	Minimum	Maximum
ACT score	1	40	13.55	2.94	10	20
	2	40	20.93	3.11	12	25
	3	40	22.55	2.33	17	25
	4	40	23.10	3.37	11	25
	5	40	24.50	1.22	20	25

ACT - Asthma control test, SD - Standard deviation

Table 4: Descriptive statistics of ACT score

	Mean	SD	SE for mean	95% CI Lower	Upper	P value
Par 1						
V1-V2	-1.38	2.960	0.468	-8.32	-5.43	0.000
Par 2						
V1-V2	-1.80	2.457	0.547	-10.11	-7.89	0.000
Par 3						
V1-V4	-1.55	2.987	0.630	-10.33	-9.21	0.000
Par 4						
V1-V5	-10.85	2.905	0.458	-11.88	-10.02	0.000

ACT - Asthma control test; SD - Standard deviation; SE - Standard error; CI - Confidence interval

Table 5: Paired sample *t* test for ACT score

	#	Percentage
ACT score < 15 (uncontrolled)		
V1	28	70.00
V2	2	5.00
V3	0	0.00
V4	0	0.00
V5	0	0.00
ACT score (5-19) (controlled)		
V1	8	20.00
V2	7	17.50
V3	8	20.00
V4	2	5.00
V5	0	0.00
ACT score > 19 (controlled)		
V1	3	7.50
V2	31	77.50
V3	29	72.50
V4	35	87.50
V5	40	100.00

ACT - Asthma control test

Table 6: Asthma control by ACT score

There was significant increment (from 7.5% to 100%) in controlled asthma from baseline to visit 5.

All patients had a better asthma control as shown by:

1. Significant reduction in daytime symptoms
2. Significant reduction in nocturnal symptoms
3. Significant reduction in limitation of daily activity
4. Significant reduction in need for rescue medication
5. A better asthma control as per patients self-perception of level of control of asthma.

An improvement in all above factors was reflected by an improvement in ACT score which is a net total of all these factors.

Thus, there was a significant improvement in asthma control as demonstrated by significant improvement in ACT score.

FEV₁

There was a significant improvement in the mean FEV₁ at all 5 successive visits. $P < 0.005$ suggests statistically significant improvement in FEV₁ in each visit compared to first visit [Table 7] and [Table 8], [Figure 6].

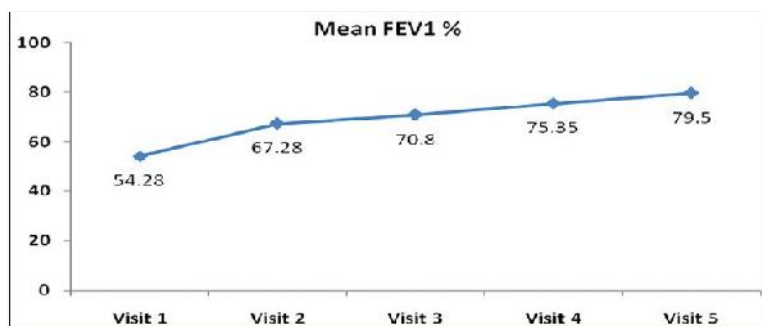


Figure 6: Graph showing improvement in mean forced expiratory volume in 1 s during follow-up visits

Parameters	Visit	N	Mean	SD	Minimum	Maximum
FEV ₁ %	1	40	54.28	12.56	24	79
	2	40	67.28	12.90	37	95
	3	40	70.80	15.71	8	96
	4	40	75.35	13.74	35	94
	5	40	79.50	9.81	53	99

FEV₁ - Forced expiratory volume in 1 s, SD - Standard deviation

Table 7: Descriptive statistics of FEV₁%

	Mean	SD	SE for mean	95% CI		P value
				Lower	Upper	
Pair 1						
V1-V2	-13.00	11.03	1.74	-16.53	-9.47	0.000
Pair 2						
V1-V3	-16.53	15.57	2.46	-21.51	-11.54	0.000
Pair 3						
V1-V4	-21.08	13.30	2.10	-25.33	-16.82	0.000
Pair 4						
V1-V5	-25.23	12.22	1.93	-29.13	-21.32	0.000

SD - Standard deviation, SE - Standard error, CI - Confidence interval, FEV₁ - Forced expiratory volume in 1 s

Table 8: Paired sample *t* test for FEV₁%

PEFR

There was a significant improvement in the mean PEFR at all five successive visits [Table 9] and [Table 10], [Figure 7].

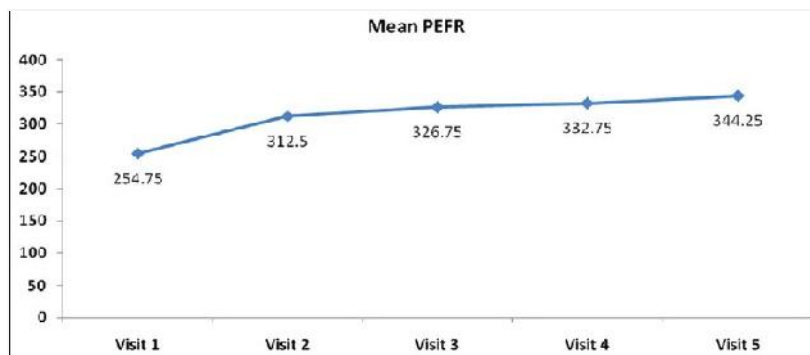


Figure 7: Graph showing improvement in mean peak expiratory flow rate during follow-up visits

Parameters	Visit	N	Mean	SD	Minimum	Maximum
PEFR	1	40	254.75	71.07	150	450
	2	40	312.50	86.82	150	500
	3	40	326.75	79.53	160	500
	4	40	332.75	89.47	180	520
	5	40	344.25	80.03	200	550

SD - Standard deviation, PEFR - Peak expiratory flow rate

Table 9: Descriptive statistics of PEFR

	Mean	SD	SE for mean	95% CI		P value
				Lower	Upper	
Pair 1						
V1-V2	-57.75	41.79	6.61	-71.11	-44.39	0.000
Pair 2						
V1-V3	-72.00	41.89	6.62	-85.40	-58.60	0.000
Pair 3						
V1-V4	-78.00	52.10	8.24	-94.66	-61.34	0.000
Pair 4						
V1-V5	-89.50	46.52	7.36	-104.38	-74.62	0.000

SD - Standard deviation, SE - Standard error, CI - Confidence interval, PEFR - Peak expiratory flow rate

Table 10: Paired sample *t* test for PEFR

Step-down of therapy

Thirty four out of 40 patients (85%) achieved normal lung functions ($FEV_1 > 80\%$) while on therapy. Hence, in these 34 patients therapy was stepped down. (Dose of budesonide and formoterol decreased to 4 puffs of 100 mcg/8 mcg daily instead of 8 puffs) [Table 11], [Figure 8] and [Figure 9].

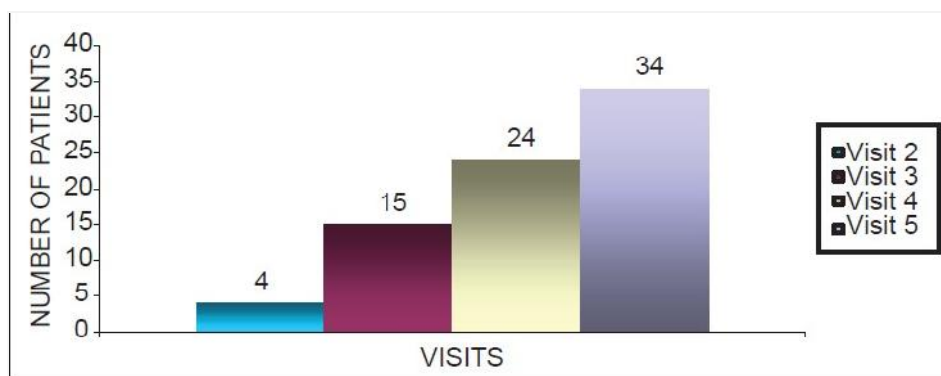


Figure 8: Bar diagram showing number of patients stepped down during follow-up visits

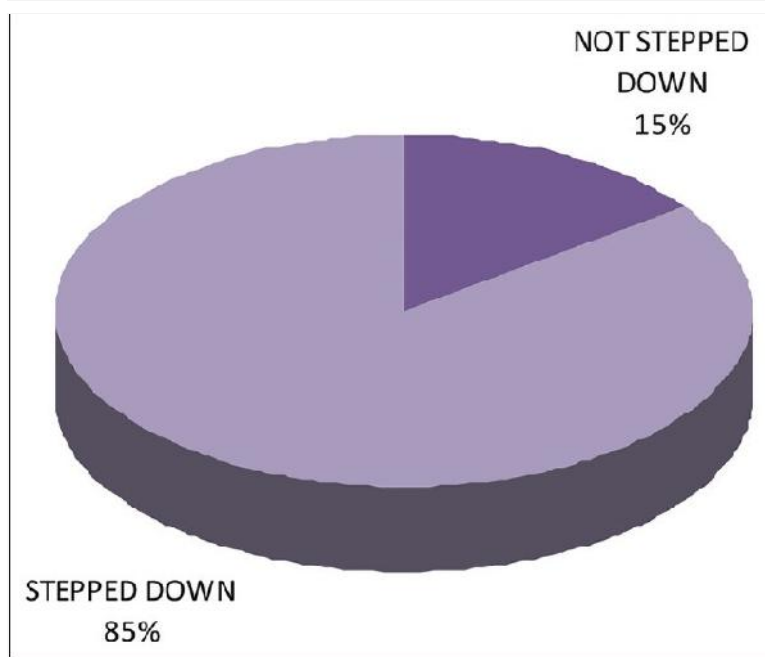


Figure 9: Pie chart showing percentage of patients stepped down

Visits	Number of patients stepped down
2	4
3	15
4	24
5	34

Table 11: Step down therapy

Improvement in subjective parameter (ACT score) and objective parameters (FEV1 and PEFR) persisted even after step down of therapy after achieving control and normal lung function.

Six out of 40 patients (15%) were not stepped down as they continued to have partially controlled asthma.

Number of acute exacerbations

- Three out of 40 patients had acute exacerbation during therapy
- All the exacerbation were mild (as per GINA guideline), none requiring hospitalization
- Reasons for exacerbations:
- In two patients it was non-compliance to inhaler therapy due to non-affordability
- In one patient the cause of exacerbation was upper respiratory tract infection
- All of these were successfully managed on an outpatient basis by stepping up of the dose to the baseline maintenance dose and additional 5 day course of oral macrolide antibiotic in the patient having upper respiratory tract infection.

Improvement in compliance

- A salient feature of this study was a considerable improvement in compliance to therapy on the part of patients
- The reasons for improved compliance were simplicity of therapy. (Single inhaler for maintenance and rescue) and also cost-effectiveness.

Discussion



We began this endeavor with an intention to assess the efficacy of SMART using adjustable dosing in managing persistent asthma. In our study, patients received therapy with an inhaler containing a combination of beclomethasone/budesonide and formoterol which was used both as maintenance and rescue therapy. Although on this therapy the patients were followed-up at 1 month, 3 months, 6 months and 1 year. At each visit, the control of asthma was assessed by subjective and objective parameters as per GINA guidelines

Therapy was accordingly stepped up, stepped down or kept the same for each individualized patient as per level of control; i.e., adjustable variable dosing. Thus SMART approach and adjustable/variable dosing were two highlights of our study.

The study group consisted of 40 patients - 20 men and 20 women in the age group 18-80 years; mean age being 43.8 years. 13 patients were moderate persistent bronchial asthma and 27 severe persistent bronchial asthma. SMART therapy was shown to be highly efficacious in achieving asthma control. The improvement in asthma as assessed by subjective (ACT score) and objective (FEV1 and PEFr) parameter was as follows:

- There was an improvement in ACT score and FEV1 and PEFr at each successive visits and the improvement in these parameters at each successive visits was shown to be statistically highly significant ($P < 0.0001$).
- More the duration of SMART therapy higher the values ACT score, FEV1, PEFr achieved.
- At the end of 1 year of SMART therapy all 13 patients of moderate persistent asthma and 22 of 27 patients of severe persistent bronchial asthma had achieved controlled asthma and normal lung functions (FEV1 > 80%).
- 90% and 100% of patients at visits 4 and 5 had ACT score more than 19. Also patients who achieved control of asthma were stepped down successfully to half the dose and were controlled at same.
- 24 out of 40 (60%) and 34 out of 40 (85%) patients were stepped down until 6th month and 1 year after SMART therapy.

Only three patients had mild exacerbations. In two out of three patients reason for exacerbation was non-compliance due to non-affordability, who was managed with only step up of therapy. In 3rd patient, the exacerbation was due to upper respiratory tract infection which was managed with antibiotic therapy along with step up of therapy. Thus, our study showed that SMART approach achieved control of asthma with minimum ICS doses without increasing risk of exacerbation.

Similar to our study, various other studies have evaluated benefits and drawbacks of this approach. There are currently eight published studies investigating the SMART approach. [\[9\],\[10\],\[11\],\[12\],\[13\],\[14\],\[15\],\[16\]](#) The first 3 studies compared SMART to higher maintenance dose of budesonide. These studies show decrease in number of exacerbation as well as improvement in FEV1 and symptoms with SMART approach. These could be expected, since the FACET study already showed the combination therapy is superior to treatment with ICS alone. [\[5\]](#)

Further studies have compared the SMART approach to fixed dosing with fluticasone/salmeterol [\[17\],\[18\]](#) One study compared the SMART approach using a maintenance dose of budesonide/formoterol (320 mcg/9 mg) bid with an additional dose of budesonide/formoterol (160 mcg/4.5 mg) as needed to fixed dosing with fluticasone/salmeterol (500 mcg/50 mcg) bid. [\[19\]](#) In that study, the SMART approach had a better outcome for the number of exacerbation without a difference in lung function. In addition, the mean dose of ICS was lower with SMART (792 mcg budesonide vs. 1000 mcg fluticasone). Finally, an open label study was carried out by Vogelmeier *et al.* [\[16\]](#) They compared SMART to fixed dosing with fluticasone/salmeterol. With the SMART approach, the budesonide/formoterol maintenance dose could be titrated in accordance to normal clinical practice to either 100 mcg/4.5 mcg bid or 320 mcg/9 mcg bid. In addition, patients were allowed to use budesonide/formoterol 100 mcg/4.5 mcg as needed. With fluticasone/salmeterol, the dose could also be titrated to 100 mcg/50 mcg bid, 250 mcg/50 mg bid and 500 mcg/50 mcg bid. This study again showed a reduced exacerbation rate in favor of SMART approach, while the doses of ICS used were similar (mean 653 mcg budesonide/day vs. 583 mcg fluticasone/day).

In our study, we used variable adjustable dosing strategy with SMART approach. Various studies have evaluated the benefits and drawbacks of this approach. Three studies have directly compared

the adjustable maintenance dosing strategy with budesonide/formoterol to a fixed dose fluticasone/salmeterol. ^{[19],[20],[21]}

In the CONCEPT study, Fitzgerald *et al.* found a lower number of exacerbation and less symptoms in patients using fixed dose fluticasone/salmeterol 250 mcg/50 mcg bid compared to budesonide/formoterol adjustable maintenance dosing. ^[20] However, the CONCEPT study used a different adjustable maintenance dosing scheme with step down the dose of budesonide/formoterol that was lower than that used in all other studies with adjustable maintenance dosing (budesonide/formoterol 160 mcg/4.5 mg once daily vs. bid), which may well explain the favorable results with the fixed dosing regimen. Indeed, two subsequent studies using the advocated step down approach showed no difference in asthma control between fluticasone/salmeterol (250 mcg/50 mcg) bid and budesonide/formoterol adjustable maintenance dosing. ^{[19],[21]}

Treatment with single inhaler containing both an ICS and LABA has the advantage that it simplifies the management of asthma patients and this is likely to increase patient compliance. ^{[22],[23]} In agree with this, Rosenhall *et al.* found a lower number of withdrawals during their 12 month study after treatment with budesonide and formoterol in a single inhaler compared to treatment administered through separate inhalers. ^[24] In a similar way compliance on the part of patients was found to be significantly improved in our study which can be considered as a big plus point toward this treatment approach.

Hence, we suggest that SMART approach of asthma management with adjustable dosing should be used more frequently in the future for appropriate patients. But more studies with large sample size in Indian setup need to be done with longer duration of follow-ups to be able to formulate locally useful guideline for asthma management as the majority of international guidelines are based on studies done in developed countries where affordability and other socio-economic factors may be totally different.

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