

Comparative Efficacy of Budesonide by Different Delivery Devices in Bronchial Asthma

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ABSTRACT

Aims& Objective: To assess the relative efficiency of budesonide administered from different delivery devices to adult patients of chronic stable bronchial asthma as measured by pulmonary function test parameters.

Materials and Methods: This prospective study was undertaken to assess the relative efficiency of budesonide administered from different delivery devices to adult patients of chronic stable bronchial asthma as measured by pulmonary function test parameters. Fifty subjects were administered budesonide (1 mg) via nebulizer, budesonide (400 microgram) by metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler consecutively each week for four weeks under direct supervision. Pulmonary function test was done before and one hour after administration of the drug on each visit.

Results: No significant difference in Peak expiratory flow rate ($P=0.77$), forced expiratory volume in one second ($P=0.95$), forced vital capacity ($P=0.24$) and forced expiratory volume in one second and forced vital capacity ratio ($P=0.22$) was seen after giving budesonide by different devices.

Conclusion: Budesonide delivered by different devices (nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler) have similar effect on lung function in patients of chronic stable bronchial asthma and may be used interchangeably.

KEY WORDS: Budesonide; Comparative Study; Asthma

INTRODUCTION

Inhaled corticosteroids are the most effective drugs for the treatment of asthma and they represent first-line therapy for all patients with persistent disease, irrespective of disease severity.^[1] The clinical benefit of inhaled

corticosteroids therapy is determined by a complex interplay between the nature and severity of the disease, the type of drug and its formulation, and characteristics of delivery device together with the patient's ability to use the device correctly.^[2] Studies have demonstrated their efficacy in reducing symptom, frequency

and severity of asthma exacerbations and asthma mortality. Inhaled corticosteroids are marketed with different delivery devices, which have different lung deposition properties, in vivo dosage accuracy and dose variability.^[3] The major advantage of inhaled therapy is that drugs are delivered directly into the airways producing higher local concentrations with significantly less risk of systemic side effects.

Inhaled medications for asthma are available as pressurized metered dose inhaler, metered dose inhaler with spacer, breath-actuated metered dose inhaler, dry powder inhalers, soft mist inhalers and nebulized or wet aerosols. In most of studies the inhaled corticosteroids for the treatment of bronchial asthma have been administered by one or two of the devices as stated above. To the best of our knowledge there is no Indian study comparing clinical efficacy of budesonide delivered via nebulizer, metered dose inhaler and dry powder inhaler in patients of chronic stable bronchial asthma.

With inhaled corticosteroids being the mainstay of anti-inflammatory treatment in asthma, it is necessary to determine the comparative efficacy of different corticosteroids delivered through different inhaler devices. The present study was undertaken to assess the relative efficiency of budesonide administered from different delivery devices to adult patients of chronic stable bronchial asthma as measured by pulmonary function test parameters.

MATERIALS AND METHODS

This prospective eighteen months study was conducted among clinically diagnosed patients of chronic stable bronchial asthma from out patient department of Tuberculosis and Chest Diseases, Era's Lucknow Medical College and Hospital, Lucknow. Individuals of either sex aged 18 years and above, who were residents of the local area and had a history of bronchial asthma for at least 6 months comprised the study unit. Approval for the study from the Institutional ethical committee was obtained and written and informed consent from all patients was taken.

Sample size was calculated to be 36 on the basis of prior observations reported in a previous study^[4] using the formula: $n = (\sigma_1^2 + \sigma_2^2) (Z_{1-\alpha/2} + Z_{1-\beta})^2 / d^2$ where $\sigma_1 = 3.4$, $\sigma_2 = 4.7$, $d = 3.4$, $Z_{1-\alpha/2} = 1.96$, $Z_{1-\beta} = 1.28$, $\alpha = .05$ and $\beta = 0.1$ (power 90%). But assuming loss to follow up cases to be 40% (10% for each step), the initial recruitment was calculated to be 46 which was further rounded off to 50 cases.

The subjects fulfilling the following criteria were considered to be suffering from chronic stable bronchial asthma as defined by American Thoracic society 1987.^[5]

- i. History suggestive of bronchial asthma
- ii. No acute exacerbation (episodes of progressive increase in shortness of breath, cough, wheezing, or chest tightness, or some combination of these symptoms) within the past one month
- iii. No history of receiving any corticosteroid therapy for past one month
- iv. Baseline forced expiratory volume in one second (FEV₁) less than 80% of predicted value
- v. Increase in FEV₁ equal or more than to 12% and peak expiratory flow rate (PEFR) equal or more than to 20% of baseline value 15 minutes after bronchodilator therapy.

Patients with past history of hypersensitivity to budesonide, history of treatment of asthma within four weeks prior to study were excluded. Pregnant and lactating females, subjects with hepatic, cardiac, renal and respiratory disorders and those with an upper respiratory tract or acute sinus infection within four weeks prior to enrollment were also excluded. Individuals with a smoking history of >10 pack-years and those on immunotherapy who required a change in dosage regimen within 12 weeks prior to enrollment were also excluded.

All study subjects underwent pulmonary function tests before and one hour after drug administration. Inhaled Salbutamol 200 mcg was administered on first visit (day-1) to assess bronchodilator reversibility and to fulfill the criteria of bronchial asthma. A single dose of Budesonide 1mg by nebulizer was given on the

second visit (day-8). On the third visit (day 15), a single dose of Budesonide 400mcg by metered dose inhaler was given and on the fourth visit (day 22) a single dose of Budesonide 400mcg by metered dose inhaler with spacer was administered. Finally on the fifth visit (day 29) a single dose of Budesonide 400mcg by dry powder inhaler.

After a standardized initial evaluation, which included complete history taking, clinical examination, investigations, asthma symptom score and spirometry, patients were requested to follow up every week for 4 weeks. Each patient was given a card in which as needed salbutamol inhalation was to be mentioned by the patients themselves and they were requested to bring the card along with them when they came after one week. Each patient was given a diary card to encircle asthma symptoms.

The severity of Asthma was assessed by symptom score as mentioned by Calverley et al (2005)^[6] that included major complains of asthma i.e. (i) shortness of breath, (ii) cough (iii) chest tightness (iv) night time awakening. The individual score of above four parameters were added up to get the cumulative asthma score. Graded scoring system was used to note patients complain and severity.

Spirometry was done at the beginning of study. Before spirometry it was ascertained that the patient had not taken inhaled β_2 agonist (salbutamol) therapy for at least 6 hours, theophylline therapy for at least 24 hours, and antihistamine therapy for at least 48 hours and coffee for at least 4 hours. Spirometry was performed with standard techniques and evaluated for validity according to American Thoracic Society criteria (1995)^[7] using Medspiror (Medsystems Private Limited, Chandigarh). At least three spirometry maneuvers were done and highest FEV₁ value was noted. Patients who had FEV₁, less than 80% of predicted value were administered inhaled salbutamol 200mcg by nebulizer. Fifteen minutes after salbutamol administration spirometry was repeated and those patients who had an increase of at least 12% absolute FEV₁ and at least 20%

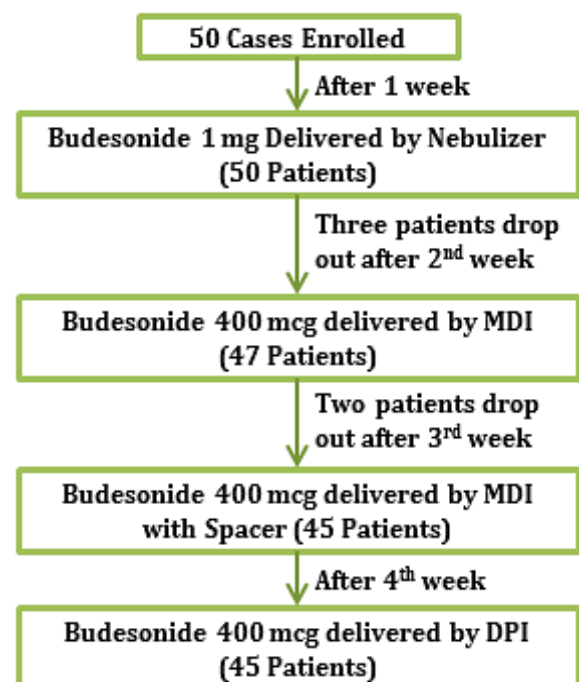
PEFR were labeled as suffering from bronchial asthma and enrolled in the study. Pre and post medication pulmonary function test (PFT) reports were collected. Thus in all, patients had to visit the department for 5 times including nomination, registration and 4 follow up visits.

Data entry and statistical analysis was done using statistically package of social science (SPSS) software (version 17.0). Paired “t” test, ANOVA and post hoc turkey’s test were used. P values less than 0.05 were considered significant.

RESULTS

Initially 50 patients were enrolled in the study out of which, 3 did not turn up after second visit and 2 did not turn up after third visit. None of the patients experienced an acute exacerbation of asthma during the study period. Thus finally 5 patients were excluded due to loss to follow up and the data of the remaining 45 subjects (27 males and 18 females) was analyzed (Figure 1). Twenty four (53.3%) individuals were aged between 18-40 years, 17 (37.7%) individuals were aged between 41-60 years and 4 (8.9%) individuals were aged between 61-70 years. The mean age of the patients was found to be 42 years.

Figure-1: Study Design and Execution



Mean asthma scores calculated from diary card entries varied between 1.97 to 2.09 on days of visits. There was no significant difference in patient's asthma symptom score per week at day 1, 8, 15, 22 and 29 ($P>0.05$). Since there was no significant change in pulmonary function test parameters (before the giving budesonide) at week-2, week-3, week-4, week-5, which shows that the patients were suffering from chronic stable bronchial asthma and there was no significant modification in the disease process during the course of the study. No significant change in the asthma symptom scores and use of rescue medication during the study periods also shows that there was no acute exacerbation and the patients were stable. [Table-1]

Table-1: Asthma Symptom Score of the Patients

	Shortness of breath	Cough	Chest Tightness	Night time awakening	Total
Day 1	0.78±0.73	0.68±0.63	0.36±0.48	0.26±0.44	2.09±0.79
Day 8	0.73±0.62	0.71±0.59	0.40±0.49	0.24±0.43	2.08±0.70
Day 15	0.76±0.61	0.64±0.57	0.33±0.47	0.24±0.43	1.98±0.75
Day 22	0.77±0.63	0.64±0.61	0.36±0.48	0.24±0.43	2.02±0.43
Day 29	0.73±0.57	0.68±0.63	0.33±0.47	0.22±0.42	1.97±0.72
ANOVA					
F=	0.056	0.108	0.143	0.059	0.252
P=	0.994	0.979	0.966	0.908	0.908

Pretreatment values of peak expiratory flow rate varied between 30- 47%, 31- 48 %, 33- 50 % and 33- 48 % before giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) respectively. There was no significant difference in PEFr values at week 2, 3, 4 and 5, before giving the drug by different devices ($P>0.05$). [Table-2]

Pretreatment values of forced expiratory volume in 1 second varied between 61 - 74%, 60 -77%, 62 -75% and 58 - 77% before giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) respectively. There was no significant difference

in FEV₁ values at week 2, 3, 4 and 5, before giving the drug by different devices ($P>0.05$). [Table-3]

Table-2: Effect on Peak Expiratory Flow Rate (PEFR) (Predicted %) after Giving Budesonide by Different Devices

Devices		PEFR	
		Pre-treatment Value (Mean± S.D)	Post-treatment Value (Mean± S.D)
Nebulizer		39.71 ± 4.03	43.49 ± 3.76
Metered Dose Inhaler		40.33 ± 4.11	43.04 ± 4.18
Metered Dose Inhaler with Spacer		41.07 ± 4.54	43.87 ± 4.19
Dry Powder Inhaler		40.18 ± 3.59	43.01 ± 3.13
ANOVA	F value	0.85	0.38
	P value	0.46	0.77

Table-3: Effect on Forced Expiratory Volume in 1 Second (FEV₁) (Predicted %) after Giving Budesonide by Different Devices

Devices		FEV ₁	
		Pre-treatment Value (Mean± S.D)	Post-treatment Value (Mean± S.D)
Nebulizer		67.36 ± 2.97	72.58±3.37
Metered Dose Inhaler		67.42 ± 4.81	72.13±4.79
Metered Dose Inhaler with Spacer		68.20 ± 3.79	72.49±3.97
Dry Powder Inhaler		68.18 ± 4.78	72.16±4.96
ANOVA	F value	0.58	0.13
	P value	0.63	0.95

Pretreatment values of forced vital capacity varied between 82 - 98%, 82 - 101%, 84 - 102% and 84 - 103% before giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) respectively. There was no significant difference in FVC values at week 2, 3, 4 and 5 before giving the drug by different devices ($P>0.05$). [Table-4]

Table-4: Effect on Forced Vital Capacity (FVC) (Predicted %) after Giving Budesonide by Different Devices

Devices		FVC	
		Pre-treatment Value (Mean± S.D)	Post-treatment Value (Mean± S.D)
Nebulizer		90.64±3.94	95.67±4.59
Metered Dose Inhaler		90.33±4.89	94.20±5.39
Metered Dose Inhaler with Spacer		92.16±5.09	96.27±5.35
Dry Powder Inhaler		92.36±5.45	96.11±5.98
ANOVA	F value	2.01	1.39
	P value	0.11	0.24

Pretreatment values of FEV₁/FVC varied between 0.68 - 0.82%, 0.70 - 0.83%, 0.66 - 0.83% and 0.66 - 0.83% before giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) respectively. There was no significant difference in FEV₁/FVC values at week 2, 3, 4 and 5, before giving the drug by different devices (P>0.05). [Table-5]

Table-5: Effect on FEV₁/FVC (Predicted %) after Giving Budesonide by Different Devices

Devices		FEV ₁ /FVC	
		Pre-treatment Value (Mean± S.D)	Post-treatment Value (Mean± S.D)
Nebulizer		0.74±.03	0.76±.04
Metered Dose Inhaler		0.75±.03	0.76±.03
Metered Dose Inhaler with Spacer		0.74±.03	0.75±.03
Dry Powder Inhaler		0.73±.04	0.75±.04
ANOVA	F value	0.41	1.49
	P value	0.75	0.22

One hour after giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) there was highly significant increase in PEFR (P<0.001). The percentage change in PEFR was highest after giving budesonide by nebulizer (37 - 50%) followed by dry powder inhaler (33 - 50%),

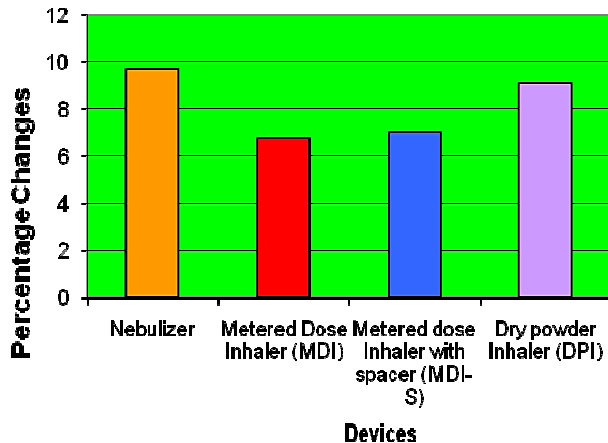
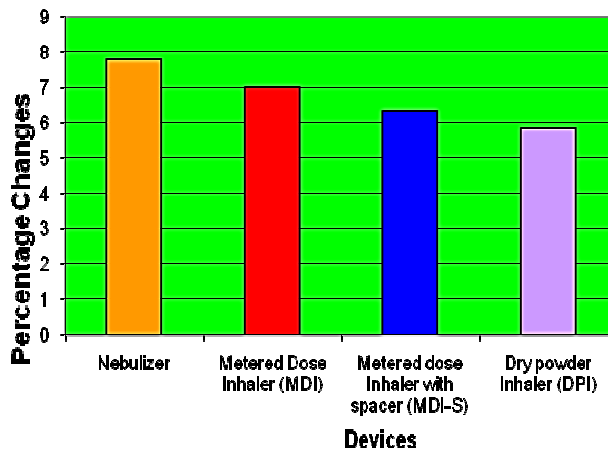
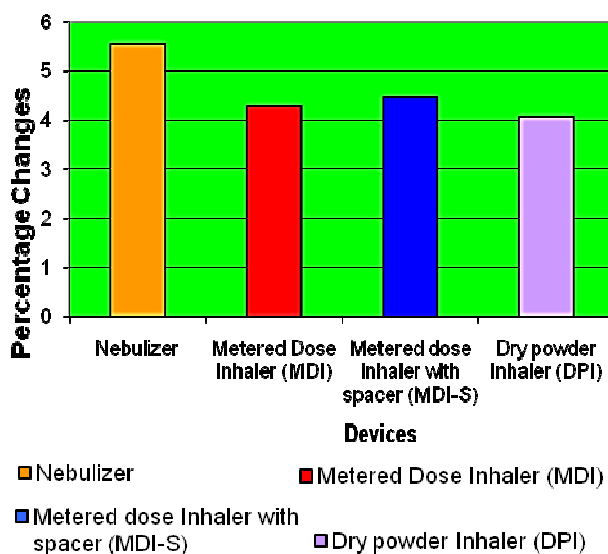
metered dose inhaler with spacer (36 - 53 %) and metered dose inhaler (36 - 50 %). However there was no significant difference in the PEFR after giving budesonide by any of the devices (P>0.05). [Figure 2]

One hour after giving budesonide by the different devices at week 2, 3, 4 and 5, there was highly significant increase in FEV₁ (P<0.001). The post treatment values of FEV₁ ranged between 66 - 82%, 63 - 81%, 64 - 79% and 66 - 82% by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler respectively, the difference being statistically insignificant (P>0.05). [Figure 3]

One hour after giving budesonide by different devices at week 2, 3, 4 and 5, there was highly significant increase in FVC (P<0.001). The percentage change in FVC ranged between 87 - 106%, 87 - 105%, 86 - 106% and 87 - 107% by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler respectively, the difference being statistically insignificant (P>0.05). [Figure 4]

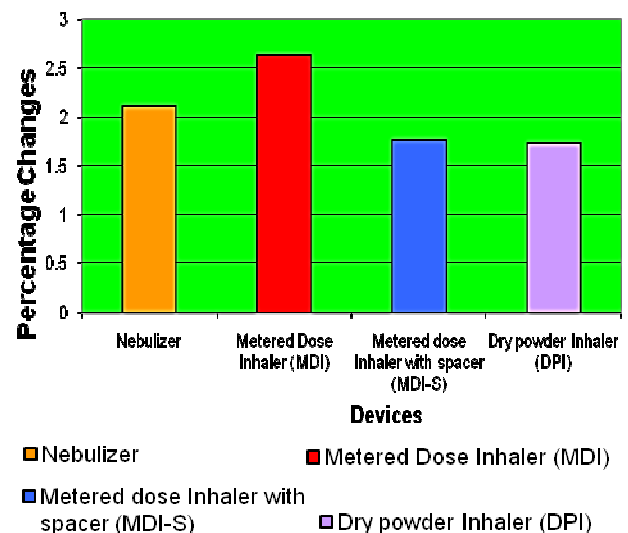
One hour after giving budesonide by different devices at week 2, 3, 4 and 5, there was highly significant increase in FEV₁/FVC (P<0.001). The percentage change in FEV₁/FVC ranged between 0.69 - 0.84%, 0.71 - 0.85, 0.67 - 0.84% and 0.67 - 0.84% by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler respectively, the difference being statistically insignificant (P>0.05). [Figure 4]

The pulmonary function parameters showed a highly significant increase one hour after giving budesonide by any of the devices evaluated. There was no significant difference in post treatment values of peak expiratory flow rate (P=0.77), forced expiratory volume in one second (P=0.95), forced vital capacity (P=0.24) and forced expiratory volume in one second and forced vital capacity ratio (P=0.22) after giving budesonide by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler respectively at day 8, 15, 22 and 29. This shows a similar efficacy of budesonide delivered via the different devices studied.

Figure-2: Percentage Change in PEFR 1 Hour after Budesonide Inhalation via Different Devices**Figure-3: Percentage Change in FEV₁ 1 Hour after Budesonide Inhalation via Different Devices****Figure-4: Percentage Change in FVC 1 Hour After Budesonide Inhalation via Different Devices**

The pulmonary function parameters showed a highly significant increase one hour after giving budesonide by any of the devices evaluated. There was no significant difference in post

treatment values of peak expiratory flow rate ($P=0.77$), forced expiratory volume in one second ($P=0.95$), forced vital capacity ($P=0.24$) and forced expiratory volume in one second and forced vital capacity ratio ($P=0.22$) after giving budesonide by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler respectively at day 8, 15, 22 and 29. This shows a similar efficacy of budesonide delivered via the different devices studied.

Figure-5: Percentage Change in FEV₁/FVC 1 Hour after Budesonide Inhalation via Different Devices

DISCUSSION

To the best of our knowledge there is no Indian study comparing clinical efficacy of budesonide delivered via nebulizer and dry powder inhaler in patients of chronic stable bronchial asthma. Our study for the first time compared the effect of budesonide delivered via nebulizer, metered dose inhaler, metered dose inhaler with spacer and by dry powder inhaler on lung functions and revealed that these devices have a similar effect on the lung function in patients of chronic stable bronchial asthma.

Higher incidence of chronic stable bronchial asthma was found among those aged between 18 to 40 years in our study. This is in conformity with the results of previous surveys which show that bronchial asthma occurs in all ages with one half cases occurring before age of 10 years and another third before age 40 years.^[8] Out of 45

patients enrolled the majority (60%) were males in the current study. Previous studies however have shown that in adulthood prevalence of asthma is greater in women than men, reason for which is not clear.^[9] The reason for higher enrollment of males in this study is partly due to exclusion of pregnant and lactating women and partly due to the larger male and female sex ratio as per Census 2001.^[10]

One hour after giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) there was highly significant increase in PEFr in our study. The percentage change in peak expiratory flow rate was 9.27 ± 3.39 with nebulizer, 6.79 ± 2.01 with metered dose inhaler, 7.03 ± 2.98 with metered dose inhaler with spacer and 9.11 ± 3.28 with dry powder inhaler.

Edinger et al (2006)^[11] demonstrated that the PEFr predicted percentage increased from 42 to 56% after a single dose of budesonide given by nebulizer although the change was insignificant. This can be attributed to the smaller sample size (16 patients) and higher proportion of females (Female: male ratio=13:3) in their study. The effect of gender on response to inhaled corticosteroid in patients of asthma needs to be explored.

Several studies have demonstrated an increase in peak expiratory flow rate after giving budesonide by nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler over a period of 1 to 12 weeks.^[12-16]

No significant difference in the PEFr was found after giving budesonide by any of the different devices used in our study which is in agreement with the study of Bisgaard et al (1998)^[12] that compared the effect of budesonide given as nebulized suspension versus metered dose inhaler in adult asthmatics. Spirometry at their clinic revealed no statistically significant difference between the treatments. Effect of 1mg budesonide by nebulizer was significantly more

than that of budesonide by metered dose inhaler plus spacer only in evening peak expiratory flow rate. Engel et al (1989)^[13] also demonstrated that there was no significant difference in peak expiratory flow rate at clinic and evening peak expiratory flow rate after giving budesonide by metered dose inhaler or dry powder inhaler, however morning peak expiratory flow rate found from patient's diaries showed significantly higher values in the group receiving budesonide through dry powder inhaler. Reason of different effects of delivery devices on morning evening peak expiratory flow rate needs to be further investigated.

One hour after giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) there was a highly significant increase in FEV₁ in our study. Kerwin et al (2008)^[14] observed a significant increase in FEV₁ when budesonide was given by dry powder inhaler as compared to placebo. There was no significant difference found in the FEV₁ after giving budesonide by any of the devices used in our study. Engel et al (1989)^[13] compared inhaled budesonide delivered either via pressurized metered dose inhaler or turbuhaler and found that there was no significant difference in FEV₁ between the two treatments. Bisgaard et al (1998)^[12] compared the efficacy of budesonide as a nebulized suspension versus pressurized metered dose inhaler in adult asthmatics and revealed no statistically significant difference between the treatments.

One hour after giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4), dry powder inhaler (week-5) forced vital capacity also increased significantly. Although the percentage change in forced vital capacity was highest with nebulizer, followed by metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler but there was no significant difference in the FVC after giving budesonide by any of the devices. Engel et al (1989)^[13] compared inhaled budesonide delivered via pressurized metered dose inhaler and turbuhaler

and found no statistically significant differences in FVC.

One hour after giving budesonide by nebulizer (week-2), metered dose inhaler (week-3), metered dose inhaler with spacer (week-4) and dry powder inhaler (week-5) there was highly significant increase in forced expiratory volume in one second and forced vital capacity ratio (FEV_1/FVC). There was no significant difference found in the FEV_1/FVC after giving budesonide by any of the devices. Previous studies on inhaled budesonide by different devices in patients of chronic stable bronchial asthma have not reported the effect on FEV_1/FVC .

The present study found no significant differences on spirometric variables after giving budesonide via nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler. They may be used interchangeably depending on availability, cost and compliance of the patients.

CONCLUSION

Budesonide delivered by different devices (nebulizer, metered dose inhaler, metered dose inhaler with spacer and dry powder inhaler) have similar effect on lung function in patients of chronic stable bronchial asthma and may be used interchangeably.

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