

Comparison of clinical effects of beclomethasone dipropionate & budesonide in treatment of children with mild persistent asthma: A double-blind, randomized, controlled study

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Received September 4, 2015

Background & objectives: Various inhaled corticosteroids (ICSs) are available to control the symptoms of asthma. Although beclomethasone dipropionate (BDP) and budesonide (BUD) are one of the oldest ICSs, their wide availability and low cost make them attractive options in developing countries. Due to lack of consensus on which of the two drugs is better for controlling mild persistent asthma, we undertook this study to compare the efficacy of these two drugs by measuring the change in percentage predicted forced expiratory volume in one second (FEV₁) from baseline in children with mild persistent asthma.

Methods: A double-blind, randomized, parallel group study was conducted in children 7-15 yr of age with newly diagnosed asthma. Of the 85 cases of mild persistent asthma, 42 received BUD while 43 received BDP at a dose of 400 µg/day using pressurized metered-dose inhaler with valved spacer for two months. The outcomes measured were change in FEV₁, symptom scores and side effects.

Results: There was a significant ($P < 0.05$) improvement in FEV₁ in BUD group ($98.43 \pm 4.63\%$) than in BDP group ($95.65 \pm 5.66\%$) at the end of two months of treatment. The mean symptom scores in BUD group (0.28 ± 1.22) and BDP group (0.43 ± 1.52) were comparable after two months. No side effects were seen in either group.

Interpretation & conclusions: FEV₁ was significantly greater in BUD group than BDP group. Improvement in symptoms and incidence of side effects were similar. Our findings indicate that both BDP and BUD can be used effectively in the management of children with mild persistent asthma. [CTRI No: CTRI/2013/03/003495].

Key words Beclomethasone dipropionate - budesonide - forced expiratory volume in one second - metered dose inhaler - mild persistent asthma - symptom score

Asthma is a common childhood illness characterized by chronic airway inflammation. This chronic inflammatory nature of the disease needs to be checked on time to prevent long-term irreversible impairment of pulmonary function¹. Uncontrolled asthma reduces the quality of life of children by retarding the growth², inability to exercise³, loss of sleep and frequent absences from school⁴.

There are various medications available to control the underlying inflammation such as inhaled corticosteroids (ICSs), oral steroids, leukotriene modifiers, chromones and theophylline. Of these, ICSs are considered as the most effective therapy for all levels of persistent asthma¹. Their success is based on their ability to improve asthma symptoms and quality of life⁵, low systemic bioavailability and lesser side effects⁶. The various ICSs available are beclomethasone dipropionate (BDP), budesonide (BUD), ciclesonide, flunisolide, fluticasone and mometasone. Among these, BUD and BDP are widely used in developing countries due to their better cost-benefit ratio. However, it is still a matter of debate as to which of these two drugs is a better drug in terms of efficacy. Various *in vitro* studies have shown differences in their pharmacokinetic properties. Receptor affinity of BDP is higher while *in vitro* potency of BUD is greater^{7,8}. It is unclear whether these differences translate into any clinical significance.

The available data on the comparison of clinical effects of these two drugs in children have mostly come from small crossover studies that included less than 30 children⁹⁻¹². Majority of these studies have poorly defined inclusion and exclusion criteria and have used different delivery devices with or without the spacers. One of these studies has shown significantly higher forced expiratory volume in one second (FEV₁) during BUD treatment¹², while others have shown only slightly higher FEV₁ during BUD treatment⁹⁻¹¹. A meta-analysis of crossover studies done in children and adults did not demonstrate a significant difference between BDP and BUD for FEV₁, morning peak expiratory flow (PEF), evening PEF, asthma symptoms or rescue beta-2 agonist use, over a dose range of 400-1000 µg¹³.

At present, BUD is being used for the treatment of mild persistent asthma in our hospital. However, the low cost and wide availability of BDP make it an attractive alternative¹⁴. Moreover, due to lack of consensus on which of the two drugs is better for controlling mild persistent asthma, We conducted this

study to compare the clinical effects of the two drugs so as to help to develop standardized guidelines. The objective of our study was to compare the efficacy of these two drugs in terms of improvement in pulmonary function in children with mild persistent asthma, measured by change in predicted FEV₁ from baseline.

Material & Methods

This parallel group double-blind, randomized, controlled trial (RCT) was conducted in the department of Pediatrics, Dr. Ram Manohar Lohia Hospital, New Delhi, India between November 2011 and November 2012 after approval by the Institutional Ethical Committee. The trial was registered in the Clinical Trials Registry of India No: CTRI/2013/03/003495.

Participants: Children with newly diagnosed mild persistent asthma aged 7-15 yr attending wards, outpatient department and chest clinic were included in this study. Mild persistent asthma was defined as asthma symptoms occurring more than once a week but not daily, exacerbations affecting activity and sleep, nocturnal symptoms greater than or equal to once a month and FEV₁ ≥80 per cent of the predicted. Cases fulfilling the above definition and showing an improvement of ≥12 per cent in FEV₁ after 15 min of administration of four separate doses of 100 µg of salbutamol metered dose inhaler (MDI) with valved spacer were considered eligible¹⁵. Children who received oral, parenteral or inhaled steroids during the last one month; children with any underlying chronic illness including cystic fibrosis, pneumothorax, chronic suppurative lung disease, tuberculosis, congenital heart diseases and any other chronic systemic illness; those unable to use inhaler with spacer or perform spirometry and children with lower respiratory tract infections in the last one month were excluded from the study. Written informed consent was obtained from parents of all the children.

Interventions- how and when they were administered: Children with newly diagnosed asthma were randomly assigned to study (BDP) and control (BUD) groups. Children allocated to BUD group received BUD 200 µg one puff twice a day b.i.d. and children in BDP group received BDP 200 µg one puff b.i.d. from an MDI with a valved spacer. Allocation of children to one of these groups was based on computer-generated simple randomization by an independent person. After selecting the cases and recording the absolute and

percentage predicted values of FEV₁, patients were given these medicines for two months.

Outcome measures: The primary outcome of our study was to compare the clinical effects of inhaled BDP and BUD by comparing the change in percentage predicted FEV₁ after two months of therapy. The secondary outcomes were to compare symptom scoring for day and night time symptoms, limitation in daily activities, absence from school, need for rescue salbutamol inhaler, number of exacerbations since the last visit, need for an emergency visit and incidence of side effects. The definitions used for this study were as follows: FEV₁ is the volume of air exhaled in the first second of a forceful expiration. Symptom score was done by the end of each month using a validated Asthma Therapy Assessment Questionnaire (ATAQ)^{16,17}. Major side effects observed in the study were cough, hoarseness of voice and candidiasis. These side effects were assessed clinically by history and physical examination on each visit.

The patients' clinical history and physical examination findings were noted. We used vitalograph portable spirometer which was calibrated for volume once daily with an airtight 3 l calibrated syringe with an accuracy of 15 ml¹⁸. Since valid spirometric measures are dependent on patient's ability to perform properly a full, forceful and prolonged expiratory manoeuvres, spirometry was done after properly explaining the correct method to the patients, and the best of three spirometry attempts was recorded. After recording the absolute and percentage predicted values of FEV₁, patients were given the medicines for next two months which included random number coded MDI and salbutamol MDI (rescue medication). The same type of valved spacers was used for the delivery of drug from the MDI. Parents were explained to maintain daily symptom diary for day and night symptoms, the number of acute exacerbations, use of rescue medication, visits to the emergency department, limitation in daily activities and absence from school.

Children were followed up at two weeks, first and second month. Compliance to medicines was checked at every visit, as well as telephonically every week. Every month symptom scoring and spirometry were done. The patients were labelled as having controlled asthma if ATAQ score and FEV₁ showed improvement during the two months follow up. Those who were not fulfilling these criteria were planned to be stepped up

and withdrawn from the study. Any patient developing acute exacerbation was advised to take 2-4 puffs of salbutamol MDI with valved spacer every 20 min for the first hour¹⁵ and immediately visit the emergency department for further management. Oral steroids were allowed for acute exacerbation management.

Sample size: There are no previous studies on the comparison of BUD versus BDP in children with mild persistent asthma. Therefore, we hypothesized that if a mean difference in FEV₁ in BDP was lower than two per cent in comparison to BUD, it would be considered non-inferior to BUD. Sample size of 39 per group was calculated based on the assumption of at least a mean difference of two per cent in FEV₁ (%) at second month between the two groups, a standard deviation (SD) of 3² or effect size of 0.67, a two-sided alpha of 0.05, beta of 0.80, a power of 80 and 10 per cent as lost to follow up.

Randomization:

Sequence generation: (i) Randomized sequence was generated using computerized random number generator. (ii) Randomization list was prepared by biostatisticians not involved in the study and was kept with them.

Randomization-allocation concealment: Serially numbered, sealed, identical opaque envelopes containing the random numbers were kept at the study site as per the allocation sequence.

Randomization-implementation: The randomization was done as soon as the cases were enrolled in the study. The research staff assigned each case the next serial number corresponding to the randomization code of the intervention.

Randomization-blinding: A person independent of the study prepared the medicines. After removing their labels, both the medicines were painted with red colour and covered with similar coloured caps. Study labels containing random numbers were put on the medicines. The treating paediatricians selected the cases, assessed them and advised these medicines. The random number coded medicines were distributed by the staff nurse. Once the statistical analysis was done; the identity of the two drugs was revealed to the treating paediatrician by the person who prepared the medicines. The participants and the treating paediatrician both were blinded to the intervention.

Statistical analysis: Data were collected using a predesigned proforma. Statistical testing was conducted

with the Statistical Package for the Social Science system version SPSS 17.0 (Chicago, IL, USA). Chi-square test and Fisher's exact test (used where expected frequency was <5) were used for categorical variables and Wilcoxon rank-sum test or Student's *t* test was used for continuous variables depending on whether they were normally distributed or not. Analysis was performed according to the intention to treat principle.

Results

Of the 90 patients screened, 85 children with mild persistent asthma were enrolled and randomized. Forty three children received BDP, while 42 received BUD. Three children were lost to follow up from BDP group and two from BUD group (Figure). The baseline demographic and clinical characteristics of the study groups are presented in Table I. The two groups had comparable baseline characteristics including the baseline spirometric parameters, *i.e.* FEV₁.

Primary outcomes: At the end of two months, mean FEV₁ in BDP group was 1.55 ± 0.39 l, while in BUD group was 1.74 ± 0.42 l with corresponding percentages of 95.65 ± 5.66 and 98.43 ± 4.63,

respectively (Table II). When the two groups were compared, there was a significant ($P < 0.05$) improvement in FEV₁ in BUD group [mean difference: -2.78; 95% confidence interval (CI): -5.08 - -0.48] as compared to BDP group (Table II).

Secondary outcomes: The mean symptom score in BDP group at baseline was 4.30 ± 0.75 and in BUD group was 4.28 ± 0.85. On intergroup comparison of symptom score after two months of treatment, improvement in BDP (0.43 ± 1.52) and BUD groups (0.28 ± 1.22) was similar (mean difference: 0.15; 95% CI: -0.46 - -0.76, $P = 0.638$) as shown in Table III. No side effects were observed in either group.

Some additional parameters were also observed in our study including PEF rate at the end of the first and second month, number of acute exacerbations, limitation of physical activities, sleep disturbance, school absenteeism, use of rescue medication and visit to emergency department (Table III). There was significant improvement in PEF in both group BDP (3.32 ± 0.89 l, 3.68 ± 1.19 l) and group BUD (3.89 ± 1.14 l, 4.12 ± 1.10 l) after the first and second month of treatment. When both

Table I. Comparison of baseline parameters of the study population

Parameters	Mean±SD		Unadjusted OR/mean difference (95% CI)
	Group BDP (n=40)	Group BUD (n=40)	
Age (yr) (mean±SD)	10.36±2.26	10.08±3.24	0.28 (-0.96-1.52)
Sex			
Male	25	29	1.27 (0.76-2.12)
Female	15	11	1.27 (0.76-2.12)
Height (cm), mean±SD	135.10±13.92	133.46±13.46	1.64 (-4.46-7.74)
Weight (kg), mean±SD	27.55±8.17	28.28±8.99	-0.73 (-4.55 - -3.09)
Age of onset of asthma symptoms (yr), mean±SD	5.28±3.62	4.64±3.55	0.64 (-0.96 - -2.24)
Cough	40 (100)	40 (100)	-
Wheezing	20 (50)	16 (40)	0.81 (0.52-1.28)
Breathlessness	33 (82.5)	31 (77.5)	0.86 (0.52-1.42)
Chest pain	8 (20)	13 (32.5)	1.35 (0.88-2.09)
Allergic rhinitis	13 (32.5)	16 (40)	1.17 (0.76-1.82)
Sinusitis	1 (2.5)	0 (0.0)	0.32 (0.01-8.22)
FEV ₁ (l), mean±SD	1.33±0.32	1.39±0.33	-0.06 (-0.20-0.08)
FEV ₁ (% predicted), mean±SD	81.77±1.66	82.45±1.44	-0.68 (-1.37-0.01)
Symptom score, mean±SD	4.30±0.75	4.28±0.85	0.02 (-0.34-0.38)

Values in parenthesis are percentages. BDP, beclomethasone dipropionate; BUD, budesonide; FEV₁, forced expiratory volume in one second; OR, odds ratio; CI, confidence interval

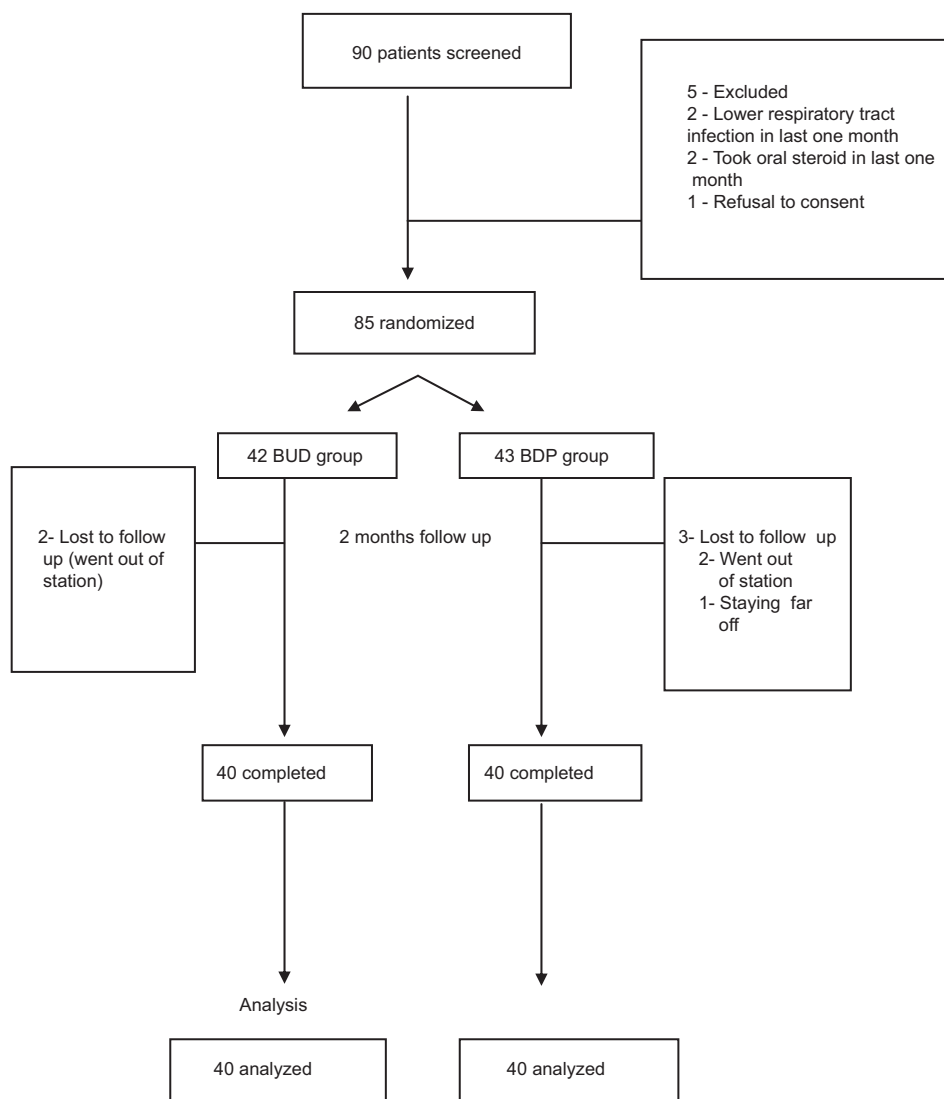


Figure. Flow chart, showing study design. BUD, budesonide; BDP, beclomethasone dipropionate.

groups were compared, BUD group had significantly better improvement in PEF than BDP group ($P < 0.05$) after first and second month (Table IV). However, other additional parameters did not show significant difference between the two groups (Table III).

Discussion

In this double-blind, randomized, single centre study, greater improvement was reported in patients' FEV₁ treated with 400 µg/day of BUD MDI as compared to 400 µg/day of beclomethasone MDI administered through valved spacer with comparable improvement in symptoms of asthma without any side effect after two months of treatment.

Mild persistent asthma constitutes the largest group of children with persistent asthma¹. The previous clinical studies comparing inhaled BDP and BUD in asthmatic children have shown no clear advantage in terms of efficacy of either drug⁹⁻¹². However, many clinico-pharmacological studies have suggested that BUD has better topical to systemic glucocorticoid activity ratio than BDP, and BUD may be preferred where high doses ICSs are required to control asthma¹⁹.

In 1982, Field and colleagues⁹ conducted a study on 31 severely asthmatic children aged between 4 and 14 yr requiring regular inhaled steroid prophylaxis. Fifteen children used BUD through pressurized aerosol

Table II. Primary outcome measures of the study population

Parameter	Mean±SD or n (%)		Mean difference (95% CI)
	Group BDP	Group BUD	
FEV ₁ baseline (l)	1.33±0.32	1.39±0.33	-0.06 (-0.20-0.08)
Baseline (%)	81.77±1.66	82.45±1.44	-0.68 (-1.37-0.01)
First month (l)	1.46±0.33	1.62±0.36*	0.16 (0.01-0.31)
First month (%)	90.18±3.99	92.10±2.57*	1.92 (0.43-3.41)
Second month (l)	1.55±0.39	1.74±0.42*	-0.19 (-0.37 - -0.01)
Second month (%)	95.65±5.66	98.43±4.63	-2.78 (-5.08 - -0.48)

*P<0.05 compared to BDP group. BDP, beclomethasone dipropionate; BUD, budesonide; OR, odds ratio; CI, confidence interval; FEV₁, forced expiratory volume in one second

Table III. Secondary outcomes of the study population

Parameter	Mean±SD or n (%)		Unadjusted OR/mean difference (95% CI)
	Group BDP (n=40)	Group BUD (n=40)	
Symptom score baseline	4.30±0.75	4.28±0.85	0.02 (-0.34-0.38)
Symptom score 1 st month	0.75±1.06	0.48±0.75	-0.27 (-0.68-0.14)
Symptom score 2 nd month	0.43±1.52	0.28±1.22	0.15 (-0.46-0.76)
Number of acute exacerbations	2 (5)	0	-
Rescue medication	5 (12.5)	2 (5)	0.55 (0.17-1.80)
Emergency visits	1 (2.5)	0	-
Limitations of physical activities	5 (12.5)	2 (5)	0.55 (0.17-1.80)
Sleep disturbances	5 (12.5)	2 (5)	0.55 (0.17-1.80)
School absenteeism	5 (12.5)	2 (5)	0.55 (0.17-1.80)

Values in parenthesis are percentages. BDP, beclomethasone dipropionate; BUD, budesonide; OR, odds ratio; CI, confidence interval

Table IV. Peak expiratory flow values of the study population

Parameter	Mean±SD or n (%)		Mean difference (95% CI)
	Group BDP	Group BUD	
PEF baseline (l)	3.19±0.80	3.46±0.94	0.27 (-0.11-0.66)
Baseline (%)	82.02±1.89	82.37±1.48	0.35 (-0.40-1.10)
First month (l)	3.32±0.89	3.89±1.14*	0.57 (0.12-1.02)
First month (%)	90.9±3.11	92.2±1.87*	1.30 (0.16-2.44)
Second month (l)	3.68±1.19	4.12±1.10*	0.44 (-0.07 - -0.95)
Second month (%)	95.75±6.04	98.62±3.99*	2.87 (0.59-5.15)

*P<0.05 compared to BDP group PEF, peak expiratory flow; BUD, budesonide; CI, confidence interval; BDP, beclomethasone dipropionate

with a spacer inhaler, while 12 used BDP through Rotahaler. FEV₁ and symptom score in the BUD group were 83.4 ± 22.9 l and 13.6 ± 16.5, while the values of the same parameters in BDP group were 78.5 ± 25.1 l and 17.2 ± 19.3, respectively. This comparison did not show any significant difference although there was a consistent tendency towards greater benefit from

BUD⁹. In another study conducted by Springer *et al.*¹⁰ on 10 asthmatic children in each group who were already on treatment with steroids were given a total daily dose of 400 µg each of BDP and BUD through a conventional pressurized aerosol without a spacer. The comparison of FEV₁ and symptom score between the two groups showed no significant difference¹⁰. In a

study by Baran *et al*¹¹ on 21 chronic asthmatic children, aged 4-14 yr who were on regular ICSs for their control, BUD group received 100 µg b.i.d. through spacer inhaler, while BDP group received 100 µg b.i.d. through dry powder inhaler. On analysis, it was found that compared with placebo, FEV₁ was significantly better with BUD ($P < 0.05$), but no significant effect could be detected with BDP¹¹.

Our study also reflected improvement in the quality of life of the asthmatic children, especially those receiving BUD. In the BUD group, though there was a reduction in sleep disturbance, school absenteeism, limitation of physical activities, less number of children requiring emergency visits and rescue medication, but this difference was not significant. There was a significant increase in PEF at the end of the first and second month in the group receiving BUD. However, daily home monitoring of PEF rate was not possible as patients could not purchase the peak flow meter.

The strengths of our study were the study design, proper blinding and objective primary outcome. It was an adequately powered RCT in children with mild persistent asthma and the results favoured BUD which is commonly prescribed in most regions of the world. Thus, our results can be generalized to most settings. However, one important limitation of our study was the short follow up period of two months during which we did not expect the compliance to be as poor as would be the case in case of a lengthier time period.

In conclusion, our study showed improvement in patients' FEV₁ treated with 400 µg/day of BUD MDI as compared to 400 µg/day of beclomethasone MDI administered through spacer with valve over a period of two months. However, comparable improvement in symptoms of asthma was observed in both the groups. No significant safety concerns were identified. BUD was found to be slightly more effective than BDP. It can be suggested that both BDP and BUD can be used effectively in the management of children with mild persistent asthma.

Acknowledgment

Authors acknowledge Dr T.P. Yadav and the hospital administration for providing inhalers, Sister Chanci as the nursing staff for the distribution of medicines and the pharmacist Shrimati Sagar for the preparation of the drug. Authors thank Shrimati Parul Takkar for helping in statistical analysis and Dr. Neha Patharia for collection of review material.

Conflicts of Interest: None.

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