

Once vs Twice-Daily Administration of Inhaled Budesonide for Mild and Moderate Well Controlled Childhood Asthma

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ABSTRACT

Background: Simplifying dose schedules may improve adherence and morbidity associated with asthma. There is limited data on the effects of once-daily budesonide treatment using a metered dosage inhaler (MDI) and a spacer on asthma symptoms and lung function in children, however.

Method: This study was conducted in POF Hospital Wah Cantt Pediatrics Department between Jan 2022 to March 2022. This Study compared the impact of inhaled budesonide doses given once daily versus twice daily on asthmatic children's symptoms, lung function, and bronchial hyperresponsiveness. This research uses a randomised, single-blind, parallel clinical trial. Budesonide was administered to individuals using an MDI at a daily dose of either 800 mg or a fractionated dose of 400 mg twice a day for 12 weeks. For the statistical analysis, we employed both independent and paired sample tests.

Results: Asthma symptoms significantly decreased in both groups. However, the once-daily group considerably outperformed the twice-daily group in terms of treatment adherence, reduction in BHR, and improvement in asthma symptoms ($p < 0.05$). No significant variations in spirometric characteristics, morning peak expiratory flow, or plasma cortisol levels were discovered between the two groups.

Conclusion: It has been shown that treating symptoms and improving BHR with one daily dose of 800g of inhaled budesonide delivered by MDI + spacer is more effective than dividing it into two doses of 400g each. The differences found in this study may have resulted from patients in the once-daily group adhering to their treatment more closely.

Keywords: asthma, once, twice budesonide, wheezing

INTRODUCTION

The current standard of care for treating asthma with inhaled corticosteroids (ICS) applies to patients of any age. The condition can be managed effectively with ICS, but the treatment must be continued over time. Optimal clinical and functional results with minimum side effects in children rely on several patient and therapy-related characteristics. Simplified dosage regimens (such as once-daily delivery), excellent inhaler technique, regular patient monitoring, and education on medication adherence are needed. (1, 2) Dry powder inhalers (DPI) containing budesonide once day are equally effective as using them twice daily for controlling asthma in children, according to research. The financial, emotional, and therapeutic benefits to the whole family could be substantial. (3-5) Additionally, it has been discovered that long-term administration of budesonide once daily (200 or 400g) to children and adults with recently discovered mild persistent asthma is safe and well tolerated. (6, 7)

Although there is a sizable body of knowledge about once-daily budesonide DPI administration in children, less is known about whether the same disease-controlling effectiveness may be accomplished in children by giving generic budesonide by MDI + spacers. It would enable inhaled corticosteroids to be administered to patients who are not able to use DPI and be more cost-effective, especially in developing countries where DPI devices still cost much more than MDIs.

The effects of once vs twice daily dose of budesonide MDI plus spacer on symptoms of asthma, function of lungs, & methacholine responsiveness in children with mild to moderate asthma were assessed.

METHODS

Participants: Fifty children with atopic asthma from families with poor socioeconomic status were treated by our hospital's pediatric respiratory medicine service and participated in this study. They did not recently have any exacerbations of their moderate to severe continuing asthma, they had no history of an acute respiratory infection in the four weeks before to randomization, and they had not recently used systemic steroids. They were all

receiving treatment with routine inhaled steroids up to 800 micrograms of MDI beclomethasone dipropionate (or an equivalent) per day, as well as on-demand inhaled salbutamol, all of which were administered through a plastic spacer that had been unsealed.

Study design: This study was a 12-week, parallel, two-group, randomized, single-blind clinical trial. Children and mothers received training in forced vital capacity procedures, symptom recording, and breathing technique over the course of a four-week trial period (mainly wheezing and cough). Children were divided randomly into two research groups after the run-in. Budesonide MDI, 400-mcg was inhaled by one group, and 800 mcg was inhaled by the other group, once daily in the morning. Both groups took salbutamol on demand to treat acute symptoms. An enormous plastic spacer without valves was used to inhale MDI aerosols through the mouth. Mothers were given instructions on how to clean the appliance with detergent to reduce electrostatic charge. All aerosols (budesonide and salbutamol) were inhaled using the same technique. After the canister was shaken, the MDI aerosols were pushed into the spacer and then slowly inhaled by mouth from the remaining volume to entire lung capacity. This was followed by holding the breath for ten seconds and then gently breathing out. After receiving an inhalation of budesonide, patients were given the instruction to gargle with water.

Clinical assessment: In a span of 12 weeks, children were expected to come to our clinic every 30 days. Complete physical examinations were performed at each visit, and the parents' reports of their child's wheezing in the two weeks before to each appointment were registered and used for analysis.

Pulmonary function testing: Using a heated pneumotachograph and the Medgraphics CPF-S processing system, spirometric measures were taken at the beginning (baseline) and conclusion of the trial. Prior to the methacholine challenge, baseline values were acquired on each test day. The best spirometric values were chosen in accordance with the ATS criteria for acceptability and reproducibility, and forced capacity exercises were performed in triplicate. (8) Twelve hours before lung function testing, short-acting beta 2 adrenergic agonists were discontinued, and inhaled steroids were permitted as directed by study doctors. None of the

patients were using oral steroids, long-acting adrenergic agonists, antihistamines, or theophylline.

If the patient's FEV1 was within or above 80% of the predicted value, a methacholine challenge test was performed using a modified tidal breathing technique. Using a Hudson 1730 updraft 2 nebulizer with a fill capacity of two millilitres, methacholine chloride solutions in normal saline were nebulized at room temperature for two minutes. The solutions were held at a temperature of four degrees Celsius. The nebulizer was driven by air at a pressure of fifty pounds per square inch (psi) and a flow rate of six litres per minute. Subjects performed all manoeuvres while standing. The output of nebulizers under the aforementioned operating circumstances ranged from 340 to 360 mg/min. Through a mouth tube with a volume extension piece, methacholine aerosol was administered.

Methacholine concentrations ranging from 0.03 to 8 mg/ml were inhaled over the course of two minutes after breathing in normal saline. FEV1 measurements were made 30 and 90 seconds after inhalation. Every 5 minutes, concentrations were doubled until the FEV1 value fell by more than 20% from the post-saline value (PC20). Then, using a large volume valved spacer, four puffs (400g) of salbutamol were administered sequentially.

Adherence to treatment: The reports from both the parents and the children, in addition to the weight of the canister, were used to assess the rate of treatment adherence. To determine which group of children adhered better to their treatment plan, the amount of weight on each MDI canister that was given to them and then collected at each matching appointment was recorded.

Morning plasma cortisol: Both at the beginning (randomization) and end of the trial, fasting blood samples were taken for plasmatic morning cortisol. Plasma cortisol was measured using a radio-immunoassay, with normal values being those between 5 and 25 g/dl.

Data analysis: Between-visit asthma symptoms, as reported by the parents (yes or no), were calculated as a categorised clinical score for comparison between the beginning of treatment and the end of treatment. Before any calculations were performed, methacholine concentrations were logarithmically converted, and PC20 was then estimated by linearly interpolating between the last two points with the use of a computer software. In this investigation, significant changes in PC20 methacholine DD values included those of one or more. LogPC20 was calculated by subtracting the starting value from the final value and then dividing by log2 to get the number of double log-concentrations, which was then used to assess the degree to which bronchial responsiveness to methacholine had changed. After receiving inhaled corticosteroids, the trigger increased by 1 DD, which meant that twice as much trigger was required to produce the same decrease in FEV1. For paired and independent samples, statistical analysis uses analysis of variance (ANOVA), a parametric and nonparametric test. Statistical significance is determined by p<0.05 (two-tailed) and presented as mean and 95% confidence interval (95% CI). The study was carried out with the Hospital's Ethics Committee's approval, and all parents provided complete, written, and signed consent. Results 44 of the original 50 enrolled youngsters finished the study. Three from each group of six children were withdrawn for the primary reasons that they did not want to continue the study and did not show up for one or more of the scheduled visits. Height and weight did not significantly differ across groups.

table I summarizes demographic, lung function, and other patient data. Both groups' clinical outcomes dramatically improved by the conclusion of the research. Despite the fact that the once-daily budesonide group had a significantly lower number of children who were still experiencing asthma symptoms at week 12 than the twice-daily group (chi-square 4.29, p=0.038)

When compared to the group of children who inhaled budesonide once daily (74.4%; 95%CI 68.9-79.9%), the overall measured adherence (by canisterweight) was considerably lower for the children who breathed the medication twice daily. Although

treatment compliance was reported to be higher than 85% in both groups, there was little agreement between reported and estimated compliance (kappa = 0.13). Spirometric and PEFr readings at baseline and discharge did not significantly differ between groups or between groups.

For all of the research groups, there was no obvious change in mean methacholine PC20 between admission and discharge. PC20 rose from 0.68 mg/mL to 1.48 mg/mL in youngsters who inhaled budesonide once daily, although not significantly. The once-daily group showed a major improvement compared to the twice-daily group. At the beginning and end of the trial, plasma cortisol levels did not differ substantially across groups. Neither mothers nor study participants reported adverse drug effects.

Table 1: demographic, function' lungs and values of morning plasma cortisol for two study groups at entry & discharge

	Once daily		Twice daily	
	Entry	End	Entry	End
Mean age	10.7		10.8	
Gender	14/8		13/9	
Weight	45.2	46.01	44.19	44.9
Height	143.4	144.6	141.4	142.6
PEFR	329.1	330.2	335.5	337.5
FVC	111.2	113.2	112.1	112.7
FEV1	104.4	1.7.4	109.6	109.5
FEF	88.9	92.9	99.9	96.2
FEV1/FVC	93.8	95.2	97.9	97.5
PC20	0.68	1.48	1.22	1.02
Cortisol	12.89	13.39	13.30	14.59

DISCUSSION

For the treatment of mild to severe asthma, this trial demonstrates that 16 weeks of treatment with either once-daily (800g) or twice-daily (400g BID) MDI budesonide are equally beneficial. In contrast to twice-daily administration, once-daily budesonide significantly improved BHR and was more effective in reducing asthma symptoms. This latter result has previously been documented with inhaled corticosteroids, mostly delivered by DPI in children and adults, and may be related to the much greater adherence to therapy shown in the group of children who inhaled budesonide once day. In a randomised, double-blind, placebo-controlled, multicenter research, the budesonide turbobaler (200g or 400g once daily for 12 weeks) was as effective as placebo.(9)

accordance to the findings of a multicenter, randomized, double-blind, placebo-controlled study that included 274 asthmatic children ranging in age from 6 to 17 years old. In dosages up to 800g per day, once-day budesonide regimens show equivalent efficacy to twice-daily regimens, according to a recent meta-analysis on the effectiveness of budesonide provided once daily vs twice daily in patients with mild to severe asthma. The authors of the study have suggested that once-daily regimens may have benefits in terms of patient compliance and satisfaction.(7) In the long run (up to three years) A large prospective randomized study found that patients with mild persistent asthma who had recently developed the condition benefited from once-daily administration of DPI budesonide (200–400 mg), as this improved the patients' ability to maintain asthma control and reduced the frequency of severe exacerbations. (6) Even with better asthma treatment procedures, the disease is still associated with high rates of morbidity and death, and non-compliance with prescribed therapies is a major contributing factor. There is growing agreement that maintaining strong adherence to a treatment regimen is essential for achieving the desired clinical and functional control of the condition, both in everyday medical practice and in research. Despite the challenges in measuring adherence, doctors and researchers should make an attempt to do so when recommending asthma medication to patients. The estimated adherence to MDI inhalation treatment (69% or 50% by canister weight) is much lower than the reported adherence (80%) by mothers or children. This difference has been demonstrated using a number of different methods. However, using inhaled

steroids from a DPI that has a dosage monitor built into the device also resulted in poor adherence (68 percent).(10)

Studies show that poor adherence is a predictor of asthma morbidity, but that doctors may mitigate most of the risks by elaborating on asthma regulations, fostering open lines of communication with caregivers, and dispelling myths about the harmful consequences of asthma medicines..(11)

It is debatable how inhaled budesonide affects asthmatic children's lungs because of the contrasting findings of two sizable long-term controlled studies. (12) After 1 and 3 years of the study, START11 observed that the treatment group significantly improved their pre-bronchodilator and postbronchodilator FEV1percentage values compared to the control group when taking the budesonide turbo-haler 200mcg once daily. However, compared to placebo, continued daily treatment with 200 mcg of budesonide turbobaler twice a day had no discernible effect on lung function as determined by the FEV1 following bronchodilator usage. The short duration of the study's observation period—3 months—as well as the fact that lung function in both groups was more than 85% predicted at the time of randomization may help to explain why none of the inhaled budesonide treatment modalities used in the current study had any effect on changing lung function. There is some contentious information in this regard. According to some authors, taking DPI budesonide once day for three months significantly improved lung function and symptoms when compared to placebo18. Others who have used the identical dosages and administration method over an extended period of time have not observed any appreciable changes in lung function in asthmatic youngsters. According to a comparable long-term study, the budesonide DPI treatment group significantly outperformed the placebo group after 1 and 3 years of the trial in terms of both pre bronchodilator and post bronchodilator FEV1% values. A large percentage of children with moderate to severe stable asthma have good lung function and minimal symptoms while having BHR and ultimately airway inflammation. According to research, the majority of silent asthmatics still show BHR and symptoms of airway inflammation, and the severity of the airway inflammation and the severity of the asthma in children's BHR would be related. (13) High doses of inhaled corticosteroids (mean dosage 1,000g, range 400-2,000g daily) lowered BHR in individuals with corticosteroid naïve asthma compared to low doses within 2-8 weeks, but it was unclear whether lower doses would have the same impact. (14) In a meta-analysis of inhaled corticosteroids, it was determined that a significant improvement in BHR can be achieved with a minimal dose and duration of treatment.

It is commonly established that each asthmatic patient should have a unique treatment plan intended to manage their symptoms, enhance their pulmonary function, reduce bronchial hyperresponsiveness, and require rescue medication as little as possible. High doses of inhaled corticosteroids (mean dosage 1,000g, range 400-2,000g daily) lowered BHR in individuals with corticosteroid naïve asthma compared to low doses within 2-8 weeks, but it was unclear whether lower doses would have the same impact. It has been shown that the larger dose of inhaled steroids was noticeably more effective at reducing severe exacerbationseven when low and high doses had equivalent effects on symptoms and peak flows.(15) In this trial, 800g per day was used, a dose that has been shown to be effective in controlling symptoms and improving BHR. Both groups found it to be safe and well tolerated. Using MDI plus spacer to administer budesonide once a day may be beneficial for asthmatic children in terms of compliance with treatment, a cost-effective alternative, and make it

easier for younger children who cannot inhale medications from DPI to receive long-term treatment.

CONCLUSION

According to the findings of this research, it was determined that the administration of 800g of inhaled budesonide once day by MDI + spacer was superior to the practice of dividing the dosage into 400g doses twice daily for the purpose of symptom management and improvement of BHR. One possible explanation for the differences that were discovered is that patients who received once-daily inhalation budesonide had a better rate of compliance with their treatment.

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