

# Efficacy and cost effectiveness of inhaled steroids in asthma in a developing country

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## Abstract

**Eighty six children with troublesome wheezing were studied, in a semipropective clinical trial with the patients acting as their own controls, to assess the efficacy and cost effectiveness of inhaled steroids. Improvement in school attendance, hospitalisations, breakthrough wheezing, and acute severe attacks were used to assess clinical efficacy. Expenditure for the family, on a cost of illness framework, before and after treatment, was used to estimate cost effectiveness. Highly significant numbers of patients showed improvement in clinical parameters, confirming efficacy. Mean monthly cost before inhaled steroid treatment was Rs 2652.33 (£36.33) and Rs 449.42 (£6.16) after starting treatment. The mean cost per unit satisfaction (cost utility value) which was Rs 255.54 (£3.50) before starting prophylaxis came down to Rs 5.42 (£0.07) after starting treatment. There are no previous reports of cost-benefit assessment of inhaled steroids in childhood asthma. It is concluded that, even for developing countries with financial constraints, inhaled steroid treatment for prophylaxis of asthma is a cost effective and rational form of treatment.**

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Childhood asthma is a disease with the widest possible spectrum of severity varying from mild episodic attacks to severe persistent disease.<sup>1</sup> Very frequent attacks or perennial forms of the disease lead to marked disruption of normal lifestyles for the affected child as well as the parents.<sup>2</sup> Most of those who are severely affected need continuous medication, not only to allow them to lead normal or near normal lives but also to prevent potentially fatal severe acute exacerbations.<sup>3</sup> To compound the present situation further, there are disturbing reports of a rising incidence of asthma all over the world.<sup>4</sup>

Up to the present time, the inflammatory basis of asthma is well established as a fact,<sup>5</sup> and anti-inflammatory drugs are being used more and more in affected children. They have even been advocated as a first line form of treatment for prophylaxis of moderate to severe asthma.<sup>6</sup> There is undisputed evidence, from all over the globe, of clinical benefits of inhaled steroid treatment for childhood asthma.<sup>7,8</sup> However, these drugs are quite expensive and especially for developing countries with poor financial

resources, cost of drugs is a major factor on which general availability and common use of any drug would be based.

Sri Lanka is a developing country with a gross national product per capita of Rs 21 641.00 (£296.45) at current prices.<sup>9</sup> For comparison, the same per capita index for Great Britain is £11 108.90 (Rs 810 949.70)<sup>10</sup> and for India it is £205.15 (Rs 14 976.00).<sup>9</sup> There is a free national health service in Sri Lanka managed entirely by the state and a separate, fee levying, private health service. Up to the present time, inhalers containing corticosteroids are not freely available on prescription in the hospitals of the national health service. They are quite expensive and are available only for direct purchase through the private pharmaceutical industry and the private hospitals.

This study was undertaken in a hospital in the private sector in Sri Lanka, not only to assess how effective inhaled steroid treatment is in a real life clinical setting, but also to ascertain how beneficial it is cost wise in the long term management of children with troublesome asthma. The findings would be of relevance even to the hospitals of the national health services of Sri Lanka and other developing countries, as cost saving would be even more important to these institutions where fees are not levied.

## Subjects and methods

The study was carried out over a period of four years from January 1990. Eighty six consecutive children with wheezing that disrupted their normal lives were studied in a semipropective design with the patients acting as their own controls, before and after starting inhaled steroid prophylaxis. None of them had had inhaled steroid treatment in the past. They had one or more of the following predetermined admission criteria for inclusion into the study: (1) Perennial asthma with wheezing every day. (2) Frequent episodic attacks of wheezing occurring more often than once in three weeks. (3) Repeated hospital admissions for wheezing, more frequently than once in three months. (4) Loss of schooling of more than two days per month, due to acute wheezing.

Complete clinical details of the patients including present and past history were obtained at the beginning of the study. Specific information about loss of schooling, hospitalisations, documented acute severe attacks, and breakthrough wheezing over the last year on present treatment were specially noted. Past treatment over the last year and the current medications were also documented. A

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Table 1 Frequency distribution (number of patients) of the starting doses of beclomethasone dipropionate and budesonide

	Daily dosage ( $\mu\text{g}$ )		
	300	400	600
Beclomethasone dipropionate	7	15	26
Budesonide	7	18	13
Total	14	33	39

complete physical examination was carried out in the first instance.

The mother and father of the child were interviewed before starting the child on inhaled steroids and details of all expenses incurred in the treatment of the child for the past year were recorded. This procedure included costs of medical consultations, drugs, hospital admissions, travelling, direct and indirect loss of revenue for the parents in employment and businesses necessarily incurred as a result of the child's illness and any other incidental expenses. The expenditure was calculated on a cost of illness framework taking into account health service costs and indirect costs. The final value was averaged out and documented as the mean monthly cost per patient.

The mother of each child was also requested to plot on a standard 10 cm linear visual analogue scale, the point at which she would place the child as regards parental satisfaction of the response to the current treatment before starting inhaled steroids. The reference line had 0 at the left hand corner representing zero or poor satisfaction and 100 at the right hand corner denoting perfect satisfaction. The point marked by the mother was carefully measured and the percentage satisfaction score before starting inhaled steroids for each child was noted. The average for the initial satisfaction score for the study population before starting inhaled steroids was then calculated.

The children were started on inhaled steroids, allocated randomly into either beclomethasone dipropionate or budesonide. At the beginning of treatment they were admitted to hospital for two days and child and mother were both intensively trained in the correct use of the inhalers. Subsequently their progress was followed up at monthly intervals. All metered dose inhalers were used with a spacer and the dry powder formulations used a Rotahaler. The inhaler technique was repeatedly checked during the monthly visits. The usual starting dose was 300, 400, or 600  $\mu\text{g}$  per day of either drug, the selection of dosage being made on clinical severity. The frequency distribution of the starting doses of

both drugs is given in table 1. This dose was reduced to a maintenance dose once the patients had shown a sustained clinical improvement, in most cases three to six months after starting treatment. Any other medications that the child was receiving at the start of the study were gradually withdrawn. The progress was determined by assessing improvement in school attendance, hospitalisations, incidence of breakthrough wheezing, and acute severe attacks.

One year after starting treatment with inhaled steroids, the parents were interviewed again and the costs were calculated for the first year on inhaled steroids using the same cost of illness framework. The mean monthly cost for each patient and the total study population were then calculated. Percentage satisfaction was reascertained by using a new 10 cm line and the mean for the satisfaction score after treatment for the entire series calculated. The mean monthly cost before treatment divided by the initial mean satisfaction score represented the mean monthly cost per unit satisfaction before starting inhaled steroid treatment and the mean monthly cost after treatment divided by the mean after treatment satisfaction score denoted the mean monthly cost per unit satisfaction on inhaled steroid treatment.

#### ANALYSIS

The details of each patient were entered into a specially designed analytical program, INH.REC of Epi Info 5 in a Compaq Contura Laptop computer, and were analysed using the standard facilities of Epi Info 5. All comparisons of loss of schooling, hospitalisations, incidence of breakthrough wheezing, acute severe attacks, satisfaction scores, mean monthly costs, and costs per unit satisfaction were made on the same patient population before and after starting inhaled steroid prophylaxis. The observations were treated as on a matched design. The significance of statistics was based on  $\chi^2$  analysis and paired *t* tests.

#### Results

Eighty six patients were enrolled into the study; all kept their regular monthly appointments and none were lost to follow up. There were 52 boys and 34 girls (M:F=1.53:1). A history of atopy was obtained in 48 (55.8%) while 61 (70.9%) had a positive family history for asthma in a first degree relative. Forty seven (54.6%) had a history of atopy as well as a positive family history for asthma. Thirty four (39.5%) had the first attack of wheezing in the first two years of life and 38 (44.2%) developed the first attack between 2 and 5 years of age. Thus 72 out of 86 (83.7%) developed the first attack of asthma during the first five years of life. Mean age at onset was 3.4 years and mean age of starting inhaled steroid prophylaxis in this study was 7.4 years. Eighty four children were on oral  $\beta$  agonists and 72 were on oral theophyllines, both drugs on a long term basis, up to the beginning of the study. Eighty one of

Table 2 Analysis of improvement in clinical parameters ( $n=86$ )

	Before treatment	After treatment	Significance	
			<i>p</i> Value	Odds ratio (95% CI)
Loss of schooling	81	4	<0.001	155 (49.5 and 485.31)*
Breakthrough wheezing	82	26	<0.001	113 (32.03 and 398.64)*
Hospital admissions	77	4	<0.001	147 (46.05 and 469.27)*
Acute severe attacks	75	4	<0.001	143 (44.34 and 461.17)*

95% CI=95% confidence interval.

\*0.5 is added to all four cells as one contains a zero<sup>24</sup> and the lower limit of CI is taken as significant.<sup>25</sup>

86 (94%) of the patients had repeated courses of intravenous and oral steroids up to the start of the study. None of them were on long term low dose systemic corticosteroids.

The analysis of clinical parameters used, namely loss of schooling, breakthrough wheezing, hospital admissions, and acute severe attacks is given in table 2. Beclomethasone dipropionate was used in 48 (55.8%) and budesonide in 38 (44.2%). The mean starting dose for beclomethasone dipropionate was 485.42 µg per day and for budesonide was 450.00 µg per day. It was possible to reduce the starting dose to the maintenance dose on average after 5.94 months for beclomethasone dipropionate and 5.45 months for budesonide. The average maintenance dose was 300.00 µg for beclomethasone dipropionate and 260.53 µg for budesonide. Sixty seven (77.9%) of the patients showed an excellent response with no further loss of schooling, breakthrough wheezing, hospital admissions, or acute severe attacks. Thirteen (15.1%) of them showed a good clinical response with no loss of schooling, hospitalisations, or acute severe attacks but they had mild or moderately severe attacks of breakthrough wheezing with upper respiratory tract infections. These were easily controlled on short courses of oral β agonists and systemic steroids were not required in any of them. Six (7%) of the patients showed a poor response with continued attacks of frequent breakthrough wheezing, disruption of schooling, acute severe attacks, and hospitalisations.

The mean monthly cost, before starting on inhaled steroid treatment, was Rs 2652.33 (£36.33). This was reduced to Rs 449.40 (£6.16) after treatment. The average satisfaction score before treatment was 14.59% and after treatment was 90.21%. The mean cost per unit satisfaction before treatment was Rs 255.54 (£3.50) and it was reduced to Rs 5.42 (£0.07) after treatment.

It was possible to slowly tail off inhaled steroids in 19 patients after varying periods of freedom from symptoms, namely 18 months (seven patients), 24 months (nine patients), and 36 months (three patients). In each patient, the inhaled steroid was withdrawn very slowly over six to nine months. These patients have remained under further observation for periods varying from 12 to 24 months and are free of asthmatic symptoms up to the present time.

### Discussion

The children in this study belonged to a highly selective group with moderate to severe asthma. They had marked restriction of normal lifestyles and were either regularly unwell or chronically ill. Children belonging to this group have been shown to have growth retardation,<sup>11</sup> exercise intolerance,<sup>12</sup> poor school performance,<sup>13</sup> and they are known to be at risk of succumbing to an acute severe attack.<sup>14</sup> Many authorities have advocated inhaled steroid prophylaxis for children who suffer from this type of moderate to severe asthma.<sup>15-17</sup>

The association of atopy, family history, and asthma is well known.<sup>18</sup> This study also confirmed this connection. Most of the patients started to wheeze in the first five years of life with a mean age at onset of 3.4 years. There was a very significant delay in starting these children on inhaled steroid prophylaxis, the mean age of starting it being 7.4 years. This pattern is seen very often in Sri Lanka mainly due to concerns regarding costs of inhaled steroids in the first instance and fears of adverse effects of prolonged treatment in the second.

The response of the patients, as judged by the reduction in loss of schooling, breakthrough wheezing, hospitalisations, and the occurrence of acute severe attacks, was quite impressive. This obviously contributed to the high levels of satisfaction on the part of parents and the excellent compliance with the treatment. However, six patients showed an unsatisfactory response, confirming the notion that though they are very useful drugs, inhaled corticosteroids are not a panacea for all ills in childhood asthma.

The costs were calculated on a cost of illness framework that has been advocated for the calculation of expenses incurred during an illness.<sup>19</sup> The satisfaction scores plotted using a 10 cm linear analogue scale is a method used for analysis of subjective variables.<sup>20</sup> There was a very significant reduction in the expenditure for the family by at least 80% after the institution of inhaled steroid treatment. This was obviously due to the drastic reductions obtained in breakthrough wheezing, acute severe attacks, and hospitalisations. The satisfaction scores obtained showed that the parents were quite satisfied with the progress of the children. Although there is no absolutely foolproof way of assessing degrees of human suffering in monetary terms, the costs per unit satisfaction in the cost utility analysis is a reflection of the benefits derived. There was a very significant reduction of this value in the study. It indicated that although the parents were far from satisfied with the treatment received earlier, the costs were enormous. The use of inhaled steroids not only produced far superior degrees of satisfaction but also reduced the recurrent expenditure drastically, both of which are reflected in the markedly reduced costs per unit satisfaction after inhaled steroid prophylaxis.

One interesting aspect of the study was the marked reduction in repeated hospitalisations of the patients studied. It has been shown that the cost of inpatient care for a child at Lady Ridgeway Hospital for Sick Children, Colombo, Sri Lanka is, on the average, Rs 349 (£4.78) per day.<sup>21</sup> It is a government managed non-fee levying teaching hospital. The amount of money that would be saved by reduction of admissions of asthmatic children alone would be sufficient to justify the use of inhaled steroids in the more severely affected children.

These results are very significant in view of the absence of any cost-benefit or medical audit studies on the use of inhaled steroids in childhood asthma in the world literature. As far as it is possible to ascertain, this is the first

report of cost-benefit analysis of inhaled steroids in the prophylaxis of moderate to severe childhood asthma.

The patients studied were from the higher social classes and they were able to afford private medical attention. The excellent compliance rate of the patients in this study probably reflects the higher levels of education and intelligence of this particular social class among the general population. The very high literacy rate of around 88% that is found in Sri Lanka is likely to be another factor that contributed to this level of compliance. This study was not originally designed to look at the undesirable effects of inhaled steroids and as such, no comment could be made on this aspect of treatment. However, the mean starting doses and the mean maintenance doses of both beclomethasone dipropionate and budesonide were well below the levels at which side effects are known to occur.<sup>22 23</sup>

### Conclusion

This study clearly demonstrates the clinically efficacy and cost effectiveness of inhaled steroid prophylaxis in moderate to severe childhood asthma. The findings would be of significance not only to developing countries with their own financial problems but also to the more developed nations that are showing a reawakening of interest in medical audit and cost-benefit ratios of different treatment methods.

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### Commentary

In any society the connection between value and costs must be made with regard to all forms of health care. To determine whether the value of a health activity is worth its costs should be made not only by professionals but also by the people who will actually receive the value (experience the benefits and harms) and pay the costs.<sup>1</sup> Perera's paper examines the efficacy and cost effectiveness of inhaled steroids in asthma in Sri Lanka, a developing country with severe resource constraints. Relatively high cost treatment may be justified in this setting if the cost-utility value to the patient is reduced by the treatment. Perera has shown this effect in the population of patients he studied, but one cannot conclude that inhaled steroid treatment for prophylaxis of asthma is a cost effective treatment in all developing country settings without considering some of the limitations of the study.

The sample studied was small (n=86) even though the results showed strong cost-utility improvements. Of potentially greater importance is the unrepresentativeness of the patients studied. As noted at the end of the paper, the subjects were mostly from the upper income groups (being self selecting because of fee paying). By the same token, the application of the results to the public sector would apply disproportionately to members of lower income groups. The potential significance of differences in education/literacy is acknowledged. It seems possible, however, that the effectiveness of treatment and the extent of the benefits could be affected quite substantially by other income related factors such as nutrition, home environment, and morbidity from other causes. This may also limit the extent to which the results could be applied to other developing countries.

Similarly, the fact that the subjects were users of the private health sector may well mean that their previous treatment is unrepresentative of public sector patients. All but two of the subjects were on oral  $\beta$  agonists, all but 14 on oral theophyllines, and all but five had had repeated courses of intravenous and oral steroids. This suggests that at least 75% had all three forms of treatment during the control period. Essentially, the analysis is a comparison of the proposed treatment with this alternative regimen, which is almost certainly different from the pattern of treatment in the public sector in Sri Lanka or elsewhere in