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Research Article

Comparison of Inhaled Fluticasone and Oral Prednisolone in Children with Mild to Moderate Exacerbation of Acute Asthma

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Abstract

Objective of the Study: 1. Primary objective: To study and compare the improvements in parameters e.g. FEV1 (Primary outcome) and PEFR, SaO_2 and RR (Secondary outcome) in children with mild/moderate exacerbation of Asthma after experimental therapy i.e. inhaled fluticasone or oral Prednisolone till 4hrs of therapy. 2. Secondary objective: To compare relapse or hospitalization in next 7 days.

Material and Method: Study area: Hospital based study, conducted in Base Hospital, Delhi Cantt. Tertiary care hospital with 2 units of Pediatrics with attached Pediatrics emergency service. There is concern about safety of repetitive courses of systemic corticosteroids. Many children therefore receive inhaled corticosteroid during acute exacerbation of asthma The efficacy of inhaled corticosteroids in the treatment of severe acute asthma in children is not known. This study is about comparison of inhaled and systemic corticosteroid in improving respiratory parameters in children with mild to moderate exacerbation of asthma. Study population: Urban Children of both sexes in the age group of 5 - 12 years who are k/c/o asthma in mild/moderate exacerbation of symptoms visiting Pediatric emergency service. Sample size and sample technique: 100 children 5 years of age or older k/c/o asthma in mild/moderate exacerbation of symptoms. Data collection technique and tools: The study was conducted between January 2011 to March 2013. Informed consent was taken from the parents. Performa covering personal history, family history, living conditions, known allergies and current as well as previous treatments was elicited. Physical examination including anthropometric measurements was performed at the initial visit. The 100 children with mild/moderate exacerbation of Asthma underwent Peak expiratory flow rate measurement (PEFR Meter- Photo 2) and spirometry using Compact Spirometer (MIR-Medical International Research, REF-spirolab II, 125-00155 manufacturer - Italy- Photo -3) and vital monitoring. Data analysis: 1. Independent t test for comparison between two drugs. 2. One way ANOVA for hourly data for both drugs (1, 2, 3, 4 hours). 3. All the data will be expressed as Mean ± S.D

Salient Findings: 1. In this study children with mild to moderate asthma had shown significant improvement in pulmonary function tests with protocol based treatment. 2. Complaints like cough, wheeze, tightness in the chest, shortness of breath significantly decreased after protocol based treatment and counseling. 3. Oral prednisolone compared better than inhaled fluticasone as there is statistically significant improvement in primary outcome i.e. FEV1 in Prednisolone group as compared to inhaled fluticasone. 4. After improvement in symptoms, counseling the children as well as parents and explaining the benign nature of the disease in majority

cases. The improvement in their pulmonary functions and no relapse in home phase of the study show effectiveness of the intervention.

Conclusion: To conclude, in this study oral prednisolone proved to be better than inhaled fluticasone in children with mild to moderate exacerbations as the primary outcome i.e. FEV1 is statistically significant. However, the improvement in secondary outcome is not statistically significant. There was no relapse in next 7 days in both the groups in home phase of the study and follow up with education and psychological counseling improved the quality of life in our group of asthmatic children. These measures also alleviated the negative emotions and psychological distress associated with asthma. It was evident as study has shown improvement in objective measures of pulmonary function.

Recommendations: 1. High dose of inhaled steroid cannot replace oral prednisolone in acute exacerbation of Asthma. 2. Children with asthma show significant improvement in pulmonary function tests with protocol-based treatment. 3. MDI with spacers are as effective as nebulizers for the delivery of bronchodilators in the management of acute asthma and are more advantageous in children. 4. Although pharmacological intervention to treat established asthma is highly effective in controlling symptoms and improving quality of life, every attention should be paid to the measures to prevent this chronic disease. 5. Children as well as their parents needs to be educated and counseled in addition to the conventional pharmacologic treatment. Compliance to treatment can only be ensured with proper counseling and addressing complaints of parents and children.

Keywords: *Fluticasone; Prednisolone; Acute Asthma*

Introduction

Acute asthma is a common medical emergency in children. Systemic corticosteroids can decrease rates of hospitalisation among patients with acute asthma [1,2] although this statement is controversial to a certain extent [3,4]. However, there is equal concern about safety of repetitive courses of systemic corticosteroids [5-7]. Unlike β2 agonist, inhaled steroids e.g. highly potent Fluticasone propionate are generally thought to be safe, the inhalation route can be used easily in any setting and many children already receive inhaled corticosteroid during acute exacerbation of asthma. Regarding the efficacy of inhaled corticosteroids in the treatment of severe acute asthma in children, little is known, and there is conflicting evidence in the literature about the role of inhaled corticosteroids in management of severe acute asthma. So, this study was planned to compare the efficacy of high dose 1 mg of inhaled Fluticasone delivered by nebulisation with that of Prednisolone 2 mg/kg per orally administrated in children 5 years of age or more at the time of initial assessment and standard doses of both drugs during follow up in mild and moderate exacerbation of asthma.

Aim and Objective

Primary objective: To compare forced expiratory volume in first second (FEV1) (primary outcome) and peak expiratory flow rate (PEFR), SaO_2 and respiratory rate (RR) (secondary outcome) in children with mild and moderate exacerbation of asthma after experimental therapy i.e. inhaled Fluticasone or oral Prednisolone till 4hrs of therapy.

Secondary objective: To compare relapse or re-hospitalization over next 7 days after last day of therapy.

Materials and Methods

Study design: Randomized control open-labelled study by using computer generated random list (Random allocation software supporting block randomization).

This study is a Hospital based study done at Pediatrics and emergency department, Base Hospital, Delhi Cantt. Over 2 years (January 2011 to March 2013). Hundred (100) children (5 - 12 years old), diagnosed as mild and moderate exacerbation of asthma were enrolled, based on an estimated standard deviation of 15 for the change in the percentage of the predicted FEV1 in the Prednisolone group. In order to allow detection of a 10-percentage point difference between the groups in the degree of improvement in FEV1 (as a percentage of the predicted value) from base line to 240 minutes and to maintain an alpha error of 0.05 and a beta error of 0.10.

Exclusion criteria:

1. Children with other known chronic illnesses.
2. Known psychological or mental problems.
3. Children with first wheezing episode who had not previously received bronchodilator therapy or who had taken oral prednisone within last seven days of the visit.
4. Children taking 1000 µg or more of inhaled Beclomethasone di-propionate or Budesonide per day or 500 µg or more of inhaled Fluticasone per day.
5. Children of parents who are unlikely to give a reliable history or bring the child for regular follow-up.

Details of methodology

This study was conducted with approval from the ethical review committee of this institution; written consent was taken from the parent, after explaining the details about the study and risk involved. A structured proforma which includes patient particulars, detailed history related to asthma onset, triggers, previous number of episodes, family history, living conditions, known allergies, treatment history and contact number was recorded. Physical examination including vital monitoring and anthropometric measurements was performed and recorded.

All enrolled children underwent PEFR measurement (using PEFR Meter-Photo 2) and spirometry using Compact Spiro meter (MIR-Medical International Research, REF-Spirolab II, 125-00155, manufacturer-Italy-Photo-3). FEV1 and FVC were recorded according to the recommendations of American Thoracic Society [8]. The study group was categorized as mild, moderate and severe asthma based on IAP guidelines [9] those with low FEV1 (relative to percentage of predicted) and PEFR between 40 - 80% predicted; variability 20 - 30% and in whom result could be evaluated.

All were nebulized with salbutamol 2.5 mg and ipratropium bromide 250 microgram and oxygen @ flow of 6 - 7 liters per minute once, at the time of first contact. They were then randomized by using computer generated random list. In experimental therapy children received one dose of either inhaled fluticasone high dose 1mg through nebulization or oral prednisolone @ 2 mg /kg (maximum, 60 mg) and then three nebulizations with 2.5 mg of salbutamol and Ipratropium bromide @ 250 microgram at 20, 40, 60 minutes. These children were subsequently assessed hourly up to 4 hours.

Upon improvement, their parents were counselled about the techniques in using asthma devices by demonstrating hands on respiratory models, posters, handouts and educational CDs following the ALPAC method recommended by WHO (Ask, Listen, Praise, Advise, and Check). Children were discharged after four to six hours of admission.

All the parents and children were counselled regarding course of the disease and discharged with advice to continue to receive either Fluticasone or Prednisolone according to their group assignment (the home phase of the study), e.g. those in the Fluticasone group received Fluticasone 100 microgram per puff twice a day by MDI with spacer for 7 days, whereas children in Prednisolone group received Prednisolone 1 mg/kg/day (maximum 40 mg/day) once daily in morning after meals for 7 days. All patients also received inhaler Salbutamol 100 microgram per puff, 2 puffs TDS for seven days. Other patients who refused to participate were kept to assess the generalization of the study. On day 8, clinical assessment and pulmonary function testing of children was done.

Data analysis

After data collection, data was entered in excel and analyzed. Frequency and percentage tables were used for presentation of result. Mean median, standard deviation and inter quartile range was calculated for quantitative data. Independent t test was used for comparison between two drugs, and one way ANOVA for comparison of data (hourly readings) within the group of both the drugs (1, 2, 3, 4 hours).

Results and Discussion

Out of hundred children, twenty nine children had family history of asthma,allergic rhinitis or atopic dermatitis.

Fifty six children had mild intermittent asthma, ten children had mild persistent asthma, thirty four children had moderate persistent asthma.

The details of the primary and secondary variables and clinical features of children both in baseline and during experimental phase is mention in table 1-3 and figure and home phase of therapy in children with mild and moderate exacerbation of asthma is detailed in table 4.

Enrolment Characteristics of patients	Group I Inhaled Fluticasone (n = 51)	Group II Oral Prednisolone (n = 49)
Mean age in years	8.05 ± 1.95 (5 - 12)	8.94 ± 1.99 (5 - 12)
Male	40	41
Female	11	8
Weight in kg (mean ± SD)	28.17 ± 8.85 (range 17 - 58)	32.10 ± 11.44 (range 17 - 58)
Height in cm (mean ± SD)	126.84 ± 10.62 (range 110 - 148)	133.51 ± 10.90 (range 111 - 148)
Mean age in years at onset of illness	6.09 ± 1.64 (4 - 10)	6.67 ± 1.95 (4 - 10)
Complaints at the time of presentation		
Cough, wheeze	34	28
Cough, wheeze, dyspnea	11	19
Cough, wheeze, dyspnea, running nose	6	2
Triggers		
Cold wind	2	1
Cold wind and seasonal	14	15
Seasonal	17	16
Seasonal and exercise	3	1
Viral infection	15	16
Number of episodes of exacerbation per year		
< 5	16	21

≥ 5 - 7	28	16
≥ 8	7	12
Day time symptoms		
< 1/week	39	29
≥ 1/week	12	20
Nocturnal awakening		
< 2/month	35	23
≥ 2/month	16	26
FEV1	2.12 ± 0.28 (1.7 - 2.8)	2.12.18 ± 0.28 (1.6 - 2.8)
PEFR	263.6 ± 51.07 (150 - 400)	274.7 ± 47.47 (150 - 400)

Table 1: *Baseline demographic variables and clinical features of children.*

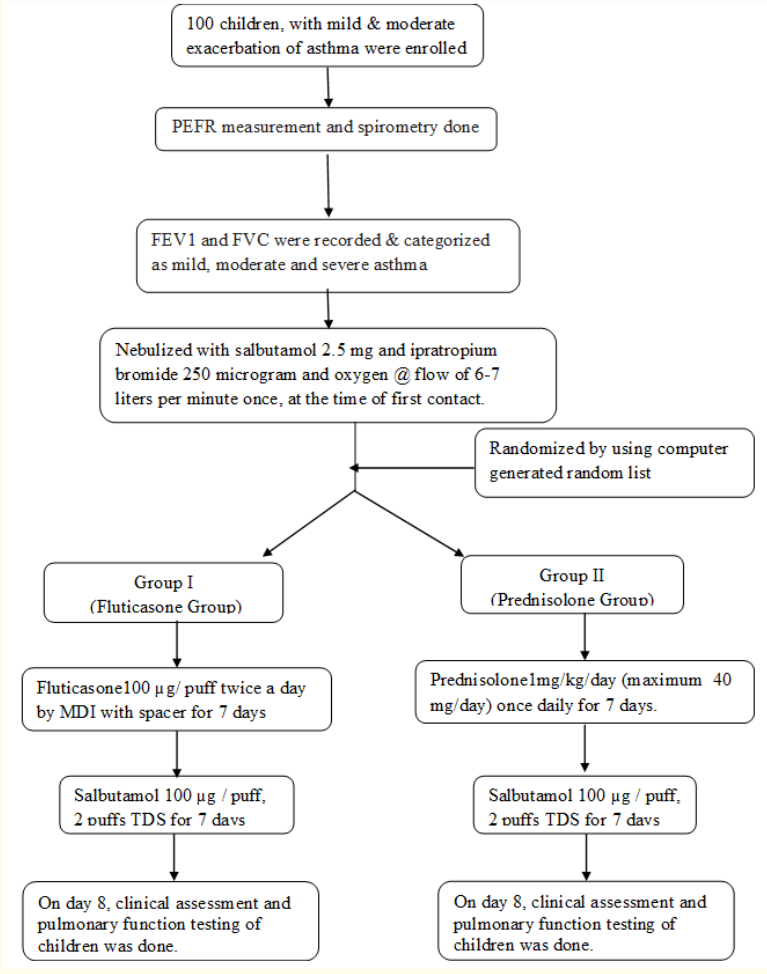

Figure 1: *Profile of patient used for recruitment and enrolment into the study.*

FEV1	Inhaled Fluticasone (n = 51)	Oral Prednisolone (n = 49)	Statistical significance* Student t-test (independent)
At admission. after nebulisation	2.17 ± 0.26	2.30 ± 0.25	< 0.01 S
60 minutes	2.35 ± 0.28	2.50 ± 0.23	< 0.01 S
120 minutes	2.51 ± 0.31	2.66 ± 0.26	< 0.01 S
180 minutes	2.66 ± 0.33	2.81 ± 0.26	< 0.05 S
240 minutes	2.81 ± 0.33	2.95 ± 0.26	< 0.05 S

Table 2: *Mean FEV1 (primary outcome) at different intervals during therapy.*

Parameter in different intervals	Inhaled fluticasone (n = 51)	Oral prednisolone (n = 49)	Statistical significance*
At admission			
PEFR	273.52 ± 53.24	294.30 ± 44.35	<0.05 Significant
SaO_2	91.96 ± 0.48	92.04 ± 0.644	>0.05 N.S.
RR	50.90 ± 5.59	51.59 ± 5.59	>0.05 N.S.
60 minutes			
PEFR	282.25 ± 47.80	309.10 ± 47.64	>0.05 N.S.
SaO_2	93.90 ± 0.500	94.02 ± 0.381	>0.05 N.S.
RR	46.84 ± 4.87	47.53 ± 5.00	>0.05 N.S.
120 minutes			
PEFR	296.80 ± 52.54	311 ± 50.95	>0.05 N.S.
SaO_2	94.98 ± 0.316	94.98 ± 0.478	>0.05 N.S.
RR	43.37 ± 4.95	44.49 ± 4.80	>0.05 N.S.
180 minutes			
PEFR	309.70 ± 55.28	323.9 ± 52.78	>0.05 N.S.
SaO_2	95.98 ± 0.51	96.06 ± 0.775	>0.05 N.S.
RR	41.1 ± 4.78	42 ± 4.98	>0.05 N.S.
240 minutes			
PEFR	320.00 ± 51.22	334.6 ± 52.36	>0.05 N.S.
SaO_2	96.35 ± 0.62	96.35 ± 0.805	>0.05 N.S.
RR	37.49 ± 3.65	37.84 ± 4.18	>0.05 N.S.

Table 3: *PEFR, SaO_2 and respiratory rate at different interval during therapy.*

**Student independent t-test, no statistically significant difference was found on comparing PEFR, SaO_2 and respiratory rate measured at different intervals in the two groups. However, mean PEFR measured at regular intervals was found to be higher in oral Prednisolone group as compared to that in inhaled Fluticasone group.*

Comparison of PEFR, SaO_2 and respiratory rate measured at hourly interval from baseline to final follow up i.e. at 1 hour, 2 hour, 3 hour and 4 hour within both the groups showed by using One way analysis of variance (ANOVA) significant improvement in all these parameters.

Parameter observed	Inhaled fluticasone (n = 51)	Oral prednisolone (n = 49)	Statistical significance*
Relapse (72 h/day)	0	0	
PEFR after 7 days	338.90 ± 46.30	358.16 ± 45.58	< 0.05 Significant

Table 4: *Home phase of therapy in children with mild & moderate exacerbation of asthma*

**Student t-test (independent)- oral prednisolone is slightly better than inhaled Fluticasone group (p < 0.05).*

The mean FEV1 recorded at different intervals during therapy in oral Prednisolone group as compared to that in inhaled Fluticasone group was statistically significant. We also found PEFR, SaO2 recorded at different intervals during therapy to be slightly higher and Respiratory rate improved in oral Prednisolone group as compared to that in inhaled Fluticasone group. Although there was no relapse after 7 days in both the groups, home phase of the study showed oral Prednisolone to be slightly better than inhaled Fluticasone.

Objective measures of pulmonary function (using - PEF-Meter and spirometry) were used to evaluate initial status and subsequent improvement with use of pharmacotherapy, although there is no gold standard tool to assess this.

Pulmonary functions were objectively measured using PEF-Meter and spirometry which requires high degree of patient cooperation and also reasonably good pulmonary reserve to perform the tests. Therefore, interpretation of these objective measures could have been hampered by subjective factors, particularly in younger children. Besides, the readings reflect a one-time measurement of the child's status unless recorded serially, which is often not feasible in home-based care.

Manjra., *et al*. (2000) in randomized, double-blind study on 321 children with acute exacerbation of asthma, evening peak expiratory flow (PEF) over 7 days, and PEF recorded in clinic showed significantly greater increase in the Fluticasone group as compared to Prednisolone group. PEF was measured which is less sensitive indicator of small airway obstruction and symptom score may be overestimated [10] Saito M (2017) using high-dose nebulized Budesonide and oral Prednisolone in children < 3 years of age with mild asthma exacerbation found same number days for improvement (5 ± 0) and days of oxygen use (2 ± 0) [11].

Although it is difficult to make diagnosis of asthma in young children, Saito M has used very stringent criteria for the same to match the cohort.

Both single high-dose Fluticasone and Prednisolone treatment resulted in a significant improvement in asthma score ($p < 0.0001$), PEF ($p < 0.0001$), and FEV1 ($p < 0.0001$) at the end of the six-day period [12]. Razi CH (2015) in a double-blind, placebo-controlled and parallel-group trial on 100 children aged 7 - 72 months admitted with asthma exacerbation and clinical asthma score (CAS) of between 3 and 9, showed that adding inhaled Budesonide to standard treatment of asthma exacerbation with oxygen inhalation and β2-agonist, anti-cholinergic and oral corticosteroid therapy, decreased the overall duration of hospital stay [13].

However, Schuh (2006) studied a convenience sample of 69 healthy children 5 to 17 years of age with acute mild to moderate asthma and found that airway obstruction in children improved faster on oral than on inhaled corticosteroids. Although the sample size was smaller [14].

Schuh (2000) in another double-blind, randomized trial involving 100 children five years of age or older reported that children with severe acute asthma had higher increase in FEV1, FVC, and PEFR, and lesser re-hospitalization when treated with oral Prednisone as compared to inhaled Fluticasone [15].

Rodrigo (2006) reported that inhaled steroids caused vasoconstriction of mucosal blood vessels and decreased blood flow and airway obstruction causing improvement in symptoms and spirometric values. However, this effect is rapid, transient and dose dependent so requires repeated administration of high dose of inhaled steroids at short intervals [16].

The major strength of study was no drop out on follow up. It could be due to proper education and counselling given along with conventional pharmacologic treatment resulting in good compliance as shown by improvement in pulmonary function tests during home phase of therapy and no relapse on follow up after 7 days and also because the study population consisted of children of defence employee staying in known defence accommodations in Delhi.

Conclusion

In this study on 100 children with mild to moderate exacerbation of asthma comparison of improvement in FEV1 with oral Prednisolone as compared to that with inhaled Fluticasone was statistically significant. To conclude, oral Prednisolone proved to be better than inhaled Fluticasone in children with mild to moderate exacerbations. The improvement in pulmonary functions and no relapse in home phase of the study in inhaled Fluticasone group show its effectiveness. To extrapolate the observations, a greater number of studies are needed to prove the efficacy of inhaled Fluticasone in asthma exacerbations.

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