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Preliminary, Comparative, Randomized, Open Labeled Trial, Evaluating Efficacy and Safety of Add-On Effects of Oral Prednisolone and Deflazacort to Inhalational Salbutamol in Patients of COPD

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ABSTRACT

Objective: To compare safety and efficacy of add-on effects of oral Prednisolone and oral Deflazacort to inhalational salbutamol in Patients of stable COPD. ***Materials and Methods:*** Sixty patients of COPD fulfilling ATS criteria were randomized to two treatment regimens for 2 weeks. In R1 patients received prednisolone 30 mg and in R2 patients received Deflazacort 36 mg in the morning. Patients in both regimens received Salbutamol (Inhalational 200 µg one puff QID). ***Statistics:*** Paired 't' Test was used for before and after treatment comparisons. ***Results:*** With R1, FEV1 changed from 1.0953 ± 0.382 to 1.155 ± 0.3701 ($P < 0.05$); with R2, it changed from 1.1227 ± 0.412 to 1.226 ± 0.3530 ($P < 0.001$). With R1 fasting blood sugar changed from 77.11± 8.026 to 80.51± 8.0987 ($P > 0.05$); With R2 it changed from 76.81± 6.3456 to79.00± 5.3071($P > 0.05$). With R1, total cholesterol increased from 196±10 to 216±17 ($P < 0.05$), LDL cholesterol increased from 107±9 to 124±14 ($P < 0.05$), HDL cholesterol increased from 53±4 to 56±3($P > 0.05$), Triglyceride levels decreased from 177±33 to 151±14 ($P>0.05$); With R2, total cholesterol increased from 195±5 to 191±12 ($P>0.05$), LDL cholesterol decreased from 105±13 to 101±9 ($P >0.05$), HDL cholesterol increased from 46±3 to 56±4 ($P <0.05$), Triglyceride levels decreased from 170±19 to 152±19 ($P >0.05$). With regimen R1 CRP changed from 4.9±1.3 to 3.3±1 ($p<0.05$) with regimen R2 CRP changed from 4.7±1.5 to 3±1.2 ($p<0.05$). ***Conclusion:*** Deflazacort should be used instead of Prednisolone in COPD patients requiring corticosteroid therapy.

INTRODUCTION

Chronic respiratory diseases account for 4 million deaths annually. 300 million people currently suffer from asthma. Globally 2.5 lakh people die of asthma every year & it is the most common non-communicable disease in children. 65 million have moderate to severe chronic obstructive pulmonary disease (COPD). More than 3 million died of COPD in 2005, which is 5% of all deaths globally that year. COPD is projected to become the third leading cause of death by 2030[1]. The BOLD study found the overall prevalence of COPD to be 5.7 - 23% in men aged > 40 yrs & 4.2 - 20.7% in women aged > 40yrs. Prevalence at Srinagar Centre was estimated at 17.3% in men aged > 40 yrs. And 14.8% in women aged > 40 years [2]. The INSEARCH study found the prevalence of Ch. Bronchitis in India at 3.5% & the prevalence of Asthma at 2.05% [3].

For the diagnosis and assessment of COPD, spirometry is the gold standard as it is best standardized, reproducible and objective way of measuring airflow limitation [4]. Patients with COPD typically show a decrease in both forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). A post-bronchodilator FEV1/FVC <70 % confirms the presence of airflow limitation that is not fully reversible.

Etiology of COPD is multifactorial, smoking, indoor & outdoor air pollution, occupational dust and chemicals, genetic factors, respiratory infections, socioeconomic status, nutrition and asthma. The single most important known causative factor of COPD is cigarette smoking [5]. Inhalation of cold air has been found to worsen airway obstruction in sensitive patients with COPD [6].

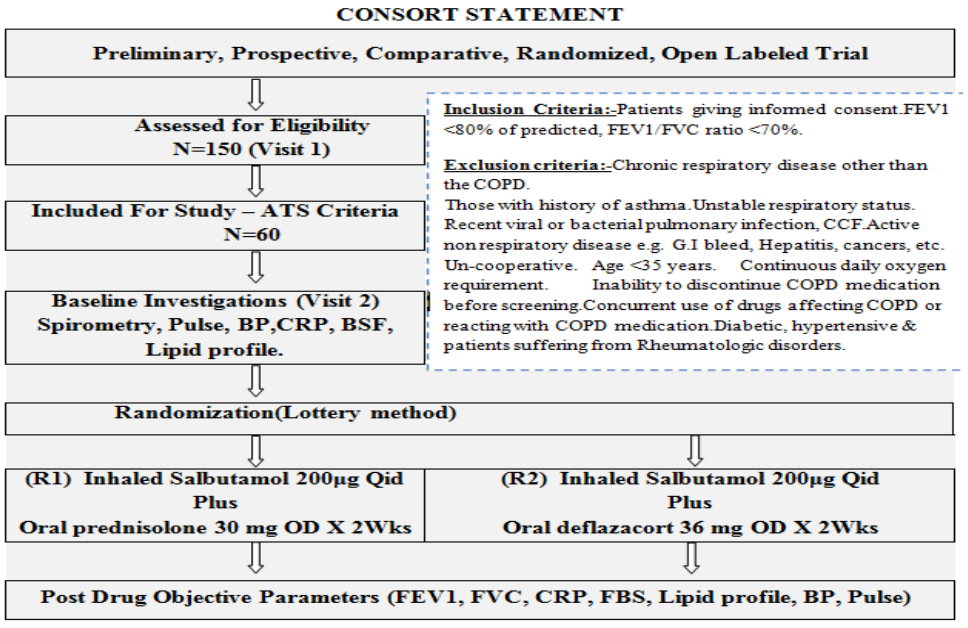
Local and systemic inflammation is implicated in the pathogenesis and maintenance of COPD; therapeutic strategies meant to halt or reverse inflammation are desirable. Non pulmonary manifestations of COPD suggest a systemic disorder that is likely mediated by circulating inflammatory cells and inflammatory cytokines. The use of inhaled or systemic corticosteroids has been the cornerstone in anti-inflammatory therapy in all settings of COPD [7]. Short term oral corticosteroid at higher doses in stable COPD produces statistically significant benefits in lung function, symptoms and exercise capacity, but currently their long term use is precluded because of adverse effects associated with their long term use [8].

Deflazacort an oxazoline derivative of prednisolone has been shown to possess similar efficacy in improving pulmonary function in acute exacerbations of COPD[9] and in acute moderate asthma or asthma crisis[10]. Deflazacort has lesser metabolic side effects in terms of worsening of lipid profile, derangement of glucose metabolism, reduction in bone mass and fat accumulation [11,12]. The aim of this study was to compare the add-on effects of two different oral corticosteroids prednisolone & deflazacort in equipotent doses to inhalational salbutamol in COPD patients.

Efficacy of the drugs was compared by assessing changes in various spirometric parameters (FEV1,FVC,FEV1/FVC%) and CRP while safety and tolerability was compared by assessing the changes in blood sugar, lipid profile, pulse, B.P and percentage of side effects with the two regimens.

MATERIALS METHODS

After approval from board of studies, the study was carried out at Govt. Chest Diseases Hospital Srinagar J&K. Informed written consent was taken from the patients found fit for the study. The patients who consented were followed by detailed history and clinical examination to confirm the initial diagnosis of COPD. The patients were asked to stop all bronchodilator drugs for at least 12 hours before initial spirometric testing [13]. Before doing pre-drug spirometry pulse and B.P were recorded [14].



The Spirometer used was PC based RM Medispiror which exceeded ATS criteria for accuracy and precision. Spirometry was performed according to American Thoracic Society (ATS) guidelines [15].

RESULTS

The Male: Female ratio was 2:1 (Table 1). The highest percentage of study population was in the age group of 61-65 years (28%) (Table 1) 90% patients were either smokers or ex-smokers and 10% patients were non-smokers. In smokers 43% were males and 5% were females. In ex-smokers group 53% were males and 75% were females. In non-smoker group 5% were males and 10% were females (Table 1). Maximum numbers of patients (51.66%) were having an illness of 2-4 years duration (Figure 2).

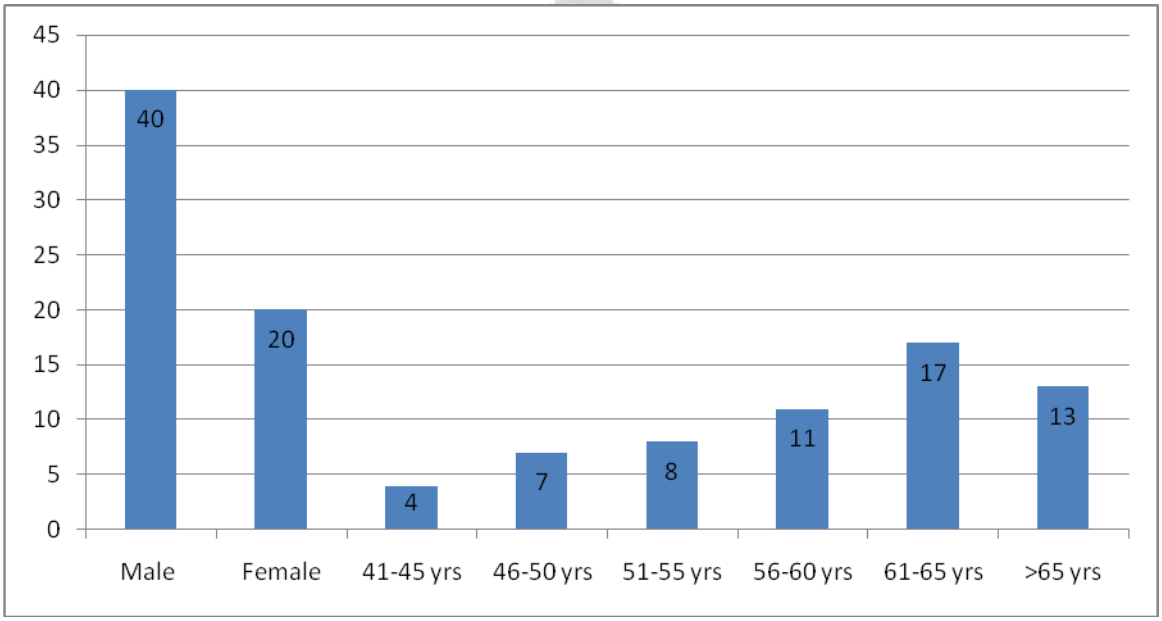


Figure 1: Sex and Age Distribution of Study Population

Table 1: Smoking Status of Study population

STATUS	MALES		FEMALES		TOTAL	
	No.	%	No.	%	No.	%
SMOKERS	17	43	1	5	18	30
EX-SMOKERS	21	53	15	75	36	60
NONSMOKERS	2	5	4	20	6	10

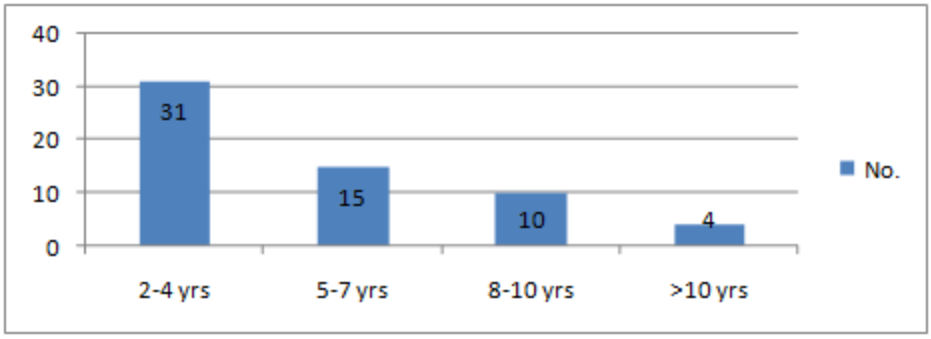


Figure 2: Distribution of Study population by Duration of illness in years

Table 2: Pre-Test and Post-test Parameters of Study Population

Parameter	Regimen	Before Treatment Mean±S.D	After Treatment Mean±S.D	t	P
FEV1	R1	1.0953± 0.382	1.155± 0.3701	5.741	<0.05
	R2	1.1227± 0.412	1.226± 0.3530	5.351	<0.001
FVC	R1	2.1813 ± 1.071	2.587± 1.1873	2.102	<0.05
	R2	1.9653 ± 0.800	2.2350± 0.757	2.184	<0.05
FEV1/FVC%.	R1	53.462± 18.163	59.685± 18.511	0.065	<0.05
	R2	52.890± 18.080	60.995± 19.330	1.043	<0.05
Pulse	R1	79.642± 15.648	83.034± 14.322	0.51	>0.05
	R2	80.553± 11.485	82.00± 13.076	0.59	>0.05
Systolic BP	R1	122.13± 8.85	124.50± 7.39	0.346	>0.05
	R2	122.40±7.40	122.800± 8.32	0.742	>0.05
Diastolic BP	R1	78.066± 5.445	78.266± 4.883	0.532	>0.05
	R2	78.400± 4.966	78.0956± 5.44	0.841	>0.05
Blood Sugar	R1	77.11± 8.026	80.51± 8.0987	0.3508	>0.05
	R2	76.81± 6.3456	79.00± 5.3071	0.7253	>0.05
CRP (mg/l)	R1	4.9±1.3	3.3±1	0.065	<0.05
	R2	4.7±1.5	3±1.2	1.043	<0.05
Total cholesterol (mg/dl)	R1	196±10	216±17	20±9	<0.05
	R2	195±5	191±12	–4±6	>0.05
HDL-cholesterol (mg/dl)	R1	53±4	56±3	3±3	>0.05
	R2	46±3	56±4	10±2	<0.05
LDL-cholesterol (mg/dl)	R1	107±9	124±14	17±7	<0.05
	R2	105±13	101±9	–4±5	>0.05
Triglycerides (mg/dl)	R1	177±33	151±14	–26±28	>0.05
	R2	170±19	152±19	–18±22	>0.05

With regimen R1, FEV1 changed from 1.0953 ±0.382 to 1.155 ±0.3701. With regimen R2, FEV1 changed from 1.1227±0.412 to 1.226 ± 0.3530. The FEV1 changes in both the regimens were statistically significant. With regimen R1, FVC changed from 2.1813 ± 1.071 to 2.587± 1.1873. With regimen R2, FVC changed from 1.965±0.800 to 2.2350 ± 0.757. The FVC changes in both the regimens were statistically significant. With regimen R1, FEV1/FVC % changed from 53.462± 18.163 to 59.685± 18.511. With regimen R2, FEV1/FVC % changed from 52.890± 18.080 to 60.995± 19.330. The FEV1/FVC % changes in both the regimens were statistically significant. With regimen R1 pulse changed from 79.642± 15.648 to 83.034±14.322 and with R2 from 80.553± 11.485 to 82.00± 13.076. The changes in both the regimens were statistically insignificant. With regimen R1, the change in systolic BP was from 122.13± 8.85 to 124.50± 7.39 and with regimen R2 the change was from 122.40± 7.396 to 122.800± 8.32. Both the regimens showed statistically insignificant changes. With R1 diastolic B.P. changed from 78.066± 5.445 to 78.266± 4.883 while as with R2 the change was from 78.400± 4.966 to 78.0956± 5.44. None of the regimens showed statistically significant changes in Diastolic B.P. With regimen R1 fasting blood sugar changed from 77.11± 8.026 to 80.51± 8.0987. With regimen R2 fasting blood sugar changed from 76.81± 6.3456 to79.00± 5.3071. The changes were insignificant in both the regimens. With regimen R1 CRP changed from 4.9±1.3 to 3.3±1 ($p<0.05$) with regimen R2 CRP changed from 4.7±1.5 to 3±1.2 ($p<0.05$). The changes in CRP levels were significant in both the regimens. With regimen R1, total cholesterol increased from 196±10 to 216±17. LDL cholesterol increased from 107±9 to 124±14. HDL cholesterol increased from 53±4 to 56±3. Triglyceride levels decreased from 177±33 to 151±14. The changes in total and LDL cholesterol were statistically significant ($P<0.05$). While the increase in HDL cholesterol and Triglyceride levels were statistically insignificant ($p>0.05$). With regimen R2, total cholesterol increased from 195±5 to 191±12. LDL cholesterol decreased from 105±13 to 101±9. HDL cholesterol increased from 46±3 to 56±4. Triglyceride levels decreased from 170±19 to152±19. There was a significant increase in HDL cholesterol whereas changes in total cholesterol, LDL cholesterol and triglyceride levels were not significant. In R1 and R2 regimen 21% and 18 % experienced side effects respectively. Increased appetite & epigastric pain were the commonest side effect with both regimens R1 and R2 followed by water retention (Table 3).

Table 3: ADR's observed with both regimens

Regimen	With side effects			Without side effects		
	No.	%		No.	%	
R1	6	21		23	79	
R2	5	18		23	82	
PERCENTAGE SIDE EFFECTS OF BOTH REGIMENS						
	Increased appetite	Epigastric pain	Hypertension	Water retention	Insomnia	Nervousness
R1	13.79%	10.34%	6.89%	6.89%	3.44%	3.44%
R2	10.71	7.14%	X	3.57%	3.57%	3.57%

DISCUSSION

A number of different pharmacological agents are being used to treat patients of COPD. Pharmacotherapy is used to control symptoms reduce the frequency and severity of exacerbations, improve health status and exercise tolerance [16].

The existing medications of COPD do not modify the long term decline in lung function [17], although there is some evidence that regular treatment with β2-agonists, inhaled glucocorticoids, and their combinations can decrease the rate of decline of lung function [18].

Bronchodilators are central to the management of COPD [5]. Beta agonists, anticholinergics, methylxanthines are all effective bronchodilators. They are given either on as needed basis for relief of persisting or worsening symptoms or on a regular basis to prevent or reduce symptoms. Beta-2 agonists are most widely used bronchodilators for COPD. They cause significant increase in FEV1, PEFR and symptom score [19].

Corticosteroids improve the response to bronchodilator and decrease dyspnea in stable COPD [5]. Short term oral corticosteroids in stable COPD produces statistically significant benefits in lung function, symptoms and exercise capacity [20]. Reduced lung function in COPD is associated with increased levels of systemic inflammatory markers which may explain the high prevalence of systemic complications such as cachexia, osteoporosis, and cardiovascular diseases among patients with COPD and reduction in systemic inflammation may have important patho-physiological and therapeutic implications for subjects with stable COPD [21].

In the present study it was observed that spirometric values improved significantly in both treatment arms. (Table 3, 6, 7) with regimen R1, FEV1 changed from 1.0953 ±0.382 to 1.155 ±0.3701. FVC changed from 2.1813±1.071 to 2.587±1.1873. FEV1/FVC% changed from 53.462±18.163% to 59.685±18.511%. These changes were statistically significant ($p<0.05$). With regimen R2, FEV1 changed from 1.1227±0.412 to 1.226 ± 0.3530. FVC changed from 1.9653±0.800 to 2.2350±0.757 FEV1/FVC% changed from 52.890±18.080% to 60.995±19.330%. These changes were statistically significant ($p<0.05$). These results correlate well with the studies conducted by other workers.

Callahan *et al* (1991) in a meta-analysis oral corticosteroid therapy for patients with stable COPD concluded that patients with stable chronic obstructive pulmonary disease receiving oral corticosteroid therapy have a 20% or greater improvement in baseline FEV1 [22].

Bergin-Zimmermann (1995) while comparing the therapeutic efficacy and tolerability of deflazacort and prednisone, in the short term management of exacerbations of chronic obstructive pulmonary concluded both drugs showed a statistically significant improvement of both, lung function and clinical symptoms, after 7 and 14 days [9].

Gartner S *et al* (2004) found that deflazacort and prednisolone showed similar efficacy in improving pulmonary function and in producing clinical improvement in the management of acute moderate asthma in children[23].

CONCLUSION

Although prednisolone and deflazacort are equally efficacious as evidenced by improvement in spirometric parameters & decrease in CRP, but due to adverse deterioration of lipid profile with prednisolone and favorable improvement with deflazacort not only in total cholesterol and LDL, but also elevation in HDL, deflazacort should be used instead of prednisolone in COPD patients requiring corticosteroid therapy.

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REFERENCES

1. WHO: Chronic Respiratory diseases. Available from:http://www.who.int/respiratory/en.Assessed on 10-3-2015.
2. Burney P, Koul P. A et al. Thorax 2014;69:465–473.
3. S.K Jindal. Insearch study. Int J Tuberc Lung Dis.2012;16:1270–7.
4. Pauwels RA, Buist SA, Calverley PM, Jenkins CR, Hurd SS. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. Am J RespirCrit Care Med. 2001;163(5):1256-1276
5. Man SF, McAlister FA, Anthonisen NR, Sin DD. Contemporary management of chronic obstructive pulmonary disease: Clinical application. JAMA 2003; 290(17):2313-6.
6. Miller JS, Nairn JR, Unkles RD, MCNeil RS. Cold air and ventilatory function. Br. Med. J. Dis. Chest 1965; 59:23.
7. Jeremy AF, Omar AM, Zab M. Inhaled and systemic corticosteroids in chronic obstructive pulmonary disease. Proceedings of American Thoracic Society 2008; 5:506–512.
8. Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2005; (3):CD005374.
9. Bergin-Zimmermann, Kathrin Andrea. Deflazacort versus prednisone in the treatment of acute exacerbations of chronic obstructive pulmonary diseases. (1995). doi: 10.3929/ethz-a-001511895.
10. Chapela R. Comparative study of the effectiveness of 2 oral corticoids in the control of severe crisis of bronchial asthma: deflazacort and prednisone. Rev Alerg Mex. 1995; 42(4):64-8.
11. Lippuner K, Casez JP, Horber FF, Jaeger P. Effects of deflazacort versus prednisone on bone mass, body composition, and lipid profile: a randomized, double blind study in kidney transplant patients. J ClinEndocrinolMetab. 1998; 83(11):3795-802.
12. Bruno A, Pagano G, Benzi L, Di Ciani G, Spallone V, Calabrese G *et al*. Change in glucose metabolism after long-term treatment with deflazacort and betamethasone. Eur J ClinPharmacol. 1992; 43(1):47-50.
13. Nishimura K, Koyama H, Ikeda A, Sugiura N, Kawakatsu K, Izumi T. The Additive effect of theophylline on a high dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. Chest 1995; 107:718-23.
14. Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kutta K, Della Cioppa. Comparison of the efficacy, tolerability, and safety of formoterol dry powder & oral, slow release theophylline in the treatment of COPD. Chest 2002; 121:1058-69.
15. American Thoracic Society. Standardization of Spirometry 1994 update: Statement of the American Thoracic Society. Am J RespirCrit Care Med 1995; 152:1107-36.
16. Fabbri L, Hogg JC, Jenkins C, Nizankowska E, Sullivan , Molen TD, Weel CV. Global initative for chronic obstructive lung diseases.-2006.
17. Anthonisen NR, Connent JE, iley JP, Altose MD, Bailey WC, Buist AS *et al*. Effects of smoking intervention and use of an inhaled anticholinergic bronchodilator on rate of decline of FEV1. The Lung Study. JAMA 1994; 272(19):1497-505.
18. Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, Vestbo J, Knobil K, Yates JC, and Calverly PM. Effects of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J RespirCrit Care Med. 2008 Aug 15; 178(4):332-8.
19. Sestini P, Renzoni E, Gray R, Poole P, ram FS. Short acting beta 2 agonists for COPD (Cochrane review) Cochrane Database syst. Review 2000(3):CD001495.
20. Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary

disease. Cochrane Database Syst Rev. 2005; (3):CD005374.

21. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta analysis.Thorax 2004; 59:574–580.
22. Callahan CM, Dittus RS, Katz BP. Oral Corticosteroid therapy for patients with stable COPD. A meta-analysis. Ann Intern Med 1991; 114(3):216-223.
23. Gartner S, Cobos N, Perez-Yarza EG, Moreno A, De Frutos C, Linan S *et al*. Comparative efficacy of oral deflazacort versus oral prednisolone in children with moderate acute asthma. Anales de pediatria 2004; 61(3):207-212.