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ORIGINAL ARTICLE

Role of Oral Prednisolone in the Acute Exacerbation of Bronchiectasis

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Abstract:

Background and Objectives: *The clinical efficacy of oral corticosteroid treatment has not been evaluated in the treatment of bronchiectasis, despite the presence of chronic airway inflammation. Not much randomized controlled trials have been conducted in this aspect and not much data is available, especially with respect to patients of Bangladesh. This study was designed to see the effect of Oral Prednisolone in Bronchiectasis during acute exacerbation.*

Methods: *This double blind, a prospective, randomized controlled trial (RCT) was carried out in NIDCH, Dhaka during the period from June 2009 to May 2010. A total of 64 patients of Bronchiectasis with acute exacerbation, were enrolled in two groups randomly: 'Steroid' group (n=32, 19 M, mean±SD age 42.06 ± 15.02 years) and 'Placebo' group (n=32, 25 M, mean±SD age 37.06 ± 11.99 years). After blinding, 'Steroid' group patients were given oral Prednisolone (30 mg/ day) for 2 weeks followed by 2 weeks tapering and 'Placebo' group patients, who were regarded as control, were given 'matched' Placebo for the same duration, in addition to standard treatment of Bronchiectasis, and effect was seen at 7th day, 14th day and 30th day.*

Results: *In both groups, baseline characteristics were almost similar. Clinical outcome at different time interval showed that addition of oral Prednisolone to the standard treatment of Bronchiectasis resulted in enhanced clinical improvement, especially in cough (at day 7, p=0.001, NNT=1.8), sputum volume (at day 7, p=0.040, NNT=2.7, at day 14, NNT=4.6), sputum purulence (at day 14, p=0.003), dyspnoea (At 14 days, p=0.003), and fever (at day 7, p=0.010) earlier (mostly at day 7), compared to standard treatment alone. Not much improvement was noted in appetite, CBC and Spirometric parameters. Exacerbation was seen in 2 (6.3%) cases in 'Steroid' group, as compared with 9 (28.1%) cases in 'Placebo' group (p=0.020). Only minor side effects (including dyspepsia, weight gain and acne) related to corticosteroid use were noted, which was statistically insignificant, implicating its safety at short term use.*

Conclusion: *Oral prednisolone is beneficial for acute exacerbation of bronchiectasis as an adjunct to the standard treatment, which gives earlier improvement, thereby decreases the morbidity, hospital stay as well as treatment cost.*

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Background

"Bronchiectasis" originates from Greek literally meaning 'stretching of the windpipe'. It may be defined as chronic necrotizing infection of the bronchi and bronchioles leading to or associated with abnormal dilatation of those airways.[1] It is characterized by irreversible destruction and dilatation of medium sized subsegmental bronchi from about 4th to 9th generations[2], generally associated with chronic bacterial infection. It is increasingly recognized as a major cause of respiratory morbidity especially in developing countries[3,4,5] and in some ethnic populations of affluent countries[6,7]. People with bronchiectasis have significant morbidity; with poor exercise tolerance, recurrent primary health care presentations, repeated hospital admissions and frequent school absenteeism. Bronchiectasis is associated with more rapid lung function decline and without treatment almost always results in shortened life expectancy[8]. Although once considered to be an orphan disease with fading relevance in the developed world in the late 20th century, Bronchiectasis is now being diagnosed with increasing frequency in North America and around the globe[9]. The prevalence of bronchiectasis in the United States and worldwide, including Bangladesh, is unknown.

Bronchiectasis is often regarded as the final common path for a wide spectrum of diseases. Even after extensive investigations the aetiology of non-cystic fibrosis (CF) bronchiectasis remains unknown in 50%[8,10,11]. The high proportion of patients with idiopathic aetiology reflects our poor understanding. The dominant clinical features of bronchiectasis are disabling productive cough, dyspnoea, occasional haemoptysis and presence of other respiratory signs (clubbing, chest wall deformity, wheeze or crepitations on auscultation)[12], often in association with recurrent acute exacerbations. An exacerbation is defined as subjective and persistent (>24 hour) deterioration in at least 3 respiratory symptoms (including cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain), with or without fever (>37.5°C), radiographic deterioration, systemic disturbances, or deterioration in physical signs in the chest (including crackles and dullness on auscultation and percussion, respectively).[3]

Regarding pathogenesis, recent data have revealed three important interactive pathogenic and interactively components in bronchiectasis, namely- infection with respiratory pathogens, inflammation with intensive leukocyte infiltration and enzymatic components released from the neutrophils as well as the bacteria. These interact to perpetuate the continued airway destruction in bronchiectasis. The current management includes the promotion of bronchial hygiene, the reduction of bronchial inflammation, administration of antibiotic aimed at pathogen, surgery where indicated and miscellaneous measures (like – O_2 therapy, vaccines etc.). In our study, Standard treatment of Bronchiectasis was referred to as the usual recognized treatment of bronchiectasis followed all over the world, which includes – Bed rest, Anti-pyretic, Antibiotic, Postural drainage and Chest physiotherapy.

Regarding Steroid use in Bronchiectasis, RCTs in young patients with Cystic Fibrosis have shown improvements in clinical and physiological parameters (bronchial hyper-responsiveness, respiratory symptoms, and spirometric parameters) with extended courses of alternate-day Steroids, but with significant adverse effects particularly on growth rates in males. [13] There are only few controlled studies of the use of Inhaled Corticosteroid in non-CF bronchiectasis with limited benefits.[14] Although asthma, COPD, and bronchiectasis are similar in symptoms, airway inflammation and airflow obstruction, Corticosteroid treatment is only of proven clinical benefit in asthma where it improves lung function and exacerbation frequency. Such efficacy is unclear in COPD and previously unexplored in bronchiectasis. As asthma like symptoms are common in bronchiectasis, the use of Corticosteroids may be beneficial in reducing exacerbations, symptoms and pulmonary decline.

Rationale

Bronchiectasis is a global problem and in Bangladesh, as a result of widespread Tuberculous infection, many patients suffer from it with significant morbidity with frequent acute exacerbations. The clinical efficacy of oral corticosteroid treatment has not been evaluated in acute exacerbation, particularly in non-CF bronchiectasis, despite the presence of chronic airway inflammation. Not much randomized controlled trials had been conducted in this aspect and not much data is available, especially with respect to patients of Bangladesh. So this randomized, double blind study has been designed to evaluate the clinical efficacy of treatment with Corticosteroid in patients with acute exacerbation of bronchiectasis. This trial is one of the first of such kind, particularly in the people of Bangladesh.

Hypothesis

Treatment with Corticosteroid hastens the improvement of acute exacerbation of Bronchiectasis.

Objectives

General objective was to find out the ideal treatment of Bronchiectasis during acute exacerbation.

Specific objectives were to know whether the oral Corticosteroid therapy can hasten the resolution of acute exacerbation of Bronchiectasis, reduce the 24 hours sputum volume & sputum purulence, improve the symptoms of the patients and the Spirometric parameters in the short term, and to find out the efficacy of the oral Corticosteroids in reducing frequency of acute respiratory exacerbations during the study period.

Ethical Implications

The study protocol was approved by the institutional ethical committee in NIDCH, Dhaka. Informed written consent was obtained from the patients after elaborate explanation of the purpose of the study. No invasive procedure or investigation was done for this study. No monetary compensation was provided to the patients because of loss of their time. All information gathered was kept secret and was only be used for medical research and analysis.

Materials and Methods:

This double blind, placebo-controlled, prospective, randomized controlled trial (RCT) was carried out in both Indoor and Outdoor of National Institute of Diseases of Chest and Hospital (NIDCH), Dhaka during the period from June 2009 to May 2010. A total of 64 patients[15], both male and female, diagnosed as acute exacerbation of Bronchiectasis, were enrolled according to the inclusion and exclusion criteria in two groups randomly. It was a simple random sampling using 64 random number cards obtained from Random number table. Each random number was assigned to either Placebo or Prednisolone by the helper of the study. Patient picked a card with a random number at the time of enrollment and got either Drug or Placebo for the whole length of the study (1 month). The investigator remained blinded in the whole process. Each group contained 32 patients (32 cases and 32 controls). 'Steroid' group patients (n=32, 19 M, mean±SD age 42.06 ± 15.02 years) were given Corticosteroid in the form of oral Prednisolone and 'Placebo' group patients (n=32, 25 M, mean±SD age 37.06 ± 11.99 years) were given 'matched Placebo' (not containing Steroid). In addition, Standard treatment of Bronchiectasis was given to both groups and effects were seen at 7^{th} day, 14^{th} day and 30^{th} day. Total 8 patients (5 from 'Steroid' group and 3 from 'Placebo' group), mostly female, did not come for follow-up at 1 month, despite repeated contact over Telephone. So, another 8 patients were included in the study according to selection criteria to maintain the total number of sample size to 64.

Several variables were used in the study. **Sputum purulence** were scored as[3] - **0** = absence of sputum, **1**= completely transparent, **2** = almost transparent, **3** = translucent but colourless, **4** = opaque and milky white, **5** = grey, **6** = pale green, **7** = moderately green and **8** = dark green sputum. Dyspnoea were scored according to Medical Research Council (MRC) dyspnoea scale[16].

Selection criteria of subjects:

Inclusion criteria

- Patients with proven Bronchiectasis, preferably by HRCT, were recruited with written informed consent.
- Presence of acute exacerbation of bronchiectasis
- Daily sputum production >10 ml
- Age between 18 to 65 years.
- No sex difference was made.
- Participants, who gave consent and willing to comply with the study procedure, were included.

Exclusion criteria

- Patients not willing to enroll in the study
- Unreliable clinic attendance
- Regular usage of Inhaled or Oral corticosteroids due to any cause, like – Bronchial asthma
- Known unstable systemic diseases (e.g.- cardiovascular diseases), Cystic fibrosis and Malignancy
- Active Tuberculosis.
- Severe haemoptysis
- Pregnancy

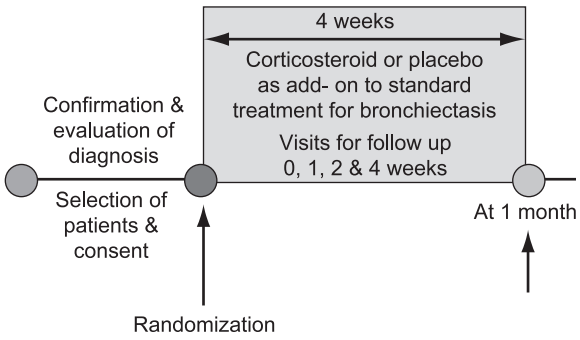
Study design and Steps of the study procedure: This is a randomized, placebo-controlled, double-blind, hospital based clinical trial comprised of:

(1) Screening phase: During this phase, each subject was evaluated with history and physical examination for eligibility in the study. A questionnaire proforma was prepared and filled up and patients were selected according to inclusion and exclusion criteria. Certain investigations were done on admission and also at 1 month, including – CBC, Spirometry and Sputum examination (including Sputum purulence score). Informed written consent was taken from each patient after explanation.

(2) 2- Weeks Clinical & Run-in phase: After selection, patients of diagnosed Bronchiectasis with acute exacerbation were grouped into two: 'Steroid group' and 'Placebo group' and were randomized to receive either Steroid or Placebo. 'Steroid' group patients were given oral Prednisolone (30 mg/day) for 2 weeks followed by 2 weeks tapering and 'Placebo' group patients were given 'matched Placebo' for the same duration. In addition, the standard treatment of acute exacerbation of Bronchiectasis was given (already described). Both groups were given Tab. Levofloxacin (500 mg) daily PO for 10 days empirically for all exacerbations. If the condition was severe from the beginning or in case of clinical deterioration, injectable antibiotics were given after hospitalization, if not already hospitalized. Medications were provided to the patients and were asked to take regularly. Investigator involved in monitoring the study remained blinded throughout the study period.

(3) 2- Weeks Follow-up phase: Patients were followed up and reviewed clinically as well as by certain investigations during the treatment phase at 7th day, 14th day and 30th day and results were compared with the baseline value to see the effect of the drugs. During follow-up, both subjective and objective variables were seen.

All data relating the diagnosis, management and outcome were collected, recorded and properly stored in the pre-designed data collection sheet and compiled. After properly scrutinized, edited and recorded systematically, data were processed and analyzed using SPSS (Statistical Package for Social Sciences) version 15.0.0. to find out the role of Corticosteroid in the management of acute exacerbation of Bronchiectasis. The level of significance was 0.05 and Probability value (p) <0.05 was considered as level of significance in all cases.



Results & Observations

Table-I

Distribution of the study population according to cough by groups (n=64)

	Cough	Groups		p value
		Placebo	Steroid	
On admission	Present/ Increased	32 (100.0)	32 (100.0)	
At 7 days	Improve/ Resolved	0 (0.0)	9 (28.1)	0.001*
	Static/ No change	13(40.6)	22 (68.8)	
	Increased	19(59.4)	1(3.1)	
At14 days	Improved/Resolved	9(28.1)	29(90.6)	0.001*
	Static/ No change	23 (71.9)	3(9.4)	
At1 month	Improve/ Resolved	22 (68.8)	26(81.3)	0.435*
	Static/ No change	7 (21.9)	5(15.6)	
	Increased	3 (9.4)	1(3.1)	

*Chi-square (c^2) test was done to measure the level of significance.
Figure within parenthesis indicates in percentage.

Table II

Distribution of study population according to fever by groups (n=64)

	Fever	Groups		p value
		Placebo	Steroid	
On admission	No fever	1 (3.1)	3 (9.4)	0.613**
	Irregular/ intermittent	29 (90.6)	27 (93.7)	
	Continued/persistent	2 (6.3)	2 (6.3)	
At 7 days	Improved/absent	3 (9.4)	12 (37.5)	0.010*
	Irregular/intermittent	26 (81.3)	20 (62.5)	
	Continued/persistent	3 (9.4)	0 (0.0)	
At 14 days	Improved/absent	31 (96.9)	32 (100.0)	0.999**
	Irregular/intermittent	1 (3.1)	0 (0.0)	
At 1 month	Improved/absent	29 (90.6)	28 (87.5)	0.999**
	Irregular/intermittent	3 (9.4)	4 (12.5)	

*Chi-square (c^2) test was done to measure the level of significance.
**Fisher's Exact test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Table-III

Distribution of study population according to Dyspnoea grade by groups (n=64)

Dyspnoea	Groups		p value
	Placebo	Steroid	
On admission	3.16 ± 0.88	3.28 ± 0.73	0.539*
At 7 days	2.50 ± 0.72	2.34 ± 0.65	0.366*
At 14 days	2.00 ± 0.44	2.06 ± 0.72	0.675*
At 1 month	1.91 ± 0.69	1.84 ± 0.81	0.740*
Percent of improvement from admission to 7^{th} days	18.85 ± 15.69	27.97 ± 14.38	0.018*
Percent of improvement from admission to 30^{th} days	37.08 ± 19.52	42.71 ± 19.94	0.259*

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

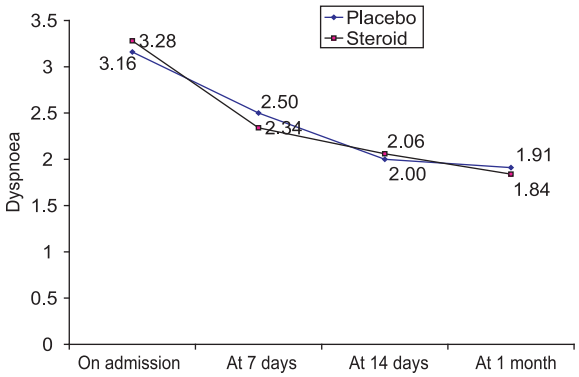


Fig.-1: *Line chart of changes of Dyspnoea grade at different time interval by groups*

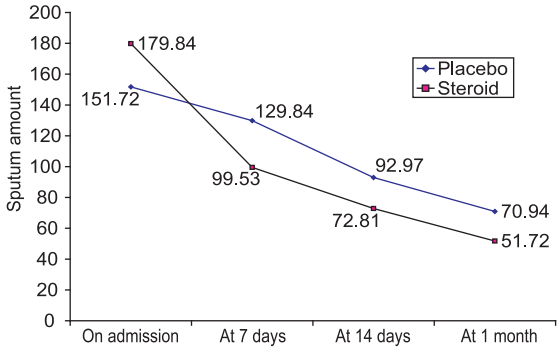


Fig.-2: *Line chart of changes of Sputum volume at different time interval by groups*

Table IV

Distribution of study population according to Sputum amount by groups (n=64)

Sputum amount	Groups		p value
	Placebo	Steroid	
On admission	151.72 ± 59.39	179.84 ± 100.77	0.179*
At 7 days (in ml)	129.84 ± 49.88	99.53 ± 64.79	0.040*
At 14 days (in ml)	92.97 ± 40.66	72.81 ± 102.13	0.304*
At 1 month (in ml)	70.94 ± 36.49	51.72± 57.50	0.115*
Percent of improvement from admission to 7th days	14.37 ± 4.92	44.27 ± 16.01	0.001*
Percent of improvement from admission to 30th days	54.05± 10.93	74.26± 17.43	0.001*

*Chi-square (c^2) test was done to measure the level of significance.

Table-V

Distribution of study population according to sputum purulence score by groups (n=64)

Sputum purulence	Groups		p value*
	Placebo	Steroid	
On admission	4.41 ± 0.50	4.69 ± 0.74	0.079
At 7 days	2.75± 0.80	2.44 ± 0.62	0.086
At 14 days	1.56± 0.56	1.19 ± 0.40	0.003
At 1 month	1.41 ± 0.91	1.34 ± 0.90	0.784
Percent of improvement from admission to 7^{th} days	38.13 ± 14.07	48.04 ± 11.26	0.003
Percent of improvement from admission to 30^{th} days	67.97 ± 20.04	71.57 ± 15.88	0.429

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

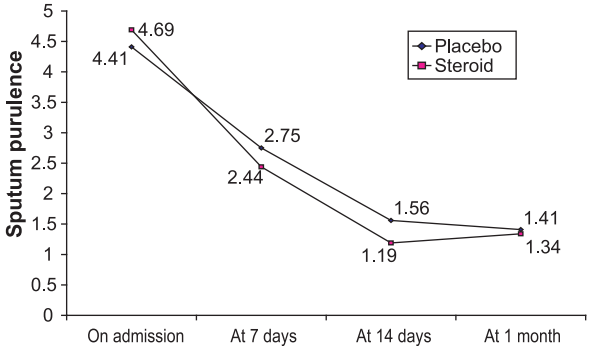


Fig.-3: *Line chart of changes of Sputum purulence at different time interval*

Table VI

Distribution of study population according to spirometric parameters by groups (n=64)

Spirometric parameters		Groups		p value
		Placebo	Steroid	
FEV_1	On admission	54.86 ±10.60	52.53 ±14.93	0.475*
	At 1 month	57.91 ±10.19	56.78±16.46	0.741*
FVC	On admission	73.07±8.85	66.80 ±16.19	0.059*
	At 1 month	76.50 ±7.34	72.37±14.70	0.160*
FEV1/FVC	On admission	67.76 ±9.36	72.01 ±13.40	0.146*
	At 1 month	72.72 ±8.36	76.25 ±10.85	0.150*

*Chi-square (c^2) test was done to measure the level of significance. Figure within parenthesis indicates in percentage.

Table-VII

Calculation for CER, EER, RRR, ARR & NNT

	Day	CER	EER	RRR	ARR	NNT
Cough	For7^{th} day	59.4%	3.1%	94.8%	56.3%	1.8
	For 30^{th} day	9.4%	3.1%	67.0%	6.3%	15.9
Sputum amount *	For 7^{th} day	93.8%	56.3%	39.98%	37.5%	2.7
	For 30^{th} day	40.6%	18.8%	53.6%	21.8%	4.6
Sputum purulence**	For 7^{th} day	53.1%	50.0%	5.8%	3.1%	32.2
	For 30^{th} day	15.6%	12.5%	19.9%	3.1%	32.2

[CER - Control Event Rate, EER -Experimental Event Rate, RRR -Relative Risk Reduction, ARR - Absolute Risk Reduction, NNT - Number Needed to Treat]

*Considering that e"75 ml of sputum production/day as significant or severe

** Considering Sputum purulence score e"3 as severe or significant

Discussion:

This study was conducted with intent to establish the efficacy of oral prednisolone as an adjuvant for the treatment of exacerbation bronchiectasis. The main outcome measures were clinical improvement, especially change in general wellbeing (including change in cough, sputum volume, sputum purulence, grading of dyspnoea, improvement of fever, appetite), change in laboratory inflammatory markers, (including total count of WBC & ESR) and Spirometric parameters (including FEV_1, FVC and FEV_1/FVC).

It was seen that in both groups, baseline characteristics were almost similar, which includes age, sex, religion, economic status, sputum volume and purulence score, haemoptysis, grading of dyspnoea, presence or absence of fever, anorexia, weight loss, chest pain, post-TB status, ESR, total WBC count and Neutrophil count and Spirometric values (FEV1, FVC & FEV1/FVC). Among 64 patients, total 44 males and 20 females participated in the study with a Male: Female ratio of 2.2:1. The mean age of placebo and steroid group was 37.06 ± 11.99 and 42.06 ± 15.02 years respectively.

Clinical outcome at different time interval showed that addition of oral Prednisolone to the standard treatment of Bronchiectasis results in improved clinical outcome faster than the standard treatment alone. The results of the study showed that addition of oral Prednisolone enhanced clinical improvement, especially in cough, sputum volume, sputum purulence, dyspnoea and fever, earlier (mostly at day 7), compared to standard treatment alone, thus this therapy could decrease the morbidity, hospital stay as well as treatment cost.

The Control event rate (CER), Experimental event rate (EER), Relative risk reduction (RRR), Absolute risk reduction (ARR) and Number needed to treat (NNT) of the patients were also calculated. In case of cough, at day 7, the NNT is 1.8 which is highly significant; this means that at day 7, at least one patient will be benefited in reduction of cough when 2 patients are treated. At day 30, the NNT is 15.9 which is somewhat significant; that means for

getting benefit of reduction of cough, at least 16 patients will needed to be treated. For sputum amount, at day 7, the NNT is 2.7 which is highly significant. At day 30, the NNT is 4.6 which is also highly significant. For sputum purulence, the NNT is 32.2 at day 7 and at day 30 which is not much significant clinically.

Not much improvement was seen in appetite, CBC, ESR, Spirometric parameters (including- FEV1, FVC and FEV1/FVC).

In addition, exacerbation was seen in 2 (6.3%) cases in 'Steroid' group, as compared with 9 (28.1%) cases in 'Placebo' group, which is statistically significant (p=0.020), although the duration of this study was short, i.e. only one month.

At 1 month, side effects related to corticosteroid use were noted in 10 (31.3) patients in 'Steroid' group. The side effects were minor, like – Dyspepsia, aggravation of peptic ulcer, weight gain and acne. The difference between two groups is not significant (p=0.070). No major side effects were noted, implicating safety of oral corticosteroid in short term use.

Sputum culture and sensitivity was neither done at baseline nor done at follow-up visit, because a few comparable studies performed in patients with non-cystic fibrosis bronchiectasis have shown that successful treatment does not depend on the eradication of the organisms responsible for acute exacerbation state.[17,18,19] Spirometric parameters were not chosen as major end point in the study, although Spirometry was done to see the changes with addition of Oral steroid, because study by Hill SL, et al.[20] shown that patients with bronchiectasis have a significant improvement in clinical symptoms without a significant change in FEV_1.

For a successful research it is needed to see the concordance of clinical and microbiological response simultaneously. So, large scale study is needed to see clinical and microbiological efficacy. In addition, this was an uncontrolled trial, so the frequency and dose of drug as well as its safety in long term use cannot be definitely recommended in this time.

Conclusion:

So, the findings of this study permit to conclude that Oral prednisolone is more effective than the placebo for acute exacerbation of bronchiectasis as an adjunct to the standard treatment, which gives earlier clinical improvement, especially in case of symptoms, sputum volume and sputum purulence, and hence reduce the morbidity as well as hospital stay.

Recommendation

- Oral Prednisolone can be recommended for the acute exacerbation of Bronchiectasis in the short term, as an effective adjuvant to the standard treatment.
- Further large scale multi-centred study with longer period follow-up should be carried out to see long term efficacy and safety profile of oral prednisolone in Bronchiectasis.

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