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RESEARCH ARTICLE

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Open Label Observational Comparative Efficacy Study of Ceftriaxone and Levofloxacin in COPD Exacerbations

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ABSTRACT

Background: Chronic Obstructive Pulmonary Disease (COPD) is a common preventable and treatable disease. Part of the natural history of the disease is an exacerbation characterized by severity of dyspnoea, increased sputum volume, and purulence. Antibiotics are given to most patients with Acute Exacerbation Chronic Obstructive Pulmonary Disease (AECOPD). **Objectives:** This study examines the clinical efficacy of ceftriaxone and levofloxacin in patients with AECOPD. It is an open label, observational comparative study. The study compares the efficacy of 1 gm ceftriaxone intravenous infusion BD and oral 500 mg levofloxacin OD for 5 days based on clinical parameters, investigates the healthcare utilization of the study population during hospitalization and looks into the cost comparison between the treatment groups. **Methods:** The clinical improvement and resolution was measured using the Borg scale for dyspnoea to quantify its severity. The sputum volume and sputum purulence were also quantified by scales. The measurements were done on day 1, 3 and 5. **Results:** Improvement and resolution of dyspnoea, sputum purulence, and oxygen saturation were similar with empirical intravenous ceftriaxone and oral levofloxacin therapy. Intravenous Ceftriaxone was significantly beneficial with p value of 0.009 in resolving sputum volume compared to levofloxacin. Treatment failure was observed in 23.5% ceftriaxone and 4.5% levofloxacin treatment groups; both were associated with low rate of relapse requiring hospitalization. Among these patients, the time to next exacerbation was within 3 weeks. **Conclusion:** This study has shown comparable clinical efficacy between ceftriaxone and levofloxacin in AECOPD. The ceftriaxone regimen is certainly costlier than the levofloxacin regimen due to higher acquisition, nursing, and infusion fee.

Key words: Acute Exacerbation Chronic Obstructive Pulmonary Disease, Ceftriaxone, levofloxacin, Borg scale, Anthonisen criteria.

INTRODUCTION

Rational use of antibiotics has always been a grave concern in the treatment of various infectious diseases.[1] The role and choice of antimicrobials in the treatment of exacerbations of COPD have been a matter of controversy even though they are widely used. Antimicrobials are given to most patients with acute exacerbations of COPD, but the efficacy of antimicrobial therapy has been questioned.

Though one can be quite confident that antimicrobials are useful in moderate to severe exacerbations of COPD, there is considerable discussion as to antimicrobial choice, especially for initial empirical therapy.[2-4]

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As most exacerbations nowadays are treated without obtaining sputum bacteriology, this initial empirical choice often becomes the only choice made for antimicrobial use in exacerbations. Results of the antimicrobial comparison trials should guide the recommendations for appropriate empirical antibiotic treatments in exacerbations. Though a large number of such trials have been conducted, in the vast majority, antimicrobial choice does not appear to affect the clinical outcome. This is contrary to expectations that antimicrobials with better *in vitro* and *in vivo* antimicrobial efficacy and pharmacodynamic and pharmacokinetic characteristics should show superiority in clinical outcomes.[5]

Most clinical trials of antibiotics were performed for regulatory approval and are designed for demonstrating equivalence rather than differences between antibiotics. Although antibiotics provide benefits compared with placebo in acute exacerbation of COPD, further studies are required to assess different classes of antibiotics in a specific clinical situation.[6]

Studies must examine clinical efficacy more stringently based on a classification system (Anthonisen criteria) that would help select patients most likely to benefit from the antibiotic. Since comparative trials showed clinical equivalence and not clinical superiority, differences among antibiotics should be made perceptible regarding considering clinical efficacy (improvement plus resolution), requirement of an additional antibiotic (failure), time to next exacerbation (relapse) and advantages in terms of cost.[7]

Ceftriaxone was chosen based on the local experience of clinical resolution. Levofloxacin was chosen as trials have demonstrated that *in vitro* microbiological superiority of flouroquinolones does translate to greater *in vivo* effectiveness[8-9] It also attains high intra pulmonary drug Concentrations.[10]

Short course antibiotic therapy (5 days) was practiced rather than conventional therapy (7 days), as it has improved compliance, minimization of cost, waste, less side effects, and potential for generation of antimicrobial resistance. Five day levofloxacin has comparable efficacy with 10 day levofloxacin in CB and COPD.[8] Five day therapy with various cephalosporins is as effective as 10 day therapy in patients with various respiratory tract infections.[11]

At present, no study has been carried out to investigate of the differences in efficacy, pattern of healthcare utilization of the study population during hospitalization, and cost comparison between the two antibiotics in COPD patients hospitalized with a current type I or a type II (Anthonisen criteria) exacerbation. Ceftriaxone belongs to the class of cephalosporin antibiotics and the levofloxacin belongs to the class of flouroquinolone antibiotics. Hence, in this study, we have compared the comparative efficacy of these two antibiotics in the treatment of COPD patients.

METHODOLOGY

Study Design

This was a Open label, Concurrent, Observational, and Non randomised study to determine the efficacy of intravenous Ceftriaxone 1 g b.d (5 days) and oral levofloxacin 500 mg o.d (5 days) in AECOPD, based on the clinical response to the treatment of hospitalized patients. The study was approved by the Hospital Ethics Committee (PSG Hospitals, Coimbatore, and Tamil Nadu).

Study Population with inclusion and exclusion criteria

Patients eligible for inclusion were aged 18 years or older with a history of or newly diagnosed COPD, hospitalized with a primary diagnosis of AECOPD (defined according to the American thoracic Society). The patient's current infection was categorized into two principal types. Type 1 Anthonisen criteria: presence of increased dyspnoea, sputum volume, and sputum purulence and Type 2 Anthonisen criteria: presence of 2 of the afore mentioned 3 symptoms.[12] Treatment regimen was with either ceftriaxone 1 g bd or levofloxacin 500 mg od for 5 days.

Patients with any of the following characteristics were excluded:

(1) Received recent antibiotic therapy (30 days prior) or had other lower respiratory tract illness (pneumonia, bronchiectasis, tuberculosis, cystic fibrosis, pulmonary malignancy) detected clinically. (2) Type 3 Anthonisen criteria: presence of one of the afore mentioned 3 symptoms and one or more of the following findings (fever >100.4^{0}F or 380°C without other cause , increased wheezing , increased cough, or increased respiratory rate compared with the stable baseline condition). (3) Need for concomitant antibiotic agents with a spectrum of activity similar to that of study drugs. (4) Cephalosporin or Flouroquinolone allergy. (5) Malabsoprtion syndrome, Immune compromised, history of epilepsy, or lowered seizure threshold. (6) Pregnancy, lactation, psychiatric patients. (7) Recently participated in a clinical trial.

Therapy

The patients initiated their therapy with intravenous ceftriaxone 1 g o.d and oral levofloxacin 500 mg o.d and were observed from day1 to day 5 for the administration of the drug. The use of bronchodilators, corticosteroids, and mucolytics was permitted throughout the study.

Clinical Assessment

All the patients were hospitalized for at least 5 days. Evaluations were performed at day 1 (initiation of antibacterial therapy), day 3 (to test improvement), and day 5 (to test resolution).

Severity of dyspnoea: Breathlessness is a subjective sensation, and like pain, it needs to be perceived and reacted to. This was evaluated based on the Borg scale[12] for dyspnoea, which measures the patient's perception of his breathlessness as depicted in Table 1.

Sputum purulence and volume

Sputum was collected over a 24-h period by patients at 9 am on day1, before 9 am on day 2 of admission, and stored in clear sterile plastic (60 mL) containers at room temperature. Patients were instructed to completely empty the contents of their mouth before they expectorated to ensure that there was minimal contamination by saliva. The 24-h sputum volume was graded as depicted in Table 2.[13-14] The sputum purulence was determined by a scoring system as depicted in Table 3.[14-16]

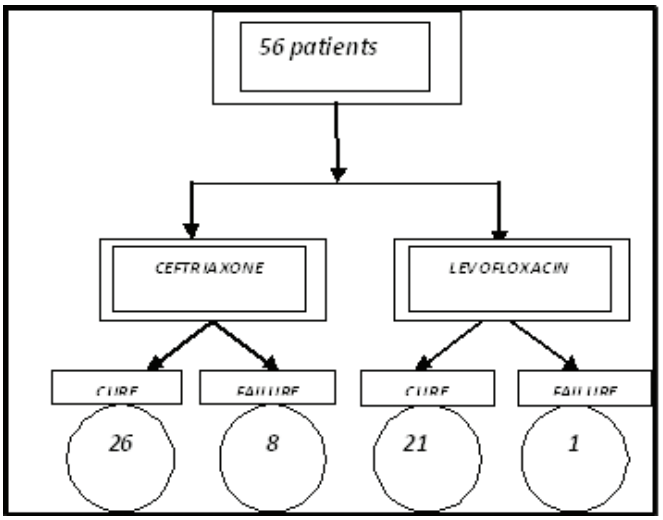

Figure 1: Treatment Details of Patients

Safety Assessment

Drug safety was assessed in all patients, who received at least one dose of the interventional drug. Adverse events were ranked by the investigator in terms of their severity (mild, moderate, severe, or serious and life threatening) and their relationship to the interventional drug (probable, possible, remote, or none).[17]

Efficacy assessment

- **Improvement:** Reduction in severity or number of signs and symptoms of infection.

Table 1: Borg scale

Score	Severity
0	Not breathless at all
0.5	Very very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	----------
7	Very severe breathless
8	----------
9	Very very severe (almost max)
10	Maximum

Table 2: Sputum volume

Score	Volume
1	0-10ml
2	10-20 ml
3	20-30 ml
4	30-40 ml
5	40-50 ml
6	>50ml

Table 3: Sputum purulence

Score	Sputum purulence
0	Absence of sputum
1	Completely transparent
2	Almost transparent
3	Translucent but colorless
4	Opaque and milky white
5	Grey
6	Pale green
7	Moderately green
8	Dark green

Table 4: Patient Demographics

	Ceftriaxone (%) (n=34)	Levofloxacin (%)(n=22)
Mean age±SD (years)	66.2±8.1	65.2±8.0
Sex Male Female	 34/34 (100) 0/34 (0)	 22/22 (100) 0/22 (0)
Race-South Asian	34/34 (100)	22/22 (100)
Education status Literate Ill-literate	 30 (88.2) 4 (11.7)	 20 (90.0) 2 (10)

Table 5: Presentation of Exacerbation

Variables		Ceftriaxone n (%)	Levofloxacin n (%)
COPD (%) Past history		34 (100)	22 (100)
Medication compliance	Yes	21(61.7)	13 (61.7)
	No	13 (38.2)	8 (36.3)
Number of infective exacerbations in the previous year	0	27 (79)	18 (81.8)
	1	5 (14.7)	2 (9)
	≥2	2 (5.8)	2 (9)
Severity of infection	Type I	32 (94.1)	19 (86.3)
	Type II	2 (5.8)	3 (13.6)
	Type III	0	0
Onset of current Exacerbation	0–4 days prior therapy	9 (26.4)	9 (40.9)
	4–7 days prior therapy	2 (5.8)	4 (18.1)
	≥7 days prior therapy	23 (67.6)	8 (36.3)
Sputum culture sensitivity	Performed	22 (64.7)	8 (36.3)
	Not performed	12 (35.2)	12 (54.5)
Medications given for Patients	Systemic glucocorticoids	32 (94)	22 (100)
	Inhaled glucocorticoids	5 (14.7)	4 (18.1)
	SABA+LAMA	32 (94)	21 (95.4)
	LAMA	24 (70.5)	9 (40.9)
	Xanthine derivatives	25 (73.5)	10 (45.4)
	Inhaled glucocorticoids+LABA's	20 (58.8)	7 (31.8)

- **Resolution:** Disappearance of acute signs and symptoms with no additional or alternate antibiotic therapy needed.
- **Failure:** Insufficient lessening of signs and symptoms of infection, necessitating additional or alternative antibiotic therapy.
- **Efficacy:** The ability of the study drug to produce both improvement and resolution.

The clinical parameter was evaluated on day 1, day 3, and day 5. Improvement was the difference of values on day 3 from day 1. Resolution was the difference of values on day 5 from day 1. Efficacy was the sum of both improvement and resolution. Efficacy was calculated for the ceftriaxone study population and levofloxacin study population for severity of dyspnoea, sputum purulence, and sputum volume, and oxygen saturation.[17]

Cost comparison of brands

The utilization of various brands of ceftriaxone and various brands of levofloxacin was recorded. The cost comparison of the utilized brands was performed separately. The brand with the lowest nett treatment cost was favoured.

Economic analysis

The analyses are based on recording health care utilization during the hospital stay in monetary units and then mean

Table 6: Co-morbidities of the study Population

Morbidity	Ceftriaxone n (%)	Levofloxacin n (%)
Hypertension	10 (29.4)	5 (22.7)
Diabetes mellitus	15 (44.1)	8 (36.3)
Chronic Respiratory failure	6 (17.6)	4 (18.1)
Pulmonary Arterial Hypertension	4 (11.7)	2 (9)
Corpulmonale	4 (11.7)	1 (4.5)
Diabetes Neuropathy	2 (5.8)	0
Old Pulmonary tuberculosis	4 (11.7)	2 (9)
Dilated cardio myopathy	2 (5.8)	0
Ischemic Heart Disease	2 (5.8)	0
Left Ventricular dysfunction	2 (5.8)	0
Renal failure	1 (2.9)	0
Coronary artery disease	2 (5.80	1 (4.5)
Hemorrhoids	1 (2.9)	1 (4.5)
Beningn Prostrate hypertrophy	2 (5.8)	2 (9)
GERD	2 (5.8)	5 (22.7)
Alcohol dependence syndrome	1 (2.9)	2 (22.7)
Arthritis	0	1(4.5)
Liver cirrhosis	0	1(4.5)
Steroid Abuse	0	1(4.5)
Atrial Fibrillation	1 (2.9)	0
Allergy	2 (5.8)	0
Parkinsonism	1 (2.9)	0
Anemia	6 (17.6)	5 (22.7)
Depression	1 (2.9)	0

Table 7: Incidence of Treatment–Emergent Adverse Events

Nature of event	Severity	Relationship	Ceftriaxone n (%)	Levofloxacin n (%)
Hypokalemia	Mild	None	6 (17.6)	1(4.5)
Hyponatremia	Mild	None	1(2.9)	0
Pedal edema	Severe	None	0	1(4.5)

Table 8: Variables of Cost of treatment with the various brands of ceftriaxone

Brand	Brand X n=16	Brand Y n=8	Brand Z n=2
Cost per unit	48.76	64.01	78.39
Units consumed per day	2	2	2
Treatment days	5	5	5
Total cost	7801.60	5120.80	1567.80
Mean cost±SD	487.6±22.08	640.1±25.3	783.9±27.9

Table 9: Variables of Cost of treatment with the various brands of levofloxacin

Brand	Brand A (n=17)	Brand B (n=4)
Cost per unit	8.79	7.92
Units consumed per day	1	1
Treatment days	5	5
Total cost	747.15	158.4
Mean cost±SD	43.95±6.6	39.6±6.2

Table 10: Healthcare utilization in general care	
Study group	**Mean Hospitalization cost±SD**
Ceftriaxone n=20	9169.4±21.41
Levofloxacin n=17	7617.1±21.16
P value	<0.0001

Table 11: Healthcare utilization in special care	
Study group	**Mean Hospitalization cost±SD**
Ceftriaxone n= 6	18157.5±55.01
Levofloxacin n=4	16586.4±64.39.
P value	<0.001

patient costs were calculated separately for the two groups and compared statistically using an unpaired student's t test.

Statistical Analysis

Categorical values, including demographics and medical characteristics, were summarized descriptively in frequencies and percentages. The efficacy was calculated for each clinical parameter (severity of dyspnoea, sputum purulence, sputum volume, and SP02 for ceftriaxone and levofloxacin study populations.) The statistic unpaired t test was applied.

RESULTS AND DISCUSSION

Patient Demographics

In the current study we observed patients with complicated or severe AECOPD and used specific clinical measures to compare the efficacy of Ceftriaxone and Levofloxacin (Figure 1). Patients observed in this study had a mean age of 66.05 years. Majority were male and 89% were literates with a history of past or current smoking (83.8%) (Table 4).

Presentation of AECOPD

All patients had clinically documented AECOPD; 91% of which were classified as Type I Anthonisen criteria and 9% were type II Anthonisen criteria. The compliance results state 87.5 % had a past history of COPD out of which 69.6 % were compliant and 30.3% were non-compliant with inhaler medication (Table 5).

The exacerbation results state that 28.5% had more than 1 infective exacerbation in the previous year. Co morbid disease information states that 82.1% had a history of co-morbid disease (Table 6). The mean duration of symptoms for the current exacerbation of COPD was 7 days in both groups.

Sputum culture sensitivity was performed for 53.5% Patients in the study population out of which pre therapy pathogen was isolated in 16% (Streptococcus.pneumonia (3), Pseudomonas aeruginosa (1) Candida species (2), Klebseilla.pneumonia (2), Hemophilus. Influenza (1).

Throughout the study, patients received concomitant Systemic glucocorticoids (96%), Inhaled glucocorticoids (16%), SABA+LAMA (94.6%), LAMA (58.9), Xanthine derivatives (62.5%), Inhaled glucocorticoids plus LABA's (48.2%) (Table 5).

Clinical Response

The comparison of efficacy based on clinical improvement and resolution of the 4 parameters: sputum purulence, sputum volume severity of dyspnoea, and oxygen saturation is as follows.

Sputum Purulence

The improvement plus resolution (Efficacy) of sputum purulence in ceftriaxone and levofloxacin treated patients has a p value 0.6012 (95% C.I, -1.2 to 2.1). Neither had superior efficacy over the other.

Sputum Volume

The improvement plus resolution (Efficacy) of sputum volume in ceftriaxone and levofloxacin treated patients has a p value 0.0009 (95% CI, 1.4 to 5.8). Ceftriaxone had a superior efficacy over Levofloxacin.

Severity of Dyspnoea

The improvement plus resolution (Efficacy) in Severity of dyspnoea in ceftriaxone and levofloxacin treated patients has a *p* value 0.1297 (95% C.I., -2.9 to 0.38). Neither had superior efficacy over the other.

Oxygen Saturation

The improvement plus resolution (Efficacy) in oxygen saturation in ceftriaxone and levofloxacin treated patients has a p value 0.3175 (95% C.I,-0.9 to 2.9). Neither had superior efficacy over the other.

Safety and Adverse Events

The most common abnormal laboratory variables were leukocytosis, neutrophilia, deranged glycemic index,

anemia, hyperkalemia, hyponatremia, and hypocalcemia. The frequency of abnormal laboratory variables was very similar between the two treatment groups (Table 7). There were no reports of photosensitivity, convulsions, tendnitis, or other adverse events sometimes associated with flouroquinolone antibiotics. The frequency of abnormal laboratory variables was very similar between the two treatment groups, concordant with the reported work done.[17]

In conclusion this study has shown comparable clinical efficacy between 5 day courses of twice-daily Ceftriaxone 1g injection and once daily levofloxacin 500 mg oral tablet in acute exacerbations of COPD, in concordance with the work.

Cost Analysis

Ceftriaxone

The study population received Brand X, Brand Y, and Brand Z for the treatment. T variables of cost of treatment with the various brands of ceftriaxone are presented in Table 8.

Statistical analysis of cost

The cost of Brand X 1 g injection and Brand Y 1 g injection has a p value of less than 0.0001 (95% confidence interval; -173.2919 to -131.7081). The cost difference is extremely significant. Statistical analysis of cost for Brand X verses Brand Y.

The cost of Brand X 1 g injection and Brand Z 1 g injection has a p value less than 0.0001 of (95% confidence interval; -332.0542 to -260.5458). The cost difference is extremely significant.

Levofloxacin

The study population received Brand A, Brand B for the treatment. The variables of cost of treatment with the various brands of Levofloxacin are presented in Table 9.

Statistical analysis of cost

The cost of Brand A 500 mg oral tablet and Brand B 500 mg oral tablet has a p value 0.2460 (95% confidence interval; -3.2551 to 11.9551). The cost difference is not considered significant.

Among ceftriaxone treated patients, reduction in cost can be achieved by prescribing Brand X 1g injection and among levofloxacin treated patients it can be achieved by prescribing either Brand A 500 mg oral tablet or Brand B 500 mg oral tablet.

Health Care Utilization

The treatment groups were segregated into general ward treatment and special ward treatment. In the general ward, 20 patients from the ceftriaxone treatment group and 17 patients from the levofloxacin treatment group were admitted. In the special ward, 6 patients from the ceftriaxone treatment group and 4 patients from the levofloxacin treatment group.

Mean cost of a patient hospitalized with AECOPD under general care has been determined as Rs 9169.4 ± 21.41 for ceftriaxone treatment group and Rs 7617.1 ± 21.16 for levofloxacin treatment group. (Table 10). Mean cost of a single patient hospitalized with AECOPD under special care has been determined as Rs 18157.5 ± 55.01 for ceftriaxone treatment group and Rs 16586.4 ± 64.39 for levofloxacin treatment group. (Table 11).

CONCLUSION

The selected patients for this study were at higher risk for complications based on their age (66.05 years) and high rate of past or current smoking (83.3%). All patients had clinically documented AECOPD, 91% of which were classified as Type I Winnipeg criteria and 9% as type II Winnipeg criteria. With regards to co morbidities, the prevalence was highest for Diabetes mellitus (48.9%) and hypertension (31%) among both the groups.

This study showed that improvement and resolution of dyspnoea, sputum purulence, and oxygen saturation were similar with empirical intravenous ceftriaxone and oral levofloxacin therapy. Intravenous Ceftriaxone was significantly beneficial with p value 0.009 in resolving sputum volume compared to levofloxacin. Treatment failure was more with ceftriaxone compared to levofloxacin. Both were associated with low rates of relapse requiring hospitalization with time to next exacerbation less than 3 weeks. The incidence of treatment induced adverse events did not differ between the treatment groups.

The broad spectrum antibacterial activity of both ceftriaxone and levofloxacin against the major bacterial pathogens in AECOPD, potential lower costs of 5 day regimen, and the likelihood of patient compliance make them valuable and viable therapeutic options.

Comparable clinical efficacy between 5 day courses of intravenous Ceftriaxone and oral Levofloxacin 500 mg

in AECOPD was observed. The mean costs of a patient hospitalized with AECOPD in the ceftriaxone group, both in general and special care were more than the corresponding costs in levofloxaicn group.

Ceftriaxone regimen is costlier than levofloxacin regimen owing to the high acquisition, nursing, and infusion fee of the former. Reduction in cost can be achieved by prescribing Brand X 1 g injection in ceftriaxone treated patients. As for levofloxacin, its once daily dosing and low cost makes it an acceptable treatment choice for AECOPD.

LIMITATIONS

The limitations of the study were the small number of subjects. Also, patients weren't observed when stable to establish a baseline comparison in order to reliably distinguish between clinical improvement and resolution following improvement. There was insufficient data to permit meaningful comparison of the bacteriologic efficacy of the antibiotics. The concurrent therapy was not controlled it could have owed to the masking of the differences between antibiotics

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CONFLICT OF INTEREST

The author declare no conflict of interest.

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