COMPARISON OF CLINICAL CURE RATE FOR DOXYCYCLINE AND LEVOFLOXACIN IN TREATMENT OF ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Objectives: To compare the clinical cure rate for doxycycline and levofloxacin in treatment of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and explore the response in relation to gender.

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital Rawalpindi, from Nov 2015 to Jun 2016.

Methodology: In this study, indoor patients diagnosed with acute exacerbation of chronic obstructive pulmonary disease were enrolled through consecutive sampling and randomized into two groups through lottery method. Patients were randomly assigned to oral doxycycline 100 mg twice daily or oral levofloxacin 500 mg once daily for five days. The clinical and laboratory assessments of the patients were done on the 7th day to note response as clinical cure or clinical failure.

Results: Mean age of the sample was 52 ± 5.5 years. Clinical cure was observed in 156 (84.8%) patients. Cure rate was found to be significantly higher in levofloxacin group as compared to the doxycycline group (91.3% vs. 78.3% respectively) (p=0.014). Significantly higher cure rate was observed for levofloxacin than doxycycline in males (p=0.026). No significant difference in the cure rate was noticed among the two treatment groups in females (p=0.289).

Conclusion: Clinical cure rate for acute exacerbation of chronic obstructive pulmonary disease with levofloxacin was significantly higher in the sample as compared to doxycycline. The males from the sample showed similar difference in cure rate for the two drugs.

Keywords: Acute exacerbations, Chronic obstructive pulmonary disease, Doxycycline, Effectiveness, Levofloxacin.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death worldwide[1]. It is a chronic inflammatory disease of the lungs characterized by partially reversible obstruction to the airflow from lungs. Important symptoms include difficulty breathing, cough, sputum, wheezing, and chest tightness. It results from prolonged exposure to smoke and other irritating gases initiating inflammatory response in bronchial linings, excessive mucous production, and impaired movement of cilia.

COPD has two variants that may be present simultaneously in the same patient but with different proportions. Chronic bronchitis is defined as excessive cough and sputum production on most days for at least 3 months during at least 2 consecutive years. On the other hand, emphysema is characterized by long standing breathlessness resulting from damage to the lung tissue and destruction of air spaces. Chronic bronchitis more often involves larger airways while emphysema tends to affect smaller airways and alveoli. Complications of COPD include pneumothorax, recurrent lung infections, muscle wasting, osteoporosis, bronchiectasis, respiratory

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failure, cor pulmonale, lung cancer, and depression.

Clinically, COPD has a chronic disabling course punctuated by acute exacerbations, which tend to occur more frequently during winter months. Acute exacerbations are manifested as increased sputum production, increased purulence of sputum, and worsening of shortness of breath with or without fever requiring a change in treatment. Acute exacerbation of COPD (AECOPD) is a major cause of COPD morbidity, mortality, and treatment expenditure. AECOPD reduces quality of life, expedites disease progression, and increases risk of death.

There are several causes of AECOPD but the most frequent are infections of the tracheobronchial tree, non-compliance with medication, allergens, and air pollutants (e.g. tobacco smoke, ozone, occupational exposures)[1-3]. Organisms mainly isolated from these patients are *Haemophilus Influenzae*, *Streptococcus pneumoniae*, *Moraxellacatarrhalis*, atypical pathogens, and respiratory viruses[4].

Management of AECOPD always includes cessation of smoking, controlled oxygen therapy, inhaled beta-2 agonists, inhaled anticholinergics, systemic steroids, methylxanthines in non responders, and mechanical ventilation if required. Since bacterial infections are the primary cause of AECOPD, antibiotic therapy is usually an integral part of treatment for AECOPD. Studies have shown a better cure rate for AECOPD with antibiotics in comparison with the placebo[2,5-7]. More specifically, antibiotic treated patients had lower rates of in-hospital mortality and readmission for AECOPD and fewer requirements of mechanical ventilation during hospital stay[2,7]. Data also suggest that antibiotic treatment during AECOPD might significantly prolong the interval for subsequent exacerbations[8].

There are two groups of recommended antibiotics in the treatment of AECOPD. First-line antibiotics include amoxicillin, tetracyclines, azithromycin, and clarithromycin and the second-line antibiotics include levofloxacin, moxifloxacin, and amoxicillin-clavulanate[2,9]. Meta-analyses suggest that a five-day course of antibiotic therapy is as effective as long-term therapy[10]. Some studies have shown better efficacy of second-line agents than first-line agents. Two different studies have shown a success rate of 80%[11] with doxycycline and 92%[12] with levofloxacin in AECOPD.

Pakistan is a country with a very high disease burden of COPD and a population with low income and poor health facilities. No comparative studies were done in the past between first and second-line antibiotics in patients with AECOPD. Empirical therapy was usually started straight away with second-line drugs with the assumption that they were more effective without any evidence for superior efficacy of a particular drug or a group of drugs. Comparison of relatively inexpensive but recommended first-line doxycycline with expensive second-line levofloxacin in patients with AECOPD was thus the main objective of this study with a view to suggest more rational and cost-effective protocol in this resource limited country. The comparison of response in relation to gender was a secondary aim of the study.

METHODOLOGY

It was a quasi-experimental study conducted in the department of Internal Medicine at Pak Emirates Military Hospital Rawalpindi from November 2015 to June 2016. Prior to start of the study, the ethical approval was obtained from the hospital ethics committee. We calculated a sample size of 92 in each group, using World Health Orgnaization sample size calculator with level of significance: 5%, power of test: 80%, anticipated first population proportion: 92%[12], and anticipated second population proportion: 80%[11].

The nature of the study and its advantages and limitations were explained to the patient/ guardian and a written informed consent was taken before inclusion in the study. Indoor patients diagnosed with AECOPD were enrolled through consecutive sampling and randomized

into two groups by lottery method. The AECOPD was defined[13-15] as sustained worsening of symptoms which were acute in onset and characterized by temperature >100°F, increased sputum quantity as observed by the patient, breathing rate >30/min, white cell count >11 x 10^9/L, and C-reactive protein (CRP) levels >10 ng/ml. Patients complicated with pneumonia, bronchiectasis, ischemic heart disease, chronic liver disease, congestive cardiac failure, chronic renal failure, and known allergy to the drugs under study were excluded.

All the study related information was collected on a pre-designed proformas. Baseline information of the patients and clinical presentation was noted. Baseline laboratory tests including total leukocyte count and CRP and chest x-rays were performed at the time of admission and after seven days of intervention. Patients were randomly assigned to oral doxy-cycline 100mg twice daily or oral levofloxacin 500mg once daily for five days. The clinical and laboratory assessments of the patients were measured on the seventh day. The effectiveness of antibiotic treatment in terms of resolution of AECOPD (clinical cure)[14] was defined by the presence of any four of the following six clinical and laboratory parameters:[14-16].

1. Temp <99°F
2. Decrease in respiratory rate by 20%
3. Restoration of oxygen saturation to 88-92% on air
4. Decreased sputum quantity observed by the patient
5. Total leukocyte count ≤11 x 10^9/L
6. CRP levels ≤10 ng/ml

Failure to achieve at least four of the above-mentioned parameters was considered as clinical failure[14].

The Statistical Package for Social Sciences ver 20.0 was used for all analyses. The means and standard deviations were calculated for age. The frequencies and percentages were calculated for gender. The Pearson's chi-square test was applied to compare outcome (clinical cure or clinical failure) among the two treatment groups (doxycycline versus levofloxacin), before and after stratification into male and female. A *p*-value <0.05 was considered significant.

RESULTS

Mean age of the patients was 52 ± 5.5 years in a sample of 184 patients. Male preponderance was observed in the sample i.e. 106 (57.60%) vs 78 (42.4%) females. In both groups (doxycycline group versus levofloxacin group) males were found to be in higher percentage, i.e. 55 (59.8%) and 51 (55.4%) respectively. Clinical cure was observed in 156 (84.8%) of the patients (figure).

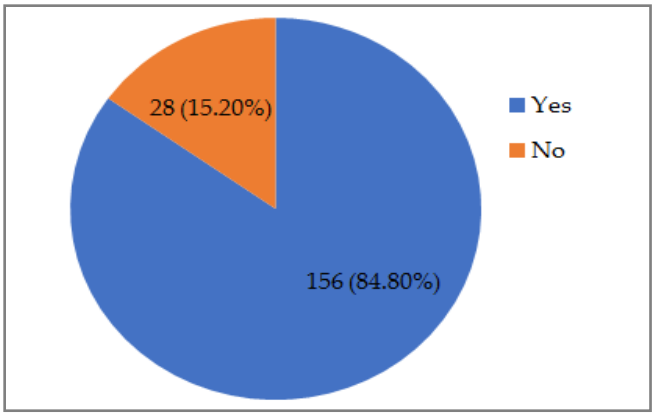

Figure: Overall effectiveness of the treatment.

Clinical cure was observed in 84 (91.3%) of levofloxacin group as compared to 72 (78.3%) in the doxycycline group (*p*=0.014) (table-I). Similarly, significantly higher rate of clinical cure was observed in levofloxacin group versus doxycycline group among males (table-II) (*p*=0.026). No significant difference in the clinical cure rate was observed in the two treatment groups (doxycycline versus levofloxacin) in females (table-III) (*p*=0.289).

DISCUSSION

In this study, the overall effectiveness of treatment (clinical cure) was noticed in majority of the patients which is comparable to previous studies suggesting better cure rates with antibiotic therapy[5-7]. Clinical cure was seen significantly higher in levofloxacin group as compared to doxycycline group.

In the relevant medical literature, levofloxacin has always been a better drug than doxycycline in improving clinical outcome and prolonging exacerbation-free interval, though there had been no direct comparison. Seven-day regimens of oral levofloxacin have demonstrated

Table-I: Comparison of effectiveness with respect to group (n=184).

Group	Effectiveness		*p*-value
	Clinical cure n (%)	Clinical failure n (%)	
Doxycycline	72 (78.3)	20 (21.7)	0.014
Levofloxacin	84 (91.3)	8 (8.7)	

Table-II: Male patients & comparison of effectiveness with respect to group (n=106).

Group	Effectiveness		*p*-value
	Clinical Cure n (%)	Clinical Failure n (%)	
Doxycycline	36 (65.5)	19 (34.5)	0.026
Levofloxacin	43 (84.3)	8 (15.7)	

Table-III: Female patients & comparison of effectiveness with respect to group (n=78).

Group	Effectiveness		*p*-value
	Clinical Cure n (%)	Clinical Failure n (%)	
Doxycycline	36 (97.3)	1 (2.7)	0.289
Levofloxacin	41 (100)	0 (0)	

favorable clinical outcomes in 92%, 92%, 94%, and 96% of clinically evaluable patients, which were better than the compared antibiotics including azithromycin, ceftriaxone, and cefuroxime axetil[4,12,17,18]. Similarly, a ten-day regimen has been found to have a clinical cure rate of 94.6%[19] and 87.4%[20] respectively.

Considering doxycycline, a satisfactory clinical response was seen in 80%, 91.2%, and 80% of the tested individuals in three randomized controlled trials respectively[11,21,22]. However, in the third trial, the primary clinical endpoint of clinical success on day 30 was not met and doxycycline treatment had no effect on lung function or systemic inflammation (measured by serum CRP levels) at 10th or 30th day[22]. Similarly, in another randomized double-blind trial, the median time to next exacerbation was shorter (148 days) in the doxycycline group compared with the placebo group (161 days)[23]. Thus, on comparing the mean percentage of clinical efficacy in above reported trials for doxycycline and levofloxacin, the mean efficacy percentage for levofloxacin (93.4%) was significantly better than mean efficacy percentage for doxycycline (83.7%) (p=0.031). This compliments our observation that levofloxacin was more efficacious than doxycycline in treatment of AECOPD.

While comparing the two genders, a significant difference in the efficacy of drugs was observed in male patients. On the other hand, the difference did not reach a statistically significant value in case of females. Males and females can be expected to respond differently in terms of efficacy and adverse effects to the same drug in the same doses. Females have a higher percentage of body fat than males that can affect the volume of distribution of certain drugs[24]. Gender differences in the activity of cytochrome P450 and uridine diphosphate glucuronosyl-trans-ferase enzymes and renal excretion, results in differences in clearance of active drug metabolites[24]. Thus, the response to a drug may differ among the two genders. Needless to say, that the observed clinical cure rate was excellent with both antibiotics in females, so, the first-line treatment among doxycycline and levofloxacin should be based on cost-effectiveness, availability, and side effect profile in case of females.

CONCLUSION

Clinical cure rate for AECOPD with levofloxacin was significantly higher in the sample as compared to doxycycline. The males from the sample showed similar difference in cure rate for the two drugs but the females displayed similar response to both drugs.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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