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Original Research Article

Effectiveness and safety evaluation of oral cefixime and moxifloxacin fixed dose combination in lower respiratory tract infections

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ABSTRACT

Background: Scientific literature advocates the need for combination therapies in combatting lower respiratory tract infection (LRTI). Cefixime (400 mg) and moxifloxacin (400 mg) fixed dose combination (FDC) is currently approved in India for the management of LRTI, but data related to its real world usage is lacking. The present study was designed to understand the real world use (effectiveness and safety) of this FDC in LRTI.
Methods: This retrospective study was conducted at out-patient departments of 5 hospitals between August 2018 and January 2019. After ethics committee approval, data of adults LRTI patients who received FDC of cefixime (400 mg) and moxifloxacin (400 mg) for at least 72 hours was collected. Improvement in LRTI symptoms (cough, sputum volume and purulence, fever, dyspnea, pleuritic chest pain, sleep disturbance, fatigue) were scored at baseline and follow-up using a 5-point severity scale. White blood cell (WBC) counts at baseline and end-of-treatment were compared.
Results: Data of 190 patients having mean age 42.33+16.15 years was evaluated. Majority were males (61.58%), with commonest LRTI infection being community acquired pneumonia (CAP) (84.21%). Commonest clinical symptom reported (97.37%) was cough. All patients showed improvement in symptoms and significant improvement in all mean symptom scores were noted ($p<0.05$). Of the 30 patients having WBC above normal range, 29 showed a decrease in count at end of treatment. No adverse events were reported.
Conclusions: Oral FDC of cefixime (400 mg) and moxifloxacin (400 mg) was efficacious in improving all symptoms reported by LRTI patients without causing any adverse event.

Keywords: Antibiotic resistance, Cefixime, Fixed drug combination, Lower respiratory tract infection, Moxifloxacin

INTRODUCTION

Lower respiratory tract infections (LRTI) is a broad term which encompasses various diseases like community-acquired pneumonia (CAP), acute bacterial exacerbations of chronic bronchitis (AECB) and acute maxillary sinusitis. The 2015 study on the Global Burden of Disease (GBD 2015) states that LRTIs are the 4th most

common cause of mortality.[1] The yearly CAP incidence is estimated to be between 5–11 per 1000 population, and the numbers are considered to be higher in older population.[2] A substantial reason for morbidity as well as mortality in both, the developed as well as the developing nations like India is attributed to LRTIs.[3]

Community-acquired LRTIs caused by Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae, as well as other typical and atypical pathogens, continue to be amongst the commonest conditions for which patients seek physician assistance. Management of RTI poses a major challenge for the physicians, mainly due to the presence of antibiotic resistance, especially to the most commonly found pathogen Streptococcus pneumoniae.[4] Various factors like inadequate public health infrastructure, increasing incomes, surging disease burden, and unregulated availability of low-cost antibiotics have led to a swift increase in the prevalence of resistant infections in India.[5] India was the world's largest consumer of antibiotics in the year 2010, and this increased antibiotic usage is the key factor contributing to increasing resistance in the country.[6]

β-lactam and fluoroquinolone classes of drugs are chiefly involved and recommended in the treatment of RTIs. However these endorsed classes of antibiotics have their shortcomings, especially when used individually. β-lactams have been found to have no activity against atypical pathogens, and almost half of the Streptococcus pneumoniae pathogens have been found to be resistant to them.

Fluoroquinolones have shown an augmented potential for developing resistant strains, especially the gram negative bacteria.[7] Citing these reasons, it has been advocated in scientific literature as well as by clinicians that combination therapies may help in combatting the issue of inadequate RTI management.

Cefixime (400 mg) and moxifloxacin (400 mg) fixed dose combination (FDC) is currently approved by primary drug regulatory body, which is Central Drug Standard Control Organization (CDSCO), in the management of lower respiratory tract infections (LRTI). It has an enhanced activity against clinically important Gram-positive, Gram-negative and atypical organisms. Besides the enhanced activity, the other advantages of this particular FDC include multimodal action, prevention of emergence of drug resistance, as well as increased compliance for the therapy.[8]

Despite the presence of cefixime + moxifloxacin FDC in the Indian market, there is a lack of data regarding the real-world usage of this combination. The present study was designed to understand the real-world use (effectiveness and safety) of cefixime and moxifloxacin fixed dose combination in LRTI.

METHODS

This was a retrospective, multi-center study conducted in five out-patient departments between August 2018 to January 2019. The study was commenced at 5 hospitals in different parts of India, with simultaneous collection of data initiated at these centers after obtaining an Independent Ethics Committee's permission (ECR/30 I /Indt/GJ/2018). All adults who had a clinical diagnosis of LRTI and had received the FDC of cefixime (400 mg) and moxifloxacin (400 mg) during the study period for a duration of at least 72 hours were considered for data collection. Patients whose follow up data was missing were excluded from the data collection process.

The demographic details noted down for the study participants included the age, gender and body weight. The diagnosis of the patient was confirmed and noted down along with the posology details of Cefixime plus Moxifloxacin combination. The primary endpoint was to assess the improvement of various symptoms which included sputum volume, sputum purulence, fever, cough, dyspnea, pleuritic chest pain, sleep disturbances and fatigue. The improvement in the LRTI symptoms were scored using a 5-point assessment scale based on the severity of the symptom, wherein a score of 5 meant complete absence of symptom and 1 meant worst severity of the clinical feature assessed (Figure 1). The scoring was done for the symptoms at days 3, 5, 7 and 10 of follow-up wherever applicable. The white blood cell (WBC) count was also looked for in the case records and were noted down if the values at the start and end of treatment were mentioned.

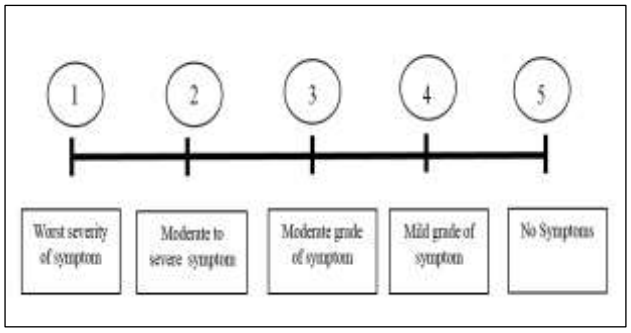


Figure 1: Symptom Severity assessment scale.

Relevant data was noted down in a Microsoft Excel master-sheet. Continuous data was represented as mean + SD while the categorical data was expressed in numerical form. The number of patients showing improvement at the follow-up days were calculated for each clinical feature and expressed in percentage form. The mean symptom scores at the follow-up days were compared with the baseline value using paired t test, with $p<0.05$ being considered significant. The patients having a baseline WBC count above the normal range were noted and their WBC count at the end of treatment was

evaluated and compared with the baseline values using paired t test.

RESULTS

A total of 190 patients were enrolled retrospectively based on the screening criteria and the data of these patients were noted down and analyzed. Majority of the patients suffering from LRTI were males (61.58%). The mean age of the patients was 42.33±16.15 years, with the median being 40 years (range: 18-92 years). The demographic details have been expressed in Table 1. The most common LRTI infection noted in the patients was community acquired pneumonia (CAP), seen in 160 patients (84.21%). 21 of the enrolled patients (11.05%) suffered from acute exacerbation of chronic bronchitis (AECB) while 9 patients (4.73%) were diagnosed with acute bronchitis.

Table 1: Demographic details of the patient (n=190).

Number of Males	117 (61.58%)
Number of Females	73 (38.42%)
Mean age of all patients (years)	42.33±16.15
Median (Range) in years	40 (18-92)
Mean weight of the patients (kilograms)	61.87±12.97

178 out of the 190 enrolled patients (93.68%) received the FDC containing 400 mg cefixime and 400 mg moxifloxacin for a period of 5 days. 7 patients (3.68%) received the FDC for a period of 10 days while 5 patients (2.63%) received the FDC as a 4-day regimen.

The commonest clinical symptom reported by the enrolled patients was cough, present in 185 out of 190 cases (97.37%). On analyzing the case record forms, 88 out of these 185 patients (47.56%) were followed-up at day 3 of treatment initiation, while 159 of these patients (85.95%) were followed-up at day 5. All the followed-up patients showed an improved assessment score. The mean improvement in the symptom assessment score was statistically significant at both, day 3 and day 5 of follow-up (Table 2 and Figure 1).

The sputum volume as well as the sputum purulence were evaluated by the physicians while the treatment of LRTI was ongoing. 113 (59.48%) out of the 190 LRTI cases complained of increased sputum volume while 94 (49.47%) patients had purulent sputum at the start of antibiotic treatment. The sputum volume decreased, and the purulence was absent in all the patients followed-up at day 3 and day 5, with significant improvement on evaluating the mean symptom score (Table 2 and Figure 1).

The improvement in fever, dyspnea and pleuritic chest pain were also calculated by evaluating the assessment scores for these clinical features. 105 patients (55.26%) reported presence of fever, 78 patients (41.05%) reported with dyspnea while 87 patients (45.79%) had pleuritic chest pain. At the follow-up done on day 3 and/or on day 5, all the patients showed a decreased grade or absent fever as well as alleviated dyspnea and pleuritic chest pain (Table 2 and Figure 1). The mean assessment scores were also significantly improved on day 3 and day 5 follow-up.

The impact of the cefixime-moxifloxacin combination on the quality of life (QoL) parameters like sleep disturbance and fatigue showed positive results. Before the start of treatment, 84 patients (44.21%) complained of sleep disturbance due to underlying illness while 74 patients (38.95%) complained of fatigue due to the illness. On follow-up, all patients reported improved sleep and lack of fatigue, and based on the assessment scoring there was statistically significant improvement on day 3 or day 5 of follow-up ($p<0.05$) (Table 2 and Figure 1).

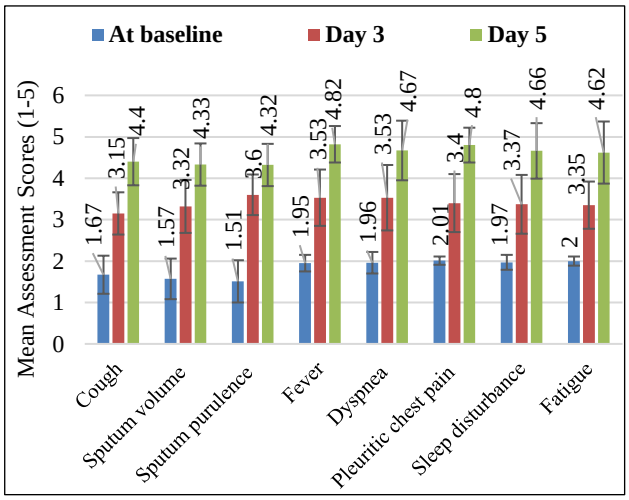


Figure 1: Mean assessment score for the clinical symptoms assessed in patients with LRTI (N=120).

A graphical representation of the improvement of various LRTI symptoms assessed in this study, based on the 5-point assessment scale (Table 2 and Figure 1).

Out of the 190 patients whose data was evaluated, case records of 66 patients had been assessed for WBC count at both, baseline and end of treatment. 30 of these patients had a WBC count more than the ULN (4000-11,000/mm3) at baseline before start of treatment. 29 out of these 30 patients (96.67%) showed a decrease in their WBC count at the end of antibiotic therapy, out of which 20 had a WBC count in the normal range while 9 others still had WBC count above the normal defined range (Table 3).

A statistically significant decrease in the mean WBC count at the end of antibiotic treatment, as compared to the baseline (Figure 2).

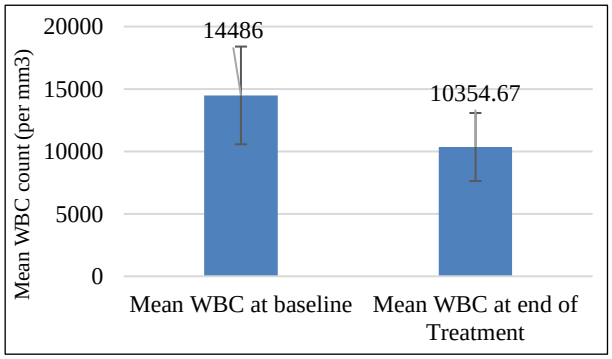
Table 2: Mean assessment symptoms scores for the enrolled patient with LRTI.

Parameters	Mean score at Baseline [A] (n)	Mean score at Day 3 [B] (n)	Mean Score at Day 5 [C] (n)	P value	
				A vs. B	A vs. C
Cough	1.67±0.46 (185)	3.15±0.51 (88)	4.40±0.57 (159)	<0.001*	<0.001*
Sputum Volume	1.57±0.49 (113)	3.32±0.64 (56)	4.33±0.51 (110)	<0.001*	<0.001*
Sputum Purulence	1.51±0.51 (94)	3.60±0.49 (38)	4.32±0.51 (94)	<0.001*	<0.001*
Fever	1.95±0.20 (105)	3.53±0.68 (73)	4.82±0.44 (87)	<0.001*	<0.001*
Dyspnea	1.96±0.26 (78)	3.53±0.79 (56)	4.67±0.72 (61)	<0.001*	<0.001*
Pleuritic Chest Pain	2.01±0.10 (87)	3.40±0.70 (64)	4.80±0.42 (68)	<0.001*	<0.001*
Sleep Disturbance	1.97±0.18 (84)	3.37±0.71 (53)	4.66±0.67 (74)	<0.001*	<0.001*
Fatigue	2±0.11 (74)	3.35±0.57 (65)	4.62±0.75 (69)	<0.001*	<0.001*

A = Mean score at baseline, B = Mean score at day 3, C = Mean Score at day 5.
P value less than 0.05 considered significant by paired t test

Table 3: WBC Count of patient with lower respiratory tract infections (n=30).

Parameter assessed	Number of patients
Patients with abnormal WBC count (more than 11000/mm3) at baseline	30
Patients with normalized WBC count (more than 11000/mm3) at end of Rx	20 (66.67%)
Patients showing a decrease in WBC count at end of treatment compared to the baseline	29 (96.67%)



P<0.05 considered significant by paired t test

Figure 2: Mean WBC Count at baseline and end of treatment (n=30).

None of the patients whose data were included in the study reported any adverse event.

DISCUSSION

The worldwide burden of LRTI is growing by-the-minute. The two most commonly encountered LRTIs in the out-patient departments are CAP and AECB. The number of new cases of CAP encountered per year is approximately 5-11 per 1000 population, and is amongst the leading causes of morbidity as well as mortality.[2,3] Despite the presence of multiple anti-microbial agents, the bacterial agents are developing resistance to these drugs and making them ineffective.[9] The increase in the cases of antimicrobial resistance in India can be attributed to various factors like irrational usage of antibiotics, inadequate dosage or treatment duration and self-medication of such agents by patients due to easy availability. Rational antibiotic combination therapy can serve as one of the important interventions to tackle this growing issue of antibiotic resistance. Beta lactam antibiotics and fluoroquinolones are considered as the first line antibiotics for treatment of LRTI. However, individually, beta lactams have negligible activity against atypical microorganisms and there is an increased emergence of Streptococcal isolates resistant to these antibiotics.[8] Similarly, there is an increased chance for the gram-negative organisms to develop resistance to fluoroquinolones. Therefore, the combination of these two classes of drugs in LRTI will help the patients in providing them a multimodal empiric coverage with probably additive effect, increasing the patient compliance and tackling the issue of antibiotic resistance. Though the FDC of cefixime and moxifloxacin is approved by the CDSCO in the management of LRTI, the real-world evidence with regards to the efficacy and safety of this FDC is limited. Hence, this retrospective study was conducted to fulfil this crucial void.

In this study, the most common LRTI noted was CAP, and majority of these patients (93.68%) received the medication for 5 days. The commonest clinical feature noted in these patients was cough (97.37%), followed by increased sputum volume, fever, sputum purulence, pleuritic chest pain, sleep disturbance, dyspnea and fatigue. These findings give an idea about the LRTI presentation and treatment pattern at various Indian OPDs. On evaluating the symptom scores of these patients, it was found that 100% of the patients showed improvement after a course of cefixime 400 mg-moxifloxacin 400 mg FDC, in all the clinical features assessed. The FDC treatment was able to bring down the WBC count in all but one assessed patient. According to the case records of the patients enrolled, none of the patients suffered from any kind of adverse event throughout the duration of taking the antibiotic regimen, indicating that the FDC is not only efficacious but safe as

well. Thus, this study shows that the intake of cefixime plus moxifloxacin FDC led to global improvement in the patients' health.

The efficacy of moxifloxacin as monotherapy in LRTIs have been evaluated in a few published studies. A study by Rahmel et al, found that moxifloxacin is a safe and an effective antibiotic in patients with severe CAP and provides an extended spectrum coverage of severe CAP inducing bacteria.[10] In a similar cohort analysis done by Gabriel Lee et al, moxifloxacin treatment in CAP patients was found to be associated with lower treatment failures as compared to levofloxacin in Taiwanese population.[11] Some studies have also compared fluoroquinolones with beta lactams, but the results have been inconsistent. In a meta-analysis by Mao An et al, the microbiological treatment efficacy rates of moxifloxacin was found to be superior to those of beta lactam based monotherapy and the safety of these two regimens was found to be comparable.[12] However, in a Nigerian study by Ige et al, cefixime was found to be superior than ciprofloxacin in providing the bacterial cure, symptomatic relief and radiological improvement in CAP patients.[13] The comparative data between beta lactams and fluoroquinolones, though inconsistent, show the efficacy of these classes of drugs in LRTI management.

The dilemma on whether to use monotherapy or combination therapy to treat LRTIs has always given rise to debates amongst clinicians. Some meta-analyses have tried to solve this query, with limited success. A meta-analysis published by Vardakas et al. included studies which had evaluated LRTI patients receiving fluoroquinolones, beta lactams or macrolides as monotherapy or in combination. The authors found that monotherapy was related to a higher mortality as compared to combination therapy, but this difference was not statistically significant. It was noted that the North American studies showed greater mortality with monotherapy, and this more evident in retrospective studies. The same meta-analysis also pointed out that macrolides could have been considered an appropriate treatment option in the early 90s, but in the current situation there is increased resistance to this class of drug and the inclusion of old studies may have affected the outcome of the meta-analysis. The meta-analysis also mentioned about the dearth of studies with patients having mild to moderate LRTI, as majority had studied patients with severe grade of LRTI.[14] In another meta-analysis by Raz-Pasteur et al, the efficacy of fluoroquinolone monotherapy was compared with their combination with beta-lactams. However, no significant difference was observed in relation to overall outcomes. However, once again, the two studies included in the analysis had a small number of patients who were suffering from severe CAP and were admitted in ICU.[15] On literature search, very few studies were found which have tried to explore the real world experience of antibiotic usage in mild to moderate LRTI. Hence, this study is a step in the right direction to evaluate the usage of a beta lactam and fluoroquinolone combination which is approved for usage by the primary regulatory body of India.

This study had a few limitations. Since this was a single-arm study, the results could not be compared with other monotherapies or combination regimens. In the future, researchers can plan prospective, randomized and controlled studies to add to the real-world evidence in relation to the usage of cefixime and moxifloxacin combination in managing mild to moderate LRTI.

CONCLUSION

In a real-world setting, the oral fixed dose combination of cefixime (400 mg) and moxifloxacin (400 mg) was found to be efficacious in improving all the symptoms reported by patients suffering from LRTI, without causing any adverse event.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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