

Evaluation of Efficacy and Safety of Fixed Dose Combination of Ceftazidime-Tobramycin in Comparison with Ceftazidime in Lower Respiratory Tract Infections

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Abstract: Lower respiratory tract infections are major cause of morbidity and mortality. Objectives were to evaluate efficacy and safety of fixed dose combination (FDC) of Ceftazidime and Tobramycin in comparison with Ceftazidime alone in patients with lower respiratory tract infections. Patients (n=240) were randomly distributed in two arms: one arm was treated with Ceftazidime(1g)-Tobramycin(120mg) and other arm was treated with Ceftazidime (1g) alone. Patients were clinically, radiologically and bacteriologically evaluated. Clinically successful outcome was seen in 88.4% of the patients in Ceftazidime-Tobramycin treated group as compared to 61.2% in Ceftazidime alone treated group. In Ceftazidime-Tobramycin treated group, majority of pathogen isolated were *H.influenzae* (35%), *P. aeruginosa* (24.16%), *K. pneumoniae* (16.66%) and *M. catarrhalis* (24.16%), whereas in Ceftazidime alone treated group majority of pathogen isolated were *H.influenzae* (33.33%), *P. aeruginosa* (20%), *K. pneumoniae* (18.33%) and *M. catarrhalis* (28.33%). In Ceftazidime-Tobramycin treated group (98%), a significantly higher bacterial eradication was observed than Ceftazidime alone treated group (79%). Radiological improvement was also superior in Ceftazidime-Tobramycin treated group. No major adverse events were observed. Results showed that fixed dose combination of Ceftazidime Tobramycin is superior than Ceftazidime alone in the treatment of lower respiratory tract infections.

Key Words: Ceftazidime, tobramycin, *P. aeruginosa*, LRTI.

INTRODUCTION

Lower respiratory tract infections (LRTI) are very common in general practice and comprise of bronchitis and pneumonia [1]. It is associated with considerable mortality and morbidity worldwide. It is fifth and sixth cause of death in USA and UK [2]. Many patients especially elderly and those dehydrated can't expectorate lower respiratory tract secretions and therefore don't produce samples acceptable for bacterial culture. Even when suitable sample is available culture results are available after 2-4 days [3]. For these reasons initial therapy is empirical and treatment of LRTI's put significant therapeutic challenge. Owing to increase in resistance and change in resistance pattern relevant pathogen may not be susceptible and therapy with single antibiotic may promote antimicrobial resistance.

Ceftazidime belongs to cephalosporin group of antibiotics. It interfere with the ability of bacteria to form cell wall leading to bacterial death [4]. Its synergistic combination with tobramycin extends antibacterial spectrum [5]. Keeping it in view, this study was planned to evaluate comparative efficacy and safety study of Ceftazidime-Tobramycin combination in comparison with ceftazidime alone.

PATIENTS AND METHODS

Patients

Hospitalized patients (n=240, more than 18yrs of age) of either sex suffering from lower respiratory tract infections

participated in an open labeled, two arm, comparative, multi-centre trial conducted at Dr. R N Cooper Municipal General Hospital, Mumbai, Seth G S Medical College, Mumbai, SMT. NHL Municipal Medical college, Ahmedabad, and D Y Patil Medical college, Kolhapur.

Inclusion Criteria

Patients with confirmed diagnosis of lower respiratory tract infections and who did not receive either of the antibiotics in previous 72h were enrolled in the trial. The diagnosis of LRTI required isolation of bacteria from blood culture and at least two of following: fever (>100F), cough, production of sputum, leukocytosis (>12000 wbc/mm³ or >15% bands) or upper tract symptoms (flank or back pain or costovertebral angle tenderness) and radiographic abnormality. Patients willing to give informed consent were included.

Exclusion Criteria

Patients were excluded, if they had received intravenous antibiotic >24 hrs. Patients hypersensitive to the study drug or related drugs, pregnant and lactating women were also excluded. Patients with renal and hepatic insufficiency were also excluded.

Randomization

Patients were randomly allocated to two groups. The randomization was done in blocks of 120 patients Fig. (1). Randomization list was prepared before starting the study and random treatment assignment was placed in serially-labeled sealed envelopes. The assignment was opened when patients had met all the inclusion and exclusion criteria and written consent was available. One group of patients were treated

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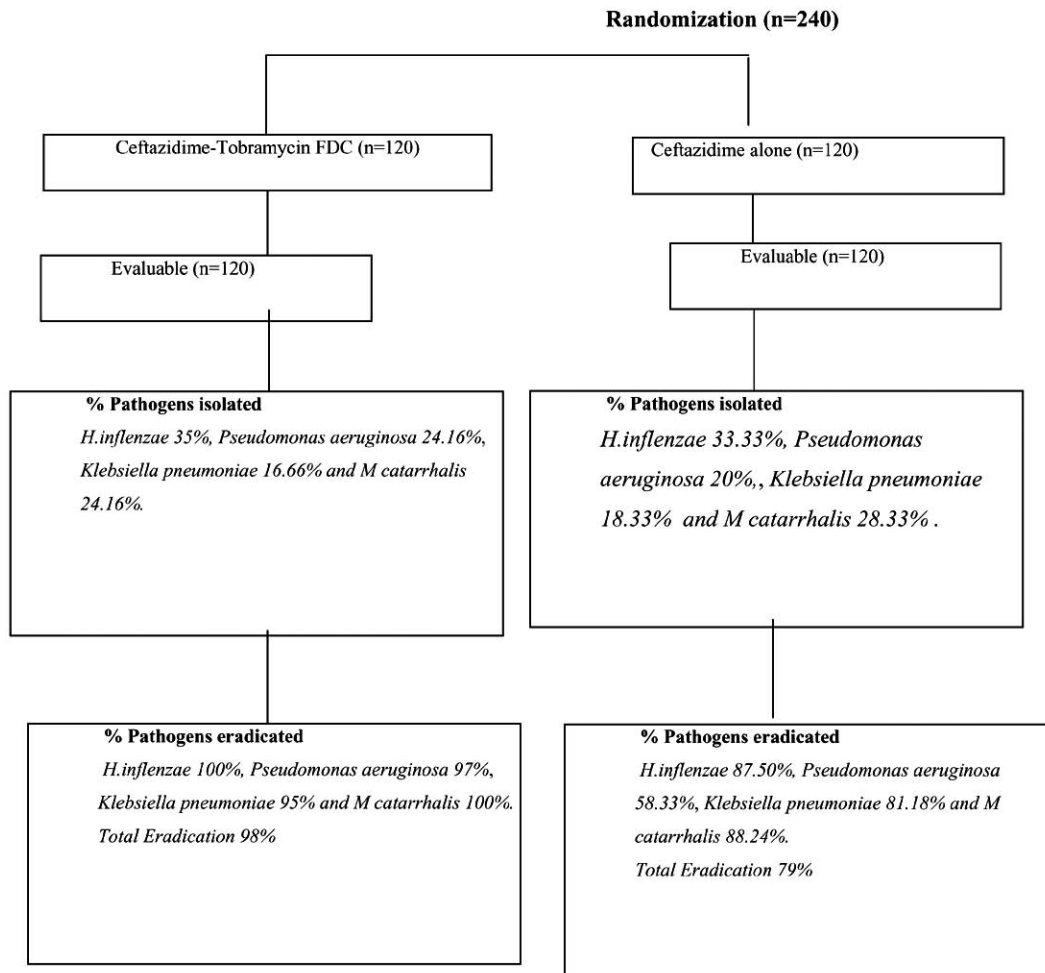


Fig. (1). Randomization flow chart.

with intravenous injection of Ceftazidime-Tobramycin FDC 1.120 g and other group of patients were treated with intravenous injection of Ceftazidime alone 1g for 7 days.

Supportive therapy was given as per the standard case management guidelines prepared by WHO programme for the control of ARI.

EVALUATION

Clinical Evaluation

All the patients receiving at least 1 dose of the study drugs were evaluated on an intent to treat basis. The patients were considered cured, if there was disappearance of originally observed symptoms or infection; clinically improved, if there was clear recovery or partial disappearance of original symptoms and no further requirement of antibiotic therapy.

If there was worsening of the infection symptoms or treatment with other antibiotics was required, it was considered as failure. Patients withdrawn from the study at any time, whether due to inadequate response or adverse events was also considered as failure.

Bacteriological Evaluation

Bacteriological evaluation was done in terms of presence or absence of bacteria in sputum. The patients were consid-

ered completely cured, if no pathogens were observed in the bacteriological culture and incompletely cured/persistence, if pathogens still persisted in the bacteriological culture.

The trial was conducted in accordance with declaration of Helsinki and was approved by ethics committee.

Safety Evaluation

All the adverse events were recorded and rated for severity and relationship to the study medication. Day to day fluctuations in any pre-existing conditions were not considered as adverse events. However, significant exacerbations or worsening of pre-existing conditions were also recorded. Drop out cases with reasons (non-compliance, side effects or others) were noted. Any abnormal laboratory values were also noted.

Statistical Methods

Categorical data between the baseline and post treatment values were compared with chi square test and continuous data was compared with the t - test .

RESULTS

Both treatment groups were balanced with respect to the baseline demographic characteristics: gender, age and num-

ber of patients. Out of 240 patients enrolled in the study, 120 patients were randomized to each group. Ceftazidime-Tobramycin treated arm had 92 male and 28 female volunteers while Ceftazidime treated arm had 88 male and 32 female volunteers.

Pneumonia was diagnosed in 100 (84%) of Ceftazidime-Tobramycin treated group and in 86 (72%) of Ceftazidime treated group. Bronchitis was diagnosed in 20 (16%) of Ceftazidime treated group and 34 (28%) of Ceftazidime treated patients.

Clinical Evaluation

Clinically successful outcome was seen in 88.4% of the patients in Ceftazidime-Tobramycin FDC treated group as compared to 61.2% in ceftazidime alone treated group, with significant reduction in symptoms of dyspnoea, fever, cough, sputum, hemoptysis and chest pain in the patients (Fig. 2).

In Ceftazidime-Tobramycin FDC treated group 11.6% of the patients did not show clinical improvement as compared to 38.8% in Cefepime alone treated group.

Radiological evaluation was also done on day 0 and day 7. In Ceftazidime-Tobramycin treated group 93% of patients showed radiological improvement whereas in Ceftazidime alone treated group 76% of patients showed the improvement (Fig. 2).

Bacteriological Evaluation

In both the groups, single baseline pathogen was isolated from 85% of patients. Two or more pathogens were isolated from 42% of patients in Ceftazidime-Tobramycin treated group and 44% of patients in Ceftazidime treated group. Predominant pathogens isolated were *H. influenzae*, *P. aeruginosa*, *K. pneumoniae* and *M. catarrhalis*.

In Ceftazidime-Tobramycin treated group, a significantly higher number of patients (98%) showed elimination of bacterial infection than Ceftazidime alone treated group (79%). In Ceftazidime-Tobramycin treated group 100% eradication of *H. influenzae* (42/42) and *M. catarrhalis* (29/29) was observed. Eradication of *P. aeruginosa* and *K. pneumoniae* was 97% and 95% respectively. In Ceftazidime alone treated

group, eradication of *H. influenzae*, *P. aeruginosa*, *K. pneumoniae* and *M. catarrhalis* was 87.5%, 58.33%, 81.18% and 88.24% respectively (Figs. 2, 3).

Safety Evaluation

No significant change in liver function tests, renal function tests were observed on completion of treatment as compared to base line values on screening. All the patients from both the arms tolerated the trial medication without any major adverse events that needed discontinuation.

DISCUSSION

LRTI were the leading cause of deaths among all infectious diseases in 2002, and accounted for 3.9 million deaths worldwide and 6.9% of all deaths that year. Antibiotics are often thought to be the first line treatment in lower respiratory tract infections and it is important to use appropriate antibiotic selection based on the infecting organism and to ensure this therapy changes with the evolving nature of these infections and the emerging resistance to conventional therapies [6].

Treatment with an aminoglycoside in combination with a β -lactam is the usual first-line therapy for Acute Pulmonary exacerbations in patients with Cystic fibrosis [7]. Ceftazidime and Tobramycin combination therapy is considered by some clinicians to be the clinical standard [8]. Cade *et al.*, reported that microbiological eradication in 52% of LRTI patients on treatment with Ceftazidime. The favorable clinical response rate was observed in 74% of piperacillin-tazobactam treated patients whereas it was 50% for Ceftazidime treated patients. The bacteriological response between the treatment group was 65% for piperacillin tazobactam and 38% for Ceftazidime treated groups [9].

In the present study, the Ceftazidime Tobramycin group showed much better clinical (88.4%) and bacteriological response (98%) rates. Many anaerobes are known to be intrinsically resistant to Ceftazidime. In the Ceftazidime alone treated group clinical response rate was 61.2% and bacterial eradication rate was 79% respectively. Pathogenwise eradication was also better in Ceftazidime Tobramycin FDC treated group than Ceftazidime alone treated group. This

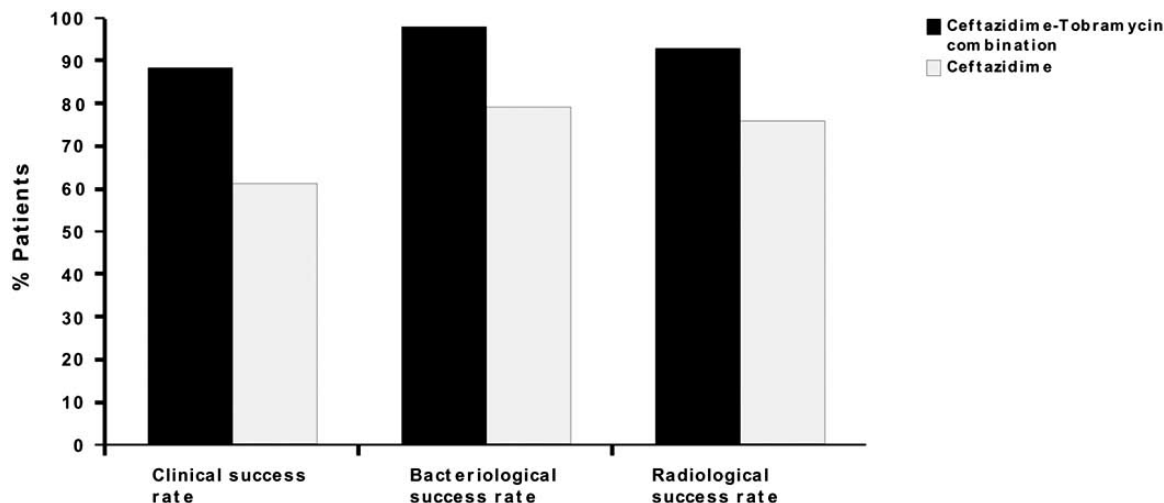


Fig. (2). Comparative evaluation of the two treatment groups.

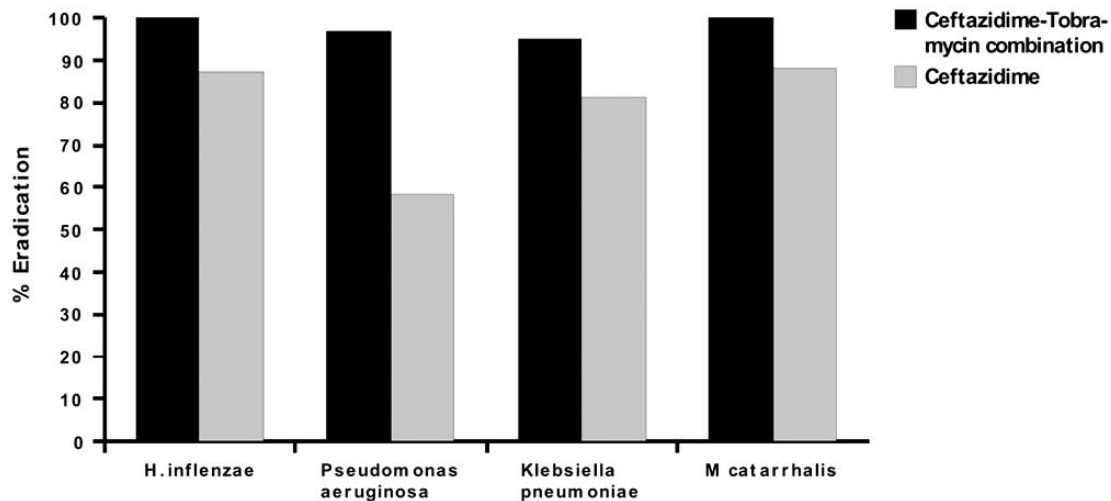


Fig. (3). Pathogenwise comparative bacterial eradication.

superimacy of the combination was also seen in radiological evaluation which was significantly better in Ceftazidime - Tobramycin FDC treated group than Ceftazidime alone treated group.

Clinical and bacteriological success obtained in the present study was better than earlier reports. An open labeled, randomized comparative multicentre study was conducted in USA and Canada to compare the efficacy of Piperacillin & Tazobactam plus Tobramycin with Ceftazidime plus Tobramycin in patients with LRTI. The clinical success rate in Piperacillin/Tazobactam treated group was 74% and in Ceftazidime treated group it was 50%. Eradication of baseline pathogen in piperacillin tazobactam group was 66% and in ceftazidime treated group it was 88% [10]. In another study on pneumonia patients, clinical response rate was 80% and 88% in cefepime and ceftazidime treated groups respectively where as bacteriological response rate was 85 and 73% in cefepime and Ceftazidime treated groups [11]. Hollander *et al.*, established synergism between Tobramycin and Ceftazidime against *pseudomonas aeruginosa* strain and suggested infections due to resistant pseudomonas strains could be treated by synergistic combination of these drugs [5]. Moreover it has also been reported that simultaneous dosing of Ceftazidime and Tobramycin had better efficacy than Tobramycin followed by Ceftazidime [12]. Even in febrile neutropenic patients Ceftazidime -tobramycin combination was more effective than ceftazidime alone treated group [13].

No significant change in liver and renal function tests were observed on completion of treatment as compared to baseline values. No major adverse events were observed and all the patients well tolerated the study medications. There are different views of toxicity of Tobramycin. In a patients of bacteremia and osteomyelitis, liver enzymes rose when Tobramycin therapy was initiated, markedly increased when the Tobramycin dose was increased, then resolved upon discontinuation of therapy [14] where as safety data from a study on patients with cystic fibrosis demonstrated that both meropenem and Ceftazidime, in combination with Tobramycin, were well-tolerated with a notably low incidence of nausea and/or vomiting, diarrhea, and skin rashes. The utility of

combination therapy with a -lactam plus an aminoglycoside in the treatment of LRTI was also supported [15].

In conclusion, fixed dose combination of Ceftazidime-Tobramycin is more effective and as safe as Ceftazidime alone in treatment of lower respiratory tract infections.

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