

ASSESSMENT ON EVALUATION OF SAFETY AND EFFICACY OF CEFOTAXIME AND CEFTRIAXONE IN LOWER RESPIRATORY TRACT INFECTIONS- A COMPARATIVE STUDY

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ABSTRACT

Back ground: Lower respiratory tract infection (LRTI) is a broad terminology which includes bronchitis, pneumonia, acute exacerbations of chronic obstructive pulmonary disease, chronic bronchitis. World Health Organization (WHO) globally high burden of disease study estimated that (LRTIs) cases are around 429.2 million, episodes of illness and accounts for 94.5 million incapacity adjusted life years. In adults aged > 59 years, it causes 1.6million deaths. Beta-lactamase producing bacteria present a major problem in treating LRTIs. The objective of this study was to assess and evaluate safety, efficacy of ceftriaxone versus cefotaxime injection as an alternative

therapeutic option for treatment of in patients (5-65 years) with LRTIs. **Methods:** This is a randomized and comparative study, performed for a period of six months a total of 110 inpatients with lower respiratory tract infections, from ESI hospital within the age range of 5-65 years. Patients received ceftriaxone or cefotaxime injection intravenously during the treatment. **Results:** There was no difference between the two groups in demography or disease characteristics ($p > 0.05$) at baseline. Efficacy was evaluated in a total 110 patients. Both the treatment groups were comparable in response rate at the end of the therapy ($p > 0.05$). Clinical success rate was 94.8% and 88.5%, respectively for ceftriaxone and cefotaxime. Both the study medications were safe and well tolerated in the study population. **Conclusion:** In conclusion, ceftriaxone administered was found to be little more effective

when compared with cefotaxime therapy. However, further studies with a large number of patients are required to confirm these findings with more robust microbiological evaluation.

KEYWORDS: LRTI, Ceftriaxone, Cefotaxime, Randomized.

1. INTRODUCTION

Respiratory tract infections are the most often reported infectious disease in human being. Based on the part of respiratory system affected they are conventionally divided into upper respiratory tract infections and lower respiratory tract infections (LRTIs).^[1]

Acute LRTIs are one of the common clinical problems in community and hospital settings. Beta lactam antibiotics, macrolides, and fluoroquinolones are regularly prescribed medicines for the management of Acute LRTIs. Macrolides are time-tested and effective agents for the treatment of LRTIs. World Health Organization (WHO) global burden of disease study estimated that lower respiratory infections (LRTIs) where 429.2 million episodes of illness worldwide and accounts for 94.5 million incapacity adjusted life years. In adults aged more than 59 years, it causes 1.6 million deaths annually (WHO, 2012).

Lower respiratory tract infections (LRTI's) are one of the most common cause of morbidity and mortality arising from infectious diseases both in the developed and developing countries.^[2] In the South-East Region, respiratory tract infection accounts for 34.60% deaths which is of total 3,941,000 deaths in the world.^[3]

Lower respiratory tract infection (LRTI) is a wide terminology which includes bronchitis, pneumonia, acute exacerbations of chronic obstructive pulmonary disease/chronic bronchitis, and acute exacerbation of bronchiectasis. In LRTI lower part such as larynx, bronchi, trachea and lung parenchyma of the respiratory system is affected. LRTI is not a single disease, it includes a group of specific infection they differ from epidemiologies, pathogeneses, clinical presentations, and outcomes. The aetiology and symptomatology of respiratory diseases differ with age, gender, season, the type of population at risk, and other factors. LRTIs are usually the first infection to occur after birth and pneumonia is too often the final illness to occur before death.^[4,5]

The role of antibiotics in the management of larger population of patients with LRTI is less clear. The standard antibacterial treatments for lower respiratory tract infections in the past have been macrolides, in particular macrolides, the penicillins, or cephalosporins. Adverse

drug reactions (ADRs) lead to a number of medical and monetary consequences, e.g. they extend hospital stay, increase the cost of treatment and exposure to possible harm and death nearly two-fold. Thus, there is a compelling need to create awareness among physicians and patients towards the need for ADR monitoring^[6]

Based on anatomical region infected, Lower Respiratory tract infection are classified They include:

- Bronchitis
- Bronchiolitis
- Pneumonia

Among these most common are bronchitis and pneumonia.^[5]

Sign and Symptoms of Lrti

Bronchitis	Bronchiolitis	Pneumonia
<ul style="list-style-type: none"> • Malaise, • Headache, • Coryza, • Sore throat and • Cough 	<ul style="list-style-type: none"> • Productive cough • Difficulty breathing, • Fever with chills, • Chest pain, • Dyspnoea, • Fatigue, and • Confusion. 	<ul style="list-style-type: none"> • Malaise, • Fever, • Chills, • Rigors, • Cough, • Dyspnoea, and • Chest pain.

Causes of Lrti

BRONCHITIS	BRONCHIOLITIS	PNEUMONIA
<p>The causes of acute bronchitis include: viruses, that cause colds and <u>flu</u>. exposure to substances that irritate the lungs, such as tobacco smoke, dust, fumes, vapours, and air pollution. bacterial infection</p> <p>The causes of chronic bronchitis chronic smoking. long-term exposure to air pollution, dust and fumes</p>	<p><i>Respiratory syncytial virus (RSV)</i> <i>Adenoviruses</i> <i>Influenza viruses</i></p>	<p>Bacteria. Eg: Streptococcus pneumoniae. Bacteria-like organisms. Mycoplasma pneumoniae also can cause pneumonia. Fungi. The fungi that cause it can be found in soil or bird droppings and vary depending upon geographic location. Viruses. Viruses are the most common cause of pneumonia in children younger than 5 years.</p>

Riskfactors of Lrti

BRONCHITIS	BRONCHIOLITIS	PNEUMONIA
<ul style="list-style-type: none"> • Cigarette smoke. • Low resistance • Exposure to irritants on the job. • Gastric reflux. 	<ul style="list-style-type: none"> • Infants younger than^[3] months of age • Premature birth • An underlying heart or lung condition • A depressed immune system • Exposure to tobacco smoke • Never having been breast-fed — breast-fed babies receive immune benefits from the mother • Contact with multiple children, such as in a child care setting • Living in a crowded environment 	<p>The two age groups at highest risk are:</p> <ul style="list-style-type: none"> • Children who are 2 years old or younger • People who are age 65 or older <p>Other risk factors include:</p> <ul style="list-style-type: none"> • Being hospitalized. • Chronic disease. like asthma, COPD or heart disease. • Smoking. • Weakened or suppressed immune system. People have HIV/AIDS, chemotherapy or long-term steroids are at risk.

Treatment of Lrti

Bronchitis	Bronchiolitis	Pneumonia
<p>Analgesics (aspirin, acetaminophen, ibuprofen), Cough suppressants (Dextromethorphan-for mild cough)</p> <p>Codeine-more severe coughs)</p> <p>Antibiotics and Bronchodilators.</p> <p>In children aspirin should be avoided due to the possible association of development of Reye's syndrome.</p> <p>Regular use of antibiotic is discouraged to treat acute bronchitis.</p>	<p>Based on the causative organism antibiotics is given and in case of severe infection with respiratory syncytial virus, antiviral like Ribavirin is used.</p>	<p>Antibiotics including(Piperacillin/tazobactam, Cephalosporins, Levofloxacin, Imipenem, Meropenem)are used to treat bacterial pneumonia. Analgesics (aspirin, acetaminophen, ibuprofen), Cough suppressants (Dextromethorphan-for mild</p>

2. METHODOLOGY

Study Design: It is A Prospective **Comparative**, Observational, Study.

Study Period: The Present study was conducted for a period of **Six months from October 2018 to March 2019.**

Study site: The Present study was conducted in **General Medicine Department** at ESI hospital, Indiranagar, Bangalore.

Sample size: The In- Patients admitted in hospital during the study period of six months
[N=110 Patients.]

CRITERIA

Inclusion criteria

- Patients with aging 5 years -65 years.
- Patients suffering from LRTI and having previous history of medical, medication problems.
- The Patients who are willing to participate in the study.

Exclusion criteria

- Patients who are not willing to Participate in the study.
- Pregnancy.
- Lactation.
- Cancer Patient.

Source of Data

All the patients satisfying the inclusion criteria were selected from General medicine department for the present study. All the required data was collected from patients through Data collection form, personal interview, case sheets and treatment charts.

Method of collection of data

All the patients satisfying the inclusion criteria were selected from General medicine department in ESI hospital, Indiranagar. After thoroughly explaining the study methodology to the subjects, and included in the study. Informed Consent was taken from each patient, the necessary information was collected by interviewing the patients and parents using the following annexures.i.e., Consent form, Data collection form, Questionnaire etc.,

Statistical tools: Prism Graphic Pad and Microsoft excel are used to analyse the result.

3. RESULT

A total of 58 patients were randomized to receive ceftriaxone injection and 52 patients received cefotaxime injection. This study enrolled 63 males and 47 females(Table :1). The diagnosis of LRTI was radiologically confirmed by chest X-ray showing consolidation in all

these patients, and none of the patients had interstitial infiltration. The demographic and baseline characteristics were comparable ($p > 0.05$) for both the treatment populations. There was no marked difference in between the two groups in either signs and symptoms of disease or disease status at baseline (Table1).

SAMPLE SIZE N= 110

Table 1: Demographic details of the patient.

Sex	Number	Percentage
Male	63	57.27%
Female	47	42.72%

Table 2: Age wise distribution.

Age	Number	Percentage
5-15	29	26.4 %
15-25	16	14.5 %
25-35	12	11 %
35-45	15	13.6 %
45-55	18	16.4 %
55-65	20	18.1 %

In this study(n=110) LRTIs was commonly reported in age group 5-15 years(26.4%) and it is followed by 35-45 years(13.6%) and 25-35 years (11%).

Table 3: Number of patients suffering from diseases.

Disease	Number	Percentage
Bronchitis	56	51 %
Bronchiolitis	29	26.4 %
Pneumonia	25	22.7 %

Out of 110 patients 51% bronchitis, 26.4% bronchiolitis and 22.7% pneumonia are reported.

Table 4: Comparison of signs and symptoms present at baseline.

Symptom	Ceftriaxone	Percentage	Cefotaxime	Percentage
Presence of cough	58	100%	52	100%
Presence of dyspnoea	56	96.5%	51	98%
Fever (body temperature $\geq 38^{\circ}\text{C}$)	51	87.9%	45	86.5%
Presence of crepitations	46	79.3%	44	84.6%
Presence of bronchial breathing	8	13.8%	6	11.5%
Presence of sputum	48	82.7%	44	84.6%

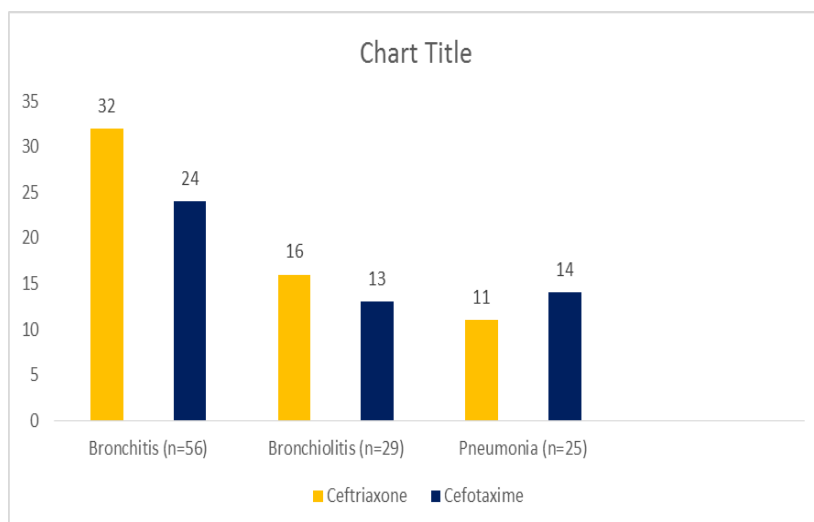


Figure 1: Prescribing pattern of ceftriaxone and cefotaxime in LRTI.

Among in patients with bronchitis(n=56), bronchiolitis (n=29) and pneumonia(n=25) are treated with ceftriaxone 32,16 and 11 and cefotaxime 24,13 and 14 respectively(Figure1). Effectiveness was evaluated in all (n=102) patients.

Table 5: Clinical response and results of equivalence comparisons at the end of the therapy.

Treatment group	Cure + improvement (%)	Failure (%)	P Value
Ceftriaxone (n=58)	55 (94.8%)	3 (5.2%)	0.709
Cefotaxime (n=52)	46 (88.5%)	6 (11.5%)	

Table 5 shows that a successful clinical response (clinically cured/improved) had been achieved in 94.8% patients treated with ceftriaxone injection and in 88.5% patients treated with cefotaxime injection. Clinical failure occurred in 3 patients (5.2%) patients from the ceftriaxone injection group and 6 (11.5%) patients from the cefotaxime injection group.

No additional antibiotics were given along with study medication. None of the patients was given any oral follow-through antibiotics after they were discharged from the hospital. The two treatments were also comparable ($p > 0.05$) in terms of clinical response rate across age. At the final stage of the therapy visit there was marked reduction in baseline signs and symptoms of infection across the therapy groups. There was no significant difference in resolution of signs and symptoms across the two treatment groups.

Those patients who received at least one dose of study medication were included in the safety analysis. A total of 110 patients were analyzed. Twenty seven (26.5%) reported 77 adverse

events during the study. Some patients reported more than one adverse event. The adverse events reported in this study are shown in Table 6.

Table 6: Adverse events reported in both the treatment groups*.

Adverse event	Ceftriaxone (n=58)	Cefotaxime (n=52)
Injection site reactions (swelling, redness, pain, a hard lump, or soreness)	9	11
Skin rash	7	6
Nausea	3	2
Vomiting	6	4
Diarrhoea	8	5
Headache	1	3
Dizziness	3	5
Overactive reflexes	2	0

* Some patients reported more than 1 adverse event.

The commonly reported adverse events were injection site reaction(15% in ceftriaxone group vs 21.1% in cefotaxime group), skin rash (12% in ceftriaxone group vs 11.5% in cefotaxime group) and diarrhoea(13.8% in ceftriaxone group vs 9.6% in cefotaxime group). Less common adverse events were headache (1.7% in ceftriaxone group vs 5.7% in cefotaxime group) and overactive reflexes(3.4% in ceftriaxone group). In the reported adverse events were of mild-to-moderate intensity and possibly seen in the study drugs. The incidence of adverse events with ceftriaxone was slightly more to that reported in the cefotaxime (Table 6).

4. DISCUSSION

LRTIs are common problems in day-to-day clinical practice. Antimicrobial therapy is a principal management component for these diseases. It is often difficult to diagnose and differentiate atypical infections from that of typical infections. Clinical findings and radiological imaging may help to suspect atypical infections. The study done by Ashok Mahashur which explains that In country like India, it is often difficult to confirm the atypical infection even in the laboratories because of the inherent properties of atypical bacteria, limited access to the sophisticated laboratory methods, and cost. In such a scenario, physician often resorts to empirical therapy with antimicrobial agents. With growing evidence of antimicrobial resistance, empirical treatment is becoming more difficult. The antimicrobial agent is often selected based on the patient profile, local resistance pattern, availability of the medicine, and cost. In some cases, especially those with severe illness, combination therapy

may be required. In such patients, combination of macrolide and beta-lactam antibiotic is a suitable option.^[16]

In the present study, ceftriaxone injection was slightly more effective as cefotaxime therapy in patients with LRTIs. Both the study treatments were effective with good clinical response rates. Both the treatments showed comparable clinical response ($p < 0.05$) across the six age groups studied. The clinical outcome in our study for ceftriaxone is comparable to those reported in previous studies.^[15] This is the first randomized, comparative evaluation of ceftriaxone combination with cefotaxime injection in LRTI patients of 5-15 years age group. Although the response rates for both the drugs were statistically similar, more patients were clinically cured in the ceftriaxone group than in the cefotaxime group (94.8% vs 88.5%, respectively). Most adverse events reported were of mild-to-moderate intensity. The adverse event reported in this study for ceftriaxone as well as cefotaxime are Injection site reactions (swelling, redness, pain, a hard lump, or soreness), Skin rash, Nausea, Vomiting, Diarrhoea, Headache, Dizziness and Overactive reflexes. The adverse events reported in the ceftriaxone group were similar to those reported in the for patients receiving cefotaxime.

It is still difficult to detect the causative pathogen in patients with acute LRTIs, and antibiotic therapy in such patients is almost always empirical. Ceftriaxone provides a good choice for the treatment of LRTI inpatients of age group 5-15 years.

5. CONCLUSION

In conclusion, ceftriaxone administered was found to be as safe and effective as cefotaxime therapy. However, further studies with a larger number of patients are required to confirm these findings with more robust microbiological evaluation. Understanding the profile of lower respiratory tract infection is very important. Steps should be taken to combat the various modifiable risk factors of malnutrition and prevention of further complication. Effective implementation of immunization and national health programs and also training of health personnel at subcentre level in early recognition, treatment and referral to higher centre plays a pivotal role in reducing the morbidity and mortality associated with LRTI.

6. RECOMMENDATIONS

If the LRTI is self limited then it is suggested that the use of antibiotics is restricted, since the excess use of antibiotic may lead to antibiotic resistance.

Smoking should be avoided because cigarette smoke may increase the risk of LRTIs.

Get vaccinated. Many cases of LRTIs result from influenza, a virus. Getting a yearly flu vaccine can help protect you from getting the flu. You may also want to consider vaccination that protects against some types of pneumonia.

Wash your hands. To reduce your risk of catching a viral infection, wash your hands frequently and get in the habit of using alcohol-based hand sanitizers.

Wear a surgical mask. If you have COPD, you might consider wearing a face mask at work if you're exposed to dust or fumes, and when you're going to be among crowds, such as while traveling.

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