Original Article

Treatment of ventilator-associated pneumonia with piperacillin-tazobactum and amikacin *vs* cefepime and levofloxacin: A randomized prospective study

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Abstract

Study Objectives: To compare the survival benefits and cost effectiveness of cefepime-levofloxacin (C-L) as an alternative empirical antibiotic therapy for ventilator associated pneumonia (VAP) with the most widely recommended combination of piperacillin-tazobactam and amikacin (P-T-A). **Design:** Prospective, observational, cohort study. **Materials and Methods:** A total number of 879 patients were admitted in the ICU during 1st April 2004 to 31st March 2005 and were screened for the study. Ninety-three patients were clinically suspected to develop early onset VAP. The patients were randomly divided into two groups receiving Cefepime-Levofloxacin (C-L) or Piperacillin-Tazobactam-Amikacin (P-T-A) as empirical antibiotic therapy. Treatment outcome was compared between the groups, which included ICU mortality, duration of mechanical ventilation, duration of ICU stay and total cost incurred on antibiotics. **Results:** The epidemiological characteristics including mean age and APACHE II score were comparable between the two groups. The mortality rates in the two groups were similar. The duration of mechanical ventilation was shorter in C-L group (5-8 days) as compared to P-T-A group (6-11 days). Also, the mean duration of ICU stay was reduced in C-L group (16±2.1 days) as compared to P-T-A group (19±3.4 days). Further, the overall cost of antibiotics in C-L group was 1/3rd of the cost in P-T-A group. Eleven patients were found to be receiving inappropriate antibiotics and seven patients developed ARF during the course of antibiotic therapy. These patients were excluded from the study. **Conclusion:** Cefepime-Levofloxacin combination is an effective alternative to piperacillin-tazobactam-amikacin for empirical treatment of VAP. It reduces the duration of mechanical ventilation, number of days of ICU stay and overall cost of antibiotics

Key words: Antibiotics, cefepime, levofloxacin, piperacillin-tazobactam, ventilator associated pneumonia

Introduction

Ventilator associated pneumonia (VAP) is associated with prolonged mechanical ventilation, increased duration of intensive care unit (ICU) stay and highest mortality rate of all hospital acquired infections.[1,2] These patients are often treated empirically with antibiotic regimens based on suspected pathogens. Empirical treatment is dependent on individual patient factors and bacterial culture-sensitivity pattern of individual Intensive Care Units.

Selection of appropriate antibiotics in the initial stages is an important determinant of clinical outcome.[3] Various studies have shown that as much as 50% of antibiotic use is inappropriate.[4,5] Use of appropriate antibiotics

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directed towards the most prevalent organism not only improves the cure rate and survival but also reduces the emergence of resistant strains. Most of these empirical therapies are directed towards Gram-negative aerobic bacteria and *Staphylococci*.

Many authorities recommend piperacillin-tazobactam as the most effective agent in the empirical treatment of VAP.[6] However, the widespread use of piperacillin-tazobactam as empirical therapy has led to the development of resistance.[7] Recently a combination of cefepime and levofloxacin has been found to be highly effective against *P. aeruginosa*, *E. coli* and *S. aureus*.[8] These are found to be the most commonly isolated organisms in VAP patients.

Hence the aim of the present study was to compare the duration of mechanical ventilation, length of ICU stay, cost incurred and mortality, in patients with VAP, treated with two different groups of antibiotics (piperacillin - tazobactam and amikacin versus cefepime and levofloxacin).

Materials and Methods

The study was conducted in the Intensive Care Unit of our Institution. After obtaining approval from the institutional ethics committee, all mechanically ventilated patients who were admitted during 1st April 2004 to 31st March 2005 were screened and enrolled for the study.

Inclusion criteria

Patients, who were clinically suspected as a case of pneumonia after 48h but within seven days of initiation of mechanical ventilation, were enrolled for the study.[5] Clinical suspicion of VAP was defined as a new, progressive or persistent (>24 hours) infiltrate on chest radiograph, with two or more of the following criteria.

1. Fever>38.3°C or hypothermia <36°C.
2. Purulent endotracheal aspirate.
3. Leukocyte count >10,000/mm^3 or <4,000/mm^3.

Once VAP was suspected according to the clinical criteria, the endotracheal aspirate was sent for culture and sensitivity. The existing antibiotic regimen was changed to as per the study design. The patients were randomly divided into two groups according to the empirical antibiotic regimen prescribed. All the patients enrolled with odd numbers were designated as Group C-L and received Cefepime-Levofloxacin. Patients with even numbers were designated as Group P-T-A and received Piperacillin-Tazobactam-Amikacin. The antibiotics were continued for fourteen days in both the groups.

Exclusion criteria

Patients whose culture sensitivity reports showed resistance to the prescribed antibiotics (P-T-A or C-L) were labelled as inappropriate antibiotic therapy and were excluded from the study. The number of such patients was recorded and their antibiotics were changed according to the antibiogram. Patients with known acute renal failure or chronic renal failure (ARF/CRF) were not included in the study. Patients developing ARF during the course of antibiotic therapy were also excluded from the study.

Doctors on duty made all observations and recorded relevant data from the patients' ICU records, bedside progress charts and microbiologic reports. Patient related variables that were recorded included age, sex, diagnosis, hospital and ICU admission dates. All factors necessary for calculation of APACHE II score were also recorded. Radiologists, who interpreted chest radiographs daily, were blind to the antibiotic groups. Consultants or residents on duty, who were not a part of the study, assessed the extubation criteria and the patients were extubated after they attained extubation criteria.

The treatment variables that were subsequently recorded included - i) the date VAP was first suspected; ii) whether endotracheal aspirate culture led to change of antibiotic therapy (inappropriate therapy); iii) date of liberation from mechanical ventilation; iv) date of discharge from ICU and hospital and v) date of death, if any.

The treatment outcome compared between the two groups included - i) ICU mortality, ii) duration of mechanical ventilation, iii) duration of ICU stay and iv) total cost incurred on antibiotics.

Statistics

Baseline characteristics of patients were compared with the unpaired *t* test. Differences were considered significant if the *P* value was below 0.05.

Results

Out of 879 patients admitted in the ICU during the study period, 93 patients (C-L, n = 46 and P-T-A, n = 47) met the inclusion criteria.

Outcomes

Both the groups were comparable with respect to epidemiology and clinical characteristics [Table 1].

Total observed mortality was 37.3%. It was 39.68% in the Group P-T-A as compared to 35% in Group C-L. The difference in the incidence of mortality between the two groups was statistically insignificant though the rate was comparatively less in Group C-L [Table 2].

The duration of mechanical ventilation after the start of empirical therapy was 6.3±1.6 days in the Group C-L as compared to 8.2±2.1 days in P-T-A Group. This difference achieved statistical significance (*P*-value<0.05) [Table 3].

Further, the mean ± SD duration of ICU stay was 16±2.1 days in CL Group as compared to19±3.4 days in PTA Group. The difference was statistically significant (*P*-value<0.05) [Table 3].

Eight patients were found to be receiving inappropriate antibiotics, as the organism isolated from their endotracheal aspirate was resistant to the empirical regimen used. Nine patients in the study cohort developed ARF during the course of therapy and had to be excluded from the study [Table 2].

Patient factors such as high APACHE II score on admission, immunocompromised state and hepatic failure were associated with increased mortality in both the groups [Table 4].

Pathogens

Endotracheal aspirate was obtained from all patients. The most commonly isolated organisms were *P. aeruginosa*, *Staphylococcus aureus* and *E. coli* [Table 3].

Cost effectiveness

As evident in [Table 5], C-L combination is more economical than P-T-A. The average cost of antibiotics

Table 1: Epidemiologic and clinical characteristics of both the groups

Parameters	C-L (n=46)	P-T-A (n=47)
Age (years)	45.2±5.1	43.6±6.2
Sex (M/F)	25/21	28/19
APACHE II	18±2	16±3
Duration of mechanical ventilation before onset of VAP	5±1.4	4±2.8
Indications for mechanical ventilation		
Exacerbation of COPD	18	20
Abdominal sepsis	11	8
Organophosphate poisoning	2	1
Snake bite	3	5
Emergency abdominal surgery (Post-operative)	5	6
Pneumonia	4	2
Trauma	4	4
Total	47	46

VAP - Ventilator associated pneumonia, COPD - Chronic obstructive pulmonary diseases

Table 2: Characteristics of patients included in the study cohort

Parameters	C-L	P-T-A
No. of patients with clinically suspected VAP	47	46
Inappropriate therapy	5	3
Patients excluded because of acute renal failure	4	5
Average duration of mechanical ventilation after suspicion of VAP (days)	6.3±1.6	8.2±2.1
Average duration of ICU stay (days)	16±2.1	19±3.4
Incidence of death	35%	39.68%

VAP - Ventilator associated pneumonia, ICU - Intensive care unit

Table 3: Organisms isolated from clinically suspected ventilator associated pneumonia patients in both the groups

Organisms	Group C-L (n = 47)	Group P-T-A (n = 46)
P. aeruginosa	20	17
Staphylococcus aureus	11	14
E. coli	7	10
Acinetobacter	3	2
Klebsiella	2	2
Streptococcus species	3	2

Table 4: Patient factors associated with high mortality in both the groups

	C-L		P-T-A	
	No. of patients	Mortality	No. of patients	Mortality
Hepatic failure	6	4	5	4
Immunocompromised state	3	2	3	2
Apache II >20	2	1	2	1

Table 5: Comparison of average cost of antibiotic in both the groups

Average cost of antibiotics (Rs.)	C-L	P-T-A
Per day	554.30	1689.80
Per patient	7760.20	23657.20

incurred in C-L group was Rs. 554.30 per day per patient as compared to Rs. 1689.80 in the P-T-A group. Hence, the cost incurred in C-L group was approximately 1/3rd to that of P-T-A group.

Discussion

Antibiotics are one of the costliest categories of drugs used in the ICU. Its use has become mandatory as it influences the patient outcome in the ICU. Patient outcome also depends upon early, appropriate and adequate administration of empirical antibiotics.[6,9] However, there are no specific guidelines regarding empirical antibiotic treatment of VAP.[6] Initially various authorities investigated single drug therapy as the empirical treatment of VAP.[10,11] Because of development of resistance and high mortality associated with monotherapy, use of two antibiotics directed against most commonly isolated organisms is recommended now.[12,13] Recently, the most frequently recommended combination therapy includes antipseudomonal penicillin plus betalactamase inhibitor along with fluoroquinolones or aminoglycosides.[6]

It is very difficult to conduct a study free from bias. However, in our study we took certain steps to make it bias free. The patients fulfilling the clinical criteria of VAP were randomly divided into two groups. VAP criteria were applied by consultants who were not a part of the study. Further, patients in both the groups were taken off the ventilator when they met a well-defined extubation criteria assessed by consultants or residents who were independent. Even the radiologist commenting on chest radiographs was made blind to the groups.

In the present study the survival outcome was similar in both the groups. However, patients treated with cefepime plus levofloxacin had shorter duration of mechanical ventilation and ICU stay as compared to piperacillin-tazobactam-amikacin combination. This may be attributed to rapid, synergistic bactericidal activity of cefepime - levofloxacin combination.[8] Further, since tazobactam is a suicidal antibiotic it can develop resistance in the parent antibiotic. The organisms isolated in our ICU might be developing resistance *in vivo* to this combination, which was not evident in the *in vitro* sensitivity investigations. As an advantage over these suicidal antibiotics, cefepime - levofloxacin combination has been shown to slow and prevent the development of resistance.[8] Contrary to our observations, other studies conducted with fluoroquinolones and cephalosporins did not show any improvement in the outcome in VAP patients.[6] This could be because the previous studies have compared second and third generation cephalosporin. Cefepime, a fourth generation cephalosporin has a structural advantage (Zwitterionic configuration) which allows faster penetration through the cell membrane of gram negative bacteria and makes it more stable against beta lactamases as compared to third generation cephalosporins.[14]

Cefepime-levofloxacin combination reduced the total cost of antibiotics to nearly 1/3 of the cost of piperacillin-tazobactam-amikacin combination [Table 5]. Reduced number of days of mechanical ventilation and ICU stay further made cefepime-levofloxacin combination a cost effective alternative to piperacillin-tazobactam-amikacin [Table 2].

In our study there was no recurrence of pneumonia after the completion of antibiotic treatment. We discharged the patients once they were symptom free.

Four patients in the cefepime-levofloxacin group and seven in the piperacillin-tazobactam-amikacin group were excluded from the study. These patients were found to be receiving inappropriate antibiotics, i.e. the isolated strains in these patients were resistant to the empirical therapy.

The patients who developed acute renal failure during the course of therapy were excluded from both the groups. They were excluded because either the dose of amikacin had to be reduced or it had to be completely avoided depending upon the level of serum creatinine. Inclusion of such patients in the cefepime-levofloxacin group would make the two groups incomparable. Further, acute renal failure is an independent risk factor for poor outcome.[15,16]

The organisms isolated in our study were similar to other study groups.[6] Diagnostic criteria of VAP and extubation criteria were similar to that used in most ICUs.[6] Patient factors such as immunocompromised state, hepatic failure, ARDS and higher APACHE II scores resulted in higher mortalities [Table 4]. It is in accordance with the clinical outcomes seen in other studies.[6,15,16]

The major limitation of our study was that it did not investigate the causative factors associated with early onset VAP. Our study was designed to investigate only the treatment outcome in two different antibiotic groups. Also we did not analyze the number of days required to make the culture negative for previously isolated organisms.

Conclusion

The results of this study indicate that combination of cefepime-levofloxacin is an effective alternative to piperacillin-tazobactam-amikacin, which is a widely accepted antibiotic regimen for the treatment of VAP. Further, cefepime-levofloxacin combination reduced the duration of mechanical ventilation, length of ICU stay, mortality and the over all cost of antibiotic therapy. However a study should be designed to evaluate the effect of these drugs in patients with ARF. Further, it should study the number of days required to make the patients culture negative with either of these combinations, which was one of the limitation of our study.

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