Original article

Cefepime/clindamycin vs. ceftriaxone/clindamycin for the empiric treatment of poisoned patients with aspiration pneumonia

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Abstract. Different antimicrobial treatments have proved to be effective in patients with aspiration pneumonia. However, resistant bacterial strains are commonly observed in hospital settings challenging the empirical treatment of these patients. In this study, we aimed to compare the efficacy of cefepime/clindamycin and ceftriaxone/clindamycin for empiric therapy of poisoned patients with aspiration pneumonia. In an open, randomized, prospective design, 140 consecutive patients aged more than 13 years, with radiographic signs of infiltration in chest radiography and dullness on percussion or pulmonary rales or ronchi in combination with at least two of the following clinical criteria were considered as eligible: fever ≥ 37°C (axillary), or hypothermia < 35°C (axillary) and leukocytosis (> 10 cells/mm^3), or leukopenia (< 3,000 cells/mm^3), a left-shift of > 10%, or purulent sputum or secretion from trachea or bronchi. Participants received intravenously either ceftriaxone 1 g q12 h and clindamycin 900 mg q8 h (group 1) or cefepime 1 g q12 h and clindamycin 900 mg q8 h (group 2). On day 5 of treatment, the number of improved/cured patients was not different between groups (OR 0.86; 95%CI 0.24 to 2.90) nor at 14 days of the study (OR 0.66; 95%CI 0.12 to 3.29). Six patients died in group 1 and 5 in group 2 (RR 0.83; 95%CI 0.28 to 2.46). In conclusion, efficacy of empiric treatment of poisoned patients with aspiration pneumonia with ceftriaxone/clindamycin was comparable to treatment with cefepime/clindamycin. (www.actabiomedica.it)

Key words: Antimicrobial agents, aspiration pneumonia, clinical research, disease management, randomized clinical trial

Introduction

Infective pneumonia following aspiration of infectious material from the oropharynx or stomach may result in life-threatening complications. Since many cases of community-acquired and nosocomial pneumonia may be due to unrecognized aspiration (1), the true incidence of aspiration pneumonia is unknown. Reported prevalence data are extremely variable, ranging from 10% to 70%, and mortality is related to the volume and content of the aspirate and is reported to be as high as 70% (2). The anaerobic pathogens most frequently isolated from patients with aspiration pneumonia include *Bacteroides, Peptostreptococcus,* and *Fusobacterium* species (3). However, most patients with aspiration pneumonia have infection with multiple organisms and therefore empirical antimicrobial treatment is usually directed to cover both anaerobic and aerobic microorganisms. An antimicrobial regimen with clindamycin, ampicillin/sulbactam, and a

cephalosporin was both well-tolerated and proved equally effective for treating patients with aspiration pneumonia and lung abscess than without a cephalosporin (4). Monotherapy with cefepime 1 or 2 g, usually administered intravenously two times daily, was as effective for clinical and bacteriological response as ceftazidime, ceftriaxone or cefotaxime monotherapy (1 or 2 g two or three times daily) in a number of randomized, clinical trials in hospitalized adults and, less commonly, in pediatric patients with moderate to severe community-acquired or nosocomial pneumonia (5). However, resistant strains are always emerging and new therapeutic alternatives are required. We therefore aimed to compare a therapeutic regimen with cefepime/clindamycin to another with ceftriaxone/clindamycin for treating patients with aspiration pneumonia secondary to drug overdose. This treatment protocol is selected according to our experience on predominant microorganisms in ICU of Loghman Hakim Hospital Poison Center.

Methods

Subjects

The study was approved by the Ethics and Research Board of the National Research Institute Tuberculosis and Lung Diseases (Trial registration: No. 416), Shaheed Beheshti University of Medical Sciences, Iran.

The study was designed as randomized and prospective clinical trial. Randomization was performed by means of a pre-designed table of random numbers for 140 patients. The table of random num-

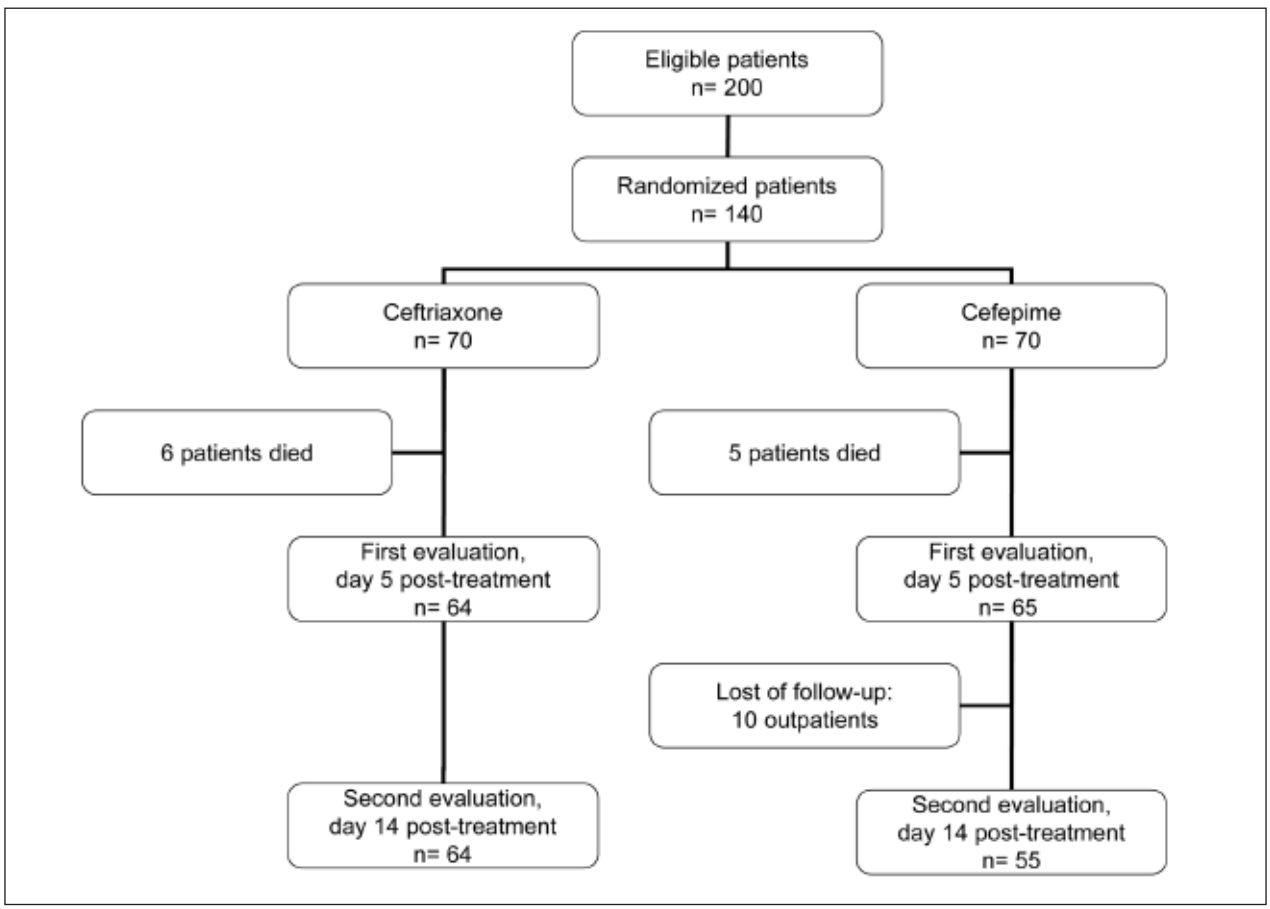

Figure 1. Flow of patients through trial. The patients who died during the study were included in the analysis of mortality rates only

bers was designed by one of the investigators who did not participate enrolling the patients or allocating them into the study groups.

The sample consisted in patients with different drug overdose toxicity hospitalized in the intensive care unite at Loghman Hakim Hospital Poison Center(LHHPC). LHHPC is a unique referral center of poisoning in Tehran,Iran. This center estimated nearly 20000 poisoned patients every year. Daily turn over in this center is 80-100 patients. Diagnosis of drug overdose toxicity performed on the basis of a drug over dose history, and confirmed by clinical signs and symptoms , and also drug urine analysis [sometimes by urine analysis for TCA by thin layer chromatography (TLC) (Clark identification)]. Most of the patients had consciousness alterations in varying degrees and received mechanical ventilation within the first 48 hours of post-admission to the hospital. Eligible patients were aged more than 13 years, and had infiltration in chest radiography and dullness on percussion or pulmonary rales or ronchi in combination with at least two of the following clinical criteria: fever ≥ 37°C (axillary), or hypothermia < 35°C (axillary) and leukocytosis (> 10 cells/mm^3), or left-shift (> 10%) leukopenia (< 3,000 cells/mm^3), or purulent sputum or secretion from trachea or bronchi. Sputum, pulmonary secretions and blood cultures were obtained before therapy. The investigator who verified eligibility criteria and enrolled the patients did not participate in the design of the table of random numbers nor allocating the patients into the study groups.

In group 1, participants received intravenous ceftriaxone 1 g q12 h plus clindamycin 900 mg q8 hours for seven to ten days duration whereas subjects in group 2 received intravenously cefepime 1 g q12 h plus clindamycin 900 mg q8 hours for five to seven days. The investigator who allocated the patients to the study groups did not participate in the design of the table of random numbers nor enrolling the patients into the study. Patients were evaluated clinically and by laboratory tests at baseline (day 0) and on days 3 and 5 of admission as well as 1-2 weeks after the patient was discharged from the hospital.

For purpose of the study, patients with poststenotic pneumonia, post-infarction pneumonia, sepsis, lung cancer or metastatic cancer, renal failure, severe blood dyscrasia or those who had received antibiotic treatment within 24 h prior to their inclusion into the study were excluded. Pregnant or lactating women were also excluded.

Study outcomes

Mortality, improvement, and cure rates were evaluated as the main outcomes on days 5 and 14 after treatment. The criteria for improvement included decreasing trend of WBC and body temperature and normal breathing sound or partial resolution of radiography. The criteria for cure included partial or complete resolution of radiographic abnormalities to a range that was considered as acceptable and complete normalization of clinical signs (body temperature ≤ 37°C (axillary) and lung auscultation), laboratory parameters of infection (WBC count ≤ 10,000 cells/mm^3) and partial resolution of radiographic abnormalities without new infiltrative changes were considered as cured. Adverse drug reactions occurring during the study period were also recorded.

Data analysis

The sample size was estimated assuming a comparison of two independent proportions in a 'negative' trial (6), with an alpha error of 0.05, a 1-β of 0.95, a 20% of maximum allowable difference, and a 90% as the proportion of respondents. These assumptions provided us with an estimated sample of a minimum of 50 cases in each treatment. A x^2 test was used for comparing gender distribution and accumulated mortality rate between groups. A Student *t* test was used to test differences between groups in terms of patients' age (years) and blood pressure at discharge. The time-course of body temperature and white blood cells was compared between groups by a two-way Analysis of Variance (ANOVA). The cure/improvement rate at 5 days of treatment as well as the number of intubated subjects at days 5 and 14 of treatment were compared by means of Fisher's exact test. Odds ratio (OR) were estimated, respectively. Statistical analyses were performed by using the software StatsDirect v. 2.5.5 (StatsDirect Ltd, Cheshire, United Kingdom), and the significant limit was $p<0.05$.

Results

The two study groups, ceftriaxone/clyndamycin (n=70) and cefepime/clyndamycin (n=70) were comparable in terms of the number of male and female subjects, their age, and the number of cases intubated at the beginning of the study (Table 1). A positive microbiological blood culture was found in 13 (18.6%) and 12 (17.1%), respectively (*P*=0.8). Microbiological blood cultures were positive to *Staphylococcus aureus* coagulase + in 3 (4.3%) patients in the ceftriaxone/clyndamycin group and in 5 (7.1%) cases in cefepime/clyndamycin group (*P* = 0.49). Furthermore, a positive tracheal culture was observed in 27 (38.6%) and 29 (41.4%), respectively (*P* = 0.7). A combination of *Staphylococcus* coagulase + and *Klebsiella pneumoniae* was found in 9 (12.9%) and 10 (14.3%), respectively (*P* = 0.8).

We did not observe any statistical difference between ceftriaxone/clindamycin and cefepime/clindamycin in the improvement/ cure rate (Table 1). In addition, whereas at the beginning of the study most patients in both groups were intubated and remained intubated after 5 days of treatment, all of them had been extubated at day 14 and were being followed-up as outpatients.

Table 1. Clinical data and clinical response to therapy with either ceftriaxone/clindamicin or cefepime/clindamicin

	Ceftriaxone (n = 70)	Cefepime (n = 70)	Statistical test	*P* value
Sex (M:F)	44:26	45:25	x^2 test	0.86
Age (yr.) [mean ± SD (ranges)]	31.5 ± 15.2 (13 – 95)	32.9 ± 14.5 (13-80)	Student *t* test	0.58
Intubated patients	67 (95.7)	66 (94.2)	Fischer's exact	0.72
Drug abuser (addict to opium)	1(1.42%)	5(7.14%)		
Temperature (°C)				
On admission	38.4 ± 0.6	38.2 ± 0.6	ANOVA	0.0005; between evaluation times
Day 3	38.0 ± 0.6	37.7 ± 0.6		0.0001; between treatments
Day 5	37.7 ± 0.5	37.4 ± 0.7		0.003; for interaction
White blood cells (/mm^3)				
On admission	12,971.0 ± 5,080.1	13,888.0 ± 4,971.2	ANOVA	<0.0001; between evaluation times
Day 3	11,285.0 ± 4,284.0	11,649.1 ± 4,233.8		0.20; between treatments
Day 5	10,155.5 ± 3,235.3	10,198.3 ± 3,903.8		
Blood pressure (mmHg) at discharge				
Systolic	111.8 ± 19.5	113.8 ± 14.4	Student *t* test	0.49
Diastolic	68.6 ± 18.7	67.9 ± 1.5	*Item*	0.77
Improvement/cure rate [n (%)]				
Day 5	90.0% (n = 63/70)	88.6% (n= 62/70)	Fischer's exact	0.79; OR 1.16 (95%CI 0.38 to 3.55)
Day 14*	93.8% (n = 60/64)	90.9% (n = 50/55)	*Item*	0.58; OR 1.50 (95%CI 0.36 to 6.56)
Intubated patients [n (%)]				
Day 5	95.7% (n = 67/70)	94.2% (n= 66/70)	Fischer's exact	0.72
Day 14	None	None		
Accumulated mortality rate [n (%)]				
Day 5	8.6% (n = 6/70)	7.1% (n = 5/70)		
Day 14	8.6% (n = 6/70)	7.1% (n = 5/70)	x^2 test	0.75; OR 1.40 (95%CI 0.39 to 5.21)

* On day 14, 10 outpatients in cefepime group were lost of follow-up

In relation to the clinical response, although differences in the patients' body temperature at the different evaluation times and between treatment groups were statistically significant (P = 0.0005 and 0.0001, respectively), they were clinically irrelevant, i.e. 1°C in average (Table 1). The number of improved/cured patients was not different between groups at 5 days of treatment (OR 1.16; 95%CI 0.38 to 3.55) or at 14 days of the study (OR 1.50; 95%CI 0.36 to 6.56). The relative risk of mortality was also not different between groups (OR 1.40; 95%CI 0.39 to 5.21). Finally, no differences were noticed between treatments in terms of white blood cells and blood pressure, and no patient showed any evidence of drug adverse reaction or drug toxicity.

Discussion

Antimicrobial therapy against anaerobic microorganism is a cornerstone for treating patients with aspiration pneumonia. In our study, ceftriaxone/ clindamycin and cefepime/clindamycin were comparable in terms of efficacy and safety for treating patients with aspiration pneumonia in an overdose population of patients. Beside the distinction between aspiration pneumonitis (acute lung injury occurring after inhalation of regurgitated gastric content) and aspiration pneumonia (developed after inhalation of colonized oropharyngeal material) (1), in our study, we observed a mortality rate of 7.9% (n= 11/140) which is comparable to the 8.5% reported among overdosed cases who had aspiration pneumonitis (7). Therefore, overdosed patients with either aspiration pneumonitis or aspiration pneumonia should be considered at a high risk of progressing to severe complications and death.

A recent study investigating the penetration of cefuroxime, cefamandole, ceftriaxone, ceftazidime and cefepime into the sputum reported that only ceftriaxone had a measurable concentration in the sputum (8). In contrast, in four trials including more than 200 children with lower respiratory tract infections, cefepime was shown to be as effective, safe and well-tolerated than ceftazidime, cefotaxime or cefuroxime (9). In addition, cefepime and ceftriaxone were comparable in safety and efficacy for the treatment of adult patients with community acquired pneumonia (10). It is therefore probably that drug penetration into sputum cannot be a proper surrogated marker of clinical efficacy of antimicrobials when treating patients with aspiration pneumonia.

Since clindamycin lacks of activity against Gram-negative bacteria, its co-administration with a second- or third-generation cephalosporin has proved to be effective when treating patients with aspiration pneumonia (4). In our study, the evaluated treatment consisted of a combination of clindamycin and a third- or a fourth-generation cephalosporin (ceftriaxone and cefepime, respectively). The two antimicrobial combinations were similar in terms of efficacy and tolerance.

Different therapeutic regimens have been reported in the literature for treating patients with aspiration pneumonia including monotherapy with cefepime or ceftriaxone (5,9), ampicillin and sulbactam (4), clindamycin and a second or third-generation cephalosporin (4), and a combination of clindamycin with a fourth-generation cephalosporin (present study). In all of these studies, a good efficacy and tolerability in addition to a lack of statistical differences between the compared groups, was reported. In adherence to the proposal by Wunderink several years ago (11), we consider that there is a need for designing cost-effectiveness analysis in future studies in order to clarify the best therapeutic alternative under different perspectives and not only regarding their anticipated good efficacy.

Conclusion

Efficacy of empiric treatment of poisoned patients with aspiration pneumonia with ceftriaxone/ clindamycin was comparable to cefepime/clindamycin. Although we didn't have significant statistical analysis in comparison by these two regimens, but according to the duration of treatment, more studies are needed to clarify the cost-effectives of these therapies.

Acknowledgements

In Tehran, Iran, the study was supported by a grant from the National Research Institute Tuberculosis and Lung Diseases, and Bristol-Myers Squibb (BMS). Participation of AAN-O was without any economic or other type of relationship with BMS.

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Accepted: 4th July 2008
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