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Penambahan Ciprofloksacin Intravena terhadap Ceftriakson sebagai Terapi Antibiotik Empiris pada Pasien Pneumonia Rawat Inap: Perbandingan Biaya dan Efektivitas

ADDING INTRAVENOUS CIPROFLOXACIN INTO CEFTRIAXONE AS AN EMPIRICAL ANTIBIOTIC TREATMENT IN HOSPITALIZED PNEUMONIA: A COMPARATIVE STUDY OF COST AND EFFECTIVENESS

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Abstract

In clinical practices the aim of adding antibiotics treatment was to improve the outcomes. The objective of this study was to assess whether adding intravenous ciprofloxacin could bear more benefit despite the cost of treatment than that of intravenous ceftriaxone for hospitalized pneumonia. This retrospective study devided patients with pneumonia into two groups; first, patients received intravenous ceftriaxone therapy only (CTX group), second, patients received combination of intravenous ceftriaxone plus ciprofloxacin (CTXCP group). There were 171 patients recruited, 106 patients received CTX treatment and 65 patients received CTXCP. The data were matched between groups by age, gender, level of payment and comorbidities. The total cost of treating hospitalized pneumonia with CTXCP was higher than CTX (p=0,000). Meanwhile, the length of stay (LOS) and length of stay antbiotic related (LOSAR) were shorter in CTX group than CTXCP (11,32 vs 13,15 days, p=0,14 and 9,26 vs 12,09 days, p=0,000). Moreover, the success rate and first line clinal failure avoided (CFA) in CTX group were better than CTXCP (81,13% vs 66,15%, p=0,027 and 71,79% vs 44,62%, p=0,000). This research concluded that adding ciprofloxacin intravenous as empiric treatment of hospitalized pneumonia did not improve outcomes but significantly increased the cost of treatment.

Keywords: pneumonia, ceftriaxone, ciprofloxacin, cost, effectiveness

Abstrak

Salah satu tujuan penambahan terapi antibiotik dalam praktek klinis adalah untuk meningkatkan hasil terapi. Namun hal tersebut dapat meningkatkan biaya perawatan. Tujuan dari penelitian ini adalah untuk mengetahui apakah penambahan terapi antibiotik ciprofloksacin akan meningkatkan efektifitas meskipun menambah biaya dibandingkan dengan monoterapi ceftriakson pada pasien pneumonia rawat inap. Penelitian ini mengambil data pasien pneumonia secara retrospektif dan membaginya menjadi dua kelompok; pertama, kelompok monoterapi ceftriakson (CTX); kedua, kelompok kombinasi ciprofloksacin dan ceftriakson (CTXCP). Sejumlah 171 pasien pneumonia yang memenuhi kriteria, 106 pasien masuk kelompok CTX dan 65 pasien masuk dalam kelompok CTXCP. Kedua kelompok memiliki karakteristik yang sama dari segi jenis kelamin, usia, jenis pembayaran, dan penyakit komorbiditas. Hasil analisis menunjukkan total biaya perawatan pada kelompok CTXCP lebih tinggi dari pada kelompok CTX (Rp. 12.120.000 vs Rp. 9.020.000, p=0,000). Perbandingan efektifitas menunjukkan lama rawat inap (*length of stay*,LOS) dan lama pemberian antibiotik saat rawat inap (*length of stay antibiotic related*,LOSAR) kelompok CTX lebih pendek dibandingkan CTXCP (11,32 vs 13,15 hari, p=0,14 and 9,26 vs 12,09 hari, p=0,000). Selain itu, tingkat keberhasilan terapi dan kegagalan antibiotik pertama (*first line clinical failure avoided*,CFA) juga lebih bagus pada kelompok CTX (81,13% vs 66,15%, p=0,027 dan 71,79% vs 44,62%, p=0,000). Dari penelitian ini dapat disimpulkan bahwa penambahan terapi ciprofloksacin

sebagai terapi empiris pada pasien pneumonia rawat inap membutuhkan biaya yang lebih tinggi namun menghasilkan efektifitas yang lebih rendah dibandingkan monoterapi ceftriakson.

Kata kunci: pneumonia, ceftriakson, ciprofloksacin, biaya, efektivitas

INTRODUCTION

Pneumonia is related with high morbidity and mortality in hospitalized patients especially in low-to-middle income countries.[1,2] Pneumonia is the third cause of death after cardiovascular diseases and tuberculosis in Indonesia. The empirical antibiotics used to treat hospitalized pneumonia are diverse. The identification of leading pathogens causing pneumonia is rarely done in clinical practice. Therefore, therapy is usually based on presumptive pathogens which frequently cause pneumonia in adult patients, clinical presentation of the patient, and the epidemiology of local pathogens.[3] Adherence to antibiotic guidelines was the most cost-effective strategy for hospitalized patients who admitted to the ward.[4]

The first-line empirical treatment of pneumonia is still being debated. Antibiotic therapy is more challenging in hospitalized pnemonia. The recommendation of empiric antibiotic on hospitalized pneumonia were respiratory quinolone (such as gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin) or third generation of cephalosporins (such as ceftriaxone and cefotaxime) combined with macrolides.[5–7] Recent evidence suggests the superiority of combination therapy compared with monotherapy for subset populations, particularly patients with severe community acquired pneumonia (CAP), bacteremic pneumococcal CAP, or intubated CAP.[7] The effectiveness of the combination therapy between fluoroquinolones and beta-lactams in hospitalized pneumonia are rarely evaluated in clinical-trials research.[8] Many studies had focused on the combination of an extended-spectrum cephalosporin plus a macrolide9. Fluoroquinolone usually used alone in moderate pneumonia, especially respiratory quinolone (e.g gatifloxacin, gemifloxacin, levofloxacin, and moxifloxacin). While, the combination of a beta-lactam (e.g cephalosporin and penicilline) with old fluoroquinolone (e.g. ciprofloxacin) was recommended for pneumonia caused by Pseudomonas.[7] The effectiveness of adding ciprofloxacin as empiric treatment in hospitalized pneumonia remains unclear and can increase the cost of treatment. The objective of this study is to compare the cost and effectiveness of ceftriaxone iv monotherapy (CTX) and ceftriaxone iv plus ciprofloxacin iv (CTXCP) in hospitalized pneumonia patients.

MATERIAL AND METHODS

This research was a retrospective study. The clinical and characteristics data were derived from medical record of hospitalized pneumonia patients in the period of January- December 2012. The study was conducted in Kariadi Public Hospital in Semarang, Indonesia. Data were devided into two groups based on their empiric antibiotic treatments; first, patients received intravenous ceftriaxone therapy only (CTX group); second, patients received combination of intravenous ceftriaxone plus ciprofloxacin (CTXCP group). The characteristics data of patients includes demographic (age and gender), type of payments, accomodation type, comorbidity diseases, and discharge information. The two groups were matched by age, gender, type of payments, and co-morbidity disease. The cost of treatment was derived from payment records which include accomodation, laboratory service, medical service, drugs and medical devices, and total cost.

The inclusions criteria of this study were patients diagnosed as pneumonia, hospitalized more than three days, patients, received ceftriaxone i.v with or without combination of ciprofloxacin i.v, was older than 18 years. Patients with aspiration pneumonia, immunocompromize disease (e.g HIV or terminal cancer), with others infectious diseases were excluded from this study. The pneumonia diagnosis was stated in medical record based on physical assesment, culture of bacteria, and posteroanterior chest X-ray. BTA test

was assessed to differentiate between pneumonia and tuberculosis.

The outcome parameters of this study were LOS (*length of stay*), LOSAR (*length of stay antibiotic related*), CFA (*first line clinical failure avoided*) and *success rate.* LOS represented the total number of days in the hospital, from the day of admission to the day of discharge, while LOSAR was the total number of days patients treated with intravenous antibiotic during hospitalization. CFA *(clinical failure avoided)* was clinical failure that can be avoided because of the first antibiotic treatment. The failure of antibiotic treatment was defined if 1) the antibiotic treatment was changed or another intravenous antibiotic was added during hospitalization, 2) the antibiotic treatment were longer than fourteen days, 3) the patients was die. Success rate was defined as a sustained improvement or resolution of the signs and symptoms of pneumonia patients, such as no additional antimicrobial therapy was indicated, it was stated by clinician on the medical record, or the intravenous antibiotic was changed into oral route.

Demographic data were presented as percentage. The mean value of LOS and LOSAR between two groups were compared using Mann-Whitney Test. Kolmogorv Smirnov was used to check the data normality. The success rate and CFA were analyzed by Chi Square test. Statistical tests performed with 95% confidence level.

RESULT

Patient profile

A total 171 patients admitted with pneumonia were included in this study. 106 (61.99%) patients were grouped in CTX and 65 patients were in CTXCP group (38.01%) (Table. 1). The two goups were matched in age, gender, type of payment and co-morbidites (p>0.05). However, sepsis complications were more common in the group CTXCP than CTX group (33.83% vs 2.38%, p = 0.044). The room type of accomodation also differed between two groups (p>0,011). CTXCP group mostly treated in a higher class than the CTX group.

The study showed that the patients were dominated by male (94.74%) rather than women. The average age of patients with hospitalized pneumonia was 56 years old with the highest percentage of aged> 40 years (84.80%). Most of the patients were covered by health insurance (56.14%) for the payments and treated in the third class ward (73.68%). The most common comorbid disease was cardiovascular disease (56.73%) (Table 1).

Cost comparations

Costs in this study was counted from direct medical costs only, while indirect costs were not included in the analysis. This study classified the cost into; cost of antibiotics, cost of accommodation, cost of laboratory tests, cost of ward, cost of drugs and medical devices, and the total cost. The cost of antibiotics in this study included parenteral and oral antibiotics, for topical antibiotics were not included in the cost components. Addition or replacement of antibiotics due to the failure of empirical therapy were also included in the cost components of antibiotics. Cost of clinical pathology and microbiology laboratory test in CTXCP group was significantly higher than CTX group (p <0.05). The study showed that the total cost of pneumonia treatment was lower in CTX group than CTXCP group. However, there was no significant differences in antibiotic cost between CTX group and CTXCP (Table 2).

Effectiveness comparations

The data showed the mean value of LOS in CTX group was shorter than CTXCP group (11.32 ± 3.69 vs 13.15 ± 4.49 days, p = 0.014). LOSAR was calculated from the length of intravenous antibiotic therapy during the hospitalization. The mean value of LOSAR in CTXCP group longer than in the CTX group (12.09 ± 4.40 vs 9.26 ± 3.52, p = 0.000).The result showed the mean of LOSAR was shorter than the value of LOS (Table 3). The results showed the proportion of CFA in CTXCP group lower than CTX group (44.62% vs 71.70%), as well as the success rate in CTX was higher than in CTXCP (Table 3).

Table 1. Characteristic and Demographic Among Hospitalized Pneumonia

Characteristics	Total (n = 171)	CTX (n = 106)	CTXCP (n = 65)	*P value
Gender				0.303
Female	9 (5.26)	4 (3.78)	5 (7.69)	
Male	162(94.74)	102 (96.22)	60 (92.31)	
Age (years, mean ± SD)		56.11±13.77	56.00±14.24	0.840
18-40	26 (15.20)	16 (15.09)	10 (15.38)	
40-60	76 (44.440	46 (43.40)	30 (46.15)	
60-80	64 (37.43)	42 (39.62)	22 (33.85)	
>80	5 (2.92)	2 (1.89)	3 (4.62)	
Type of payment				0.814
Askes	38 (22.22)	24 (22.64)	14 (21.54)	
Jamkesda	24 (14.04)	13 (12.26)	11 (16.92)	
Jamkesmas	96 (56.14)	60 (56.60)	36 (55.38)	
Private	13 (7.60)	9 (8.49)	4 (6.15)	
Room classification				0.011*
Class 1	19 (11.11)	8 (7.55)	11(16.92)	
Class 2	26 (15.20)	22 (20.75)	4 (6.15)	
Class 3	126 (73.68)	76 (71.70)	50 (76.92)	
Co-morbidities				
Cardiovascular	97 (56.73)	59 (55.66)	38 (58.46)	0.720
Diabetes mellitus	33 (19.30)	21 (19.81)	12 (18.46)	0.828
Renal impairment	25 (14.62)	13 (12.26)	12 (18.46)	0.266
Liver disease	16 (9.36)	9 (8.49)	7 (10.77)	0.619
Neoplasma	17 (9.94)	13 (12.26)	4 (6.15)	0.195
Other lung disease	42 (24.56)	25 (23.58)	17 (26.15)	0.705
Sepsis complication	25 (14.62)	3 (2.83)	22 (33.85)	0.044*

Description: if not otherwise stated, the data depicted in n (%) = number patients (percentage)
* *p* value obtained from chi square test for categorical and ordinal data types, and unpaired t test for numerical data, significant if the *p* value <0.05

DISCUSSION

The study showed that the two groups had the same criterias except sepsis complication and class of treatment. Room classification affected the cost of accomodation and the choice of branded antibiotics, while complication of sepsis implicated the severity of pneumonia disease between groups. The patients were dominated by male rather than female. Male sex is an independent factor which significantly increases the risk of pneumonia. Men are more susceptible to pneumonia due to high risk of smoking, which is higher in male.[10] Most of the patients were aged > 40 years old. Age is a risk factor for pneumonia, especially in very young age (<2 years) or very old age (> 65 years).[11] Recently, prevalence of pneumonia disease in elderly increase while the elderly population is increasing. Pneumonia morbidity and mortality rates also increased in elderly patients, especially with co-morbidities.[10]

Most of the patients were covered by insurance and treated in the third class ward. Most hospitalized pneumonia patients in this

hospital were belong to Jamkesda insurance from the government which guarantees care for third class only. Otherwise, patients with private health insurance mostly distributed in first and second class. Class treatments will affect the total cost of treatments.

Cardiovascular disease was the most frequent comorbid diseases encountered in this study. Comorbid diseases that usually affect the outcome of pneumonia treatment are cancer, diabetes, chronic obstructive pulmonary disease (COPD), asthma, and cardiovascular.[12] Chronic Heart Disease (CHD), liver disease, and cancer proven to be significantly increase the risk of pneumonia.[10]

The study showed no significant differences in antibiotic cost between CTX and CTXCP group. The define-daily dose cost of intravenous ciprofloxacin in Indonesia was 9-10 times higher than ceftriaxone. Hospitalized pneumonia were admitted to change from intravenous to oral antibiotics if there were improvement of clinical condition and able to tolerate oral therapy.[13] Cost of clinical pathology laboratory and clinical microbiology in CTXCP group was higher than CTX. It may caused by higher sepsis complications in CTXCP groups, thus required more monitoring and more routine laboratory inspection. After all, the total cost of pneumonia treatment was lower in CTX group than CTXCP groups (Table 2).

The data showed the mean value of LOS in CTX group was lower than CTXCP group. LOS of pneumonia is affected by some factors, which are intubation, emergence of abscess, bacterial pneumonia, pleural effusion, and chronic heart failure.[12] In CTXCP group, there were more cardiovascular diseases than CTX (Table 1). LOSAR was calculated from the length of intravenous antibiotic therapy during the hospitalization. LOSAR is widely used as an outcome of antibiotic therapy because it is more specific than LOS.[14,15] The result showed the mean of LOSAR is shorter than the value of LOS (Table 3).

CFA is used as one of the outcome parameters of antibiotic therapy in pneumonia.[16] The results showed the proportion of CFA in CTXCP group lower than CTX group (Table 3). Some factors that lead the failure of therapy were the increase of antibiotic resistance, children aged <2 years, elderly age> 65 years, patients receiving beta-lactam 3 months earlier, alcoholism, immunocomprimize patients due to disease or treatment.[7]

From the results can be concluded that the addition of intravenous ciprofloxacin as empirical antibiotic therapy in hospitalized pneumonia did not shorten the LOS and LOSAR and neither increase success rate and CFA. Old fluoroquinolones, such as ciprofloxacin, has good penetration on the tissue, thus it is widely used in treatment of respiratory infections.[17] As the resistance of ciprofloxacin increase, it should be avoided in less severe pneumonia, because its activities are less adequate against *S. pneumoniae*, and can lead to another fluoroquinolones resistance.[18] Resistance of ciprofloxacin against *S. pneumoniae* are more prevalent, so the Infectious Disease Society of America (IDSA) recommends respiratory fluoroquinolone for the treatment of pneumonia.[19] Ciprofloxacin in elderly is recommended only for pneumonia caused by *Pseudomonas* aeruginosa with duration of therapy of 15 days 18. Using fluoroquinolone repeatedly in outpatient therapy also increases the resistance of pneumonia.[7] The combination therapy between aminoglycoside and fluoroquinolone did not differ significantly in terms of mortality when compared with beta-lactam monotherapy as empirical or definitive therapy in patients with infection P.aeroginosa.[20]

CONCLUSION

From the study, it can be concluded that adding intravenous ciprofloxacin as empiric treatment of hospitalized pneumonia did not improve outcomes but significantly increase the cost of treatment.

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Table 2. Comparation of Cost Theraphy Between Groups

Type of Payment	Total (x 1000 rupiah)	%	CTX (x 1000 rupiah)	CTXCP (x 1000 rupiah)	*P value**
Accommodation and Consulting	1950.86±1702.62	21.6	1631.11±1204.09	2472.31±2208.20	0.004*
Laboratory					
Diagnostic	251.43±322.33		288.54±383.03	190.96±176.47	0.702
Clinical Pathology	2036.16±2148.84		1626.29±1765.2	2704.57±2533.91	0.000*
Clinical Microbiology	398.94±377.49		315.60±229.14	498.36±507.70	0.000*
Anatomical Pathology	371.56±156.48		374.26±177.37	363.00±112.76	0.129
Radiodiagnostic	580.36±740.90		631.59±868.30	495.88±459.71	0.529
Total cost of laboratory	3103.38±2447.51	34.4	2695.47±2165.56	3768.59±2737.29	0.001*
Medical Care					
Services geriatrics	175.00±66.58		177.69±65.25	171.82±68.97	0.399
Cardiac care	1818.14±3277.68		1125.20±967.59	2900.86±5183.99	0.930
Hemodialysis	2460.00±439.08		1950.00±189.40	2587.50±663.90	0.048
medical action	748.26±1657.97		742.39±1923.5	757.45±1108.98	0.001*
medical rehabilitation	154.53±95.24		150.96±93.21	159.96±99.11	0.691
medical equipment	656.68±748,40		401.67±347.47	867.97±1099.60	0.000*
Services of medical devices	556.07±508.73		501.72±472.93	630.18±548.18	0.023*
Total cost of services	1995.77±4298.62	22.1	1534.8±2347.5	2717.02±6257.86	0.005*
Drugs and Medical Devices	1963.50±3219.14	21.8	1253.0±2120.8	3100.2±4222.6	0.000*
Antibiotic					
ceftriaxone	56.93±25.44		53.76±22.14	62.11±29.46	0.049
ciprofloxacin	314.28±210.36		0	314.17±235.34	0.000*
other parenteral antibiotics	1024.36±667.49		709.15±477.34	1252.01±875.88	0.006*
oral antibiotics	4.88±3.38		5.74±3.66	3.79±2.94	0.679
Total cost of antibiotics	551.56±1401.79	6.1	231.72±950.93	1073.15±1813.91	0.000*
Total cost	9020.01±9050.14	100	7038.6±4977.7	12120±12672	0.000*

Description: Data expressed in mean ± Standard deviation, calculated the cost per patient per hospitalization
* *p value* obtained from unpaired t test if normally distributed data, and Mann Whitney test if data is not normally distributed. *p value* significant if <0.05.

Table 3. Comparation of Outcome Theraphy Between Groups

Effectiveness	CTX	CTXCP	*P value*
LOS (days)	11.32±3.69	13.15±4.49	0.014*
LOSAR (days)	9.26±3.52	12.09±4.40	0.000*
Success rate (n, %)	86 (81.13)	43 (66.15)	0.027*
CFA (n,%)	76 (71.70)	29 (44.62)	0.000*

*value p obtained from the chi-square test for categorical data and Mann Whitney test for numerical data. p value significant if <0.05.

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