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Comparative Effectiveness Study of Chloramphenicol and Ceftriaxone in the Treatment of Typhoid Fever in Children Admitted to Putri Hijau Kesdam I/Bb Hospital Medan

Eva Sartika Dasopang[1*], Fenny Hasanah[1], Teddy Kurniawan Bakri[2], Muktia Isma[1]

[1]Pharmacy Department, Faculty of Pharmacy, Tjut Nyak Dhien University of Medan, Medan, Indonesia; [2]Pharmacy Departement, Faculty of Pharmacy, Tjut Nyak Dhien University of Medan, Medan, Indonesia

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Keywords: Chloramphenicol; Ceftriaxone; Typhoid Fever; Cost Effectiveness

***Correspondence:** Eva Sartika Dasopang. Pharmacy Department, Faculty of Pharmacy, Tjut Nyak Dhien University of Medan, Medan, Indonesia. E-mail: evasartikadasopang@utnd.ac.id

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Abstract

BACKGROUND: Typhoid fever is a disease caused by Salmonella typhi bacteria, especially attacking the digestive tract. Chloramphenicol is the main drug of choice for the treatment of typhoid fever. But along with the advancement of the medical field, other medicines were developed. Ceftriaxone is an effective drug for the treatment of typhoid fever in the short term. But the price of ceftriaxone is more expensive.

AIM: The aim of this study was comparative effectiveness study of Chloramphenicol and Ceftriaxone in the treatment of typhoid fever in children admitted to Putri Hijau Kesdam I/BB Hospital Medan

METHODS: This study was conducted cross-sectionally about the treatment of typhoid fever in children who were hospitalized at TK II PutriHijau Hospital Kesdam I/BB Medan. the patient used cloramfenikol antibiotics in 13 patients and used ceftriaxone in 17 patients. Patient age ranges from 0-19 years. Antibiotic analysis is the best effectiveness using the ACER method.

RESULTS: He results of the patient characteristics show that the children of patients who suffer from typhoid fever, the highest age is 12-16 years (50%), by gender male 60% and female 40%. Patients hospitalized using chloramfenicol averaged 6.53 days (7 days) while ceftriaxon averaged 4.17 days. The average number of direct medical costs in pediatric patients suffering from typhoid fever using cloramfenikol was 3,212,776/patient while ceftriaxon 1,967,045/patient. Cost effectiveness analysis using ACER method obtained results for cloramenicenicol at 492.002/day and ceftriaxon 471,713/day

CONCLUSION: Ceftriaxone has a better treatment effectiveness compared to chloramphenicol in typhoid fever patients in children.

Introduction

Typhoid fever is an infectious disease caused by the bacterium *Salmonella typhi*. This disease is transmitted through the consumption of food or beverages contaminated by feces or urine of the infected person [1]. The characteristics of typhoid fever that continues to increase every day with a fever temperature of 38-40°C accompanied by headaches, nausea, and loss of appetite [2].

In the world, there are an estimated 16 million cases of typhoid fever every year, and cause 600,000 deaths, especially in developing countries. In developing countries typhoid fever is a public health problem, where typhoid fever is widely transmitted through water and sanitation [1]. For decades, chloramphenicol has become a drug of choice in the treatment of typhoid fever where chloramphenicol is very effective against Salmonella typhi, but with the discovery of multi drug resistance (MDR) *Salmonella typhi* in treatment using chloramphenicol [3]. In the research that was conducted by Wasfy et al., where many cephalosporin generation drugs were examined. Ceftriaxone is considered an effective drug in the treatment of typhoid fever.

Ceftriaxone is considered an effective drug in the treatment of short-term typhoid fever. The beneficial properties of this drug are that it can selectively damage the structure of germs and not interfere with the cells of the human body, has a broad

spectrum, quite good tissue penetration, bacterial resistance is still limited. But the price of Ceftriaxone drugs is more expensive [4].

Pharmacoeconomics is a description and analysis of the cost of therapy for a drug in the public health care system. Pharmacoeconomics goal is to influence policy makers and in decision making in a treatment intervention [5]. Information from the cost effectiveness analysis method (CEA) is needed to find out how much the cost of treatment for typhoid fever using the drug chloramphenicol and ceftriaxone.

Cost effectiveness analysis (CEA) is an economic evaluation method that can be used for decision making in choosing the best alternative from several alternatives. Cost effectiveness analysis is usually used to assess several alternatives whose goals or outcomes are the same. Effectiveness is measured in external units such as the number of patients recovering, the number of actions, and deaths that can be prevented [6].

Information from the cost effectiveness analysis method (CEA) is needed to find out how much the cost of treatment for typhoid fever using the drug chloramphenicol and ceftriaxone.

Material and Methods

The research methodology used in this study is a cross-sectional method. The scope of this study was typhoid fever patients of children using chloramphenicol and ceftriaxone who were hospitalized in Putri Hijau KESDAM I/BB Medan for the period January-December 2017. The number of samples included in the inclusion criteria was 30 patients. The calculation of costs was viewed from the direct medical costs incurred during hospitalization.

Data was obtained from the medical records of patients with typhoid fever of children from January to December 2017. Patients with typhoid fever who are given antibiotic treatment with chloramphenicol or ceftriaxone. Information on the value of the cost of medical services directly obtained in hospital Putri Hijau KESDAM I/BB Medan. Information on drug costs is taken from the List of Drug Prices at the Putri Hijau Pharmacy Installation in KESDAM I/BB Medan. The data were analyzed using SPSS 20.0 the presence or absence of differences in treatment effectiveness and cost effectiveness in the treatment of typhoid fever between chloramphenicol and ceftriaxone. Medical costs are directly calculated using the ACER method (Average Cost Effectiveness Ratio).

Results

Characteristics of Patients at Putri Hijau Hospital KESDAM I/BB Medan Period January-December 2017 are shown in Table 1.

Table 1: Characteristics of Patients at Putri Hijau Hospital KESDAM I/BB Medan Period January-December 2017

Information	Total (N = 30)	Percentage (%)
Age		
0-5 years (toddler)	1	3.3%
5-11 years (childhood)	7	23.3%
12-16 years (early adolescence)	15	50.0%
17-25 years (late adolescence)	7	23.3%
Gender		
Male	18	60.0%
Female	12	40.0%
Length of stay		
3-4 days	11	36.7%
5-6 days	13	43.3%
> 7 days	6	20%

Table 2 shoe the treatment characteristics of patients children typhoid fever at Putri Hijau Hospital KESDAM I/BB Medan in the period January-December 2017.

Table 2: Treatment Characteristics of Patients Children Typhoid Fever at Putri Hijau Hospital KESDAM I/BB Medan Period January-December 2017

Therapy	Drugs	Total (N = 30)	Percentace (%)
Antibiotic	Chloramphenicol	13	43.3%
	Ceftriaxone	17	56.7%
Electrolyte solution	Infus Ringer Laktat	30	100.0%
Gastrointestinal tract	Ranitidine	10	27.8%
	Omeprazole	16	44.4%
	Antasida Doen	1	2.8%
Antihistamines	Cetrizine	1	3.3%
	Tremenza	1	3.3%
Cough medicine	Ambroxol syrup	2	6.7%
	OBH syrup	1	3.3%
	Lasal Expectorant syr	1	3.3%
Diarrhea Medication	Neo Diafrom	3	10.0%
Antipyretic	Paracetamol Tablet	18	60.0%
	Paracetamol Syrup	6	20.0%
Analgetic	Inj. Novalgin	7	23.3%
Multivitamin	Neurodex Tablet	6	20.0%
Anti Emetica	Domperidon Tablet	5	16.7%
	Inj.Ondancentron	6	20.0%

Comparison of the duration of treatment in patients with typhoid fever for children using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for the period January-December 2017 is shown in Table 3.

Table 3: Comparison of the duration of treatment in patients with typhoid fever for children using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for the period January-December 2017

Chloramphenicol		Ceftriaxone	
Gender	length of stay (Day)	Gender	length of stay (Day)
Male	7	Male	4
Male	7	Female	5
Female	6	Female	3
Male	8	Male	3
Male	6	Male	5
Male	7	Male	5
Female	7	Female	4
Male	6	Male	4
Male	6	Female	4
Female	6	Female	5
Male	7	Male	5
Male	6	Male	3
Male	6	Female	4
		Male	4
		Female	5
		Female	4
		Male	4
Total	85	Total	71
Rate	6.53	Rate	4.17

Comparison of body temperature reduction in Typhoid Fever Patients of Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for Period January-December 2017 is shown in Table 4.

Table 4: Comparison of body temperature reduction in Typhoid Fever Patients of Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for Period January-December 2017

Chloramphenicol		Ceftriaxone	
Gender	Body Temperature redution (Day)	Gender	Body Temperature redution (Day)
Male	3	Male	2
Male	3	Female	3
Female	3	Female	2
Male	4	Male	2
Male	3	Male	3
Male	3	Male	3
Female	4	Female	2
Male	3	Male	2
Male	4	Female	2
Female	4	Female	3
Male	4	Male	3
Male	4	Male	2
Male	4	Female	2
		Male	2
		Female	2
		Female	2
		Male	2
Total	46	Total	39
Rate	3.5	Rate	2.3

We can see the comparison of the accompanying symptoms in patients with typhoid fever for children using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital in KESDAM I/BB Medan for the period January-December 2017 in Table 5.

Table 5: Comparison of the accompanying symptoms in patients with typhoid fever for children using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital in KESDAM I/BB Medan for the period January-December 2017

Chloramphenicol		Ceftriaxone	
Gender	Symptoms are reduced (Days to)	Gender	Symptoms are reduced (Days to)
Male	7	Male	4
Male	7	Female	5
Female	6	Female	3
Male	8	Male	3
Male	6	Male	5
Female	7	Male	5
Female	7	Female	4
Male	6	Male	4
Male	6	Female	4
Female	6	Female	5
Male	7	Male	5
Male	6	Male	3
Male	6	Female	4
		Male	4
		Female	5
		Female	4
		Male	4
Total	85	Total	71
Rate	6.53	Rate	4.17

Comparison of Inpatient Costs for Patients with Typhoid Fever Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/Medan BB Period January-December 2017 is shown in Table 6.

Table 6: Comparison of Inpatient Costs for Patients with Typhoid Fever Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/Medan BB Period January-December 2017

Chloramphenicol		Ceftriaxone	
Gender	Cost of Hospitalization (RP)	Gender	Cost of Hospitalization (RP)
Male	2.800.000	Male	1.600.000
Male	2.800.000	Female	2.000.000
Female	2.400.000	Female	1.200.000
Male	3.200.000	Male	1.200.000
Male	2.400.000	Male	2.000.000
Male	2.800.000	Male	2.000.000
Female	2.800.000	Female	1.600.000
Male	2.400.000	Male	1.600.000
Male	2.400.000	Female	1.600.000
Female	2.400.000	Female	2.000.000
Male	2.800.000	Male	2.000.000
Male	2.400.000	Male	1.200.000
Male	2.400.000	Female	1.600.000
		Male	1.600.000
		Female	2.000.000
		Female	1.600.000
		Male	1.600.000
Total	34.000.000	Total	28.400.000
Rate	2.615.384	Rate	1.670.588

Comparison of Drug Costs in Patients with Typhoid Fever in Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for Period January-December 2017 is shown in Table 7.

Table 7: Comparison of Drug Costs in Patients with Typhoid Fever in Children Using Chloramphenicol and Ceftriaxone at Putri Hijau Hospital KESDAM I/BB Medan for Period January-December 2017

Chloramphenicol		Ceftriaxone	
Gender	Drug Costs (RP)	Gender	Drug Costs (RP)
Male	625,479	Male	242,532
Male	583,559	Female	266,415
Female	599,507	Female	164,169
Male	428,124	Male	167,409
Male	901,822	Male	313,185
Male	586,800	Male	299,565
Female	582,838	Female	211,764
Male	852,089	Male	221,664
Male	494,802	Female	278,268
Female	499,140	Female	387,754
Male	629,133	Male	461,250
Male	444,618	Male	270,201
Male	538,182	Female	298,024
		Male	279,036
		Female	463,704
		Female	372,811
		Male	341,988
Total	7,766,093	Total	5,039,775
Rate	597,391	Rate	296,457

We can see the average cost of inpatient and drug costs in patients with typhoid fever in children using chloramphenicol and ceftriaxone in Putri Hijau Hospital KESDAM I/BB Medan for the period January-December 2017 in Table 8.

Table 8: Average Cost of Inpatient and Drug Costs in Patients with Typhoid Fever in Children Using Chloramphenicol and Ceftriaxone in Putri Hijau Hospital KESDAM I/BB Medan for Period January-December 2017

Chloramphenicol	Ceftriaxone
The average cost of hospitalization + drug costs in patients Rp.3,212,776/patient	The average cost of hospitalization + drug costs in patients Rp.1,967,045/patient

ACER Calculation Results for Patients with Typhoid Fever Children Using Chloramphenicol and Ceftriaxone in the Putri Hijau Hospital KESDAM I/Medan BB Period January-December 2017 is shown in Table 9.

Table 9: ACER Calculation Results for Patients with Typhoid Fever Children Using Chloramphenicol and Ceftriaxone in the Putri Hijau Hospital KESDAM I/Medan BB Period January-December 2017

Cost Item	Chloramphenicol	Ceftriaxone
Rate costs	Rp 3,212,776	Rp 1,967,045
The average patient is hospitalized	6.53 day	4.17 day
ACER (B/E)	Rp.492,002.50/day	Rp.471,713.56/day

Discussion

Typhoid fever is a disease that is closely related to environmental sanitation. Based on data obtained from 30 pediatric patients diagnosed with typhoid fever can be seen that many children at the age of 12-16 years suffer from typhoid fever 50% compared to children aged 0-5 years, 5-11 years, and 17-25 years. At the age of 12-16 years is the age of school children who have a lot of activity, and lack of attention to cleanliness. Children at school age are at the highest risk of developing Salmonella infection because the immune system is not perfect so bacteria enter the body and develop [7]. The gender of male typhoid fever of children as much as 60% of people and in female as much as 40%. Men suffering typhoid fever more than women because it is associated with male activities that are often outside the home so that the men to be infected with Salmonella more often than women [7].

Typhoid fever in children often causes patients to be treated in hospitals. The long treated in typhoid fever is the highest 5-6 days (43.3%). Patients admitted to hospital because fever typhoid range 7-14 days to reach level of healing.

In this study patients using ceftriaxone more from chloramphenicol. Ceftriaxone is considered an effective antibiotic for the treatment of typhoid fever short term. Ceftriaxone selectively can damage the structure of the germ that can kill *Salmonella typhi*, has a board spectrum, not to interfere with human body cells, germ resistance is limited and there are no harmful side effects when given to children [8], [9].

Typhoid fever often occurs on an ineffecient provision of electrolytes so that the grant should be also given intravenous fluids. In typhoid fever patients must get enough fluids, both orally and parenterally. Parenteral fluid is indicated in patients with severe pain and a decrease in consciousness and difficulty eating. Administering intravenous fluids in accordance with the guideline for the management of typoid fever [10].

Typhoid fever disease is often accompanied by other symptoms such as abdominal pain, headaches, nausea, vomiting, diarrhea, muscle pain. Symptom the most common follow up is a disorder on digestion so the use of omeprazole drug most often given [11]. Granting of proton pump inhibitor in this case omeprazole fairly safe provided in children to overcome the symptoms of digestive disorders that often follow the typhoid fever [12].

The success of the treatment can be seen from the length of patient stay hospitalized, temperature changes, disappearance of fever and reduced symptoms that follow due to the typhoid fever [11]. In this study the effectiveness of treatment was assessed based on the comparison of length of treatment, disappearance of fever and reduced symptoms that follow due to the typhoid fever between typhoid fever in children patients using Chloramphenicol and those taking Ceftriaxone. The average length of stay in typhoid fever in children using Chloramphenicol is 6.53 days and the average length of stay in typhoid fever patients using Ceftriaxone is 4.17 days. This shows that patients taking ceftriaxone have a faster treatment time than patients who use chloramphenicol. This is accordance with the research done Lili in Fatmawati Hospital Jakarta where typoid fever children patients given ceftriaxone average admitted 4.408 days [11].

Calculated the average disappearance in children patients using chloramphenicol with patients taking ceftriaxone. Then the data obtained for body temperature drop using chloramphenicol on average 3.5 days and on average using ceftriaxone at 2.3 days. This shows that typhoid fever patients who use ceftriaxone have fever faster than chloramphenicol. These data coresspond to the research done at Fatmawati hospital explained that the disappearance of fever in patients using ceftriaxone thypoid fever children with an average 3.449 days [11]. Research conducted by Susatyo stating the same thing that the treatment of children typhoid fever using Ceftriaxone 3.3 days while Chloramphenicol 5.8 days [13]. Chloramphenicol is an effective drug in the treatment of typhoid fever. But Choramphenicol is not effective in killing germs. Therefore, ceftriaxone is an effective drug in the treatment of typhoid fever in the short term [14].

Direct medical costs can be seen based on the comparison of the total cost of hospitalization between typhoid fever patients using chloramphenicol and ceftriaxone. The average cost of hospitalization for patients using cholaramphenicol is Rp.2,615,384/patient and the average cost of hospitalization in patients using ceftriaxone is Rp.1,670,588/patient. Drug costs in patients using chloramphenicol are more expensive than patients who use ceftriaxone. This happens because patients who use chloramphenicol are treated longer than patients who use ceftriaxone. So that typhoid fever patients who use chloramphenicol have to pay more than patients who use ceftriaxone. Rani 2018 do research on cost effectiveness analysis of ceftriaxone and non-ceftriaxone on typhoid fever patients get the same result that patients using ceftriaxone average hospitalization cost lower compared non ceftriaxone [15]. The average cost of drugs in patients using

cholaramphenicol is Rp.597,391.76/patient and the average cost of the drug in patients using ceftriaxone is Rp.296,457.35/patient. This shows that the cost of drugs in patients using chloramphenicol is more expensive than patients who use ceftriaxone. This happens because patients who use chloramphenicol are treated longer than patients who use ceftriaxone. So that typhoid fever patients who use chloramphenicol have to pay more than patients who use ceftriaxone.

The average cost of hospitalization + drug costs in patients using cholaramphenicol is equal to Rp 3,212,776/patient and the average cost of hospitalization + drug costs in patients using ceftriaxone is Rp 1,967,045/patient.

In the assessment of cost effectiveness analysis can use analysis with the ACER method. ACER is a cost needed to increase the effectiveness of each treatment [16]. The treatment chosen is the lowest effective cost. ACER value from chloramphenicol therapy is Rp.492,002/day while ceftriaxone therapy is Rp.471,713/day. In patients using chloramphenicol, patients must spend Rp.492,002/day and in patients using ceftriaxone, patients have to pay Rp.471,713/day to get treatment effectiveness.

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