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Cefotaxime vs ceftriaxone for the prolongation of latency period in preterm premature rupture of membranes

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Abstract

Introduction: Antibiotics are recommended as the main therapy for preterm premature rupture of membranes (PPROM). But the research on antibiotics other than the recommended macrolides regimens is still lacking. This research aims to evaluate whether there are effects differences of cefotaxime and ceftriaxone given on pregnancy with PPROM by comparing the duration of the latency period and the infants outcomes.

Material and Methods: Data was taken through medical records retrospectively at Dr. Soetomo Surabaya General Hospital, Indonesia, during the period of January-December 2017. The inclusion criteria were a history of PPROM in pregnancy <37 weeks, given cefotaxime or ceftriaxone therapy, and have labor data. The analysis was performed by the Mann-Whitney comparison test for the latency period and Fisher's exact test for infant outcomes.

Results: There were 52 samples obtained. The antibiotics used were cefotaxime 3 grams once and ceftriaxone 2 grams once. The results of the analysis showed that there were no significant differences between the types of antibiotics with the length of the latency period, with a value of $p = 0.601$ ($p>0.05$), where cefotaxime had a median of 52,67 hours and ceftriaxone was 34,17 hours. Cefotaxime was found to be more able to extend the latency period for >48 hours with a percentage of 57.8%, whereas in ceftriaxone only 42.9%. There are no significant differences in infant outcomes; infant birth weight and Apgar score among the two therapies used.

Conclusion: Cefotaxime was more preferably to be used in the Dr. Soetomo Surabaya General Hospital. Although there are no diffe-

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rences in infant outcomes between the two antibiotics, cefotaxime appears to be more able to extend the latency period for more than 48 hours which gives better prospects for fetal lung maturation. Both cefotaxime and ceftriaxone have succeeded in preventing infections in women with PPROM.

Keywords
PPROM; Antibiotic; Cefotaxime; Ceftriaxone; Cephalosporin; Latency Period.

Introduction

Premature rupture of membranes (PROM) is the rupture of the membranes before the onset of labor. In many cases, this happens in term pregnancy, but when the rupture of membranes occurs before 37 weeks gestation, this is known as a preterm PROM (PPROM) [1, 2]. PPROM complicates about 3 percent of pregnancies and leads to one-third of preterm births. This increases the risk of prematurity and leads to some other perinatal and neonatal complications, including 1 to 2 percent risk of fetal death [1].

The incidence of PPROM is not only a problem when it causes preterm labor. Women with prolonged PPROM are at higher risk for developing chorioamnionitis, which can be obtained from an increase in bacterial colonization before membrane rupture (causing PPROM) or after membrane rupture (PPROM complications) [3, 4]. The risk of infection increases with the decreasing gestational age when membrane rupture and the increasing duration of the ruptured membrane [3].

The use of antibiotics in women with PPROM has been shown to increase the latency period, which is defined as the period between ruptured membranes and onset of labor [5-8]. There is high-quality evidence that antibiotics for PPROM can reduce the risk of complications due to prematurity and the risk of maternal and neonatal infection [7, 9]. This means that antibiotics can be used at the same time to prevent the occurrence of infections and help maintain pregnancy in the PPROM to the maximum possible time or prevent preterm labor. Erythromycin is the first line choice antibiotic used for PPROM worldwide, but the recommendation was made conditional and there is no consensus regarding the best choice to this day. Cephalosporin group is another non-famous therapeutic option. Some study has already suggested that amoxicillin, 3rd generation cephalosporins, and erythromycin in the association erythromycin-amoxicillin can be used and have been shown to improve neonatal outcome [10, 11]. But the research on cephalosporin and its regimen as a PPROM therapy is still lacking.

Therefore, this study aims to evaluate whether there are effects differences between the new alternative cephalosporin antibiotics used in Dr. Soetomo Surabaya General Hospital for PPROM; cefotaxime and ceftriaxone by comparing the duration of the latency period and the infant outcomes.

Methods

Study Design and Ethics

This analytic study with a cross-sectional design took place from September 2018 - June 2019. This research was reviewed by the Health Research Ethics Committee of Dr. Soetomo Surabaya General

Hospital and has been declared "Eligible of Ethics" with certificate number 0648/KEPK/Ix/2018 on September 21st, 2018. Maternal informed consent was obtained through the help of ethics committee. We used secondary data in the form of medical records taken from the Central Medical Record and VK IRD in Dr. Soetomo Surabaya General Hospital. The population of this study was all pregnant women diagnosed with preterm premature rupture of membrane (PPROM) in Dr. Soetomo Surabaya General Hospital for January-December 2017 period. The diagnosis criteria for PPROM is the rupture of membranes without the begin of initial labor signs after 1 hour later. We used the 2017 data because that is the latest medical records which are complete for a year.

Statistical Analysis

Samples were obtained using a total sampling technique so that all parts of the population that met the inclusion criteria were taken. The inclusion criteria for this study sample are history of PPROM in pregnancies <37 weeks, given cefotaxime or ceftriaxone therapy, having delivery data, and medical records in good and complete condition. Whereas the exclusion criteria are patients who did not deliver at the Dr. Soetomo Surabaya General Hospital and medical records that are damaged and difficult to read. The independent variable in this study is the antibiotic used in pregnant women with PPROM in Dr. Soetomo Surabaya General Hospital. While the dependent variable is the length of the latent period and the outcome in infants. The time of antibiotic administration cannot be a control variable because antibiotics were given in different time frames after the rupture of membranes. These differences occur because Dr. Soetomo is a tertiary hospital so some patients came after being referred. It also depends on the time when patients decide to go to the hospital after the rupture of membranes.

The collected data was analyzed by computerization with the Statistical Package for Social Sciences (SPSS) software. Data is presented in the form of frequency distribution tables and described in narrative form. Analysis of the two variables that are thought to have a relationship is done through the Mann-Whitney and Fisher's exact statistical tests that illustrate the comparison of influences between variables.

The Mann-Whitney test was conducted to determine whether there were differences in the effect of antibiotic therapy between groups used on the latency period. At first, a chi-square test was performed to determine whether there are differences in infant outcomes between the types of antibiotics used. After the test is done, it was found that there were > 20% of tables that have an expected value of less than 5. Therefore, the p-value seen is the p-value of Fisher's exact test.

Results

Demographic Data

A total of 242 patients with history of PPROM were found in the medical records of Dr. Soetomo Surabaya General Hospital during the period of January – December 2017. Out of the total, there were only 123 patients who gave birth in Dr. Soetomo Surabaya General Hospital. Among them, there were only 52 patients who met the inclusion criteria.

In general, pregnant women with a history of PPROM are mostly in the age group of 20-35 years, which is as much as 61.5%. It is more common in multigravida women, with a percentage of 48.3%. Most PPROM occurred in the 24-31 week gestational age group, which was 40.4% and the least frequency at gestational age <24 weeks as much as 3.8%. There were 54% of samples with an estimated birth weight (EBW) ≥ 1500 grams when PPROM occurs and 46% with EBW <1500 grams.

There were 76.9% of samples that gave birth through vaginal delivery and 23.1% through cesa-

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rean section. About 51.9% of the labor happens after being induced or terminated and 48.1% occur spontaneously. There were 36.7% of babies born with low birth weight (LBW), 28.6% with very low birth weight (VLBW), 22.4% with normal weight, and 12.2% with extremely low birth weight (ELBW). The majority of the 1st minute Apgar score was low (<7) with the percentage of 55.3%, but 59.6% of the 5th minute Apgar score was more than 7. Approximately 5.8% baby died within the first 24 hours after labor. Also, we found that 100% of women with PPROM didn't suffer any infection after the rupture of membranes.

Table 1 shows the demographic data based on each antibiotic therapy used. Some of the data like the gestational age might be a moderator or intervening variable, which is a variable that can affect the dependent variable in this study or the latency period.

Antibiotic use

It was found that there were no other antibiotics used for PPROM patients at Dr. Soetomo Surabaya General Hospital apart from cefotaxime or ceftriaxone. There were only two regimens found to be used, which are cefotaxime given at a dose of 3 grams once and ceftriaxone given at a dose of 2 grams once dissolved in a 100cc intravenous NaCl 0,9% (normal saline/PZ) infusion.

The latency period consists of the time between the rupture of membranes (ROM) and antibiotic administration and the time from antibiotic administration until labor. Instead of using mean, the median was used to represent data broadly in this study because of the non-normal distribution. **Figure 1** shows that the length between the ROM and antibiotic administration was shorter and the time until labor was longer in the cefotaxime group. It can be interpreted that antibiotic was administrated sooner in the cefotaxime group and the latency period in the cefotaxime group involved more antibiotics than in the ceftriaxone group.

Table 1. Demographic data.

Demographic Data	Cefotaxime	Ceftriaxone
	n = 45 (%)	n = 7 (%)
Age		
<20 years	15.6	0
20-35 years	57.8	85.7
>35 years	26.7	14.3
Primigravida	46.3	14.3
Multigravida	53.7	85.7
Gestational Age		
<24 weeks	4.4	0
24-31 weeks	37.8	57.1
32-33 weeks	20	0
34-36 weeks	37.8	42.9
Estimated Birth Weight (EBW)		
<1500 grams	41.9	71.4
≥1500 grams	58.1	28.6
Mode of Delivery		
Pervaginam	73.3	100
Sectio caesarea	26.7	0
Terminated	53.3	42.9
Spontaneous	46.7	57.1
Infant Birth Weight		
≥2500 grams (Normal)	21.4	28.6
1500-2499 grams (LBW)	40.5	14.3
1000-1499 grams (VLBW)	28.6	28.6
<1000 grams (ELBW)	9.5	28.6
1st minute Apgar Score		
7-10	45	42.9
4-6	17.5	28.6
0-3	37.5	28.6
5th minutes Apgar Score		
7-10	62.5	42.9
4-6	12.5	28.6
0-3	25	28.6
Infant Condition		
Survive	93.3	100
Death within 24 hours	6.7	0

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Figure 1: Time Mapping between The Ruptures of Membranes (ROM), Antibiotic Administration, and Labor

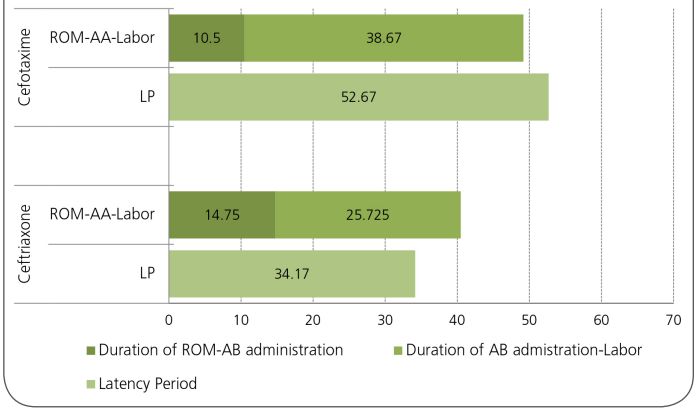

Figure 2: Percentage of Latency Period Length

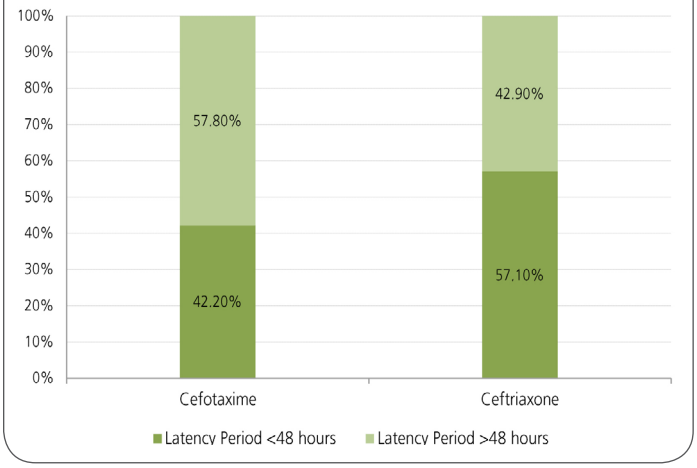

Table 2. Latency period based on gestational age and Mann-Whitney test.

Gestational Age	Median of Latency Period (hours)						*P value*
	Cefotaxime			Ceftriaxone			
Weeks	Median	Min	Max	Med	Min	Max	
<24	35,92	17,83	54	there are no samples in			0.601
24-31	74,17	7,3	200,5	127,48	34,17	193,18	
32-33	64,08	19,75	320,5	there are no samples in			
34-36	33,67	8,28	85,58	26,45	24,78	29,37	
Total	52,67	7,3	320,5	34,17	24,78	193,18	

Table 3. Infant outcomes.

Infant Outcomes	Cefotaxime		Ceftriaxone		*P value*
	N	%	N	%	
	Mean	Notes	Mean	Notes	
Birth Weight (grams)	1821,43	LBW	1471,43	VLBW	0.339
APGAR Score 1st minutes	5	Moderately depressed	5	Moderately depressed	0.711
APGAR Score 5th minutes	6	Moderately depressed	6	Moderately depressed	0.131

It was found that there were 57,8% of cefotaxime group samples which have latency period of >48 hours, whereas in ceftriaxone there were only 42,9% **(Figure 2)**

Analysis Results

The Mann-Whitney test shown a P-value of 0.601 (p >0.05), which means that there were no statistical differences. The duration of the latency period was illustrated through the median because of the non-normal distribution. If seen as a whole regardless of a certain gestational age group, the median latency period of cefotaxime group is 52 hours and 40 minutes and ceftriaxone group is 34 hours and 10 minutes. In **Table 2 & 3** there are no differences in all aspect of infant outcomes between the two antibiotics.

Discussion

The most frequently used antibiotic is cefotaxime 3 grams once given until labor. This therapeutic choi-

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ce does not match the recommendations of Indonesian Association for Obstetrics and Gynaecology (POGI) (2016) and WHO (2015), which states that erythromycin is the first choice for prophylaxis after PPROM. The difference in this use of antibiotics can be due to the administration of antibiotics adjusted to their susceptibility to the bacteria that cause infection. In the previous research, cephalosporin as first-line therapy for the care of mothers and newborns in PPROM is indicated because of the high susceptibility of *Escherichia coli* to antibiotics [12]. *Escherichia coli* was one of the most common microorganism isolated from women with PPROM along with *Staphylococcus* or *Streptococcus* species [14-16]. In addition, the most common bacteria which cause urinary tract infection (UTI) is *Escherichia coli*, where UTI is one of the causes of preterm labor in PPROM [17, 18].

The cephalosporins are divided into 3 generations according to their spectrum of activity, where activity against gram-negative bacilli increases from first- to third-generation drugs [19, 20]. Third-generation cephalosporins are preferred in many clinical situations because of their proven record of clinical efficacy, favorable pharmacokinetics and low frequency of adverse effect [21]. Cefotaxime, ceftriaxone and other cephalosporins are safe to be used during pregnancy and considered as category B by FDA [22]. Cefotaxime was found to have the best gram-positive coverage of the 3rd generation agents, but ceftriaxone was as safe and as effective as cefotaxime in treating serious bacterial infections [21, 23-25]. A study conducted in Malang, East Java, Indonesia showed that cefotaxime generally was more cost-effective than ceftriaxone which made cefotaxime more preferable [26].

It was found that cefotaxime group was able to extend the latent period longer, with a median of approximately 2 days and maximum 13 days. As seen in **Figure 1**, antibiotic in the cefotaxime group was used more effectively since the sooner administration of antibiotic after ROM occurred was associated with a better outcome [7]. Also, as seen in **Figure 2**, the median and the majority of latency period in the cefotaxime group was more than 48 hours, where 48 is the time required until the corticosteroid given has worked to stimulate pulmonary maturation [27]. This result can be caused by the majority of pregnant women treated with cefotaxime being in the 24-31 week gestational age group whereas those treated with ceftriaxone didn't have any sample in that age group as shown in Table 1 and 2. According to Melamed *et al*. [8], the duration of the latency period ranges between 0 and 59 days and is inversely proportional to the gestational age at admission. Women with a short latent period (<48 hours) are characterized by a higher rate of cervical dilatation and a higher gestational age at entry and are more likely to be nulliparous [8]. However, no other studies are comparing these 2 antibiotic regimens.

A study that also compared the latency period between antibiotics from the cephalosporin group by Fortunato *et al*. [28], stated that there was no difference in the latency period between patients treated with ceftizoxime and those given other antibiotic therapy (cefoxitin, cefazolin, ampicillin). Other studies by Lee *et al*. [29], stated that a new combination of antibiotics consisting of ceftriaxone, clarithromycin, and metronidazole was able to extend the latency period longer with a median value of 23 days, compared to the therapeutic regimen of ampicillin and/or cephalosporin alone which had a median value of 12 days.

Another comparison to be considered is the worldwide recommended erythromycin which is still recommended because there have been many studies on its effectiveness for PPROM [30]. According to WHO (2015), the choice of erythromycin was based on the findings of ORACLE I study with over 2000 women, which showed that erythromycin decreases the risk of necrotizing enterocolitis (NEC) in the newborn compared to co-amoxiclav [7]. Another study that supports the use of erythromycin sta-

ted that erythromycin was found to be associated with a decrease in the primary composite outcome (neonatal death, chronic lung disease or major cerebral abnormality on ultrasound; p = 0.08) and in single adverse neonatal outcomes (p = 0.02) when compared to placebo [31]. However, a recent study mentioned that erythromycin alone is insufficient to control the growth of Gram-positive and Gram-negative bacteria in patients with PPROM [15]. In particular, *Escherichia coli* and group B *Streptococcus* isolates showed high rates of resistance to erythromycin [15, 32].

Seelbach-Goebel [33], summarized the results of the ORACLE I trials which state that 60.9% of pregnant women given erythromycin 4x/day orally give birth within 7 days after the rupture of membranes. There were no differences in latency to delivery, incidence of chorioamnionitis, or neonatal outcomes when erythromycin was compared with other drugs from one class of macrolides, azithromycin [34, 35]. The latency period after erythromycin administration was 65,6 hours and azithromycin 61,7 hours [36].

Other regimens, amoxicillin/clavulanic acid 325 mg 4×/day orally or erythromycin 250 mg + amoxicillin/clavulanic acid 325 mg, which all mentioned in ORACLE I trial were also associated with a significantly lower rate of deliveries within 48 hours compared to placebo [33]. But a fourfold higher rate of NEC was found in both groups treated with amoxicillin/clavulanic acid [33].

Several protocols recommend other different choices of antibiotic. Some Latin American countries recommend the use of ampicillin or amoxicillin [12]. Those antibiotics also showed a significant increase in the latency period and a lower incidence of clinical amnionitis [12, 37]. But the use of ampicillin and amoxicillin was related to adverse symptoms, such as nausea, vomiting and abdominal pain [37, 38]. Thus, amoxicillin and ampicillin are often replaced by a cephalosporin in clinical practice [38].

Based on the infant outcomes, both antibiotic groups have the same low birth weight output, even though cefotaxime group has a slightly higher value. In the Fisher's exact test, p-value in lower case = 0.339 was obtained, which means there was no difference in birth weight of babies between antibiotic therapy A and B. In accordance with the ORACLE Trial I study conducted between 1994 and 2000, the use of antibiotics was not directly related to birth weight [30, 33]. But a randomized controlled trial using oral ampicillin 1 g (n = 59) vs placebo (n = 51), showed that the mean birth weight was significantly higher in those received ampicillin (2885 vs. 2336 g; $P < 0.05$) [39].

The Apgar score provides an accepted and convenient method for reporting the status of the newborn infant immediately after birth and the response to resuscitation if needed [40]. The average Apgar score both in the first minute and the fifth minute were identical between the two groups. In line with the Fisher's exact test which showed that there were no differences in the Apgar score between the two types of antibiotics used. The Apgar score is influenced by the length of the latency period. Salan [41], found that there was a correlation between the length of the latency period and the infant Apgar results with $P < 0.001$ and the Odds ratio was 8.5, which means that the length of the latent period affected the infant Apgar score with an 8.5-fold increased risk.

Conclusion

Based on this study, the most commonly used therapeutic regimen is cefotaxime 3 grams once given until labor. No differences were found in latency period and infant outcomes in terms of birth weight and Apgar scores between the use of cefotaxime and ceftriaxone. But cefotaxime appears to be more able to extend the latency period for more than 48 hours which gives better prospects for fetal lung maturation and more cost-effective than ceftriaxo-

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ne. There was no incidence of infection after the rupture of membranes with the use of these two antibiotics, which mean that cephalosporin has succeeded in preventing infections in women with PPROM. This research, however, is subject to several limitations since the sample of the ceftriaxone group was small.

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