AMPICILLIN-GENTAMYCIN WERE EQUIVALENT TO CEFOTAXIME-GENTAMYCIN THERAPY OUTCOME ON NEONATAL SEPSIS IN RURAL AREA OF WEST BORNEO

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ABSTRACT

The limited facilities in rural areas, such as Ketapang, make it hard for clinicians in charge to provide the most effective treatment while also considering preventing irrational antibiotic usage at once for neonatal sepsis. This study aimed to compare the length of stay of neonatal sepsis patients given Ampicillin-Gentamycin and Cefotaxime-Gentamycin as empiric antibiotic therapy. This was a retrospective observational study of patients admitted to Fatima Hospital, Ketapang, West Borneo, from June 2020-June, to 2021, with neonatal sepsis diagnosis based on the clinical presentation and routine blood lab. Slovin formula was used to determine the minimum sample size. Data were analyzed using Mann-Whitney Test. From 105 samples collected, the most common symptoms of neonatal sepsis found were fever (32.4%), vomitus (29.5%), and breathing difficulty (26.7%). Routine blood lab mostly showed leukocytosis with a mean of 28.369, and the mean length of hospitalization in patients given the Ampicillin-Gentamycin combination was 6.35 days. In comparison, the Cefotaxime-Gentamycin combination was 4.68 days. There was an insignificant difference in hospitalization between the two groups (p=0.274). Therefore, administration of Ampicillin-Gentamycin as empiric therapy in neonatal sepsis showed a good outcome as with Cefotaxime-Gentamycin therapy.

Keywords: Ampicillin; Antibiotic; Cefotaxime; Neonatal sepsis

INTRODUCTION

Sepsis is declared one of WHO's health priorities because of its burden and high mortality rate in certain age groups, especially neonates.[1] Sepsis is third of the most common causes of neonatal mortality in developing countries, with gram-negative bacteria as the primary pathogen. The neonatal death rate in these countries is 34 deaths per 1000 live births.[2] Neonatal sepsis is a clinical syndrome in neonates aged less than 28 days and marked with systemic infections and bacteremia. Based on the onset, neonatal sepsis is divided into early-onset if the onset is fewer than 72 hours after birth and late-onset if it occurs more than 72 hours after birth.[3]

Neonatal sepsis progresses rapidly with the tendency to cause multiorgan dysfunctions; hence early administration of antibiotics one hour after diagnosis plays the most crucial role in the therapy. Any delay in administering the antibiotic would cause a significant worsening of the neonates' mortality and morbidity, eventually causing longer hospital length of stay and an increase in hospitalization cost.[4,5] Ideally, blood culture is the gold standard for pathogen identification and antibiotics sensitivity test in treating neonatal sepsis.[6] Still, it takes days and is not always available in smaller health facilities, especially the ones in rural areas. Therefore, neonatal sepsis is diagnosed based on clinical presentation, perinatal risk factors, and simple-inexpensive supporting exam, which also applies in Fatima Hospital, Ketapang, West Borneo.

Ideally, antibiotics administration should be based on the local antibiotic sensitivity pattern, including Group B Streptococcus,

Escherichia coli, and other Gram-negative bacteria.[7,8] Almost every guideline suggests using beta-lactam (i.e., Penicillin, Cephalosporin, Monobactam, and Carbapenem) and aminoglycoside (i.e., Gentamycin) in combination as the initial empiric therapy for every suspicion of early-onset neonatal sepsis.[5,7–9] Most of these guidelines suggest administering Ampicillin and Gentamycin combination as the first line, then readjusting the therapy based on the following sensitivity analysis of the blood culture (Most clinicians add Vancomycin, Cefotaxime, or Penicillin).[10] In developing countries, almost 70% of pathogens isolated from neonatal sepsis cases showed resistance to first-line antibiotics.[11] Therefore, the Neonatal Intensive Care Unit (NICU) in some medical facilities uses Cephalosporins as the initial therapy in neonatal sepsis, considering such a resistance pattern toward ampicillin.[12,13] But unfortunately, the overuse of Cephalosporins as the first-line therapy could lead to higher antibiotic resistance.[9] This study aimed to compare the outcome of Ampicillin-Gentamycin and Cefotaxime-Gentamycin as empiric therapy administered on clinically diagnosed neonatal sepsis patients in a limited medical setting based on the differences in length of hospitalization.

MATERIAL AND METHODS

Fatima Hospital, Ketapang, West Kalimantan (INT.5/188/DIR/IV/2022), approved the collection of medical records for this study and analysis. Records were collected from neonates born in Fatima Hospital between June 1, 2020, and June 30, 2021, with ICD X code P36 (newborn sepsis). Data on the neonates' demographics, amniotic fluid color, length of hospitalization, and the empiric antibiotics administered in the first 24 hours after birth were collected. Empiric antibiotics are defined as the combination of the antibiotics given in the first 48 hours when neonatal sepsis is diagnosed, regardless of any therapeutical changes in later days of hospitalization. Antibiotic combinations were Ampicillin-Gentamycin or Cefotaxime-Gentamycin. Hospital length of stay (LOS) was counted from the date of patient's admission up to the patient's dismissal date based on clinical improvement judged by the pediatrician in charge.

Diagnosis of neonatal sepsis was established based on the patient's clinical presentation supported by available blood laboratory work based on WHO 2016 criteria of neonatal sepsis[14]; there are two clinical signs and two laboratory findings showing infection. The clinical sign could be temperature instability (>38.5ºC or <36ºC), cardiovascular disturbance (bradycardia or tachycardia), skin rash (petechial rash, sclerema), respiratory instability (apnea, tachypnea, hypoxia), gastrointestinal symptoms (vomitus, feeding intolerance), general symptoms (irritability, lethargy, hypotonia). On laboratory work, there could be found White Blood Count <40.00x10^9 cell/L or >20.000x10^9 cell/L, Thrombocyte Count <100.000 x10^9 cell/L, Glucose intolerance on two measurements showed <45 mg/dl or >190 mg/dl. This study did not include CRP, I/T ratio, and metabolic acidosis due to our hospital's limitation of such facilities or human resources.

Based on Slovin Formula, the minimum sample size needed was 105 out of 142 neonatal sepsis cases in the study period. Inclusion criteria for EOS were neonates with symptoms and signs suggestive of sepsis within 72 hours after birth in Fatima Hospital, Ketapang, West Borneo. The exclusion criteria used were neonates with a major congenital abnormality. Data distribution checked Kolmogorov Smirnov Test, and it was abnormal. Hence, the hypothetical test was done using the Mann-Whitney Test on SPSS software.

RESULT

The most clinical presentations from the collected samples were fever, vomitus, breathing difficulty, and jaundice (Figure 1). Routine blood lab mostly showed leukocytosis with a mean of 28.369+9.227.

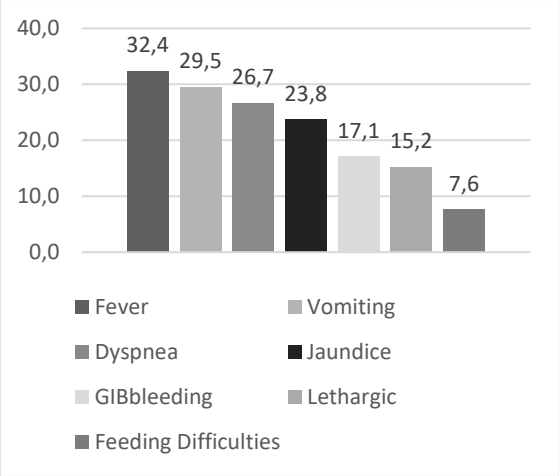

Figure 1. Percentage of Clinical Presentations

Table 1. Routine Blood Laboratory Results

Laboratorium Variables	Mean±SD
Hemoglobin	17.59±5.7
Leukocyte	28.369±9.227
Trombocyte	302.500±104.000
Blood Glucose	76.17±29.1

The characteristics of neonates groups given Ampicillin-Gentamycin and Cefotaxime-Gentamycin are shown in Table 2. Both groups showed that most of the samples taken were from term gestation age with a birth weight of >2500 grams. This study showed that neonatal sepsis occurred more frequently in Caesarean Section delivery than in those from vaginal birth. Rupture of Membrane (ROM) >18 hours found on most samples in both groups. There was an insignificant difference in the hospitalization in both groups (p=0.274).

Table 2. Sample Characteristics

Variables	Ampicillin-Gentamycin (n=46)	Cefotaxime-Gentamycin (n=59)
Gestation age		
<37 weeks	8	7
>37 weeks	38	52
Birth weight		
<2000 g	5	2
2000-2499 g	10	7
>2500 g	31	50
Delivery		
SC	27	36
PV	19	23
Green amniotic fluid		
Yes	13	11
No	33	48
ROM		
<18 hours	20	20
>18 hours	26	39

Table 3. Bivariate Analysis Results

Variables	LOS		p
	Mean±SD	Median	
Ampicillin-Gentamycin	6.35±6.95	4	0.274
Cefotaxime-Gentamycin	4.68±4.94	3	

DISCUSSION

EOS could happen due to maternal transmission, during the labor process, or during the perinatal period. There were no specific clinical symptoms in neonatal sepsis. Still, the risk factors of infection such as maternal fever (>38.0°C), preterm delivery (<37 weeks), ROM >18 hours, chorioamnionitis, maternal streptococcal infection, and inadequate antibiotic prophylaxis should be counted in addition to such clinical symptoms and be put into consideration to start the empiric antibiotics as soon as possible. Some clinical signs could be apnea, seizures, need for ventilation

assistance, signs of shock, altered behavior, hypotonia, feeding difficulties or intolerance (vomiting, excessive gastric aspirates, abdominal distention), hypothermia, tachycardia/bradycardia, respiratory distress, jaundice < 24 hours of birth, neonatal encephalopathy, unexplained excessive bleeding, thrombocytopenia, metabolic acidosis, or altered glucose homeostasis.[8] The risk factors found in this study were the ROM for more than 18 hours and clinical findings of fever, breathing difficulty, and feeding intolerance such as vomitus. Vital signs and laboratory changes can occur in neonates as part of a systemic inflammatory response to sepsis. Immune cells release cytokines and other inflammatory mediators activating the autonomic nervous system after hematogenous pathogen invasion, manifesting as changes in body temperature, respiratory drive, and changes in heart rate characteristics.[15]

The approach used in neonatal sepsis management includes infection control and prevention, early disease detection, evaluation, and administration of empiric antibiotics. The first line of antibiotics therapy was supposed to be administered within 1 hour after neonatal sepsis was diagnosed, in 24 hours after the patient's admission.[14] Study shows that therapy with antibiotics combination is superior to monotherapy, with Ampicillin and Aminoglycosides (i.e., Gentamycin) as the preferred initial therapy based on American Academy of Pediatrics (AAP) and WHO recommendation for the developing countries.[14,16] The use of such a combination was suggested since the pathogens found on EOS mostly originated from a maternal birth passage or amniotic fluid, which were dominated by gram-positive bacteria such as Group B Streptococcus and E Coli.[16] Ampicillin is a beta-lactam antibiotic with bactericidal action, which can be administered peroral or parenteral that actively kills both gram-positive and gram-negative bacteria by disrupting the biosynthesis of the cell wall that leads to the bacterial autolysis.[17]

Cephalosporins could be used as beta-lactams alternative. Studies in some countries stated the administration of the third generation of Cephalosporins directly as the empiric therapy when there was any suspicion of Ampicillin resistance.[18] A study done in the Neonatology Unit of RSUP H. Adam Malik from January 2008-December 2010 showed that the most common pathogen found in neonatal sepsis were gram-negative bacteria, such as Staphylococcus sp, Pseudomonas sp, and Enterobacter sp. These bacteria have higher resistance toward Ampicillin and Gentamycin compared to cefotaxime.[19] Cefotaxime is one of the third generations of Cephalosporins. Specifically, cefotaxime has the highest stability against β-lactamase, both penicillinase and cephalosporinase produced by these bacteria. Moreover, cefotaxime can pass through the cerebrospinal fluid; hence it could fight better against the gram-positive bacteria compared to the other third-generation Cephalosporins.

This study found the mean patient's hospital length of stay with Ampicillin-Gentamycin therapy was 6.35 days (±6.955 SD, median of four days), while the ones with Cefotaxime-Gentamycin therapy were 4.68 days (±4.964 SD, median three days). There was no statistically significant difference between these two groups' hospital length of stay based on the Mann-Whitney Test ($p=0.274$). Previous studies found high resistance in gram-negative bacteria towards Penicillin (78%) and high sensitivity towards Cephalosporins (96%),[18] but the development of cephalosporins resistance may occur when cefotaxime is routinely used for early-onset neonatal sepsis. Prolonged use of 3rd-generation cephalosporin, in general, has shown to be an independent risk factor for worse neonatal outcomes, and previous antibiotic exposure to a 3rd-generation cephalosporin was associated with the development of multidrug-resistant Gram-negative bacteremia.[20] The insignificant difference in this study suggests that Ampicillin-Gentamycin combination therapy should still be preferred as the first line of empirical treatment for neonatal sepsis.

Besides, the use of ampicillin could lower the risk of the emergence of further bacterial resistance.[18]

The study is not without limitations. First, it is a retrospective study with a broad data distribution; thus, the generalizability of our findings should be considered and may be limited only to settings similar to ours. Second, the diagnosis of sepsis was clinical, based on signs and symptoms due to our limitation of sophisticated supporting exams. Blood culture must be considered in determining the pathogen pattern causing EOS, even in rural settings. Therefore, antibiotics administration could be done with the most compatible sensitivity.

CONCLUSION

The administration of Ampicillin-Gentamycin as empiric therapy in neonatal sepsis showed a good outcome as ones with Cefotaxime-Gentamycin therapy.

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