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Original Article

Antibiotics on incidence of infection in neonates with meconium-stained amniotic fluid

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Abstract

Background The effectiveness of antibiotics for preventing infection in neonates with meconium-stained amniotic fluid (MSAF) remains unclear. Not all neonates with MSAF develop meconium aspiration syndrome (MAS) or neonatal infection. Furthermore, neonatal infection diagnosis may be difficult due to lack of symptoms. As such, clinical manifestations, laboratory results, and infection markers are important for diagnosis.

Objective To evaluate antibiotic use on the incidence of infection in neonates with MSAF.

Methods This double-blind randomized controlled clinical trial was performed at Dr. Kariadi Hospital, Semarang, Indonesia from October 2009 to March 2010. Subjects were newborns with MSAF who were diagnosed by two observers (Kappa test intraobserver agreement was 0.74) and with feces metabolites found in their amniotic fluid. Sixty-nine newborns were divided into groups I and II, comprised of 35 and 34 subjects, respectively. Group I subjects (control group) were not given antibiotics, while group II subjects (treatment group) were given combination antibiotics of ampicillin (50 mg/kg BW) and gentamicin (8 mg/kg BW), as single doses. Neonatal infection diagnosis was based on clinical manifestations, laboratory results (leucocyte count, blood culture, and I : T ratio), and the following infection markers: procalcitonin (PCT), interleukin-6 (IL-6), tumor necrosis tumor-α (TNF-α), and C-reactive protein (CRP). Chi-square and Fischer's exact tests were used for statistical analyses.

Results We found no significant differences in the incidence of neonatal infection between those who received and those who did not receive antibiotics, based on clinical manifestations, the first and second examination of laboratory marker (P=0.53), examinations of CRP, IL-6, TNF-α, and PCT either as single markers or combinations of 2, 3, or 4 markers (P> 0.05), as well as mortality rate (P=0.30).

Conclusion There is no significant difference in the incidence of infection in neonates with MSAF who received prophylactic antibiotics compared to those who did not receive antibiotics. **[Paediatr Indones. 2013;53:50-5.]**

Keywords: *meconium-stained amniotic fluid, antibiotic, neonatal infection markers*

Meconium-stained amniotic fluid (MSAF) is a natural phenomenon occurring in pregnant mothers and their fetuses. The presence of MSAF may lead to meconium aspiration syndrome (MAS), asphyxia, and neonatal infection. Newborns with MSAF are generally managed with resuscitation, antibiotics, and nursing cares. Resuscitation and breastfeeding are considered to be standard cares, but the effectiveness of antibiotics remains unclear. Recent revisions in resuscitation

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guidance for newborns with MSAF by the American Heart Association (AHA) and the American Academic of Pediatrics (AAP) recommend waiting until the newborn has been completely delivered, then assessing the child's vigor. Mucus suction for non-vigorous infants is done by laryngoscopy and an endotracheal tube.[1] A multicenter study reports that intratracheal suctioning of apparently vigorous meconium-stained infants did not result in decreased incidence of respiratory distress, compared with expectant management. They observed the complication rate of intubation to be relatively low and complications to be minor and transient in nature. They recommend that endotracheal intubation and suctioning should be performed in non-vigorous infants with MSAF, or if they need positive pressure ventilation, as well as if they develop symptoms of respiratory distress subsequent to initial assessment.[2]

The incidence of MSAF and neonatal morbidity is higher in the presence of acute inflammation of placental membranes. The presence of meconium in the amniotic fluid should alert the physician to the potential for infection and increased neonatal morbidity.[3] Approximately 13% of all live births are complicated by MSAF. Fortunately, only 5% of neonates born through MSAF develop MAS,[1,2] an estimated 25,000 to 30,000 cases and 1000 deaths related.[4]

Diagnosing neonatal infection is difficult due to the lack of symptoms, making clinical manifestations and laboratory findings important. Several infection markers may be used, such as CRP, IL-6, TNF-α, and PCT.[5-7]

The effectiveness of antibiotics for preventing infection in neonates with MSAF has been investigated with various results.[8] Antibiotics may cause anaphylaxis, lead to bacterial resistance and have other negative effects. Excessive use of antibiotics may lead to nephrotoxicity, hearing disturbances, and resistance to particular pathogens.[9,10]

Some hospital guidelines recommend intravenous antibiotics (penicillin and gentamicin) after consultation with a clinical microbiologist.[11] The Newborn Services Clinical Guideline recommends antibiotics for non-vigorous newborns with MSAF, those with persistent symptoms of MAS, and those with other risk factors for infection. Blood cultures should be performed in these cases.[12]

A study concludes that holding antibiotic treatment at the onset of infection could be fatal and is not recommended, but the concomitant use of IL-6 and CRP or TNF-α should allow antimicrobial treatment to be discontinued at 48 hours without waiting for microbiological results, provided that the infants are in good clinical condition.[13]

In Indonesia, perceptions differ on the necessity of antibiotics for newborns with MSAF. Health providers generally give antibiotics to newborns with MSAF. The discrepancy occurred in referral hospital or perinatology unit centre between giving or not giving.[14,15]

The objective of this study was to evaluate the effect of antibiotics on the incidence of neonatal infection in neonates with MSAF.

Methods

Subjects were neonates with MSAF who were admitted to Dr. Kariadi Hospital from October 2009 to March 2010, had birth weight of 2500–4000 grams, and had no clinical symptoms of sepsis at the time of enrollment, congenital malformations, premature maternal rupture of membranes (PROM), antenatal maternal infection, or cephalic presentation, and were delivered vaginally or by caesarian section, but not due to prolonged birth or birth dystocia. Subjects were recruited by consecutive sampling. Diagnoses of MSAF were determined by two clinicians (Kappa test intraobserver agreement 0.74) and amniotic fluid contained one fecal metabolite**.** Study design was double-blind, randomized, controlled trial. Randomization by block allocation was done by pharmacy staff. Group I (control group) did not receive antibiotics, while group II (experimental group) received 50 mg/kg BW ampicillin and 8 mg/kg BW gentamicin in a single dose. Both groups were given standard management. Examination done firstly as the subject dicided to be the subject usually at birth and secondly on day 3-5. The incidence of neonatal infection was made by clinical manifestations, laboratory findings (leucocyte count, blood culture and I : T ratio), and infection markers including PCT, IL-6, TNF-α, and CRP, singly or combined as 2, 3, or 4 markers. Previously determined cut off points for the infection markers were as follows: CRP > 10 mg/L, PCT >1 ng/mL, IL-6 > 44.4 pg/m, and TNF-α > 41 pg/m.[16-18] Chi-

square test and Fischer's exact test were used for statistical analyses.

Results

Subjects were 69 neonates consisting of 35 subjects in group I and 34 subjects in group II. Subjects' characteristics were recorded, including birth weight, birth length, gestational period, and type of delivery **(Table 1)**.

There was no significant difference in mean birth weight, gestational period and type of delivery between the two groups, as well as on mean length at birth.

Neonatal infection diagnoses were based on clinical manifestations, laboratory findings and infection markers. **Table 2** shows that the incidence of neonatal infection based on clinical manifestations and laboratory findings was not significantly different between groups I and II (P=0.53), with similar proportion in incidence, 8/35 and 10/35, respectively.

Single infection marker examinations were used to confirm the diagnosis of neonatal infection as shown in **Table 3**. There was no significant differences in the percentage of single positive infection markers between the groups in either the first or second examination.

Examinations of 2 marker-combination were done and the results are shown in **Table 4**.

Examinations of 3 marker-combination were done concurrently to confirm neonatal infection, as shown in **Table 5**. There was no significant differences in the incidence of neonatal infections between the two groups in the first and second examinations.

We also performed a 4 marker-combination examination in order to confirm the incidence of neonatal infection, as shown in **Table 6**. The incidence of neonatal infection between the two groups based on the combination of 4 markers (CRP, IL-6, TNF-α, and PCT) was not significantly different in the first exam (P=0.746), nor in the second exam (P=0.169).

Subjects' mortality is shown in **Table 7**. At the time of hospital discharge, the number of survivors was not significantly different in the two groups (P=0.300). Neonatal death occurred in 4 cases, 1 from group I and 3 from group II. Meconium aspiration syndrome was suspected as the cause of death in 2 cases, 1 in group I and 1 in Group II.

Table 1. Subjects characteristics

Characteristics	Group I n=35	Group II n=34
Mean birth weight (SD), gram	2900 (572.32)	3000 (522.80)
Mean length at birth (SD), cm	48 (1.80)	49 (2.09)
Sex, n		
Male	16	22
Female	19	12
Gestasional age, n		
> 41 weeks	9	10
37- 41 weeks	26	24
Type of delivery, n		
Vaginal delivery	11	10
Caesarean section	24	24
Apgar score 5th minute, n		
7-10	29	25
< 7	6	9

*T-test

Table 2. Incidence of neonatal infection based on clinical manifestations and laboratory findings

Incidence of neonatal infection	Group I n=35	Group II n=34	P value
Infection (+)	8	10	0.530**
Infection (-)	27	24	

**Chi-square test

Table 3. The incidence of infection based on single marker examinations between groups in the two examinations.

Markers	Group I 1st exam		Group II 1st exam		P value	Group I 2nd exam		Group II 2nd exam		P value
	Infection (+)		Infection (+)			Infection (+)		Infection (+)		
CRP, n (%)	1	(3)	1	(3)	0.746*	1	(3)	4	(12)	0.170**
IL-6, n (%)	14	(40)	21	(62)	0.070**	12	(34)	13	(38)	0.730**
TNF–α, n (%)	1	(3)	1	(3)	0.746*	2	(6)	7	(21)	0.070**
PCT, n (%)	12	(34)	11	(32)	0.870**	11	(46)	16	(47)	0.180**

*Fischer's exact test; **Chi-square test

Table 4. The incidence of infection based on 2 marker-combination examinations between the two groups in the first and second examinations

Markers	Group I 1st exam		Group II 1st exam		P value	Group I 2nd exam		Group II 2nd exam		P value
	Infection (+)		Infection (+)			Infection (+)		Infection (+)		
CRP and IL-6, n (%)	1	(3)	1	(3)	0.746*	1	(3)	4	(12)	0.170*
CRP and TNF-α, n (%)	1	(3)	1	(3)	0.746*	1	(3)	4	(12)	0.169
CRP and PCT, n (%)	1	(3)	1	(3)	0.746*	1	(3)	4	(12)	0.169
IL-6 and TNF-α, n (%)	1	(3)	1	(3)	0.746*	1	(3)	7	(21)	0.020*
IL-6 and PCT, n (%)	8	(23)	10	(29)	0.530**	4	(11)	10	(29)	0.060*
TNF-α and PCT, n (%)	1	(3)	1	(3)	0.746*	1	(3)	6	(18)	0.049*

*Fischer's exact test; **Chi-square test

Table 5. The incidence of infection based on combined 3 markers examination between the two groups in the first and second examinations

Markers	Group I 1st exam	Group II 1st exam	P value	Group I 2nd exam	Group II 2nd exam	P value
	Infection (+)	Infection (+)		Infection (+)	Infection (+)	
CRP, IL-6 and TNF-α, n (%)	1 (3)	1 (3)	0.746*	1 (3)	1 (3)	0.746*
CRP, IL-6 and PCT, n (%)	1 (3)	1 (3)	0.746*	1 (3)	4 (12)	0.169*
CRP, TNF-α and PCT, n (%)	1 (3)	1 (3)	0.746*	1 (3)	4 (12)	0.169*
IL-6, TNF-α and PCT, n (%)	1 (3)	1 (3)	0.746*	1 (3)	5 (15)	0.090*

*Fischer's exact test

Table 6. The incidence of infection based on a 4 marker-combination between the two groups in the first and second examinations

Markers	Group I 1st exam	Group II 1st exam	P value	Group I 2nd exam	Group II 2nd exam	P value
	Infection (+)	Infection (+)		Infection (+)	Infection (+)	
CRP, IL-6, TNF-α and PCT, n (%)	1 (3)	1 (3)	0.746	1 (3)	4 (11)	0.169*

* Fischer's exact test

Table 7. Survival in the two groups

Condition	Group I	Group II	P value
Died, n (%)	1 (3)	3 (9)	0.300*
Survived, n (%)	34 (97)	31 (91)	

*Fischer's exact test

Discussion

The objective of this study was to evaluate the effect of antibiotics on the incidence of infection in neonates with MSAF. We found no significant difference in the incidence of infection in neonates who received antibiotics compared to those who did not receive antibiotics. We observed that neonates who did not receive antibiotics were not more likely to develop an infection, based on clinical criteria and laboratory findings. Using clinical manifestations, laboratory findings, and the results of two examinations of 4 infection markers (PCT, IL-6, TNF-α, and CRP), we found that the use of antibiotics did not make a significant difference in infection incidence. Besides, the number of survivors were similar in the two groups.

Diagnostic markers are valuable as indicators of neonatal infection. Serial measurement of these markers may increase diagnostic sensitivity, and the use of a variety of markers may increase diagnostic accuracy. Past studies showed that these markers may be valuable for consideration of stopping antibiotic treatment earlier, but to date there is no diagnostic test to replace clinical judgement for continuing antibiotic treatment early on in cases of suspected neonatal infection.[6, 7, 16, 17]

Infection diagnosis based on a single marker should not be done, since no single ideal marker has been identified to confirm a diagnosis of infection.[5, 17, 18]

Therefore, in our study we used combinations of markers, in which levels at a higher than cut off point were defined as indicating the presence of neonatal infection.

In our study, the incidence of infection based on 2 marker-combination examinations IL-6 and TNF-α, in the second examination is significantly different (P=0.020), but the other markers were seen not significantly different and the incidence of infection based on a 4 marker-combination in the Group II in the second examination were 4 babies became infection, that means another 3 babies who were not infected in the first examination became infected in the second examination, but these were not significantly different

Similar to our findings, a retrospective study from Yogyakarta reported that neonates with potential infections who received prophylactic antibiotics for prevention of clinical early neonatal sepsis had outcomes similar to those who did not receive antibiotics.[19]

A Thai study on the efficacy and side effects of prophylactic antibiotics for MSAF during labor to prevent maternal and neonatal infections concluded that compared to placebo, antibiotics during labor may reduce chorioamnionitis. However, there was no evidence that antibiotics reduced postpartum endometritis, neonatal sepsis, or NICU admission. This systematic review revealed the need for better-designed, adequately powered randomized, controlled trials to assess the effect of prophylactic antibiotics on the incidence of maternal and neonatal complications.[20]

Our study was performed in a teaching hospital setting with facilities not available in primary health centers. A limitation of our study was not investigating anti-inflammatory cytokine levels. Cytokine levels may have explained why neonates with MSAF who did not receive antibiotics did not have infection, and could be a subject of further study.

We find no significant difference in the incidence of neonatal infection between neonates with MSAF who did not receive antibiotics compared to those who did receive antibiotics. Also, increased levels of PCT, IL–6, TNF-a, and CRP in neonates with MSAF who did not receive antibiotics is not significantly different from those who received antibiotics, whether analyzed singly or in combinations of 2, 3, or 4 markers.

Based on our findings, we propose that prophylactic antibiotic use in newborns with MSAF is not required. As such, these patients should be under clinical observation and laboratory examinations should be performed until a diagnosis of neonatal infection is confirmed. The examination of hematologic parameters [leukocyte count, platelet count, blood smear for toxic granulation and immature to total neutrophil ratio (I : T ratio)] available in most health facilities, as well as levels of at least 2 infection markers in neonates with MSAF at risk factor for infection should be performed. Further study should include observational, prospective cohort comparisons as part of a large, community-based study and testing anti-inflammatory cytokines in neonates with MSAF.

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