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Comparison of two different antibiotic regimens for the prophylaxisis of cases with preterm premature rupture of membranes: a randomized clinical trial

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ABSTRACT

Objectives: The aim of the study was to assess the effect of 1 g ampicillin prophylactic dosage whether it is as effective as the dosage of 2 g to prevent maternal and neonatal morbidity in a randomized manner.

Materials and methods: One hundred and fourty eight singleton pregnant women with preterm premature rupture of membranes between 21 and 33 weeks of gestation were followed-up during the study period in our institution. We compared the efficacy of two different different dosages of ampicillin. The study population was randomized into 2 groups. In the group 1, 1 g of intravenous ampicillin was given every 6 hours. In the group 2, 2 g of intravenous ampicillin was given every 6 hours.

Results: There was no significant difference between groups interms of fetal complications (RDS, icterus, mortality, sepsis, transient tachypnea of newborn and the pneumonia), rate of intensive care unit admission, fetal gender, fever, rate of clinical chorioamnionitis, high white blood cell count and the CRP, rate of cases < 30 weeks ($p > 0.05$). There was a significant difference between the groups for the rate of previous preterm premature rupture of membranes history, steroid administration and the need for tocolysis ($p < 0.05$).

Conclusions: Although antibiotics seems to be innocent, several side effects have been introduced. It is reasonable to use the lowest dosages in shortest period in order to minimize these unwanted effects.

Key words: preterm, rupture, membrane, chorioamnionitis, ampicillin, premature

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INTRODUCTION

Prelabor or premature rupture of membranes (PPROM) is defined as rupture of membranes before onset of labor [1]. One third of preterm deliveries are observed as a complication of PPROM. PPROM is associated with several complications for both neonate and the mother [1]. Most of these complications are seen in cases with PPROM before 34 weeks of gestation [2]. Latency period for the cases with PPROM under expectant management was reported to be 1.5–4.6 days [3–5]. Therefore majority of the cases deliver within 48 hours and some in 7 days following rupture of membranes [3–7]. Randomized trials have shown that neonatal complications can be reduced with prolongation of latency period [8, 9]. Evidence based data lead the American College of Obstetricians and Gynecologists (ACOG) to prepare a clinical management guideline which recommends using prophylactic antibiotics to prolong pregnancy, reduce maternal infectious morbidity and reduce infectious and gestational age dependent neonatal morbidity [1, 10]. Several antibiotic regimens have been proposed for PPROM prophylaxis including Ampicillin 2 g intravenously every 6 hours for 48 hours or 7 days alone (ampicillin 2 g intravenously every 6 hours for 48 hours or 7 days alone [11]. Dosages and the duration of prophylaxis for these kind of pregnancy complcation is still a debade.

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In this study, we tried to assess the effect of 1 g ampicillin prophylactic dosage whether it is as effective as the dosage of 2 g to prevent maternal and neonatal morbidity.

MATERIAL AND METHODS

This prospective randomized comperative study was conducted in the Department of Obstetrics and Gynecology at the Suleymaniye Women Health Research and Training Hospital, Istanbul, Turkey from January 1, 2011 to May 1, 2013. The hospital is a tertiary referral center with about 5600 deliveries per year. One hundred and fourty eight singleton pregnant women with PPROM between 21 and 33 weeks of gestation were followed-up during the study period in our institution. We compared the efficacy of ampicillin by the different dosages. The study population was randomized into 2 groups. In the group 1 (n = 84), 1 g of intravenous ampicillin was given every 6 hours. In the group 2 (n = 74), 2 g of intravenous ampicillin was given every 6 hours. Sample size was calculated according to the study by Charan J et al. with 95% CI and 80% power [12].

Diagnosis of PPROM was based on a history of leaking fluid and visualization of amniotic fluid in the vagina. If PPROM was not obvious after inspection, the diagnosis was confirmed by positive results from a nitrazine test and ultrasonographic evaluation that demonstrated oligohydramnios. Exclusion criteria were cervial dilatation more than 4 cm, PPROM for > 48 hours before admission, major fetal anomaly, chorioamnionitis, severe preeclampsia, allergic reaction to penicillin or any condition that would require the pregnancy to be terminated including maternal co-morbidity. In total, 158 patients were considered eligible for the study (Fig. 1). We compared the efficacy of two different dosages of ampicillin. The study included 2 groups. In the group 1, 1 g of intravenous ampicillin was given every 6 hours. In the group 2, 2 g of intravenous ampicillin was given every 6 hours. All antibiotics were administered until delivery or up to 7 days. The patients with 24 weeks of gestation or more were treated with antenatal corticosteroid due to prematurity. During the follow-up, vaginal culture was performed at admission. The heart rate was monitored twice a day. Ultrasound examination was performed and fetal presentation, fetal weight and amniotic fluid volume was examined daily. Biophysical scoring and Doppler velocimetry were also performed when needed. Labor induction was prohibited prior to 34 weeks. Randomization was performed by using computer program (Randomization.com). The Ethical Committee of the Bakirkoy Dr. Sadi Konuk Hospital reviewed and approved the trial protocol and all participants provided written informed consent.

Data on the characteristics of the patients including maternal age, parity were collected. Gestational age at admission, gestational age at delivery, latency period were recorded. Additionally, we measured amniotic fluid index, white blood cell (wbc) count, C-reactive protein (CRP) level, rates of clinical chorioamnionitis, neonatal sepsis, neonatal pneumonia and respiratory distress syndrome (RDS). Clinical chorioamnionitis was diagnosed based on maternal temperature ≥ 38°C and two or more of the following conditions: (1) uterine tenderness; (2) wbc count > 15 000/mm^3; (3) foul-smelling vaginal discharge; (4) maternal tachycardia

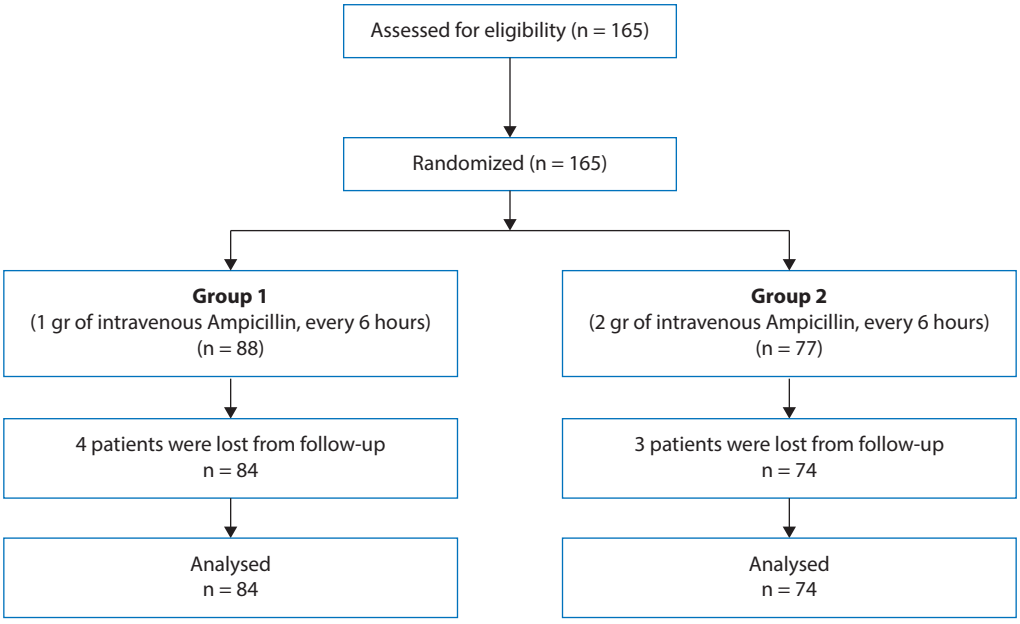

Figure 1. Flow of patients through the trial

(< 100 beats/min); and (5) fetal tachycardia (> 160 beats/min) as previously described (III). RDS was diagnosed in symptomatic infants who required ventilator support for at least 24 hours. Neonatal sepsis was diagnosed if there was a positive blood culture result obtained during the first 72 hours after birth. Pneumonia was diagnosed when an infant had compatible symptoms with diagnostic X-ray findings.

Statistical analysis was done using statistical software (SPSS 10.0 for Windows) and Student's t-test, Mann-Whitney U test, McNemar's test and Friedman variance analysis were used, as appropriate. Signifance level was defined as 0.05. Data were expressed as mean ± SD and percent (%), where appropriate.

RESULTS

Some demographic and the clinical data for the whole study population is summarized in Table 1.

There was no significant difference between groups in terms of fetal complications (RDS, icterus, mortality, sepsis, transient tachypnea of newborn and the pneumonia), rate of intensive care unit admission, fetal gender, fever, high white blood cell count (23/84 vs. 24/74) and the CRP, rate of cases < 30 weeks (23/84 vs. 22/74), the rate of previous PPROM history, steroid administration (39 vs. 55, respectively) and the need for tocolysis (10 vs. 2, respectively) ($p > 0.05$, Tab. 2). There was a significant difference between the low and high dosages groups for clinical choriamnionitis (18/84 vs. 8/74, $p < 0.05$).

DISCUSSION

In this study, we tried to compare two different dosages of same agent in cases with preterm premature rupture of membranes, our study revealed that two regimens result in similar outcomes except for the APGAR score at 1st minute, PPROM history, need for tocolyses and steroids. PPROM is seen in %2.0–3.5 of pregnancies and 1/3 of them result in preterm labor [13]. Prematurity is the most important cause of poor pregnancy outcome. Preterm deliveries account for 7 to 11% of the pregnancies [14, 15]. For that reason, management of PPROM is important for both prevention of preterm deliveries and the perinatal infections. Antibiotherapy provides interval for steroid administration. According to the literature, it is well known that steroid administration has some benefits of lower rates of respiratory distress syndrom, intraventricular hemorrhagia, necrotizing enterocolitis, need for neonatal respiratory support. Steroid administration is effective in up to 30 to 60% of the cases to prevent afforementioned complications [16, 17]. In a systematic review comparing antibiotics to placebo in the management of PPROM, analyses of the data revealed significantly lower chorioamnionitis rates (RR 0.66, 95% CI 0.46–0.96), neonatal infections (RR 0.67, 95% CI 0.52–0.85), need for surfactant administration (RR 0.83, 95% CI 0.72–0.96), need for neonatal respiratory support (RR 0.88, 95% CI 0.81–0.96) and probability of abnormal findings in cerebral ultrasound performed just before discharge (RR 0.81, 95% CI 0.68–0.98), in group under antibiotic prophylaxis [18]. Antibiotics seem to be beneficial in the management of PPROM [9, 18]. On the other hand, Cochrane review showed that antibiotics could decrease short term neonatal morbidities but not perinatal mortality [19]. There is still a concern about the optimal effective antibiotic agent and the dosage, there is still need for further studies on

Table 1. Summary of some demographic and clinical characteristics of whole study population

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. deviation
Age (years)	158	15	44	27.76	6.078
Gravidity	158	1	12	2.43	1.899
Parity	158	0	11	0.96	1.486
Gestational age at diagnosis (week)	158	19.00	36.43	31.2793	4.03371
Gestational age at delivery (week)	158	20.29	39.00	32.0371	3.81235
Interval	158	0	53	5.30	8.265
Latency period (day)	158	0	40	5.45	7.118
Initial AFI	158	0	200	60.31	34.358
Apgar score at 1 minute	158	0	9	6.20	1.780
Apgar score at 1 minute < 4	158	1	2	1.93	0.253
Apgar score at 5 minutes	158	0	10	7.78	1.744
Apgar score at 5 minutes < 7	158	1	2	1.89	0.309
Duration of hospitalization of mother (day)	158	1	42	7.55	7.152
Birth weight [g]	158	280	3380	1910.62	647.898

Table 2. Comparison summary of some demographic and clinical characteristics of two groups

Group Statistics						
	Group	N	Mean	Std. deviation	Std. error Mean	
Age (year)	Low Dose	84	27.5	5.8	0.6	
	High Dose	74	28.1	6.3	0.7	NS
Gravidity	Low Dose	84	2.5	1.9	0.2	
	High Dose	74	2.4	1.8	0.2	NS
Parity	Low Dose	84	0.9	1.3	0.1	
	High Dose	74	1	1.5	0.2	NS
Gestational age at diagnosis (week)	Low Dose	84	31	4.4	0.5	
	High Dose	74	31.6	3.5	0.4	NS
Gestational age at delivery (week)	Low Dose	84	31.8	4.2	0.5	
	High Dose	74	32.3	3.4	0.4	NS
Interval	Low Dose	84	5.5	8.5	0.9	
	High Dose	74	5	7.9	0.9	NS
Latency period (day)	Low Dose	84	5.6	8.1	0.8	
	High Dose	74	5.2	5.9	0.6	NS
Initial AFI [mm]	Low Dose	84	63.06	34.1	3.7	
	High Dose	74	57.22	34.6	4	NS
Apgar score at 1 minute	Low Dose	84	6.51	2	0.2	
	High Dose	74	5.79	1.2	0.1	< 0.05
Apgar score at 1 minute < 4	Low Dose	84	1.91	0.2	0.03	
	High Dose	74	1.96	0.1	0.02	NS
Apgar score at 5 minute	Low Dose	84	7.9	2.1	0.3	
	High Dose	74	7.5	0.8	0.1	NS
Apgar score at 5 minute <7	Low Dose	84	1.9	0.2	0.034	
	High Dose	74	1.8	0.3	0.044	NS
Duration of hospitalization of mother (day)	Low Dose	84	7.4	7.3	0.8	
	High Dose	74	7.6	6.9	0.8	NS
Birth weight [g]	Low Dose	84	1958.1	685.2	81.3	
	High Dose	74	1856.1	603.2	76.6	NS

this issue [20]. There have been studies on the antiobiotics including ampicillin, amoxicillin, azithromycin and erithromycin [9, 20, 21]. Comparison of ampicilin + erithromycin and ampicilin+azithromycin combinations revealed similar results. [21]. In an other study, eryhromycin was found to be associated with the higher risk for functional disorders and the cerebral palsy [8]. Amoxicillin-clavulanic acid combination resulted in higher rates of necrotizing enterocolitis in some studies [8, 22]. Due to the effectiveness on group B streptococcus, aerobic gram negative bacils and some anaerobic species, ampicillin is the most frequently used agent in PPROM prophylaxis [23]. According to the results of National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network trial on antibiotic therapy for reduction of infant morbidity after PPROM, ampicillin is recommended in 2 g doses for each 6 hours intervals [9]. In our study we compared two different dosages of ampicillin and found no difference in terms of maternal infections or neonatal poor outcome. The rate of chorioamnionitis was found to be higher in group under low dose protocol, however this difference did not reach statistical significance. It is well known that long duration and high doses of antibiotics may result in unfavorable outcome including allergic reactions, gastrointestinal disorders, cardiac arythmias and even mortality [24]. Major problem in using high doses of antibiotics for long time is higher risk for development of multiresistant bacterias [25, 26]. For example in England, frequently used agent erythromycin resulted in development of 35% resistant bacterias [27, 28]. In addition, overuse of antibiotics may be associated with the anaphylactic reactions during pregnancy and the peripartum period (2,7 cases/100.000 deliveries) [29–31].

Anaphylaxis is a condition that threatenes both maternal and the fetal oxygenization. According to some studies, during the fetal and neonatal period, long term and high dose antibiotic exposure may result in allergic disease and abnormal intestinal flora development that may interfere with the immune system development [32–34]. Again according to the Cochrane review, beta lactam antibiotics with or without combination of macrolide were found to be associated with the higher rates of neonatal death compared to combinations without beta lactams (RR: 1.51; 95% CI = 1.06–2.15; NNTH: 143; 95% CI = 63–1250) [19].

In conclusion, antibiotic use seems to decrease neonatal morbidity in the management of PPROM. Although antibiotics seems to be innocent, several side effects have been reported. It is reasonable to use the lowest dosages in shortest period in order to minimize these unwanted effects while the half dosage (1 g of intravenous ampicillin, every 6 hours) is as effective as the present recommendation (2 g ampicillin, every 6 hours).

Conflict of interest

The authors report no declaration of interest.

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