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Original Research

The efficacy of third-generation cephalosporin plus metronidazole versus third-generation cephalosporin plus clarithromycin in neonatal outcomes and oxidative stress markers in women with preterm premature rupture of membranes

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Summary

Purpose of Investigation: The purpose of this study is to compare neonatal outcomes and oxidative stress markers of preterm premature rupture of membranes (PPROM) treated with third-generation cephalosporin plus metronidazole (regimen A) with those treated with third-generation cephalosporin plus clarithromycin (regimen B). *Materials and Methods:* The present study included patients with singleton pregnancies with PPROM at earlier than 34 gestational weeks who were admitted to the Chonnam National University, Gwangju, Korea, between February 2007 and December 2015. Latency period, neonatal outcomes, and oxidative stress markers (including oxygen radical absorbance capacity, malondialdehyde (MDA), protein carbonyl, and interleukin-6) were compared between two groups. *Results:* Latency period from PPROM to delivery did not differ between the groups (11.0 ± 13.1 *vs.* 11.5 ± 8.6, $p = 0.791$). However, there were no significant differences in rate of latency period longer than seven days. More women were delivered after 48 hour in the regimen B group than in the regimen A group (83.6% *vs.* 94.7%, $p = 0.022$). However, there were no significant differences in rate of latency period longer than seven days. There was no significant difference in oxidative stress markers after the administration of antibiotics between regimens A and B. *Conclusion:* The present results show that there was no difference between the two regimens on the latency period and improvement of neonatal outcomes. Although there was no significant difference in neonatal outcomes, the regimen using third-generation cephalosporin plus clarithromycin may have a beneficial effect for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids and transfer to the tertiary center.

Key words: Premature rupture of membranes; Antibiotics; Oxidative stress; Latency period.

Introduction

Preterm premature rupture of membranes (PPROM) refers to the spontaneous rupture of membranes before 37 weeks of pregnancy. PPROM is responsible for 25–30% of preterm births [1]. Approximately 3% of all pregnancies in the United States are complicated by PPROM [2]. The cause of PPROM is not clearly known, but intrauterine infection is known to be one of causes. Intrauterine infection is associated with the increase in the failure of tocolytics, as well as with preterm delivery, clinical chorioamnionitis, perinatal mortality, and neonatal morbidity [3].

Administration of broad-spectrum antibiotics for women with PPROM is associated with prolongation of pregnancy and a reduction in a number of short-term neonatal morbidities [4]. Several antibiotic regimens for PPROM have proven beneficial, but it is unclear which one is best [5]. Single or combination use of amoxicillin and erythromycin is the most frequently used regimen [4, 6, 7]. Recently, a new antibiotic combination, consisting of ceftriaxone, clarithromycin, and metronidazole, prolonged the latency period and improved neonatal outcomes in patients with PPROM [8, 9]. Also, administration of ceftriaxone, clarithromycin, and metronidazole proved to be more successful than ampicillin and/or cephalosporin in the eradication of intra-amniotics inflammation/infection [10].

Oxidative stress is known to play an important role in the pathophysiology of pregnancy-related disease [11]. PPROM results from damage to collagen in the chorioamnion, which can lead to a tear in the membrane. Reactive oxygen species (ROS) are known to damage collagen in the chorioamnion and this could lead to PPROM [12]. Recent studies identify cytokine and matrix metalloproteinase activation, oxidative stress, and apoptosis as primary pathways to PPROM [13].

The purpose of study is to compare neonatal outcomes and oxidative stress markers of PPROM treated with third-generation cephalosporin plus metronidazole with those treated with third-generation cephalosporin plus clarithromycin.

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Materials and Methods

This is a retrospective cohort study that included women admitted to the Chonnam National University Hospital, Gwangju, Republic of Korea, between February 2007 to December 2015 with a diagnosis of PPROM. The inclusion criteria were: (1) singleton pregnancy, (2) gestational age < 34 weeks, (3) antenatal antibiotic treatment for at least 24 hours, and (4) availability of neonatal outcomes. Patients with clinical chorioamnionitis, fetal anomaly, and progressive preterm labor were excluded from this study.

One hundred ten patients, in group A, were treated with third-generation cephalosporin plus metronidazole for a period of seven days. Seventy-six patients, in group B, were treated with third-generation cephalosporin plus clarithromycin for a period of seven days. Maternal venous blood was obtained before antibiotic administration and on days three and seven after administration. If patients had a regular menstrual period, gestational age was determined by measuring from the first day of the last menstrual period. If patients had an irregular menstrual period or if they were uncertain of the time of their last menstrual period, it was determined based on a urine pregnancy test and ultrasonographic finding of the first trimester of pregnancy. PROM was defined as a state of membrane ruptured before the onset of spontaneous labor, and PPROM specifically referred to a membrane ruptured before 37 weeks of gestational age. Rupture of membranes was confirmed by amniotic fluid in the vaginal cavity, nitrazine paper test, and a Ferning test of the cervical mucus. The study was approved by the Clinical Trial Center at Chonnam National University Hospital, and written informed consent was obtained from all participants.

Blood samples were collected into a tube containing 3.8% sodium citrate (1 mL of citrate and 9 mL of blood), and this was centrifuged at 1000 × g for 10 minutes at 4 °C in a refrigerated centrifuge to obtain venous plasma. The separated plasma was kept frozen at -70 °C and was used within three weeks. Protein quantification in the plasma was determined by the Biuret method. Bovine serum albumin was the standard protein.

Lipid peroxides were assayed using Ohkawa's method [14], and the thiobarbituric acid (TBA) test was used for lipid peroxidation. When TBA is applied to a mixture of acetaldehyde and sucrose, it produces a 532 nm absorbing chromogen that is indistinguishable from that formed by malondialdehyde (MDA) and TBA. The MDA assay is the test most commonly used to assess the role of oxidative stress in disease. MDA is one of the several products formed during radical-induced decomposition of polyunsaturated fatty acids. The results are expressed as nmol of MDA incorporated/mg of protein based on mean absorptivity ($E_M = 1.56 \times 10^5$).

Protein carbonyl contents were determined using 2, 4-dinitrophenylhydrazine (DNPH). The supernatant fraction was divided into two equal aliquots, each of which contained approximately 1.0 mg protein. Both aliquots were precipitated with 10% trichloroacetic acid (TCA). One sample was treated with 2 N HCl, and the other sample was treated with an equal volume of 0.2%(w/v) DNPH in 2 N HCI. Both samples were incubated in 15-ml conical glass centrifuge tubes at 25°C and stirred at five-minute intervals. The samples were re-precipitated with 10% TCA, extracted with a 1:1 solution of ethanol and ethyl acetate, and reprecipitated in 10% TCA. The pellets were carefully drained and dissolved in 6 M guanidine HCI with a 20 mM sodium phosphate buffer, pH 6.5. Insoluble debris was removed by centrifugation at 6000 × g at 4 °C. The difference in the spectrum of the DNPH-treated sample *vs*. the HCl control was determined, and the results are expressed as nmol DNPH incorporated/mg protein based on the mean absorptivity of 21.0 mM cm for most aliphatic hydrazones [15].

A cytokine ELISA kit was used to measure IL-6. IL-6 antigen and biotinylated polyclonal antibody were cultured and washed out. After adding streptavidin-peroxidase, samples were re-cultured. Unbound enzymes were washed out of the samples. A substrate enzyme was added to generate a color reaction. The concentration of IL-6 was calculated by measuring the absorbance at 450 nm.

An antioxidant assay kit was used to measure the oxygen radical absorbance capacity (ORAC) levels, based on the method of Cao *et al.* [16]. In this assay system, beta-phycoerythrin (beta-PE) was used as an indicator protein, 2, 2'-azobis(2-amidinopropane) dihydrochloride (AAPH) as a peroxyl radical generator, ands 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid (Trolox, a water-soluble vitamin E analogue) as a control standard. Results are expressed as ORAC units, where 1 ORAC unit equals the net protection produced by 1 microM Trolox.

A slice of chrioamnion roll was stained by Hematoxylin and Eosin. All slides were reviewed by two pathologists without any information about IL-6. Differences were resolved by consensus. Chorioamnionitis was diagnosed when leukocyte was placed under the subamniotic space.

Data were analyzed using SPSS Version 21.0. For continuous variables, mean and standard deviation were calculated, and the Mann-Whitney U test was used. Frequency and percentage were calculated and the χ^2 test or Fisher's exact test was used for categorical variables. A p value < 0.05 was considered statistically significant.

Results

In total, 186 women with PPROM were included in this study (Figure 1). Of these women, 110 women were treated with third-generation cephalosporin plus metronidazole (regimen A), and 76 women were treated with third-generation cephalosporin plus clarithromycin (regimen B). No significant differences were detected between the two groups in mean age, parity, gestational age at PPROM, or previous preterm birth history (Table 1). The latency period (in number of days) from PPROM to delivery did not differ between the groups (11.0 ± 13.1 *vs.* 11.5 ± 8.6, p = 0.791). More women were delivered after 48 hours in the regimen B group than in the regimen A group (83.6% *vs.* 94.7%, p = 0.022). However, there were no significant differences in the rate of latency period longer than seven days (Table 2). There was no difference between the neonatal outcomes in the two groups (Table 3).

Between the regimen A group and the regimen B group,

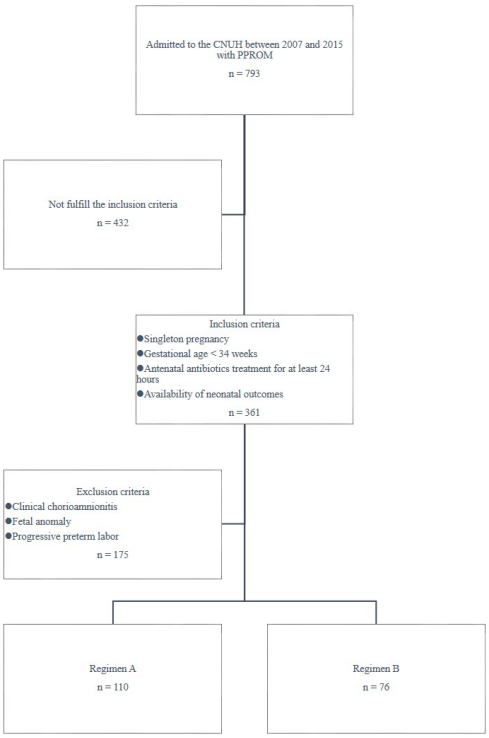

Figure 1. — Flow chart of study population.
Regimen A = 3rd-generation cephalosporin plus metronidazole.
Regimen B = 3rd-generation cephalosporin plus clarithromycin.
PPROM = Preterm premature rupture of membranes.
Values are expressed as mean ± SD. Data are presented as n (%).

there were no significant differences in lipid peroxide levels, protein carbonyl formation, ORAC, and IL-6 of the venous plasma before the antibiotics administration, day three and day seven after the antibiotic administration (Table 4).

Discussion

The purpose of the present study was to evaluate the clinical differences between antibiotic regimens in preterm PROM. The authors also evaluated oxidative stress markers, such as, ORAC, MDA, IL-6, and protein carbonyl. This study was performed because, to date, there are no optimal guidelines regarding an antibiotic regimen for preterm PROM, and there are still few comparative studies regarding antibiotic regimens.

Randomized trials by NICHD in United States used parenteral ampicillin and erythromycin for 48 hours, followed by oral amoxicillin for five days compared to placebo [7]. In a study conducted in Europe by ORACLE I, it was demonstrated that erythromycin and co-amoxiclav were used in PPROM patients to determine the optimal regimen, but only the facts of the co-amoxiclav were associated with necrotizing enterocolitis [6]. The American College of Obstetrics and Gynecology (ACOG) recommends parenteral ampicillin and erythromycin for 48 hours, followed by oral amoxicillin and erythromycin for five days [17], and the Royal College of Obstetricians and Gynecologists recommends erythromycin or penicillin [18].

PPROM infants are more likely to have neonatal morbidity than preterm infants born at the same gestational age without PPROM [19]. Neonatal outcomes have been considered to be associated with the latency period after PPROM [20]. Frenette *et al.* reported that neonatal prematurity-related morbidities were significantly decreased at the latency periods of 48 hours or more, compared to

Table 1. — *Patient characteristics.*

	Regimen A (n=110)	Regimen B (n=76)	*p* value
Maternal age (years)	31.6 ± 4.6	32.3 ± 4.8	0.074
Nulliparous (%)	58 (52.7%)	32 (42.1%)	0.154
Gestational age at PPROM (weeks)	29.4 ± 2.7	28.9 ± 2.5	0.211
Previous preterm birth (%)	10 (9.1%)	9 (11.8%)	0.542

Regimen A = 3rd-generation cephalosporin plus metronidazole; Regimen B = 3rd-generation cephalosporin plus clarithromycin . PPROM: preterm premature rupture of membranes. Values are expressed as mean ± SD. Data are presented as n (%).

Table 2. — *Pregnancy outcomes.*

	Regimen A (n=110)	Regimen B (n=76)	*p* value
Latency period (days)	11.0 ± 13.1	11.5 ± 8.6	0.791
Latency period ≥ 48 hrs (%)	92 (83.6%)	72 (94.7%)	**0.022**
Latency period ≥ 7 days (%)	64 (58.2%)	48 (63.2%)	0.495
Histology (%)			0.724
Non-specific	51 (46.4%)	36 (47.4%)	
Chorioamnionitis	52 (47.3%)	32 (42.1%)	
Amnionitis	3 (2.7%)	4 (5.3%)	
Chorionitis	4 (3.6%)	4 (5.3%)	
Cesarean delivery (%)	49 (44.5%)	32 (42.1%)	0.741

Regimen A = 3rd-generation cephalosporin plus metronidazole; Regimen B = 3rd-generation cephalosporin plus clarithromycin. Values are expressed as mean ± SD. Data are presented as n (%).

Table 3. — *Neonatal outcomes.*

	Regimen A (n=110)	Regimen B (n=76)	*p* value
Birth weight (g)	1665.1 ± 524.8	1603.6 ± 457.1	0.409
RDS (%)	47 (42.7%)	40 (52.6%)	0.183
Sepsis (early) (%)	1 (0.9%)	0 (0.0%)	1.000
Sepsis (late) (%)	3 (2.7%)	0 (0.0%)	0.271
IVH	24 (21.8%)	18 (23.7%)	0.765
PVL	2 (1.8%)	3 (3.9%)	0.400
NEC	0 (0.0%)	2 (2.6%)	0.166
CP	0 (0.0%)	0 (0.0%)	
Neonatal death	1 (0.9%)	0 (0.0%)	1.000

Regimen A = 3rd-generation cephalosporin plus metronidazole; Regimen B = 3rd-generation cephalosporin plus clarithromycin. RDS = respiratory distress syndrome; IVH = intraventricular hemorrhage; PVL = peri-ventricular leukomalacia; NEC = necrotizing enterocolitis; CP = cerebral palsy. Values are expressed as mean ± SD. Data are presented as n (%).

Table 4. — *Laboratory results.*

	Regimen A (n=110)	Regimen B (n=76)	*p* value
ORAC day 0 (μM/μL)	$112.0\times10^3 \pm 2.9\times10^3$	$105.6\times10^3 \pm 2.7\times10^3$	0.856
ORAC day 3 (μM/μL)	$98.1\times10^3 \pm 3.8\times10^3$	$111.5\times10^3 \pm 1.9\times10^3$	0.743
ORAC day 7 (μM/μL)	$113.3\times10^3 \pm 1.6\times10^3$	$105.6\times10^3 \pm 2.7\times10^3$	0.172
MDA day 0 (nmol/mg protein)	6.46 ± 1.78	6.75 ± 1.38	0.535
MDA day 3 (nmol/mg protein)	6.61 ± 1.68	6.96 ± 3.28	1.000
MDA day 7 (nmol/mg protein)	6.41 ± 1.31	7.00 ± 1.76	0.400
Protein carbonyl day 0 (nmol/mg protein)	7.86 ± 3.41	8.36 ± 2.81	0.585
Protein carbonyl day 3 (nmol/mg protein)	6.99 ± 2.14	8.60 ± 5.15	0.488
Protein carbonyl day 7 (nmol/mg protein)	7.27 ± 3.11	8.02 ± 2.55	0.360
IL-6 day 0 (ng/L)	46.36 ± 84.13	47.39 ± 66.06	0.856
IL-6 day 3 (ng/L)	54.71 ± 100.37	26.47 ± 31.66	0.535
IL-6 day 7 (ng/L)	185.17 ± 239.36	104.83 ± 173.12	0.689

Regimen A = 3rd-generation cephalosporin plus metronidazole; Regimen B = 3rd-generation cephalosporin plus clarithromycin. ORAC = oxygen radical absorbance capacity; MDA = malondialdehyde; IL = interleukin. Values are expressed as mean ± SD.

those with less than 24 hours latency [21]. Nayot *et al.* reported that a latency period more than 72 hours was associated with a lower incidence of neonatal morbidity [20]. In the present study, there was no difference in the latency period from PPROM to delivery of the antibiotic regimen groups. However more women were delivered after 48 hour in the third-generation cephalosporin plus clarithromycin regimen group than in the third-generation cephalosporin plus erythromycin regimen group. It seems to be beneficial by earning time for the administration of antenatal corticosteroid for fetal lung maturation and transfer to tertiary center.

Previously, Chang *et al.* reported that the incidence of bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH) was lower in clarithromycin group than in the erythromycin group, with no significant difference in morbidities and neurologic outcomes at two years corrected age [22]. Lee *et al.* reported that a new antibiotic regimen consisting of ceftriaxone, clarithromycin, and metronidazole prolonged the latency period, reduced acute histologic chorioamnionitis, and even improved neonatal outcome more than the erythromycin and ampicillin regimen [8]. In this study, there were no significant differences in neonatal morbidity and mortality between the third-generation cephalosporin plus erythromycin regimen group and the third-generation cephalosporin plus clarithromycin regimen group.

The exact mechanism of membrane rupture is still unknown. Oxidative stress may be associated with PROM because of the fact that increased ROS disrupts collagen [12, 23, 24]. Various etiology, such as infection/inflammation, placental bleeding, and uterine over-distention, initiates the biologic processes that damages collagen in membranes [13]. Previously, the authors evaluated the usefulness of maternal serum oxidative stress markers as predictors of delivery in preterm PROM patients. Measurements of levels of maternal serum C-reactive protein (CRP), malondialdehyde, and ORAC at admission were useful in predicting the latency period in patients with PPROM [25]. Ilhan *et al.* reported that there is a negative relationship between latency period, plasma total oxidative stress, CRP, and leukocyte counts [26]. In the present study, the authors sought to identify oxidative stress markers according to antibiotic regimens. In a manner similar to what was observed in clinical outcomes, there was no difference in the oxidative stress marker by antibiotics regimen.

The limitations of this study are related to its design as a retrospective study and its relatively small sample size. The strength of this study is in the fact that the authors attempted to evaluate the clinical outcome of different antibiotic regimens with oxidative stress markers in PPROM. There is a need for further studies comparing the clinical and oxidative stress markers in different antibiotics for PPROM.

Conclusion

The present results show that there was no difference between the two regimens in the latency period and improvement of neonatal outcomes, and they may not have any effect on the changes of oxidative stress. Although there was no significant difference in neonatal outcomes, the regimen using third-generation cephalosporin plus clarithromycin may have beneficial effects for short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids and transfer to tertiary center.

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