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Comparison of Azithromycin versus Erythromycin on Gestation Length (Prolongation of Latency Interval) and Neonatal Outcomes in Pregnant Women with Premature Rupture of the Membrane: A Randomized Clinical Trial

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Abstract

Background: Premature rupture of membrane (PROM) is an important problem among pregnant women, which leads to maternal and neonatal morbidity. This study was done to compare the efficacy of azithromycin with erythromycin on the pregnancy length and the neonatal adverse effects in mothers with PROM.

Methods: In this open-label randomized clinical trial, 194 pregnant women with PROM who referred to Akbarabadi Hospital were enrolled and randomly assigned to two groups. Group I received oral Azithromycin (1 gr/orally, Abidi Company, Iran) + Ampicillin 2 gram IV (Abidi Company, Iran) every six hours for 48 hours; then, only Amoxicillin 500 mg every eight hours for five days. and group II received intravenous Erythromycin (Abidi Company, Iran) 400 mg every six hours for seven days + Ampicillin 2 grams IV every six hours for 48 hours, then Amoxicillin 500 mg every six hours for five days. Finally, the pregnancy length and neonatal adverse effects or neonatal outcomes were compared between the two groups.

Result: There was no significant difference between the groups in mean of pregnancy length (32.5 versus 32.6 weeks, respectively, p=0.757) Also the frequency ofIntraventricular hemorrhage, Necrotizing enterocolitis, Respiratory Distress Syndrome sepsis, icter, oxygen demand, ICU admission, duration of hospitalization in the NICU, and mortality in neonate were the same between the groups. The mean of patient satisfaction (by self-report) was 9.8 and 9.5 in group I and II, respectively (P=0.001).

Conclusion: It can be concluded that oral azithromycin and intravenous erythromycin have the same effect on increasing the duration of pregnancy and reducing neonatal complications in women with PROM. But azithromycin was associated with greater satisfaction and its use is recommended.

Key Words: Azithromycin, Erythromycin, Efficacy, Gestation length, Pregnancy, Premature rupture of membrane, Prolongation of latency interval.

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1- INTRODUCTION

Premature rupture of membrane (PROM) is spontaneous rupture of amniotic membranes before initiation of labor (1). Increasing rate of preterm labor and the rate of complications in those with lower gestational age are considered as the main consequences of it (1, 2). In addition, PROM is accompanied with a four-fold increase in fetal death and three-fold raise in respiratory distress (2). Effective factors include history of preterm labor, vaginal bleeding, previous operations, smoking, and cervical insufficiency (3). Preterm labor is defined as uterine contractures with good potency and continuity to develop dilatation and progressive effacement in weeks 23 to 37 (4). In conjunction with PROM with preterm labor, the rate of maternal and neonatal complications, deculment, umbilical cord compression and prolapse, and sudden amniotic fluid discharge are expected (5, 6). The maternal adverse effects of PROM are infection and sepsis, which lead to preterm labor and the fetal and neonatal consequences include respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), malformations, cerebral palsy, blindness, deafness, and fetal death (7, 8). Corticosteroids, antibiotics, and tocolytics are among prescribed medications for PROM (9, 10). Among them, the main role of antibiotics use is to reduce infection and delay the labor progress rate (9, 10). However, the definite role of the antibiotic therapy is not yet understood specially to reduce preterm labor (9-11). The main utilized antibiotics include beta lactams, erythromycin, clindamycin, and metronidazole. However, antibiotic prophylaxis has obvious effects on increasing the pregnancy length and reducing neonatal adverse effects; but, the optimal drug, dosage, and duration of use is not yet obvious (11-18). This study was conducted to determine and compare efficacy of Azithromycin versus Erythromycin on the pregnancy length and the neonatal adverse effects in mothers with PROM. The novelty of this study is that, despite global acceptance of conservative treatment for PPROM by antibiotics, the best type of antibiotic and appropriate dose are still controversial.

2- MATERIALS AND METHODS

In this study, 194 pregnant women with PROM (in 24^{th} to 34^{th} gestational weeks) who attended Akbarabadi Hospital, Tehran, Iran between 2017 and 2018, were enrolled in this open-label randomized clinical trial. PROM and attendance to participate in the study were considered as the inclusion criteria. Major congenital anomalies, vaginal bleeding not related to pregnancy, retained placenta, allergy, dissatisfaction, and hypertension/preeclampsia were also considered as the exclusion criteria.

PROM was established by speculum examination and use of Fern & nitrazine test which was finally approved by ultrasound assessment. The participants were randomly assigned into two groups by the use of Coin tossing (Figure 1). Group I (n=97) received a single oral dose of Azithromycin (1 gr/orally), Abidi Company, Iran) + Ampicillin 2 grams IV)Abidi Company, Iran) every six hours for 48 hours; then, only Amoxicillin 500 mg every eight hours for five days. Group II (n=97) received Erythromycin (Abidi Company, Iran) 400 mg every six hours for seven days + Ampicillin 2 grams IV every six hours for 48 hours, then Amoxicillin 500 mg every six hours for five days. Two doses of 12 mg betamethasone within 24 hours were administered in both groups. The infection symptoms, labor initiation time, Non-stress test, PROM-labor interval, Apgar score, birth weight, neonatal and maternal complications including sepsis, nausea, vomiting, diarrhea, low birth weight, respiratory distress, low gestational age,

and death were evaluated in both groups. The pregnancy length was estimated by the last menstrual period and early pregnancy ultrasound. The cervical examination was done by a blind gynecologist; and also neonatal adverse effects including general examination, laboratory, cranial and abdominal ultrasound, chest radiography and Magnetic resonance imaging were determined and compared between the groups as well as pregnancy length.

2-1. Ethical Consideration

This study was approved by the ethical committee of Iran University of Medical Sciences with the code of 9411290017; and the Helsinki Declaration was respected across the study. In addition, the registration code was attained. Also, the informed consent form was received from subjectsAnd after receiving the code of ethics; she was registered in the center of clinical trials with the code of IRCT20190601043785N1.

2-2. Statistical Analysis

Data were analyzed among 194 cases by SPSS Software version 13.0. The categorical and numerical data were represented as frequency plus percentage, and mean plus standard deviation, respectively. The used tests included, Chi-Square, Fisher and Independent-sample-t tests. P-values less than 0.05 were considered statistically significant.

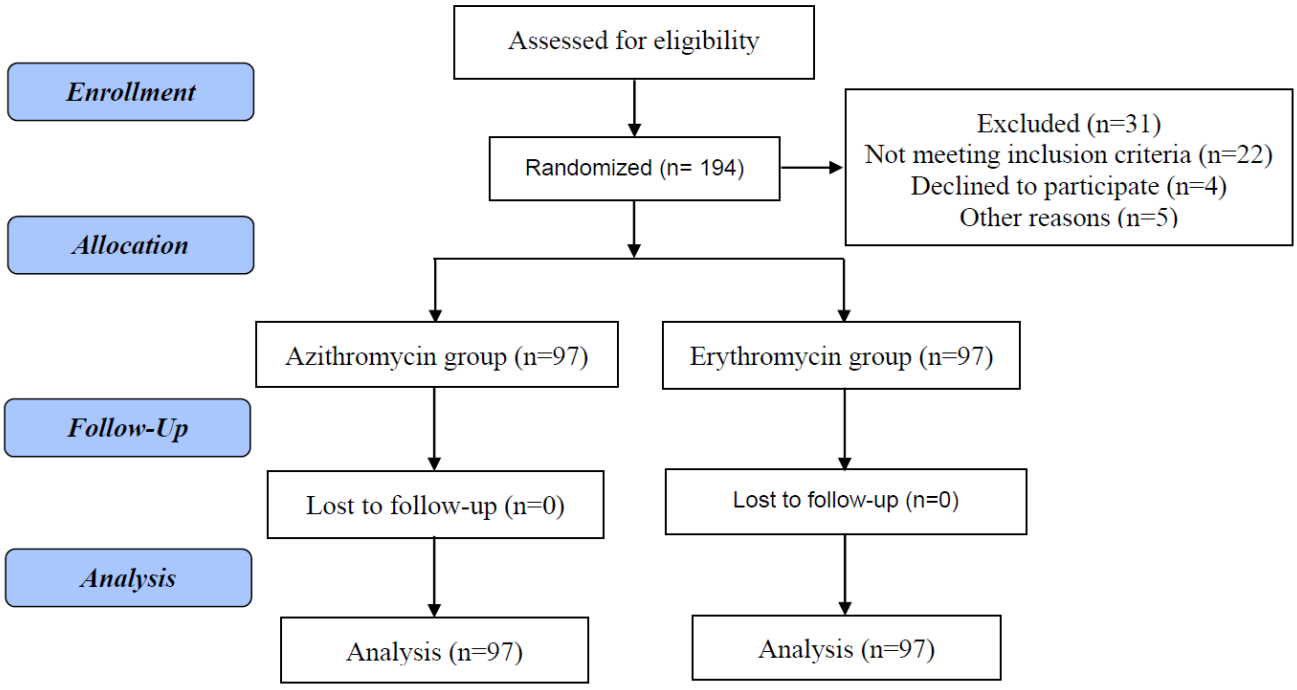

Fig 1: CONSORT (Consolidated standard of reporting trial) chart for study

3- RESULTS

The results indicated no statistically significant difference in demographic and contextual characteristics between the two groups (age, body mass index, gravidity, parity, abortion, live birth). T-test comparisons are not statistically significant and the two groups are homogeneous in terms of these variables ($p > 0.05$) (**Table 1**). Comparing AFI, PROM age, and pregnancy termination age between the two groups were not statistically different (**Table 2**).

Table-1: Demographic characteristics of participants in the two study groups

Variables	Group I (Azithromycin)	Group II (Erythromycin)	P-value
Age	30.2 ± 5.9	30 ± 6.1	0.85
Body mass index	27.4 ± 3.8	27.4 ± 3.8	0.95
Gravid	2.2 ± 1.2	2.3 ± 1.3	0.64
Parity	1.1 ± 1.0	1.2 ± 1.1	0.68
Abortion	0.3 ± 0.6	0.4 ± 0.8	0.75
Live birth child	1 ± 0.9	1 ± 0.9	0.87

Table-2: Comparing AFI, PROM age, and pregnancy termination age between the two study groups

Variables	Group I (Azithromycin)	Group II (Erythromycin)	P-value
Amniotic fluid index	5.8 ± 3.5	5.8 ± 3.5	0.92
Premature rupture of membrane gestational age	30.7 ± 2.0	30.6 ± 2.0	0.77
Pregnancy termination age	32.5 ± 2.1	32.6 ± 2.1	0.75
Birth weight	1967.7 ± 491.8	1963.8 ± 495.1	0.95
Apgar score	8.5 ± 1.5	8.4 ± 1.5	0.66

Independent-Sample ttest was used for mean and standard deviation. The cause of pregnancy termination was full-term status in 43.3% and 41.2% in groups I and II, respectively. Chorioamnionitis was seen in 10.3% in Group I compared with 12.4% in group II, without any significant difference (p=0.98). The CRP was positive in 8.2% and 5.2% in groups I, II, respectively, without any significant difference (p=0.39). Also the leukocyte count (p=0.73), heart rate (P=0.98), and body temperature (P=0.816) were the same between the groups. There was no significant diference in the satisfaction rate (by self-report) between the groups (9.8 versus 9.4 points; p-value=0.001). Vaginal delivery was the child delivery method in 39.2% and 43.3% of the participants in E and A groups, respectively, with no significant difference (P=0.560). The neonates were male in 64.9% and 67.0% in E and A groups, respectively, with no significant difference (P=0.762). The need to ICU admission was 91.8% and 93.8% in E and A groups, respectively, with no significant difference (P=0.579). Mean hospital stay was 8.4 and 8.3 days in E and A groups, respectively, with no significant difference (P=0.922). **Table 3** shows frequency of IVH, NEC, RDS, sepsis, icter, oxygen need, ICU admission, and ICU stay. The mortality rate was 6.2% and 9.3% in E and A groups, respectively, without any significant difference (P=0.420).

Table-3: Complications in neonates across the groups

Complication	Group I (Azithromycin)	Group II (Erythromycin)	Test*	P value
Intraventricular hemorrhage	3 (3.1%)	1 (1.3%)	Fisher exact test	0.62*
Sepsis	11 (11.3%)	8 (8.2%)	Chi-Square tests	0.47**
Respiratory distress syndrome	51 (52.6%)	50 (51.5%)	Chi-Square tests	0.88**
Need to oxygen	38 (39.2%)	34 (35.1%)	Chi-Square tests	0.55**
Icter	32 (33.0%)	29 (29.2%)	Chi-Square tests	0.64**
Necrotizing enterocolitis	4 (4.1%)	1 (1.0%)	-	0.37*

Data presented as n (%),* Fisher exact test, **Chi-Square tests

4- DISCUSSION

There is no statistically significant difference in terms of obstetric characteristics. In this study, the effects of azithromycin versus erythromycin were determined for pregnancy length, complications and satisfaction among mothers. It was found that, rate of complications and mean pregnancy length were the same between the groups, but the mothers were more satisfied with azithromycin. Shari Gelber et al. (19) compared azithromycin and erythromycin in PROM cases and similar to our results, they did not find any significant difference between the two groups. Amon et al. (12) reported good efficacy to reduce PROM and infection rate in the cases, which were treated with ampicillin and it may be compared in future studies with macrolides.

In another study, Johnston et al. (13) reported that mezlocillin would result in a delayed phase of labor as well as higher birth rate and Apgar score. In our study, similar results were obtained about azithromycin.

A meta-analysis (14) showed that the use of antibiotics is associated with postpartum complications and chorioamnionitis, which according to the results of the present study is the use of both antibiotics. In addition, both studies similarly showed that there is a relationship between the intense therapy of drugs and the rate of side effects (15). It was also reported that combined use of tocolytic and antibiotic would result in reduction of HMD, death, and RDS (15).

A review study by Kenyon et al. (16) showed that antibiotic use would decrease neonatal infections (RR: 0.67 CI 95%: 0.52-0.85) and also decrease the risk of chorioamnionitis (RR: 0.81 CI 95%: 0.68-0.98) and abnormal cerebral ultrasound scan before discharge from hospital (RR: 0.66 CI 95%: 0.46-0.96). Flenady et al., (17) reported that antibiotic use would lead to a decrease in the risk of maternal infection (RR: 0.74 CI 95%: 0.63-0.86) as it is seen in our study. In the same line, Mohamed et al. (18), similar to our study, showed that erythromycin and azithromycin had the same effects.

5- CONCLUSION

Finally, it may be concluded that azithromycin and erythromycin have the same efficacies in increasing pregnancy length and decreasing the neonatal adverse effects in mothers with PROM, but azithromycin is accompanied with a higher rate of satisfaction and is recommended to be used. In our study, the results did not show any significant difference between the groups. In order to achieve more clear results, it is recommended to perform this study on larger scales.

6- Conflict of interest

None.

7- REFERENCE

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