Original Article

Comparison of Feto-Maternal Outcome in Azithromycin Versus Erythromycin in Management of PPROM; A Randomized Controlled Trial

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Abstract

Objective: To compare the efficacy and safety of azithromycin with erythromycin on the duration of latency period till delivery in patients with PPROM.

Methodology: A randomized control trial study was carried out at Department of Obs and Gynae, Federal Government Polyclinic Hospital from May 2023 to May 2024. A total of 210 patients participated in the study equally distributed through lottery method in Group A (n=105) and Group B (n=105). Group A were given Azithromycin 1g once a day till 10 days meanwhile Group B were given Erythromycin 250mg 6 hourly in a day to evaluate the feto-maternal outcome of the drug. Chi Square test was used to compare the neonatal outcomes (birth weight, APGAR scores, NICU admission rates, RDS incidence, and neonatal survival) and maternal outcome (chorioamnionitis and mode of delivery (SVD vs. LSCS) between groups. P-Value ≤0.05 was considered statistically significant

Results: The study observed a significantly longer latency period in group A (5.86±5.50) while group B present (2.94±2.43) with p-value (0.0001). Similarly, Group A showed improved outcome in neonates like high APGAR score, reduced NICU admissions and chorioamnionitis rate in the patients.

Conclusion: Azithromycin 1g single-dose therapy is superior to Erythromycin in improving fetomaternal outcomes due to its enhanced convenience and maternal compliance. Its use should be considered a more effective alternative in clinical scenarios requiring antibiotic therapy during pregnancy, emphasizing better maternal and neonatal well-being.

Key words: Azithromycin, Erythromycin, PPROM, Feto-Maternal Outcome.

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Introduction

Preterm premature rupture of membranes (PPROM) is a significant obstetric condition, defined as the spontaneous rupture of the fetal membranes before 37 weeks of gestation and prior to the onset of labor.[1] PPROM complicates 3% of pregnancies and accounts for nearly one-third of all preterm births, posing a substantial challenge to maternal and neonatal health outcomes.[2] It is strongly associated with adverse consequences, including maternal infections such as chorioamnionitis, neonatal sepsis, respiratory distress syndrome, and long-term neurodevelopmental impairments in newborns.[3-4] These complications necessitate a comprehensive approach to management, aiming to prolong pregnancy (latency period) while minimizing the risks of infection and morbidity.[5]

Antibiotics are an essential component of the management of PPROM, as they help reduce the risk of ascending infections and improve perinatal outcomes by prolonging the latency period.[6] Erythromycin has been a standard choice for this indication, given its established efficacy and minimal fetal toxicity.[7] However, its short half-life requires frequent dosing (typically every 6 hours), which often

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leads to reduced patient compliance. Additionally, erythromycin is associated with significant gastrointestinal side effects, such as nausea and vomiting, which further impact adherence.[8]

Azithromycin, a second-generation macrolide, has emerged as a promising alternative. Its pharmacokinetic advantages, including a longer half-life and once-daily dosing, make it more convenient for both clinicians and patients.[9] Azithromycin has demonstrated broad-spectrum antibacterial activity and favorable tolerability in non-pregnant populations, leading to its increasing use in obstetrics.[10] Although azithromycin is gaining popularity for PPROM management, its effectiveness in improving maternal and neonatal outcomes compared to erythromycin has not been definitively established.

Given the potential benefits of azithromycin, including its simplified dosing regimen and better patient tolerability, it is crucial to explore whether it can achieve superior or equivalent fetomaternal outcomes compared to erythromycin in cases of PPROM. This study was designed to provide robust evidence through a randomized controlled trial comparing the two antibiotics. The findings are expected to inform clinical guidelines and enhance decision-making in the management of PPROM, ultimately improving maternal and neonatal outcomes in this high-risk obstetric condition.

Methodology

The study covered one-year period in the Federal Government Polyclinic Hospital as a randomized controlled trial that took place from May 2023 to May 2024 ethical approval No. FGPC.1/12/2021/Ethical committee). The patients with age between 18 years to 40 years with a singleton pregnancy, having confirmed PPROM between gestational ages of 24+0 to 33+6 weeks were included after confirmation of diagnosis. The diagnosis was based on the clinical criteria consisting of history of vaginal leakage and speculum examination showing the pooling of liquour. Nitrazine testing to confirm leaking in those with no pooling of liquour. Confirmed by the change in amniotic fluid index by ultrasound.

However, those who presented before 24+0 weeks, having fetal anomaly, active labour, excessive vaginal bleeding, cervical cerclage in the current pregnancy, chorioamnionitis on admission, placenta previa and abruption, maternal and fetal indication for delivery, allergy to macrolide antibiotics, use of antibiotics therapy within the 5 days, were excluded.

Sample size of 210(105 in each group) was calculated by 95% confidence level, 80% power of test and expected percentage of Chorioamnionitis as 25.8% with Erythromycin and 10.9% with Azithromycin.[21] In this trial, participants were divided into two groups using lottery method based on the antibiotic regimen they received: azithromycin or erythromycin. Participants in the azithromycin group were administered a single oral dose of 1g, while those in the erythromycin group received 250mg orally every 6 hours for 7 days. These dosages were selected based on established treatment protocols for preterm premature rupture of membranes (PPROM) to optimize efficacy in preventing infections and prolonging the latency period.

The azithromycin dose was administered under direct supervision to ensure compliance, with the single-dose regimen providing a practical and patient-friendly approach. For the erythromycin group, the initial dose was supervised in the hospital, followed by detailed instructions for continued 6-hourly dosing at home. Compliance was monitored through follow-up visits and telephone check-ins. Both groups received standard supportive care, including hydration, corticosteroids for fetal lung maturity (if indicated), and monitoring for signs of maternal or fetal complications. Neonatal outcomes (birth weight, APGAR scores, NICU admission rates, RDS incidence, and neonatal survival) and maternal outcome (chorioamnionitis and mode of delivery (SVD vs. LSCS) were assessed.

The data were coded, processed and analyzed by using SPSS version 25.0. Shapiro-Wilk test run to test normality of distribution. Qualitative data locality, education level, and mode of delivery were expressed in frequencies and percentage while quantitative data age, BMI, parity, and gestational age were expressed Mean±SD. Chi Square test was used to compare the neonatal outcomes (birth weight, APGAR scores, NICU admission rates, RDS incidence, and neonatal survival) and maternal outcome (chorioamnionitis and mode of delivery (SVD vs. LSCS) between groups. P-Value ≤0.05 was considered statistically significant.

Results

At the outset, there were 234 potential participants for the study. However, 24 of these women were deemed ineligible as they did not meet the selection criteria.

Among these, seven women were carrying multiple pregnancies, four had fetal anomalies considered incompatible with life, and 13 chose not to participate. Ultimately, 210 women agreed to participate and were divided evenly into two groups: Group A comprising 105 women and Group B comprising of 105 women as well. All 210 participants completed their follow-up visits until the conclusion of the study. There were no significant differences noted in socio-demographic characteristics and obstetric data between the both groups. (Table I)

Table I: Comparison of Socio-Demographic and Obstetric Characteristics Between Group A and Group B.

Variable		Group A (n=105)	Group B (n=105)	p-value
	Age in years (Mean±SD)	28.71±5.43	28.96±5.61	0.751
Locality	Urban, n(%)	29 (27.6)	21 (20)	0.191
	Rural, n(%)	76 (72.3)	84 (80)	
Education	Secondary (%)	26 (27.76)	24 (22.85)	0.890
	Basic Education (%)	54 (51.42)	55 (52.38)	
	Illiterate n(%)	25 (23.80)	26 (24.76)	
	BMI	33.29±4.11	32.80±4.17	0.340

The mean parity and gestational age at delivery were higher in Group A compared to Group B; however, the differences were not statistically significant. In contrast, there was a highly significant difference between the groups in the distribution of gestational age categories, as reflected by a p-value of 0.0001, as detailed in Table II.

Table: II: Obstetric Data of the Patients.

Variable		Group A (n=105)	Group B (n=105)	p-value
Parity		1.65±1.65	1.59±1.54	0.842
Gestational Age		32.44±2.91	31.89±3.69	0.248
Gestational Age Groups	24-28+6	9 (8.5%)	21 (20%)	0.001
	29-32+6	12 (11.42%)	33 (31.42)	
	33-36+6	84 (80%)	51 (48.57)	

The average latency period (5.86±5.50) was significantly longer in Group A than Group B (2.94±2.43), with p-value of 0.001. There were no statistically significant differences (p-value 0.35) between the two groups in terms of Chorioamnionitis rate. It was less in Group A with comparison to Group B. where SVD rate were higher in group A and LSCS in Group B (Table III)

Table III: Maternal Outcome of the Patients.

Variable		Group A (n=105)	Group B (n=105)	p-value
Latency Period (in Days)		5.86±5.50	2.94±2.43	0.001
Chorioamnionitis	Yes	9	13	0.35
	No	96	94	
Mode of Delivery	SVD n(%)	46 (44%)	32 (30%)	0.001
	LSCS n(%)	69 (66%)	73 (70%)	

The mean birth weight in Group A (2377.81±640.66) was not significantly differ in Group B (232.74± 641.05) with p-value 0.47. Furthermore, Group A presented a higher APGAR score at 5 minutes compared to Group B (p=0.000). The rate of admission to the Neonatal Intensive Care Unit (NICU) and the duration of stay in the NICU were lower in Group A than in Group B (p=0.000, 0.001; respectively). Furthermore, the incidence of respiratory distress syndrome (RDS) was significantly higher in Group B as compare to Group A (p=0.000).

Table IV: Neonatal Outcome.

Variable		Group A (n=105)	Group B (n=105)	p-value
Birth Weight (in grams)		237.81± 640.66	232.74 ± 641.05	0.47
APGAR Score at 5 minutes	<7	37 (35.23%)	77 (73.33%)	0.000
	>7	68 (64.76%)	28 (26.66%)	
NICU	Yes	28 (26.6%)	57 (54.28%)	0.04
	No	77 (73.33%)	48 (45.71%)	
RDS	Yes	24 (22.85%)	54 (51.42%)	0.000
	No	81 (77.14%)	51 (48.57%)	
Neonatal Mortality	Alive	100 (94%)	98(93%)	0.521
	IUFD	3 (2.85%)	4 (5.71%)	
	Death	2 (2.8%)	3(3.80%)	

Discussion

The patients of Group A had Azithromycin longer latency and longer gestation periods than the ones who were given Erythromycin (Group B). There weren't any significant differences between the groups regarding inflammation of the fetal membranes (chorioamnionitis) as well as mode of delivery observed in both groups. In the comparison of Group B, Group A had better neonatal outcomes. These findings are compatible with the previous study that reported a decreased risk for the development of clinical Chorioamnionitis, caesarian delivery, neonatal sepsis, and postpartum endometritis.[10]

In our study, Group A (azithromycin) demonstrated a significantly longer mean latency period (5.86±5.50 days) compared to Group B (erythromycin) at

2.94±2.43 days (p=0.0001).This finding is in accordant with the study revealed that azithromycin administration (7 days) was associated with increased latency time in PPROM by 5.8 days [interquartile range, 4.8–6.9 , P<.001).[11] However, This finding in some way not consistent with other previous study that reported insignificant differences between the groups in mean of pregnancy length but also stated that azithromycin was associated with greater satisfaction and its use is recommended in PPROM.[12] Similarly, a study specified that Azithromycin has generally replaced a 7-day course of erythromycin in current clinical practice due to its better side effect profile.[13] Another study found that higher dose of Azithromycin was associated with better maternal and neonatal outcomes as the latency period in group I was significantly higher (5.80 ± 5.44 days vs. 2.88 ± 2.37, p = 0.0001). [14]

On the other hand, Seaman et al. found no significant difference in latency duration between azithromycin and erythromycin (6.7 vs. 6.6 days, mean difference, 0.07).[15] The discrepancies may be due to variations in azithromycin dosing regimens and patient populations.

The incidence of chorioamnionitis was lower in Group A (9%) compared to Group B (13%), though the difference was not statistically significant (p=0.35). Previous studies, such as by Conde-Agudelo et al. have demonstrated that azithromycin use is associated with a reduced risk of chorioamnionitis, with an odds ratio favoring azithromycin over erythromycin.[16] This aligns with the trend observed in our study, even though statistical significance was not achieved, possibly due to the sample size.

The rates of spontaneous vaginal delivery (SVD) were slightly higher in Group A (46%) compared to Group B (34%), while LSCS was more common in Group B (68% vs. 71%, p=0.00). Similar findings were reported by Finneran et al. Who observed higher rate of cesarean delivery (48.8 vs. 29.5%, p = 0.01) in the erythromycin group.[17]

The mean birth weight between the two groups were not statistical significantly (237.81± 640.66 vs 232.74 ± 641.05, P=0.47). Group A had significantly higher APGAR scores at 5 minutes (64.76% of neonates had scores >7) compared to Group B (26.66%, p=0.000). These results are consistent with previous findings by Navathe et al. stated less necrotizing enterocolitis, Intraventricular hemorrhage; and 5-minute Apgar score <7 for the women who received azithromycin compared with the erythromycin group. [18]

NICU admission rates were lower in Group A (26.6%) compared to Group B (54.28%) and the rate of neonatal sepsis was more in group B as compared to group A (P=0.04). Similarly, the duration of NICU stay was shorter in Group A. These findings are compatible with the previous studies indicated patients receiving the azithromycin had significant advantage.[10,18] There was a higher rate of neonatal sepsis /positive neonatal blood cultures (13.6 vs. 4.1%, p = 0.05) in the erythromycin group.[17] RDS was significantly less frequent in Group A (22.85%) compared to Group B (51.42%, p=0.000).This is also corroborated by findings from Finneran et al.[17] and Navathe et al[18] highlighted that the incidence of RDS was lower in the Azithromycin group due to better fetal lung maturity at delivery.

In our study, Neonatal Mortality or survival was better in Group A, with lower rates of intrauterine fetal demise (IUFD) and neonatal deaths compared to Group B but they did not differ significantly (p=0.521). Similar outcomes were reported by Park Bae, & Chang, indicated that survival rate in the prolonged latency group did not differ from that in the short latency group (P = 0.478), and was not associated with mortality during hospitalization.[19]

Our study aligns with much of the existing literature, showing that azithromycin is superior to erythromycin in prolonging latency, reducing neonatal complications (e.g., RDS and NICU admissions), and improving neonatal survival. However, some studies reported no significant differences between the two antibiotics, possibly due to variations in methodologies, dosing regimens, and patient characteristics. These findings reinforce the need for further research to establish azithromycin as a preferred treatment in PPROM cases.

Conclusion

Azithromycin 1g single-dose therapy is superior to Erythromycin in improving fetomaternal outcomes due to its enhanced convenience and maternal compliance. Its use should be considered a more effective alternative in clinical scenarios requiring antibiotic therapy during pregnancy, emphasizing better maternal and neonatal well-being.

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