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ASSESSMENT OF INTERVENTION OF ANTIBIOTICS AMONG PATIENTS WITH PRETERM PREMATURE RUPTURE OF MEMBRANE IN A TERTIARY HOSPITAL OF KOLKATA, INDIA

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ABSTRACT

Introduction: Preterm Premature Rupture of Membrane can lead to significant perinatal mortality and morbidity. **Materials and Methods:** An intervention study was conducted with two different regimens of antibiotic on two randomized groups. Data were analysed by Students "t" test, Chi square test using SPSS version 20.0. **Results:** Majority were in the age group of 21 to 30 yrs, second gravid. Nulliparous and multiparous mothers were equally distributed. Mean duration (hrs) since rupture of membranes was 7.88 ± 3.83 hrs in group A and 9.16 ± 4.18 hrs in group B. Latency of 7 days and less was seen in 22.8% of group A population and 15.8% of group B population respectively. Azithromycin and Erythromycin groups have been observed with equal maternal and neonatal outcomes. Side-effects were found low among patients. **Conclusion:** There was no statistical difference in outcomes between two groups of antibiotic regimens in term of latency, maternal and neonatal outcome.

KEYWORDS : Intervention of Antibiotic, Preterm Premature Rupture of Membrane, No difference of two regimens

Introduction

Preterm Premature Rupture of Membrane (PPROM) is defined as spontaneous rupture of foetal membranes before 37 completed weeks of gestation and prior to the onset of labour. PPROM complicates around 2% of pregnancy but is associated with 40% of preterm deliveries. [1]

PPROM can lead to significant perinatal mortality and morbidity such as Respiratory Distress Syndrome (RDS), neonatal sepsis, umbilical cord prolapse, placental abruption and foetal death. PPROM can also lead to maternal morbidity like chorioamnionitis, postpartum endometritis, Disseminated Intravascular Coagulation (DIC), delayed menstruation, Asherman syndrome and others. [2]

The incidence of PPROM increases with the gestational age. The significance of PPROM depends on the gestational age at the time of occurrence. While most of the pregnant women near term go into labour and deliver spontaneously within 48 hours, those with PPROM have long and variable periods of latency. The length of latency period is inversely related with the gestational age. [3]

Numerous risk factors are associated with PPROM such as black race, lower socioeconomic status, past history of sexually transmitted infection, previous history of preterm delivery, polyhydramnios and multiple pregnancies. Others are procedures such as cervical cerclage & amniocentesis. [2]

The etiology of PPROM is multifactorial. This may be related to intrauterine infection (IUI), membrane dysfunction at the molecular level (due to reduced size of membrane, reduced collagen content, deficiency of type 3 collagen, reduced elasticity), genetic variation or a combination of factors. [4]

Infection appears to have an important role, either as a cause or as consequence of PPROM. Some organisms may produce collagenases, mucinases and proteases which weaken the amnion and chorion and may lead to PROM. On the other hand, infection may occur secondary to membrane rupture. Ascending infection may lead to occult deciduitis, intra-amniotic or fetal infection. [5]

A possible mechanism for the link between infection and preterm delivery is bacterial stimulation of the biosynthesis of prostaglandins, either directly via phospholipase A2 and C or indirectly via substances such as interleukin-1, tumour necrosis factor and platelet activating factor, all of which may be found in infected amniotic fluid. [5]

Evaluation & management of PPROM are important for improving neonatal outcome. The management of pregnancies complicated by PPROM is challenging, controversial and should be individualized. However, it should focus on confirming the diagnosis, validating gestational age, documenting fetal wellbeing and deciding on the mode of delivery which depends on gestational age, fetal presentation and cervical examination. [2]

Current evidence suggests aggressive antibiotic therapy which is effective for increasing latency period and reducing infectious infant morbidity. Corticosteroids can reduce many neonatal complications particularly respiratory distress syndrome and intraventricular haemorrhage. [2]

With the strong link between infection and PPROM, research has focused on the use of antibiotics following PPROM for the purpose of decreasing the complications associated with infection. Antibiotic therapy could prolong latency and improve maternal and foetal outcomes.

Treatment with antibiotics in the absence of labour has been shown to decrease the frequency of chorioamnionitis, prolong latency and decrease foetal and neonatal complications. [4] Antibiotic treatment also provides time to let corticosteroids work. Quite a few antibiotic regimens are advocated for use in PPROM.

The American College of Obstetricians and Gynaecologists (ACOG) recommends a seven days course of therapy with a combination of intravenous Ampicillin and Erythromycin followed by oral Amoxicillin and Erythromycin during expectant management of women with PPROM who are of less than 36 weeks of gestation. [6]

The present study was intended to evaluate the efficacy of combination of Ampicillin and Azithromycin with Ampicillin and Erythromycin in prolonging latency in PPROM. The usual practice is to give a single intravenous dose of Ampicillin 2 gm followed by 500 mg of Erythromycin orally six hourly for seven to ten days. The spectrum of microbial coverage of Azithromycin is similar to Erythromycin because both are macrolides. Azithromycin is often substituted for ease of administration, presumed equivalency, fewer side effects and possible decrease in cost of therapy along with once daily dosage. In this regard, it would be logical to assess and compare the efficacy of combination of Ampicillin and Azithromycin with Ampicillin and Erythromycin for prolonging latency in Preterm Premature Rupture of Membranes (PPROM).

With these backgrounds, this study was conducted to compare the efficacy of Ampicillin and Azithromycin combination and that of Ampicillin and Erythromycin in prolonging latency in Preterm

Premature rupture of Membranes and to compare the safety of Azithromycin and Erythromycin.

Materials and Methods

Study setting was Department of Gynaecology & Obstetrics, R G Kar Medical College and Hospital, Kolkata. **Study tools** used were schedule for data record, Weighing Machine, Sphygmomanometer, Ultrasonography machine; **Study period was o**ne year (1st July 2015-30th June 2016). **Study Population -** All women who were admitted in the department of Gynaecology & Obstetrics with Preterm Premature Rupture of Membranes were the study population.

Study variables were age, gravid, parity, educational level, income status, gestational age at dribbling, latency, Ampicillin and Erythromycin, Ampicillin and Azithromycin, side effects of the drugs etc.

Inclusion criteria: 1. Pregnant women of 19 yrs of age and above with preterm premature rupture of membranes and not in labour, 2. Gestational age of 28 to 34 weeks, 3. Single foetus gestation, 4. Randomization within 36 hours of rupture of membranes, 5. Cervical dilatation less than or equal to 04 cm.

Exclusion criteria-

1. Gestational age <28 weeks and>34 weeks, 2. In preterm Labour, 3. Cervical cerclage in situ, 4. Multifetal gestation, 5. Vaginal bleeding/foul smelling vaginal discharge, 6. Maternal or foetal indication for delivery, 7. Placental abnormality, 8. H/O amniocentesis, 9. Presence of chorioamnionitis clinically and/or supported by laboratory investigation, 10. Had received corticosteroid within the last seven days, 11. Had received antibiotic within the last seven days, 12. Carrying a foetus with lethal anomalies, 13. H/O foetal surgery, 14. H/O abdominal trauma, 15. On Anti Retroviral therapy, 6. Known allergy or contraindication to use of Ampicillin, Azithromycin and Erythromycin.

Sample size: Some study [7] has shown that the latency in case of PPROM treated with Ampicilin and sulbactum was 9.54 days. We hypothesized to increase the latency from 9.54 days to 12 days by treating with ampicillin and azithromycin. Keeping the alpha error to be 0.05, beta error 0.20, minimum sample size required was to be 108. Considering dropout of few cases, we did take a total sample size of 114 in our study with 57 in each arm.

Method of data collection:

Data had been collected from history, antenatal card and hospital admission record, hospital delivery log records, Neonatal Intensive Care Unit records, laboratory investigations, and also from regular daily observation of the patients. The data had been recorded in a predesigned case report proforma (schedule).

Experimental design: I. Study type – Interventional, II. Study design - Prospective Controlled Study, III. Allocation – Randomised, IV. End Point Classification - Efficacy and safety study, V. Intervention Model - Parallel Assignment, VI. Masking - Due to the nature of the study, doctor and patient were not blinded, assessor however was blinded, VII. Primary purpose – intention to treat, VIII. Randomisation – (a) Sequence Generation: Randomisation was done by computer generated list randomised in block to ensure balanced allocation. Block size was between 04 to 10. (b) Allocation concealment mechanism: Allocation concealment had been done by numbered opaque sealed envelope.

Parameters and procedures: All the patients with suggestive history of PROM like sudden gush of fluid or continued leakage of fluid per vagina, feeling wet had been admitted and diagnosis was confirmed by physical examination by checking for pooling of amniotic fluid by speculum examination and/or positive nitrazine/ferning test.(if necessary)

After taking informed consent, Patients fulfilling the inclusion criteria had been included in the study. Then, the patients were divided into two groups by randomization i.e. Group-A & Group-B by using serially numbered opaque sealed envelope technique.

Group A (Intervention group): Patients were administered dose of Inj. Ampicillin after proper sensitivity test (APST) as 02 gm IV six hourly for 48 hours. Azithromycin was added on 3rd day as 500mg orally once daily for five days.

Group B (Control group): Patients were administered dose of Inj. Ampicillin after proper sensitivity test (APST) as 02 gm IV & then six hourly for 48 hours followed by tablet Erythromycin 500 mg orally six hourly for five days.

All subjects received two doses of antenatal corticosteroid as 12 mg of injection Betamethasone IM at 24 hours interval having the first dose on admission.

All the patients were monitored daily for features of chorioamnionitis by checking pulse rate, blood pressure, temperature, uterine tenderness or any foul smelling discharge per vaginum.

Latency: In our study, the latency has been defined as the time interval from first antibiotic dose administration to the time of delivery. [4]

Schedule of data collection:

Data collection had been done at admission & during and after antibiotic administration, and after delivery. As all the patients were admitted, they were regularly assessed daily for vital signs, side effects of antibiotics (like cholestatic hepatitis, nausea, vomitting, diarrhoea, cardiac arrhythmia, fever, skin eruptions), onset of labour and the necessary data were collected.

Statistical analysis plan:

Continuous variable has been analysed by independent Students 't' test. Categorical data have been analysed by chi square or Fisher exact test as appropriate. P value of <0.05 has been considered to be statistically significant. Statistical analysis was performed using SPSS for Windows version 20.0.

Results and Analysis

During the study period 114 subjects were included and they met the inclusion criteria with PPROM in group A (n=57) who received Ampicillin +Azithromycin and group B (n=57) who received Ampicillin + Erythromycin. Their mean age was 23.3 ± 4.04 years in group A and 24.7 ± 4.13 years in group B. Majority were in the age group of 21 to 30 yrs in both the groups. The group subjects were similar in age character (Table 1).

Table 1: Distribution of study subjects according to age (n= 114)

Age in Years	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
≤ 20	22 (38.6%)	13 (22.8%)	35 (30.7%)
21 to 30	27 (47.4%)	33 (57.9%)	60 (52.6%)
≥ 31	8 (14.0%)	11 (19.3%)	19 (16.7%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Pearson's χ^2 Chi-square = 3.388, df = 2 p = 0.184

The majority of the subjects in study populations were of 2nd gravida. Mean gravidity in group A was 1.74± .695 and in group B was 2±.824 (Table 2).

Table 2: Distribution of study subjects according to Gravida (n=114)

Gravida	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
1	23 (40.46%)	17 (29.8%)	40 (35.1%)

2	26 (45.6%)	25 (43.9%)	51 (44.7%)
3	8 (14.0%)	13 (22.8%)	21 (18.47%)
4	0 (0.0%)	2 (3.5%)	2 (1.8%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Nulliparous and multiparous mothers were almost equally distributed in both the groups. Distribution of parity in both the groups was found to be non-significant [Pearson's Chi-square ($\chi 2$) = 4.891, df = 2, p = 0.087]. Mean parity was found .51 ± .539 in group A and .65 ± .694 in group B.

Among the fifty seven subjects, 36.8% and 35.1% of Group A were educated up to Middle School and Secondary Level respectively. In Group B 33.3% and 43.9% were educated up to Middle School and Secondary Level respectively.

Out of 114 subjects, 61.4% of group A and 66.7% of group B had total family income of INR 5,000 to 10,000. Only 5.3% subjects of group B and none of group A had family income of less than INR 5,000. A good number of subjects (38.6% in group A and 28.1% in group B) was found with good income (> Rs. 10000.00/month).

Table 3: Distribution of study subjects according to gestational age at dribbling (n=114)

Gestational age at Dribbling	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
28 – 31wks	35 (61.4%)	25 (43.9%)	60 (52.6%)
32 – 34 wks	22 (38.6%)	32 (56.1%)	54 (47.4%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Mean gestational age at dribbling for group A was 31 weeks and 3 days ± 1 week and 4 days while that for group B was 32 weeks ± 1 week and 2 days (**Table 3**). Gestational age at dribbling was not different in the two groups. Gestational age at dribbling of the two groups was not found to be significant at 95% Confidence Interval ($\chi^2 = 3.519$, p = 0.061).

Table 4: Distribution of study subjects according to duration since rupture of membranes at the time of admission (n=114)

Hours since rupture of membranes	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
< 12 Hours	43 (75.4%)	39 (68.4%)	82 (71.9%)
≥ 12 Hours	14 (24.6%)	18 (31.6%)	32 (28.1%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Mean duration (hrs) since rupture of membranes was 7.88 ± 3.83 hrs in group A and 9.16 ± 4.18 hrs in group B. This difference was not statistically significant ($\chi^2 = 0.695$ p = 0.404)

Majority of subjects did not have past history of PPROM which was 84.2% in group A and 78.9% for group B. Two groups for past history of PPROM showed no significant difference at 95% Confidence Interval ($\chi^2 = 0.525$, p = 0.469).

Study subjects gave a positive history of coitus during present pregnancy of which 15.8% and 14.0% were found in group A and group B respectively. These two groups for coitus at present pregnancy showed no significant difference at 95% Confidence Interval ($\chi^2 = 0.069$, p = 0.793).

To compare the efficacy of Ampicillin and Azithromycin combination and that of Ampicillin and Erythromycin combination, latency in preterm premature rupture of membranes (PPROM) in both the groups was noted.

Table 5: Distribution of study subjects according to Latency in days (n = 114)

Latency in days	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
7 and less	13 (22.8%)	9 (15.8%)	22 (19.3%)
> 7	44 (77.2%)	48 (84.2%)	92 (80.7%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Pearson's χ^2 Chi-square = 0.901, p = 0.342

Latency of 7 days and less was seen in 22.8% of group A population and 15.8% of group B population respectively. Whereas latency of >7 days was seen in 77.2% and 84.2% in group A and B respectively. Test of significance for the two groups showed no significant difference ($\chi^2 = 0.90$, p = 0.342). Mean latency after administration of Ampicillin and Azithromycin in group A was 8.65 days ± 2.303 and 9.18 days ± 2.164 in group B who were given Ampicillin and Erythromycin. An independent unpaired sample T-test (students T-test) was done for mean latency and was found to be not significant (t = 1.257, p = 0.211). (**Table 5**).

Azithromycin and Erythromycin groups have been observed for maternal and neonatal outcomes. Chorioamnionitis (10.5% vs 14.0%), Puerperal Sepsis (8.8% vs 12.3%), Birth Weight > 2 Kg (35.1% vs 47.4%), Respiratory Distress Syndrome (38.6% vs 33.3%) etc were observed in Ampicillin and Azithromycin versus Ampicillin and Erythromycin groups. There was no statistical significant difference in outcomes between these two groups.

Table 6: Distribution of side-effects of study subjects following consumption of Ampicillin with Azithromycin and Ampicillin with Erythromycin respectively (n=114)

Side effects	Ampicillin + Azithromycin (Group A)	Ampicillin + Erythromycin (Group B)	Total
Vomiting	3 (5.3%)	6 (10.5%)	9 (7.9%)
Skin rash	1 (1.8%)	0 (0.0%)	1 (0.9%)
Nausea	0 (0.0%)	3 (5.3%)	3 (2.6%)
Diarrhoea	0 (0.0%)	2 (3.5%)	2 (1.8%)
Nil	53(93.0%)	46 (80.7%)	99 (86.8%)
Total	57 (100.0%)	57 (100.0%)	114 (100.0%)

Since 7 cells have value of expected count of 5, so chi-square test was not done Vomiting was the predominant side-effect with 5.3% and 10.5% of the group A and group B respectively. Small number of group B subjects (5.3% and 3.5%) complained of nausea and diarrhea respectively. Only one subject of the total study group (n=114) complained of skin rash following intake of drugs given in group A (**Table 6).**

Discussion:

Premature rupture of membranes is a fairly common complication of pregnancy and can lead to increased maternal complications, operative procedures, neonatal morbidity and mortality. Treatment with antibiotics in the absence of labour has been shown to prolong latency, decrease the frequency of chorioamnionitis, puerperal sepsis and fetal and neonatal complications etc. This study was conducted to compare the efficacy of combination of Ampicillin and Azithromycin with Ampicillin and Erythromycin in prolonging latency in PPROM.

Socio-demographic characteristics:

Cases were selected among pregnant women aged 19 years and above who attended in OPD and ER with PPROM. Majority of the patients were in the age group of 21 to 30 years. Mean age in group A was 23.3 ± 4.04 years and mean age in group B was 24.7 ± 4.13 years. These findings were similar to the study done by Pierson et al [4] which was a retrospective comparative study of antibiotics in PPROM, conducted in the University School of Medicine, Indianpollis, Indiana in the year 2014 where mean age was 26.3 ± 6.4 years in Ampicillin + Azithromycin group and 27.4 ± 6.3 years in

Ampicillin + Erythromycin group. Another 10 years retrospective study by Okeke TC et al [2] was conducted in the University of Nigeria Teaching Hospital, Nigeria during January 1999 to December 2008, where the incidence of PPROM was highest (43%) among 26 to 30 years age group. According to the comparative study of Akter et al, 40.33% cases of PROM belonged to age group between 21- 25 yrs. [8]

Majority of study subjects were found second gravida. According to the study by Okeke TC,[2] primigravida had the highest occurrence of PPROM (29.1%). In this study, mean gravidity in group A was 1.74 ± .695 and in group B 2 ± .824. But the study by Pierson et al [4] showed mean gravidity of 3 ± 2 in both the groups.

In the present study, good number of subjects were nulliparous and about to equal was multiiparous in both the groups and there was no statistically significant differences in between two groups (p = 0.087). According to Pierson et al, [4] the mean parity was 1 ± 1 in group A and 2 ± 2 in group B.

In the study by Okeke TC [2] 29.1% subjects were nulliparous.
In the present study there were no statistically significant difference in educational level and total family income in the two groups of study population and they were comparable. The majority of the subjects were having education upto secondary level. The income was between Rs. 5000 to 10,000 in majority of the subjects. These findings were similar to the descriptive cross sectional case control study of Risk factors for PPROM by D. Kaye. [3]

Gestational age at dribbling: In the present study, gestational ages of both the groups were comparable with a difference but this difference was not significant statistically (p value = 0.061). Mean gestational age at dribbling was similar with the study by Pierson et al, [4] was comparable to another study by D. Kaye. [3]

The past history of PPROM of both the groups of the present study was not statistically significant (p = 0.469) and this was similar with the study result done by Aaron B Caughey et al. [31] We can recall the risk of recurrence of PPROM at the rate of 16 to 32% as compared with approximately 4% in women with a prior uncomplicated term delivery. Shweta Patil et al [9] of Karnataka, India, mentioned past history of PPROM in 6% of cases.

Coitus: History of coitus was present in a number of subjects in both the groups without any significant difference (p value = 0.793) but similar with the study by Shweta Patil et al, [9] where history of coitus was present in 10% of patients.

Both the groups were almost similar in time interval of dribbling after rupture of membrane without any statistical significant difference (p=0.404) between groups but majority of the subjects who presented after 12 hours of rupture of membrane were in the Erythromycin group. In the study by D. Kaye, the mean duration of hours since rupture of membrane was similar to this study. [3]

Period of latency: Period of latency was the main and primary outcome of this prospective study and this study established no statistical significant differences in maternal and neonatal outcomes between patients of Azithromycin group and Erythromycin group except in mean birth weight and NICU stay. This was in agreement with the study by Pierson et al. [4] Another study of antibiotic use in PPROM by Mercer B M, USA found similar result. [10]

Another retrospective study by Shari Gelber et al proved the same. [11]
In the ORACLE I trial, conducted in U.K among 4826 women with PPROM at < 37 weeks' gestation were enrolled and randomized into one of four oral treatment groups: (1) 325 mg Co-amoxiclav (250 mg amoxicillin and 125 mg clavulanic acid) plus250 mg erythromycin, (2) Co-amoxiclav plus erythromycin placebo, (3) Erythromycin plus Co-amoxiclav placebo, or (4) Co-amoxiclav placebo plus erythromycin placebo. Oral erythromycin was associated with prolongation of pregnancy for 48 hours when erythromycin only was compared with placebo (34.8% vs. 40.7%, *P* = 0.004). [12]

The Cochrane Collaboration published a review by Kenyon and colleagues of the use of any antibiotics versus placebo (macrolides vs placebo) following PPROM. The use of antibiotics was associated with a prolongation of pregnancy for both 48 hours (RR 0.71; 95% CI 0.58 to 0.87) and 7 days (RR 0.80; 95% CI 0.71 to0.90). [12]

Safety of Azithromycin and Erythromycin: Vomiting was the predominant side-effect with 5.3% and 10.5% subjects of Azithromycin group and Erythromycin group respectively. Subjects of Group A and B complained of Nausea and diarrhea at 5.3% and 3.5% respectively. Only one subject of the total study group complained of skin rash following intake of Ampicillin and Azithromycin, although this symptom was not felt to be an adverse effect of the drug. This study was similar with the study by Pierson et al, which showed no significant adverse effects among two antibiotic regimens. [4]

Conclusion:

There was no statistical difference in outcomes between two groups of antibiotic regimens (Ampicillin and Azithromycin versus Ampicillin and Erythromycin) in term of latency, maternal and neonatal outcome. There was improvement in several outcomes with Azithromycin, so it points toward further studies for determining efficacy of Azithromycin over Erythromycin in PPROM.

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