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"Study Of The Effect Of Chorioamniotic Membrane Sealing Drug (Amnioseal) In Premature Rupture Of Membranes: A Randomised Control Trial"

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ABSTRACT

Objective(s) : To study and compare the effectiveness of chorioamniotic Membrane sealing drug (Amnioseal) in premature rupture of membrane (PROM) with conventional treatment in terms of prolongation in gestational age and perinatal outcome.

Method(s): This randomized control trial conducted in dept. of obs and gynae, SMS Medical College, Jaipur. 210 antenatal patients (pts) with prelabour PROM recruited for the study. They divided into 2 groups of gestational age 24-30 weeks (Group A) and 31-36 weeks (Group B). These groups further subdivided into A1, A2 and B1, B2 respectively. Out of them A1, B1 were cases and A2, B2 were controls. All the patients put on rest, antibiotics, prophylactic corticosteroids and tocolytics (conventional treatment). Amnioseal added to conventional treatment in cases of A1, B1. Results observed.

Result(s) : In 24-30 weeks i.e. group A ,Mean prolongation of gestational age was 6.00 ± 3.87 wks (cases A1) versus 5.56 ± 3.46 wks (controls A2) while in 31-36 weeks i.e. group B, prolongation was 4.00 ± 2.42 weeks (cases B1) versus 3.50 ± 2.84 weeks (controls B2)(significant). In-group A mean birth weight was 1.80 ± 0.76 kg (in A1) versus 1.66 ± 0.72 kg (in A2), while 2.43 ± 0.44 kg (in B1) versus 2.20 ± 0.52 kg (in B2) (significant). Perinatal outcome was better in cases (A1 & B1).

Conclusion(s): Membrane sealing drug (Amnioseal) has a definite role in PROM as it helps in prolongation of gestational age and improves fetal outcome.

Keyword(s): - *Amnioseal,* Membrane sealing drug, premature *rupture of membranes.*

INTRODUCTION

Preterm prelabuor rupture of fetal membrane (PPROM) defined as rupture of fetal membranes prior to the onset of labour at less than 37 weeks of gestation. Premature rupture of the membranes (PROM) complicates 10% of all gestations[1] and 2-4% of preterm pregnancy.[2] In India incidence of PROM varies between 7-12%.[3] it is an important controversial dilemma for obstetricians. Extensive research has done for PROM; still the rate of preterm birth has increased by 38% since 1981.[4]

Risk factors of PROM are infections, genetic factors, zinc and vitamin C deficiency, smoking, trauma, amniocentesis,

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ante partum bleeding, lower socio-economic status, cervical incompetence, sexual contact, polyhydramnios, etc.

PROM may result to chorioamnionitis, endomyometritis, increased caesarean rate, dysfunctional labour, PPH or septic shock in mother. It may causes respiratory distress syndrome (RDS), hyperbilirubinemia, hypothermia, intraventricular haemorrhage (IVH) and necrotizing enterocolitis, fetal distress, infections, septicemia, pneumonia or urinary tract infection. Late squeals are blindness, cerebral palsy, fetal deformation syndrome or Fetal pulmonary hypoplasia (incidence of it varies 3% to 28%.[5]

PPROM can be diagnosed by history, clinical examination, pH, heat test, arborization (fern test), detection of placental alpha microglobulin-1 (amnisure test) , fetal fibronectin & α-fetoprotein detection and ultrasound .The goal of management in PPROM is prolongation of pregnancy, the most commonly accepted management is expectant management (antibiotics, tocolytics,corticosteroids).

Efforts should do to prolong pregnancy by drugs such as chorioamniotic membrane sealing drug (Amnioseal). At the same time, early identification of infection is must and appropriate intervention should be done. Amnioseal acts by making Coordination between matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases. It is a gelatin capsule combination of proapoptolic bax gene p-53 inhibitor, myristoleate with antimicrobial peptides, and cytokine, IL-10 to target the immunological system.

There are only few available studies with chorioamnitic sealing drugs, but showed better results than conventional management with antibiotics. This improved perinatal outcome with Amnioseal has prompted us to study this drug in PPROM.

METHODS

210 Antenatal patients (105 cases and 105 controls) of gestational age 24-36 weeks with leaking per vaginum (LPV) studied in Department of Obstetrics and Gynecology, Zenana Hospital, SMS Medical College, Jaipur. Sample size calculated 18 patients in each group of 24-30 wks GA. 87 patients in each group of 31-36 wks GA calculated as sample size. Out of them 2 cases and 6 controls discontinued from our study due to frank chorioamnionitis and statistical calculation done with 202 patients. We had done the Statistical analysis by using χ^2 test and 'Z' test in the all groups.

Obstetric and gynecological history had taken. Duration and amount of leaking had noted. Personal history, past history and family history had noted. Thorough and detailed examination of the patient carried out. Leaking per vaginum was confirmed by fern test. Routine investigations and ultrasonography had done. All the patients had explained about the study and drug. A prior consent was taken and then the patients were selected by randomization (alternate method). Inclusion crieteria was- ANC patients at GA 24-36 weeks with leaking per vagimum. Excluded were ANC patients with frank LPV and with active labour pain or having medical disorders. Patients were divided in 2 groups.

Group A (24-30 wks) – Who were prescribed Aminoseal (Cases A1) and who were not prescribed the drug (Controls A2).

Group B (31-36 wks) – Who were prescribed Aminoseal (Cases B1) and who were not prescribed the drug (Controls B2).

All the patients were put on rest, antibiotics, prophylactic corticosteroids and tocolytics (Nifedipine) after sending a high vaginal swab for culture sensitivity. In addition to above, the cases in Group-A1 and B1 were prescribed capsule Amnioseal in following dosage schedule: -2 Capsules-Stat, 2 Capsules-After 3 hrs f/b 2Capsules-8 hrly till next 72 hrs then 1 Capsule BD x 15 days and then1 Capsule OD x 15 days.

Monitoring of pulse, temperature, fetal heart rate and fetal movement count was done every day. Contractions and tenderness of uterus was noted 12 hourly. Vaginal discharge examined daily. Weekly ultrasound for amniotic fluid index was done. CBC & CRP had done Every 48 hrly. Fortnightly liver function tests had done. The perinatal outcome was documented.

RESULTS

In our study (87.62%) maximum women were in age group 18-27 years and 65.33% patients were from rural area . 83.66% women were Hindus, 60.39% were booked patients and 61.38% were literate, 45.54% were of lower socio-economic status and 50% of middle status, and 54.45% were primigravidas. The recurrence rate of PPROM was 58 (28.71%) and 30.69% were delivered by caesarean section (in this study). Out of 202 patients of PPROM, 93 (46.03%) cases (of Group-A1 and Group-A2) v/s 70 (30.65%) controls (of Group-B1 and Group-B2) had stoppage of demonstrable LPV after 24 hrs of treatment (Conventional and Amnioseal). Overall incidence of chorioamnionitis was 3.80% in 210 patients, whereas it was 1.94% in cases and 6.06% in control.

DISCUSSION

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A perceptible shift has taken place in management of PROM in recent years away from early induction of labour towards conservative approach. Various novel treatments for sealing of the membranes after previable PROM (e.g., fibrin/platelet/cryoprecipitate, or gel-foam instillation) have been used.

Dam Purvita et al (2010)[6] studied about Amnioseal in PROM. They stated that to counteract the immunological system, we had used a combination of proapoptotic bax gene P-53 inhibitor, myristoleate, with antimicrobial peptides, neutrophil defensins, and cytokine IL-10 enhancer.

They studied 46 cases with amnioseal and 60 controls without amnioseal with LPV in their antenatal period of 24 and 36 weeks gestation. In the 24-30 weeks group, 12 cases (A1) and 15 controls (B1) mean prolongation of gestational age was 6.16 ± 3.21 wks as against 2.66 ± 1.05 wks (significant). While in 31-36 weeks (31 cases A2 & 36 controls B2), it was 4.69 ± 0.84 wks as against 4.6 ± 0.632 wks (significant), Oligohydramnios occurred in 4 v/s 8 of A1 & B1 while 4 v/s 12 in A2 & B2 Group. The mean birth weight in A1 v/s B1 was 1.77 ± 0.66 kg v/s 1.2 ± 0.43 kg (significant), while in A2 v/s B2 it was 2.18 ± 0.56 kg vs1.76 ± 0.45 kg (significant). Associated complications were less in cases. Neonatal mortality was seen in 5 v/s 13 in A1 v/s B1 and 3 v/s 12 in A2 v/s B2. Septicemia was noted in 2 v/s 5 of A1 v/s B1, 5 v/s 8 of A2 v/s B2. Birth asphyxia was seen in 4 v/s 6 of A1 v/s B1 and 2 v/s 7 in A2 v/s B2. RDS was reported in 2 v/s 4 in A2 v/s B2 . Neonatal jaundice occurred in 8 v/s 18 in A2 v/s B2. IVH was reported in 2 v/s 4 of A2 v/s B2. Incidence of cesarean section rates were slightly higher in cases

Yet no other studies available with the use of Amnioseal more randomized controlled trials are required to assess the efficacy of the drug.

CONCLUSION

Amnioseal is a novel drug with initial promising results, it helped in sealing the membrane and stoppage of leaking in 90.29% patients with PPROM treated with Amnioseal (Group-A1, A2), thus helped in prolongation of pregnancy, prevention of infection, thereby improving maternal and Neonatal outcomes .But this is a small study. More studies and randomized controlled trials are required to see the efficacy of Amnioseal. Therefore, Amnioseal can be bringing to broader use in improving neonatal outcome in PPROM cases.

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Table-1

Distribution of study population according to Mean ± SD of Duration of Leaking Per Vaginum of Group-A1, Group-A2 and Group-B1,Group B2

	Total no. of patients	Mean ± SD Duration in hrs	P-value	Significance
Group-A1 (24-30wks)	17 cases	67.41 ± 106.07	<.05	Sig
Group-A2 (24-30 wks)	17 controls	45.70 ± 41.08		
Group-B1 (31-36 wks)	86 cases	42.77 ± 82.35	<.05	Sig
Group-B2 (31-36 wks)	82 controls	35.80 ± 70.76		

Table-1 shows that mean duration of leaking per vaginum in (Group-A1,Group-A2) was 67.41 ± 106.07 hrs & 45.70 ± 41.08 hrs and in (Group-B1 , Group-B2) it was 42.77 ± 82.35 hrs & 35.80 ± 70.76 hrs (P <.05 statistical significant).This shows mean duration of LPV was higher in cases group (A1,B1).

Table-2 ***Distribution of study population according to Mean Birth Weight of Group-A1, Group-A2 and Group-B1, GroupB2***

	Mean ± SD In Kg	P-value	Significance
Group-A1 Cases (24-30wks) 17pts	1.80 ± 0.76	>.05	NS
Group-A2 Controls(24-30 wks) 17 pts	1.66 ± 0.72		
Group-B1 Cases (31-36 wks) 86pts	2.43 ± 0.44	<.01	Sig
Group-B2 Controls(31-36 wks) 82pts	2.20 ± 0.52		

Table-2 shows that mean birth weight of newborns of Group-A1 & Group-A2 was 1.80 ± 0.76 kg and 1.66 ± 0.72 kg (P>.05 not significant) and of Group-B1 & Group-B2 was 2.43 ± 0.44 kg & 2.20 ± 0.52 kg (P<.01 significant) respectively. The mean duration of LPV was high in A1 & B1 (cases), still mean birth weight was high in cases. It shows better results of Amnioseal.

Table-3 ***Distribution of study population according to Mean ± SD of Gestational Age of Prolongation in Group-A1, Group-A2 and Group-B1, Group-B2***

	Mean ± SD In wks	P-value	Significance

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Group-A1 Cases (24-30wks) 17pts	6.00 ± 3.87	>.05	NS
Group-A2 Controls (24-30 wks) 17 pts	5.56 ± 3.46		
Group-B1 Cases (31-36wks) 86 pts	4.00 ± 2.42	<.05	Sig
Group-B2 Controls (31-36wks) 82 pts	3.50 ± 2.84		

Table-3 shows that mean prolongation was 6.00 ± 3.87 weeks and 5.56 ± 3.46 weeks in Group-A1 and in Group-A2 respectively. It was high in cases than controls. While in Group-B i.e. cases Group-B1 V/S controls Group B2 it was 4.00 ± 2.42 weeks and 3.50 ± 2.84 weeks respectively (significantly high).

Table-4

Distribution of study population According to Development of Oligohydramnios

Oligohydramnios After Treatment	Group-A1 CASE (24-30 WKS)	Group-A2 CONTROLS (24-30 WKS)	Group-B1 CASES (31-36 WKS)	Group-B2 CONTROLS (31-36 WKS)
Number of Patients with AFI < 5	8 (47.05%)	15 (88.23%)	29 (33.72%)	53 (64.63%)
Total Number of Patients	17	17	86	82

$\chi^2 = 2.946$ d.f. = 1 P > .05 NS $\chi^2 = 16.064$ d.f. = 1 P <.001 HS

Table-4 shows that (Group-A1) 8 (47.05%) cases v/s (Group-A2) 15 (88.23%) controls develop oligohydramnios (significant). Similarly, in Group-B1-29 (33.72%) out of 86 cases v/s Group-B2- 53 (64.63%) controls out of 82 were developed oligohydramnios (Highly significant).

Table-5 Distribution ***According to Perinatal Outcome of Group-A1, Group-A2 and Group-B1, Group-B2***

Perinatal Outcome	**Group-A1 17 pts**	**Group-A2 17 pts**	**P-value**	**Significance**	**Group-B1 86 pts**	**Group-B2 82 pts**	**P-value**	**Significance**
No. of Admission of newborns in Nursery	10 (58.82%)	15 (88.23%)	< .05	Sig	40 (46.51%)	62 (75.60%)	< .001	HS
Birth Asphyxia	3 (17.64%)	5 (29.41%)	> .05	NS	7 (8.13%)	19 (23.17%)	< .005	Sig

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Hypoglycemia	3 (17.64%)	4 (23.52%)	> .05	NS	16 (18.60%)	27 (32.92%)	< .05	Sig
Hypothermia	4 (23.52%)	3 (17.64%)	> .05	NS	17 (19.76%)	29 (35.63%)	< .05	Sig
Congenital Pneumonia	3 (17.64%)	4 (23.52%)	> .05	NS	7 (8.13%)	22 (26.82%)	< .005	Sig
Respiratory Distress Syndrome	6 (35.29%)	7 (41.17%)	> .05	NS	5 (5.81%)	15 (18.29%)	< .025	Sig
Neonatal Jaundice	2 (11.76%)	5 (29.41%)	> .05	NS	15 (17.44%)	28 (34.14%)	< .01	Sig
Intraventricular Haemorrhage	3 (17.64%)	4 (23.52%)	> .05	NS	2 (2.32%)	2 (2.32%)	> .05	NS
Necrotizing Enterocolitis	2 (11.76%)	5 (29.41%)	> .05	NS	0 (0.00%)	2 (2.32%)	-	-
Septicemia	3 (17.64%)	9 (52.94%)	< .05	Sig	6 (6.97%)	11 (13.41%)	> .05	NS
Neonatal Mortality	6 (35.29%)	9(52.94%)	> .05	NS	3(3.48%)	9(10.97%)	< .03	Sig

Table-5 shows that perinatal outcome was significantly better in Group B1 (cases) than Group B2 (controls). Due to more prematurity in Group A i.e. 24-30 weeks there were no significant yet better perinatal outcome was seen in cases.

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