

A Randomised Controlled Trial Determining the Efficacy of Dinoprostone Vaginal Gel for Active Management of Prelabour Rupture of Membranes at Term

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ABSTRACT

BACKGROUND

Dinoprostone gel shortens PROM–delivery interval, decreases maternal and neonatal morbidity, and thereby the hospital stay without increase in rate of caesarean section. For induction of labour, prostaglandin E2 cervical gel is quite effective and safe. We wanted to determine the safety and efficacy of dinoprostone vaginal gel in active management of PROM at term.

METHODS

This is a prospective randomised controlled trial study. We included 60 mothers, who attended labour room for induction and who fulfilled our inclusion and exclusion criteria, with their informed consent. 60 women were recruited for the trial who presented with PROM at term. Among them 30 mothers were recruited for dinoprostone gel induction group & 30 for expectant management group. All the patients were available for follow up and necessary data was collected from all the patients. Patients who delivered vaginally were followed up for 48 hrs. and those who delivered by LSCS were followed up for the next 7 days.

RESULTS

There is no statistical significance in Bishop Score at randomisation. Among 30 women selected for dinoprostone gel application, cervical ripening was noted among 83.3% of women. On the other hand only 26.7% of expectant group attended the desired score of Bishop score (>9). The difference is statistically significant (p value=.000). In this study, the average interval of induction to delivery in dinoprostone gel group is 15.17 hrs. and in expectant group it is 18.46 hrs. which is statistically lesser in dinoprostone group [asympt. sig. (2-tailed) value= 0.023 (Mann Whitney test)]. Almost 2/3rd of patients in dinoprostone gel group delivered vaginally and in expectant group 50% of the patients delivered vaginally. Rate of caesarean section was 20% and 30% in dinoprostone gel and expectant group respectively. It has been seen that post-partum fever and chorioamnionitis developed more in expectant group than in early induction group. However only chorioamnionitis is statistically significant.

CONCLUSIONS

Active management of PROM by early induction with dinoprostone vaginal gel is superior to expectant management, irrespective of cervical status.

KEYWORDS

Dinoprostone Gel, Prelabour Rupture of Membranes

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BACKGROUND

PROM is defined as rupture of membranes that occurs at term before the onset of labour. It occurs in 8-10% of cases.¹ PROM is known to be associated with multiple pregnancy, polyhydramnios, frequent digital examination, coitus, infection and altered mechanical properties of amniotic membranes etc.^{1,2} In many cases no apparent cause is evident. PROM at term pregnancy may result in immediate complications such as cord prolapse, cord compression and placental abruption and later problems like maternal and neonatal infection, interventions such as caesarean or instrumental vaginal delivery. The chance of maternal and neonatal infection increases with increased time interval between rupture of membranes and delivery of baby.³ Furthermore, intrauterine life in the presence of ruptured membranes for longer than 24 hours has been identified as a risk factor for later handicap.⁴ But if we can reduce the time interval between rupture of membranes and delivery of baby by inducing labour the risk of foetomaternal morbidity may decrease. Different methods of induction exist, of which prostaglandins are renowned for cervical ripening and myometrial stimulation. Bezircioglu et al,⁵ Krupa et al,⁶ Meikle et al⁷ etc concluded that active management of PROM by early induction is superior to expectant management irrespective of cervical status. It shortens PROM– delivery interval and decreases maternal and neonatal morbidity, and thereby the hospital stay without increase in rate of caesarean section. For induction of labour, prostaglandin E2 cervical gel is quite effective and safe.⁸ Given these considerations, we felt that such a study would be useful.

We wanted to compare the following between dinoprostone vaginal gel and expectant care-

- cervical ripening rate at 12 hours in PROM at term.
- Caesarean section rate
- time interval between rupture of membrane and delivery of baby,
- incidence & indications of caesarean delivery & Instrumental vaginal birth;
- chorioamnionitis (oral temperature >38°C during labour);
- postpartum fever (oral temperature >38°C on two separate occasions 6 hours apart at >24 hours from delivery);
- abnormal foetal heart tracing;
- meconium aspiration syndrome;
- APGAR Score at 1 min. and 5 min.;
- serious neonatal morbidity or perinatal death (e.g. infection, jaundice, seizures, respiratory distress syndrome).

METHODS

This is a prospective randomised controlled trial conducted in the Department of Obstetrics and Gynaecology, R.G. Kar

Medical College and Hospital, Kolkata, from July 2018 to June 2019 (1 year).

Inclusion Criteria

- A live singleton fetus at term,
- Cephalic presentation,
- A reactive non stress test,
- Bishop score of less than or equal to 4,
- Unscarred uterus

Exclusion Criteria

- Woman In Active Labour,
- Abnormal Fetal Heart Rate,
- Malpresentation
- Multiple Pregnancy,
- Cephalopelvic Disproportion,
- Antepartum Haemorrhage,
- Contraindication to Prostaglandin Use (Glaucoma, Asthma),
- Big Baby (>4500 Gm)

Sample Size

It has been found in a study by Bezircioglu et al⁵ that difference in the percentage of patient having a ripe cervix at 12 hrs. after Dinoprostone gel and expectant management in term PROM were 94% and 58% respectively. Assuming a cervical ripening rate at 12 hours will be similar in our study as found in the aforesaid study and keeping a type-1 error at .05 and type-2 error at .2, the required sample size in each arm will be 27 making it to total of 54. Considering a dropout of 10%, total sample size will be 60 with 30 in each arm.

Study Technique

Woman complaining of PROM at term who was given consent to participate in the study, had underwent detailed history taking and aseptic vaginal speculum examination to confirm the diagnosis. Following confirmation of the diagnosis and after doing non stress test the patients were randomised in 2 groups: induction of labour and expectant care. Randomisation was done by computer generated list randomised in block to ensure balanced allocation. Block size were between 4 to 10. Allocation concealment will be done by numbered sealed opaque envelope. In induction group dinoprostone vaginal gel was inserted into the posterior fornix. The control group was given glycerine in similar inserter as placebo and was followed until cervical ripening was achieved. Continuous Cardiotocogram monitoring was maintained throughout the induction of labour. When cervical ripening had achieved oxytocin infusion was started at a rate of 2 mu/min in both study and control group to achieve effective uterine contraction. The subsequent doses of oxytocin was titrated on the basis of uterine contraction and monitoring of foetal heart rate and CTG. Cervical ripening is defined as Bishop score >9. Uterine contractions was considered effective when it reached a frequency of more than 3 per ten minutes. Antibiotic prophylaxis against

Group B streptococcal infection was routinely administered: 2 gram of ampicillin iv stat followed by 1 gram ampicillin iv every 6 hours.

Statistical Analysis

Continuous variable was analysed by independent student t test or Mann-Whitney U test depending on the data normality. Categorical data will be analysed by Chi square or Fisher exact test, as appropriate p value of <0.05 considered to be statistically significant. Analysis was done by intention to treat principle. Statistical analysis was done by MedCalc version 12.3.0. (Mariakerke, Belgium: MedCalc software 2012).

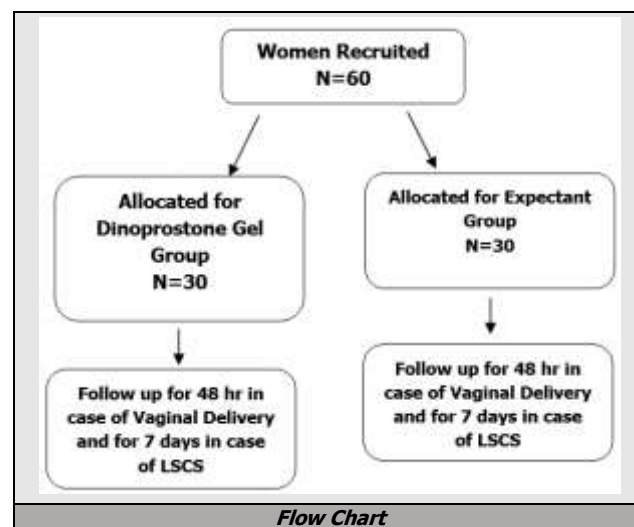
RESULTS

60 women were recruited for the trial who are presented with PROM at term. Among them 30 mothers were recruited for dinoprostone gel induction group & 30 for expectant management group. All the patients were available for follow up and data collected from all the patients. Patients delivered vaginally were followed up for 48 hrs. and those delivered by LSCS were followed up for the next 7 days.

Asymp. sig. (2-tailed) Value= 0.663(Mann Whitney test)

In our study, at randomisation 40% in both the groups had bishop score 1, 40% in dinoprostone gel group had bishop score 2 while 50% in expectant group had the same and 20% in dinoprostone gel group and 10% in expectant group had bishop score 3. But there is no statistical significance in Bishop score at randomisation. In this study mean gestational age is 39 weeks + in both the groups without any statistical significance. In our study, among 30 women selected for dinoprostone gel application, cervical ripening noted among 83.3% of women. On the other hand, only 26.7% of expectant group achieved the desired score of bishop score (>9). The difference is statistically significant (p value=.000). In this study, average interval of induction to delivery in dinoprostone gel group is 15.17 hrs. and in expectant group it is 18.46 hrs. It shows that there is reduction of almost 3 hrs. in induction to delivery time in case of dinoprostone gel group. The finding is statistically significant. In our study, almost 2/3rd of patients in dinoprostone group delivered vaginally and about 50% of the patients in expectant group. Rate of caesarean section were 20% and 30% in dinoprostone gel and expectant group respectively. About 10% of mothers required instrumental vaginal delivery in the form of forceps and 3.3% and 6.7% delivered by ventouse application in dinoprostone and expectant group respectively. There is no statistically significant difference between the two group regarding mode of delivery. In our study, maternal outcome in terms of development of chorioamnionitis and postpartum fever were studied and found to be (3.3%) in dinoprostone group. In other group, 20% developed chorioamnionitis and 13% developed postpartum fever. There is statistical significance in development of chorioamnionitis in the two groups but there is no statistical significance noted in

postpartum fever. In this study, neonatal morbidity was found to be statistically significant comparing the two groups. Neonatal sepsis is noted among 20% of cases in the expectant group whereas only 3.3% cases noted in dinoprostone gel group (p value=.046). 26.7% of neonates got admitted at NICU in expectant group whereas 6.7% neonates got admitted in dinoprostone gel group (p value=.039).



Bishop Score	Expectant (%)	Dinoprostone Gel (%)
1	12(40)	12(40)
2	15(50)	12(40)
3	3(10)	6(20)
Total	30	30

Table 1. Distribution as per Bishop Score at Randomisation

Asymp. sig.(2-tailed) Value= .663(Mann Whitney test)

Gestational Age at Induction	Dinoprostone Gel	Expectant
Mean ± SD	39.638±0.9991	39.460±0.9485

Table 2. Distribution as per Gestational Age at Induction

Z Score =-.532 Asymp. Sig.(2 Tailed)=.595(Mann- Whitney Test)

Cervical Ripening at 12 Hrs	Dinoprostone Gel (%)	Expectant (%)	p
Yes	25(83.3)	8(26.7)	0.000
No	5(16.7)	22(73.3)	
Total	30	30	

Table 3. Distribution as per Cervical Ripening at 12 Hrs.

X²=19.137 Df=1 (Chi - Square Test)

Interval of PROM to Delivery Time	Dinoprostone (%)	Expectant (%)
<12 hrs	9 (30)	5 (16.7)
12-24 hrs	13 (43.3)	10 (33.3)
>24 hrs	2 (6.7)	6 (20)
Total	24 (80)	21 (70)
Mean ± SD	15.1757±4.79590	18.4653±6.97898

Table 4. Distribution as per PROM-Delivery Interval

Z score=-2.276 asymp. sing.(2-tailed) value=.023(Mann Whitney test)

Mode of Delivery	Dinoprostone Gel (%)	Expectant (%)	p
Vaginal delivery	20 (66.7)	16 (53.3)	
Ventouse	1 (3.3)	2 (6.7)	
Forceps	3 (10)	3 (10)	0.299
LSCS	6 (20)	9 (30)	
Total	30	30	

Table 5. Mode of Delivery

X² = 1.007 df = 1 (Chi- Square Test)

Maternal Morbidity	Dinoprostone (%)	Exp (%)	χ ²	Df	p
Chorioamnionitis	1 (3.3)	6 (20)	3.976	1	0.046
Post-Partum Fever	1 (3.3)	4 (13)	1.931	1	0.165
Total	2	10			

Table 6. Distribution as per Maternal Outcome

Neonatal Morbidity	Dinoprostone (%)	Expect (%)	χ^2	Df	p
Neonatal Sepsis	1(3.3)	6(20)	3.976	1	.046
NICU Admission	2(6.7)	8(26.7)	4.248	1	.039
Total	3	14			

Table 7. Distribution as per Neonatal Outcome

DISCUSSION

In our study, at randomisation 40% in both the groups had bishop score 1, 40% in dinoprostone gel group had bishop score 2 while 50% in expectant group had the same and 20% in dinoprostone gel group & 10% in expectant group had bishop score 3. But there is no statistical significance in Bishop score at randomization (Table 1). In two other studies, Bezircioglu et al⁵ and Chung et al,⁹ there were similar results noted having no clinical significance. In this study mean gestational age is 39 weeks + in both the groups without any statistical significance (Table 2) as similar to the studies e.g., Bezircioglu et al⁵ and Chung et al.⁹

Dinoprostone gel is found to improve Bishop score in this study when applied for induction. Among 30 women selected for dinoprostone gel application, cervical ripening noted among 83.3% of women. On the other hand, only 26.7% of expectant group attended the desired score of bishop score (>9). The difference is statistically significant (p value=.000) (Table-3). Again, this is supported by various studies. In the study conducted by Smith et al¹⁰ & Chyu et al¹¹ PGE2 gel was found to improve the Bishop score. In the present study 83.3% needed only single application and only 3 patients required repeat PGE2 application. This was comparable with another prospective randomised controlled trial involving 10 women with term pregnancy done by Bezircioglu et al⁵ showed similar result where 94% of patients among study group underwent cervical ripening at 12 hrs. from induction by dinoprostone vaginal insert. In this study, average interval of induction to delivery in dinoprostone gel group is 15.17 hrs. and in expectant group it is 18.46 hrs. The finding is statistically significant (Table-4) and it is supported by many studies like Shah Krupa et al,⁶ Bezircioglu et al,⁵ Chung et al.⁹ They have concluded that immediate labour induction with prostaglandin shortens delivery interval. In another study by Dare MR et al¹² they have shown overall, women experienced a significantly shorter time from rupture of membranes to birth in the planned management groups compared with the expectant management groups.

On the contrary another study by Chung et al⁹ says that the duration of labour is not significantly different in both the groups though the patients who received prostaglandin for induction, went into labour earlier. In our study, almost 2/3rd patients in dinoprostone gel group delivered vaginally and about 50% of the patients in expectant group. Rate of caesarean section were 20% and 30% in dinoprostone gel group and expectant group respectively. About 10% of mothers required instrumental vaginal delivery in the form

of forceps in both group and 3.3% and 6.7% delivered by ventouse application in dinoprostone gel and expectant group respectively. There is no statistically significant difference between the two group regarding mode of delivery (Table 5). This observation is supported by many studies like Chung et al,⁹ Bezircioglu et al⁵, Shah Krupa et al,⁶ Rydhstrom & Ingemarsson et al,¹³ Dare MR et al.¹² Studies conducted by Mozurkewich & Wolf,¹⁴ Grant et al,³ Tan & Hannah² showed that inductions and augmentations, especially for PROM, often lead to caesarean Section. More recent studies Zanzami¹⁵ have found that in the absence of other obstetric and maternal or foetal risk factors, PROM at term is not an additional risk factor on its own. Expectant management of PROM at term enhances a patient's chance of normal delivery without an increase in fatal and/or maternal morbidity. In this study, maternal morbidity studied in terms of development of post-partum fever and chorioamnionitis. It was found to have lesser incidence of chorioamnionitis in dinoprostone group (3.3%) compared to more (20%) in expectant group. And this finding is statistically significant (p value=.046). In expectant group though post-partum fever developed more (13%) than in dinoprostone gel group (3.3%) this is not statistically significant (Table 6). This results are corroborated with findings of studies conducted by Dare MR et al,¹² Meikle et al,⁷ Poornima B et al.¹⁶ Hannah et al² which is the largest study on term PROM examined 5041 women from 72 centres throughout Canada, Israel, Australia and the UK with PROM at term have shown that an increase in maternal infectious morbidity was noted in the women of the expectant management groups, with 8.6% of the expectant groups developing clinical chorioamnionitis versus 4% in the immediate induction groups. On the other hand, there are studies those do not support the above findings like, Shalev et al¹⁷ measured a 12-hour expectant management regimen versus a 72-hour regimen; the rates of infection, chorioamnionitis and neonatal morbidity were the same in both groups. In this study, 93.3% and 66.7% of neonates had favourable Apgar score at 1 min in dinoprostone gel group and in expectant group respectively. These findings are not statistically significant. Z score=-1.733, asymp. sig. (2-tailed) value=.083 (Mann-Whitney test)

Apgar score at 5 mins was favourable and almost similar in both the groups without having any statistical significance again. Z score=-.575 asymp. sig. (2-tailed) value=.565 (Mann Whitney test) (Table 7). This finding is similar with a study conducted by Poornima B et al¹⁶ where Apgar score in both the groups found to be similar and hence not significant. In a study conducted by Bezircioglu et al⁵ they have concluded that early induction of labour could shorten the delivery time and thus reduce the risk of neonatal infection. On the other side Dare et al¹³ conducted 12 trials (total of 6814 women). In their study there was no difference for neonatal infection in both the groups. Hannah et al² & Dare MR et al¹³ showed no differences in neonatal infection rate between planned and expectant management.

CONCLUSIONS

Active management of PROM by early induction with dinoprostone vaginal gel is superior to expectant management irrespective of cervical status. It shortens PROM–delivery interval and decreases maternal and neonatal morbidity, and thereby the hospital stay, without increase in rate of cesarean section. So, in women at term with PROM if induced with dinoprostone vaginal gel as a part of active management, it is found to be quite effective and safer than expectant management in terms of delivery duration and foetomaternal outcome.

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