



Multiple Instillations of Intracervical Prostaglandin Gel for Cervical Ripening

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Abstract

The management of labour is basic to the practice of obstetrics. Induction of labour has become an integral part of modern obstetrics. The aim of induction is to achieve successful vaginal delivery where continuation of pregnancy presents a threat to the life or wellbeing of the mother or the unborn child. Unfavorable cervix is one of the main causes of failed induction. In order to overcome this, cervix should be ripened. Over the years a variety of pharmacological and physical ripening agents have been evaluated to convert a firm, rigid, long cervix to a soft, effaced and slightly dilated cervix. Among these are amniotomy, oxytocin infusion, breast stimulation, estrogen gel, mechanical and electrical devices and local and systemic prostaglandins. The present study is designed to see if multiple instillations of intracervical prostaglandin gel will improve the success of induction of labour where single instillation has failed and to compare the maternal and foetal outcome between the single instillation group and multiple instillation group.

Objectives

1. To evaluate the efficacy of instillation of more than one dose of intracervical prostaglandin E2 gel in cervical ripening.
2. To compare the maternal and foetal outcome between patients who had single instillation and multiple instillations.
3. To study the adverse effects, if any of multiple instillations of intracervical prostaglandin E2

Materials and Methods: This study was conducted in the Department of Obstetrics and Gynaecology, JIPMER, Pondicherry.

Results: Four hundred patients who were treated with intracervical PGE2 gel were included in the study. Out of this 300 patients who had spontaneous labour or adequate cervical ripening with a single instillation of PGE2 gel formed Group A and 100 patients who required multiple instillations formed Group B. Majority of the patients (more than 60%) belonged to the 21-25 years age group and were equally distributed in both the groups. There were significantly more teenagers in group B (35%) compared to Group A (18%). There was no difference between both the groups when parity was considered. The period of gestation was similar in both the groups, the mean being 40.71 weeks in Group A and 40.84 weeks in Group B. There were more indications for Pregnancy Induced Hypertension in Group B 28% as against 18% in Group A. Ninety three patients had either spontaneous labour (43%) or favourable cervix (50%) with 2 instillations making the second instillation

successful in 93% in Group B. Seven patients required 3rd instillation and out of these 3 (42.8%) had spontaneous labour and 2 (28.6%) had favourable cervix. Hence 71.4% of 3rd instillations were successful. After each instillation more multigravida had spontaneous labour. The improvement in cervical status was also better in multigravida. The change in Bishop score improved with each instillation, but this was significant only in the multigravida between first and second instillations. The cumulative improvement on Bishop score by second and third instillation was significant. About 50% of patients had cervical ripening and required oxytocin for induction of labour after first and second instillation of gel and 28.6% after the third instillation. Multigravida required less oxytocin infusion rates in Group A than primigravida. Premature rupture of membranes was the main complication in both the groups (10%). There was no difference in the incidence of meconium staining of liquor between both the groups (8% vs 5%). There were more instrumental deliveries in the multiple instillation group (29% Vs 18%). Caesarean section rates were similar in both the groups. The indications for caesarean section were similar in both the groups. The mean birth weight in Group A was 3.06 Kg and in Group B it was 3.16 Kg. Neonatal outcome was similar in both the groups

Conclusion: My study concluded that intracervical prostaglandin E2 gel is useful for cervical ripening. Some patients develop spontaneous labour with intracervical PGE2 gel. Multiple instillations of intracervical PGE2 gel are useful. Some patients have spontaneous labour while in others Bishop score improves. It is probable that teenage mothers require more than one instillation of PGE2 gel for cervical ripening. The maternal risks like infection or hyperstimulation are not increased by multiple instillations of intracervical PGE2 gel. There is no increased foetal risk with multiple instillation of intracervical PGE2 gel. Multiple instillations of intracervical gel can be beneficially used in appropriately selected cases

Keywords: Induction, Ripening, PGE2 gel.

Introduction

The management of labor is basic to the practice of obstetrics. Induction of labor has become an integral part of modern obstetrics. The aim of induction is to achieve successful vaginal delivery where continuation of pregnancy presents a threat to the life or wellbeing of the mother or the unborn child. The infant should be born in good condition within an acceptable timeframe and with minimum of maternal discomfort or side effects. It is not possible to achieve 100% success when labor is induced. Several factors influence the outcome. Unfavorable cervix is one of the main causes of failed induction. In order to overcome this, cervix should be ripened. It is well recognized that induction of labor is more successful when attempted with a ripe cervix.

Induction of labor in an unripe cervix is associated with frequent maternal complications and high rates of induction failure to the extent of 20- 50 %^{1,2} and caesarean delivery. Even when vaginal delivery is achieved these patients often have prolonged labor, with incidence of high instrumental delivery and fetal asphyxia.

Over the years a variety of pharmacological and physical ripening agents have been evaluated to

convert a firm, rigid, long cervix to a soft, effaced and slightly dilated cervix. Among these are amniotomy, oxytocin infusion, breast stimulation, estrogen gel, mechanical and electrical devices and local and systemic prostaglandins. Introduction of prostaglandins has changed the scenario of cervical ripening. Several published studies have reported significant improvement in Bishop score, more vaginal deliveries, shorter duration of labor and fewer caesarean deliveries without affecting the neonatal outcome^{3,4}.

Out of the various routes of application of prostaglandins, intracervical application has been reported to be most advantageous in terms of increased efficacy and diminished side effects^{5,6}. A single dose of 0.5 mg intracervical gel has been found to be superior to placebo in ripening the cervix. However if the ripening effect is insufficient, failure of induction and caesarean rate are nearly as high as when the cervix has been ripened with placebo. The earlier study in our institution showed a single dose instillation to be successful in 84.7% of cases.. Various authors have reported success rates ranging from 83% to 96% . The patients where attempts at cervical ripening failed often had failed induction. Many

workers have recognized the benefits of multiple instillations of prostaglandin gel in patients who do not respond to one dose. Mainprize et al⁷ and Norchi et al⁸ found 100% response rate with third instillation of prostaglandin gel. In India, Bhatla et al⁹ showed the response rate improved to 95% with second instillation and 96.5% with the third dose.

The present study is designed to see if multiple instillations of intracervical prostaglandin gel will improve the success of induction of labor where single instillation has failed and to compare the maternal and fetal outcome between the single instillation group and multiple instillation groups.

Aims and Objectives

- 1) To evaluate the efficacy of instillation of more than one dose of intracervical prostaglandin E₂ gel in cervical ripening.
- 2) To compare the maternal and fetal outcome between patients who had single instillation and multiple instillations.
- 3) To study the adverse effects, if any of multiple instillations of intracervical prostaglandin E₂

Materials and Methods

This study was conducted in the Department of Obstetrics and Gynecology, JIPMER, Pondicherry. The patients who were decided for induction of labor were included in the study. They had been admitted to the obstetric ward and a detailed history and examination had been done. They were informed about the study and their consent was obtained. There were both primigravidas and multigravidas in the group. Bishop Score was used to assess the cervical status.

Procedure

All the patients were administered 0.5mg prostaglandin gel intracervically. The commercially available gel in a prefilled syringe which contains 0.5mg was used for all the patients. After cleaning an examination was performed and assessment of

Bishop score was done. The cannula attached to the syringe was introduced into the cervix gently just short of the internal os. The plunger was then pushed gently depositing the gel into the cervical. Care was taken to minimize extra amniotic spill of gel by withdrawing the syringe while pushing the gel. The patient was kept on the bed for 30 minutes and was observed for contractions, rupture of membranes, bleeding or fetal heart rate changes.

After 6-8 hours, if the patient had not gone into spontaneous labor, a 'reassessment of the cervical status was done. If the Bishop score was less than 6, another instillation of intracervical gel was done. Again the patient was assessed after 6- 8 hours. This procedure was done either till onset of labor, change of Bishop Score to 7 or more or till 4 instillations of prostaglandin gel. If labor did not occur spontaneously and Bishop Score was 7 or more, oxytocin induction was done.

The patients who went into labor or achieved cervical ripening with a single instillation of prostaglandin E₂ gel formed Group A.

Those who required more than one instillation of prostaglandin E₂ gel formed Group.

Parameters studied

Bishop scores, change in score with each instillation of prostaglandin gel, onset of Spontaneous labor, mode of delivery, side effects of prostaglandin and maternal and complications were noted.

The details obtained were used to compare between the groups A & B using statistical methods like Chi-square test, Student t test and Fischer exact test.

Observations

Characteristics of the Patients Were

Age Distribution

The majority of the patients in both the groups were between 21-25 years of age. They were equally distributed in both the groups. There were significantly more patients in less than 20 years age group in group B (35%) compared to group A (18%). Apparently there were more primigravidas

in group B, but the difference was not statistically significant. .

Distribution of Period of Gestation

The period of gestation was similar in both the groups. More than 75% of patients in both the groups were between 38 and 42 weeks pregnant. The mean period of gestation among group A was 40 weeks and in group B, it was 40 weeks. Sixteen patients were not sure of dates but were assessed to be term by clinical examination and ultrasound before induction.

Indications for Induction of Labour

INDICATIONS	GROUP A (n=300)	GROUP B (n=100)	SIGNIFICANCE
Prolonged pregnancy	120 (40%)	35 (35%)	NS
Pregnancy induced Hypertension	54 (18%)	28 (28%)	S (P 0.03)
Oligohydramnios	33 (11%)	13 (13%)	NS
Rh Incompatibility	10 (3.3%)	6 (6%)	NS
Intrauterine growth Retardation	2 (0.66%)	0	NS
Multiple Indications	66 (22%)	12 (12%)	S (P=.02)
Others	15 (5%)	6 (6%)	NS

Most of the indications for termination were similar in both the groups. There were more patients with pregnancy induced hypertension in group B (28%) as against group A (18%) . Some patients had more than one indication for induction of labor for example, pregnancy induced hypertension or prolonged pregnancy with oligohydramnios or growth restriction.

Indications like previous history of still births nonreassuring nonstress tests were grouped together as “other” indications.

Number of Intracervical Prostaglandin Gel Instillations in Group B

Out of the 100 patients who required multiple instillations, 93 had 2 instillations and 7 required 3 instillations.

Initial Bishop Score and Outcome after Gel Instillation

	One Dose (n=400)	Two Doses (n=100)	Three Doses (n=7)
Mean Initial Bishop Score	2. 64	3 . 56	4. 57
Mean Change in Bishop Score	5. 96	6. 66	5 . 71
Spontaneous Onset of Labour	1 4 9 (37.25%)	43 (43%)	3 (42.8%)

One hundred and forty nine patients had spontaneous onset of labor after single instillation, 43 after 2 instillations and 3 patients after 3 instillation.

After 3 instillations, only 2 patients failed to go into labor or achieve a Bishop score of 7 or more. These were considered as true failures and caesarean section was done.

Bishop Score and Outcome after Gel Instillation according to Parity

	ONE DOSE		TWO DOSES		THREE DOSES	
	Primi (n=220)	Multi (n=180)	Primi (n=63)	Multi (n=37)	Primi (n=5)	Multi (n=2)
Mean Initial Bishop score	2.53	2.77	3.76	3.2	5.2	3
Mean Change in Bishop score	5.64	6.25	7.32	8.24	5.4	8.5
Spontaneous Labour	74 (33.6%)	75 (41.6%)	20 (34.5%)	23 (65.7%)	2 (40%)	1 (50%)

After each instillation more multigravida had spontaneous onset of labor than primigravida. The mean change in Bishop score was also more in multigravida with each instillation. The mean initial Bishop score before the 3rd instillation was

lower in multigravida than the mean score before the 2nd instillation. This is because one multigravida who was in this group had a very poor initial Bishop score.

Comparison of Change in Mean Bishop Score between First and Second Gel Instillations

	Mean Change After 1 st Dose	Mean Change After 2 nd Dose	Significance
Whole Group	1.87 + 0.89 (n= 100)	±2.49 (n = 57)	NS
PRIMI	2.047± 0.85 (n= 63)	5.14± 2.18 (n = 43)	NS
MULTI	1.567 ±0.89 (n=37)	5.7 ±3.44 (n= 14)	VS (P 0..0008)

The mean change in Bishop score by the second dose was much more than the mean change caused by the first dose as shown in Table. But the change when considered for the whole group was not statistically significant. Similarly when only

primigravida were considered there was no statistically significant difference in the effect of first and second doses. However the second instillation caused a significantly higher change in mean Bishop score in multigravida

Comparison of Change in Mean Bishop Score between Second and Third Gel Instillations

	Mean Change After 2 nd Dose	Mean Change After 3 rd Dose	Significance
Whole Group	5.33 ± 2.49 (n= 57)	5.25 ± 2.06 (n = 4)	NS
PRIMI	5.14 ± 2.18 (n= 43)	4.66 ±2.08 (n= 3)	NS
MULTI	5.7 ±3.44 (n== 14)	7.0 ±2.12 (n= 1)	NS

The change in Bishop score was not significant after the instillation of third dose when compared to the change after the second dose as shown in .

Comparison of Change in Mean Bishop Score between First and Third Gel Instillations

	Mean Change After 1 st Dose	Mean Change After 3 rd Dose	Significance
Whole Group	1.87+ 0.89 (n - 100)	5.71 + 3.73 (n =4)	VS (P 0.001)
PRIMI	2.047 + 0.85 (n = 63)	4.6 + 3.78 (ⁿ - 3)	s (P 0.05)
MULTI	1.57+ 0.89 (n=37)	8.5+2.12 (n - 1)	VS) (P=0.001

However as can be expected , the changes caused by the first dose alone were much lower than the changes in Bishop score after the third instillation.

This is because the change in Bishop score after the third dose is a cumulative change of second and third instillations.

Effect of Intracervical Gel on Labour

	GROUP A n =300		GROUP B n =100			
Spontaneous labor	No.	%	2 nd B No.	lose %	3 rd No.	Dose %
	149	49.67	43	43	3	42.8
Oxytocin Induced	151	50.33	50	50	2	28.6

When the whole group of multiple instillations was compared to the single instillation group, there was spontaneous onset of labor in 49.67% in

group A and 46% in group B. About half the patients in each group required oxytocin induction.

Oxytocin Requirements in ml U/mt.

	Group A (n = 140)	Group B (n = 44)	Significance
WHOLE	24.69 ± 14.61 (n= 140)	24.40 ± 13.60 (n = 44)	NS
PRIMIS	29.01± 15.20 (n=78)	24.37± 13.59 (n=33)	NS
MULTIS	19.27 ±11.87 (n = 62)	24.37 ± 14.22 (n= 11)	NS

The maximal rate of oxytocin infusion required was not different in both the groups.

Multigravidas required lower rates of oxytocin infusion than primigravidas in Group A.

Complications with Instillations of Prostaglandin E₂ Gel

Complications	Group A (n = 300)	Group B (n =100)	Significance
PROM	29 (9.66%)	10 (10%)	NS
CORD PROLAPSE	2 (0.66%)	-	NS
HYPERSTIMULATION	1 (0.33%)	-	NS
CHORIOAMNIONITIS	1 (0.33%)	-	NS

The main complication noticed in both the groups was premature rupture of membranes in about 10% of patients. There was no increase in PROM with multiple intracervical PGE₂ gel instillations. Cord prolapse occurred in two patients among Group A, Hyperstimulation and chorioamnionitis in one patient each in Group A. Surprisingly these complications were not seen in patients with multiple instillations.

Meconium Staining of Liquor

There was no difference in the occurrence of meconium staining of amniotic fluid between both the groups

Comparison of Mode of Delivery

Mode of Delivery	Group A n =300	Group B n= 100	Significance
Spontaneous Vaginal Deliveries	235 (78%)	65 (65%)	S (P 0.004)
Forceps & Vacuum	54 (18%)	29 (29%)	S (P 0.001)
Total Vaginal Deliveries	289 (96%)	94 (94%)	NS
Abdominal	11 (4%)	6 (6%)	NS

There were significantly more spontaneous vaginal deliveries in the single instillation group. On the other hand, there were more instrumental deliveries in the multiple instillation group. The rate of caesarean section was similar in both the groups.

Comparison of Indications for Caesarean Section

Indications	Group A		Group B	
	(n=11)	A (%)	(n=11)	B (%)
Foetal Distress	6	(54.5)	3	(50)
Failed Induction	-		2	(33.3)
Cord Prolapse	2	(18.18)	-	
Chorioamnionitis	1	(9)	-	
Non progress of labor	1	(9)	-	
Undiagnosed CPD		(9)	-	
Antepartum Eclampsia	-		1	(16.7)

The above table shows the indications for caesarean section in both the groups. Two cases of failed inductions were noticed in group B. Two cases of cord prolapse, one case of chorioamnionitis, one case of undiagnosed CPD and one case of nonprogress of labor were the indications for abdominal delivery among the group A patients.

Birth Weight of Babies

The mean birth weight of group A babies was 3.06 Kg and the mean of group B was 3.16 Kg. There was no significant difference between both the groups.

Foetal Complications

One still birth in group A was due to a tight loop of cord around the neck. The still birth in group B was a fresh still born for which the cause could not be ascertained. Foetal complications in both the groups were similar.

Discussion

In our study, more teenagers required multiple instillations when compared to other age groups. Mainprize et al and Norchi et al did not observe any difference in age groups who required sequential applications. The gestational age in our study was similar in both the groups. Mainprize et al also had similar observations. The mean gestational age in our study did not differ from the patients of other authors Bhatla et al, Mainprize et al.

Prolonged pregnancy was the commonest indication for induction in our study (38.75%).

Bhatla et al had prolonged pregnancy in 36.25% and Mainprize in 40%. Norchi et al, in their series had only 10% of induction for prolonged pregnancy.

In our study most of our patients either had spontaneous labor or achieved a ripe cervix with 3 instillations of PGE₂ gel. This was similar to the findings of other studies (Mainprize et al, Norchi et al, Bhatla). A significant percentage of patients developed spontaneous labor with sequential intracervical PGE₂ gel instillation. Table below shows the percentage of spontaneous labor with sequential instillations of PGE₂ gel.

Table : Spontaneous Labour After PGE₂ Gel

	1 st dose	2 nd dose	3 rd dose
Prins et al	41.5%	29%	5.9%
Mainprize et al	38%	27.7%	40%
Norchi et al	32.2%	45.2%	81.8%
Present study	37.25%	43.0%	42.8%

Our study showed a significant difference between initial Bishop Score and post instillation score. Similar findings were observed by Mainprize et al⁷, Norchi et al⁸ and Bhatla et al⁹. But Prins et al¹⁰ opined that sequential gel application was no more effective than single gel application followed by an equal period of observation.

In our study premature rupture of membranes was the main complication observed with instillation of intracervical prostaglandin gel. This was not reported by other workers. Norchi et al observed hyperstimulation of uterus in 2.2% of patients. This was observed in only 0.5% of patients of our study. Prins et al did not have any case of

hypertonus in their patients. Prins opined that hypertonus is usually associated with injudicious use of gel in women with very ripe cervixes (Bishop > 8) or in grand multipara.

We observed an increase in instrumental deliveries with multiple gel instillations. Norchi et al did not observe any increase in instrumental deliveries. About 50% of caesarean sections in our study were for foetal distress. Mainprize et al and Bhatla et al reported caesarean section for foetal distress in 33.3% of their patients. About 5% of the newborns in our study had Apgar of less than 7. The incidence of asphyxia was not affected by multiple instillations of gel. Norchi et al had similar observations in 4% of infants. Bhatla et al found no infant to have Apgar of less than 7 out of their 80 patients.

Summary

Four hundred patients who were treated with intracervical PGE₂ gel were included in the study. Out of this 300 patients who had spontaneous labor or adequate cervical ripening with a single instillation of PGE₂ gel formed Group A. One hundred patients who required multiple instillations formed Group B. Majority of the patients (more than 60%) belonged to the 21-25 years age group and were equally distributed in both the groups. There were significantly more teenagers in group B (35%) compared to Group A (18%). There was no difference between both the groups when parity was considered. The period of gestation was similar in both the groups, the mean being 40.71 weeks in Group A and 40.84 weeks in Group B. There were more indications for Pregnancy Induced Hypertension in Group B 28% as against 18% in Group A.

Ninety three patients had either spontaneous labor (43%) or favourable cervix (50%) with 2 instillations making the second instillation successful in 93% in Group B. Seven patients required 3rd instillation and out of these 3 (42.8%) had spontaneous labor and 2 (28.6%) had favourable cervix. Hence 71.4% of 3rd instillations were successful. After each instillation more

multigravida had spontaneous labor. The improvement in cervical status was also better in multigravida.

The change in Bishop score improved with each instillation, but this was significant only in the multigravida between first and second instillations. The cumulative improvement on Bishop score by second and third instillation was significant. About 50% of patients had cervical ripening and required oxytocin for induction of labor after first and second instillation of gel and 28.6% after the third instillation. Multigravida required less oxytocin infusion rates in Group A than primigravida. Premature rupture of membranes was the main complication in both the groups (10%). There was no difference in the incidence of meconium staining of liquor between both the groups (8% vs 5%). There were more instrumental deliveries in the multiple instillation group (29% Vs 18%). Caesarean section rates were similar in both the groups. The indications for caesarean section were similar in both the groups. The mean birth weight in Group A was 3.06 Kg and in Group B it was 3.16 Kg. Neonatal outcome was similar in both the groups.

Conclusions

From our study Intracervical prostaglandin E₂ gel is useful for cervical ripening. Some patients develop spontaneous labor with intracervical PGE₂ gel. Multiple instillations of intracervical PGE₂ gel are useful. Some patients have spontaneous labor while in others Bishop score improves. It is probable that teenage mothers require more than one instillation of PGE₂ gel for cervical ripening. The maternal risks like infection or hyperstimulation are not increased by multiple instillations of intracervical PGE₂ gel. There is no increased foetal risk with multiple instillation of intracervical PGE₂ gel. Multiple instillations of intracervical gel can be beneficially used in appropriately selected cases.

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