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Research Article

A Comparative Study of Safety and Efficacy of Intracervical PGE2 with Iv Oxytocin in Induction of Labor

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Abstract

This is randomized prospective observational study to compare safety and efficacy of intracervical PGE2 with iv oxytocin in the induction of labor conducted at department of Obstetrics and Gynecology, Civil Hospital, Aizawl, Mizoram, India. 200 women participated in this study which were divided into group A (study group) and B (control group) comprising of 100 women in each group. The outcome of the study was compared between the study and control groups based on different parameters- 1. bishop scoring before, after six hours, and after 12 hours of application of PGE2 gel or oxytocin induction 2. Duration of labor 3. Mode of delivery 4. Apgar scores of baby 5. incidence of complications and side effects. All women had completed the study. Cerviprime (PGE2 gel) proved to be a very effective ripening agent compared to I.V oxytocin as evident by the difference in change of Bishop score over 12 hours of cerviprime instillation, and I.V oxytocin infusion ($p < 0.005$) in Group A and B.

The duration of labor was reduced ($p < 0.005$) in women who underwent cervical ripening with intra cervical PGE2 gel. Strict intra cervical application of 0.5 mg of PGE2 gel has been shown to be safe for the parturient and the fetus as the complication like gastrointestinal upset and fetal distress is comparable in both groups ($p > 0.5$). There were 4 instances of hypertonic uterine contraction in women receiving PGE2 gel. Route of delivery was not significantly affected by pre-induction cervical ripening ($p > 0.05$) and the incidence of caesarean section and instrumental deliveries were also comparable (> 0.05). The neonatal outcome has been good in both groups with Apgar scores at 1 minute ($p > 0.2$) and 5 minutes ($p > 0.3$) being comparable. There was no instance of birth asphyxia or admission of the neonates to special care units.

The study indicates that intra cervical application of 0.5 mg of PGE2 gel (Cerviprime) is an effective primary agent, it induces labor in a significant number of women and is recommended in women with the unfavorable cervix who require induction of labor.

Keywords: *Induction of Labor; Oxytocin; Prostaglandin E2 Gel*

Abbreviations

PGE2-Prostaglandin E2; I.V.: Intravenous; gm: Gram Mg-Milligram; mu: Milliunit; min: Minute; hrs: Hours

Introduction

Modern obstetrics aims at improving the safety of the mother and the fetus during the antenatal period as well as parturition. The aim of induction of labor is to perform safe vaginal delivery at any time after the period of viability. According to the most current studies, the rate varies from 9.5 to 33.7% of all pregnancies annually [1]. However, approximately 20% of women having induction of labor end

up with caesarean delivery [2,3]. In the presence of unfavorable cervix, cervical ripening is done to increase the likelihood of successful induction [4]. Prostaglandin E2 (PGE2) given vaginally or intra-cervically has been shown to be effective for cervical ripening [5]. Oxytocin is the commonly used medication for augmentation as well as induction of labor. The side effects of oxytocin use are principally dose related; uterine tachysystole and Category II or III FHR tracings are the most common side effects. Uterine tachysystole may result in abruption placentae or uterine rupture. Relative ineffectiveness of oxytocin in women with unfavorable cervix has instigated the search for methods to improve the cervical inducibility. With unripe cervix, prolonged induction may result in an increase in both maternal and fetal morbidity. In study Prins., *et al*. the caesarean section rate for failed induction has been as high as 50% [7]. Numerous reports have pointed out the beneficial effects of locally applied PGE2 as a means of initiating cervical changes, which facilitates subsequent attempt at induction of labor [6,8,9]. In the past, the use of PGE2 was complicated by untoward systemic and local effects e.g. nausea, diarrhea, fever, uterine irritability and local irritation and as well as by the conspicuous lack of a homogenous, stable and readily available PGE2 preparation. Recently, excellent results in terms of increased efficacy and decreased side effects have been described with the use of low dose PGE2 gel, directly administered in the endocervical canal by a suitable applicator [10,11].

Induction of labor is one of the common interventions in the obstetrics and is not without risk. In many circumstances, induction of labor may either result in an increase or decrease in maternal or perinatal morbidity. These uncertainties are reflected in the wide differences in induction policies between different obstetrics units and will not be resolved till substantial evidence is accumulated from properly controlled, large randomized trials regarding the indications and methods on induction of labor. This is the prospective observational study with the primary aim to compare the safety and efficacy of intracervical PGE2 gel with I.V. oxytocin in the induction of labor, conducted at Civil Hospital, Aizawl, Mizoram, India.

Materials and Methods

This is an observational study for comparing the safety and efficacy of intra cervical PGE2 gel with I.V. oxytocin in induction of labor with descriptive design conducted at the Department of Obstetrics and Gynecology, Civil Hospital, Aizawl, Mizoram from November 2013 to November 2014. 200 pregnant women attending the birthing center who fulfilled the criteria for selection and exclusion had participated in the study. Inclusion criteria were−period of gestation 35 - 42 weeks, age 18 - 35 years, parity < 4, single live fetus in cephalic presentation, intact amniotic membranes, and bishops score < 4. Women in active labor, hypersensitive to drug or having any procedure causing scarring of uterus (e.g. previous caesarean section, myomectomy, hysterectomy), contraindications of vaginal delivery, and any medical conditions were excluded from the study

The study comprised of a study (group A) and a control (group B) group, each having 100 cases. Each woman was assigned to study after taking informed consent, detailed history, through general, systemic and vaginal examinations, proper investigations and ascertaining the indication for induction of labor. Randomization of the subject was done by allocating them alternatively to study and control group. PGE2 gel 0.5mg in triacetic base, net weight being 3 gms [cerviprime or dinoprostone gel] was applied to the endocervix of the women in the group A. After application of the gel the woman lied in the supine position for minimum for 30 minutes. After 6 hours, vaginal examinations were repeated and post PGE2 Bishops score was calculated to note the progress of labor. Dinoprostone was repeated after 6 hours for a maximum of 2 doses till the patient develops adequate uterine contraction. 6 hours were allowed to elapse before initiating oxytocin for augmentation of labor.

A note was made whenever the woman went into active labor and labor was monitored as per the labor ward protocol. Amniotomy was done as and when indicated. Intravenous oxytocin induction was done for the women not in labor after 12 hours of PGE2 gel application and labor were augmented if the women were not in active labor. I.V. Oxytocin infusion was given to these women as mentioned for the control group.

Group B was comprised of subjects who underwent oxytocin induction of labor without cervical priming with PGE2 gel. Bishop scores were calculated at initiation and every 6 hours of I.V oxytocin infusion. The progress of labor was monitored as in study group and amniotomy was done as and when indicated. I.V. oxytocin infusion, in both in group, was started at the dose of 1 mU/min and escalating dose of I.V oxytocin, doubled every half an hour, were given [e.g. 1 mU/min ,2 mU/min, 4 mU/min, 8 mU/min...]. The I.V oxytocin was titrated against the response and was increased till the woman gets good contractions lasting for 45 seconds and coming at a frequency of 3 every 10 minutes IV oxytocin infusion was not increased above a maximum of 64 mU/min.

The outcome of the study was compared between the study and control groups based on different parameters- 1. bishop scoring before, after six hours, and after 12 hours of application of PGE2 gel or oxytocin induction 2. Duration of labor 3. Mode of delivery 4. Apgar score of baby 5. Incidence of complications and side effects.

The values for the Bishop scores, duration and maximum dose of oxytocin infusion, duration of labor, duration of rupture of membranes and Apgar score has been expressed as a mean and standard deviation. To compare the means of two samples Student's t-test was used. Correlation of coefficient was calculated to know the correlation between change in Bishop score and duration of labor. Student's t-test was used to test the significance of correlation of coefficient. Z test was applied to test the equality of proportions in the data for age, parity, indications for induction of labor, period of gestation, side effects, complications and route of delivery.

Observation

This study included 200 pregnant women which has been included divided into group A and B.

Group A (study group): Comprised of 100 women who had pre-induction cervical ripening with dinoprostone gel.

Group B (control group): Comprised of 100 women who received I.V oxytocin without cervical ripening.

All women had completed the study. Observation was done based on different parameters which are-1. bishop scoring before, after six hours, and after 12 hours of application of PGE2 gel or oxytocin induction 2. Duration of labor 3. Mode of delivery 4. Apgar score of baby 5. Incidence of complications and side effects.

Bishop scoring before, after six hours, and after 12 hours of application of PGE2 gel or oxytocin induction

To know the efficacy of Cerviprime as compared to I.V. Oxytocin in induction of labor the Bishops scores in Group A were compared with Group B. The Bishop scoring done before cerviprime instillation or I.V. Oxytocin infusion is the zero-hour score and after 12 hours cerviprime or I.V. oxytocin is 12 hours score. The number of women included in Group A for assessing induction of labor were 96, as four women had undergone caesarean section before the initiation of labor. All the women in group B delivered after 12 hours of I.V. oxytocin induction, making the total number of women in this group as 100.The mean Bishop's score at 0 hour in Group A is 2.42 ± 1.00 which is statistically not significant ($p > 0.15$). The mean Bishop scores at 6 hours in Group A is 4.88 ± 0.42 and in Group B is 3.41 ± 1.1 which is statistically not significant ($p > 0.15$). The mean Bishop's score at 12 hours in Group A and Group B were 9.33 ± 1.63 and 5.76 ± 3.07 respectively and are statistically significant ($p < 0.005$). The change in Bishop's score in Group A and Group B were 6.92 ± 1.93 and 2.92 ± 2.25 respectively and were statistically significant ($p < 0.005$). In Group A only 92 women who had cervical scoring at 0 hours and 12 hours, and experienced labor are considered for assessing the correlation between change in Bishop's score and duration of labor. 4 women had emergency caesarean section for meconium stained liquor before she experienced labor and the other 4 women had emergency caesarean section for fetal bradycardia before completing 12 hours of cerviprime application (Table 1).

	Bishop score at 0 hour	Bishop score at 6 hours	Bishop score at 12 hours	Change in Bishop score
Group A (n=96)	2.42 ± 0.88	4.88 ± 0.42	9.33 ± 1.63	6.92 ± 1.93
Group B (n=100)	2.80 ± 1.00	3.41 ± 1.1	5.76 ± 3.07	2.92 ± 2.25
p value	> 0.15	> 0.15	< 0.005	< 0.005

Table 1: *Bishop scores at zero, six and twelve hours.*

The mean Bishop's score in 0 hour in primiparous and multiparous women in Group A were 2.44 ± 0.89 and 2.38 ± 0.92 respectively and were not statistically significant for p > 0.4. Similarly, in Group B mean Bishop score of 2.82 ± 1.95 and 2.75 ± 1.04 in primiparous and multiparous women respectively were not significant for p > 0.4. Change in Bishop's score in 12 hours in Group A was 6.88 ± 1.96 and 6.0 ± 1.51 in primiparous and multiparous women respectively, and is statistically not significant for p > 0.1 (Table 2).

Bishop score	Group A		Group B	
	Primiparous (n = 64)	Multiparous (n = 32)	Primiparous (n = 68)	Multiparous (n = 32)
0 hours	2.44 ± 0.89	2.38 ± 0.92 p > 0.4	2.82 ± 1.95	2.75 ± 1.04 p > 0.4
6 hours	4.71 ± 0.42	4.32 ± 0.51 p > 0.5	3.17 ± 1.22	3.00 ± 0.53 p > 0.5
12 hours	6.88 ± 1.96	6.0 ± 1.51 p > 0.15	2.65 ± 2.29	3.88 ± 2.80 p > 0.4
Change in 12 hours	6.88 ± 1.96	6.0 ± 1.51 p > 0.1	2.65 ± 2.29	3.88 ± 2.80 p > 0.05

Table 2: *Bishop scores at 0 hour, 6 hours and 12 hours and the difference between two in subgroups of primiparous and multiparous women.*

There is a negative correlation between the change in Bishop's score and duration of labor in both groups but is statistically not significant for p > 0.3 and p > 0.1 for Group A and Group B respectively (Table 3).

	Total No.	Correlation coefficient	p value
Group A	92	-0.14	> 0.3
Group B	100	-0.32	> 0.1

Table 3: *Correlation between change in bishop score and duration of labour.*

Duration of Labor

The mean duration of labor in Group A (n = 96 as 4 women had emergency caesarean section without going into labor for meconium stained liquor) was 8.99 ± 4.7 hours and in Group B (n = 100 as all women went in to labor) was 16.22 ± 5.11 hours, the difference was highly significant statistically for p < 0.0005. The mean duration of labor in Group A in primiparous and multiparous women was 9.05 ± 4.25 hours and 8.88 ± 4.25 hours respectively. Though the duration of labor was more in primiparous women, the difference was not statistically significant for p > 0.4. The calculated mean duration of labor in Group B prim parous and multiparous women was 16.74 ± 5.27 hours and 15.03 ± 4.97 hours respectively, but the difference was not significant statistically for p > 0.2 (Table 4).

Group	Duration of labor in total no. of women (hrs)	Duration of labor in primiparous women (hrs)	Duration of labor in multiparous women (hrs)
A	(n = 96) 8.99 ± 4.7 p < 0.0005	(n = 64) 9.05 ± 4.24 p > 0.4	(n = 32) 8.88 ± 4.25
B	(n = 100) 16.22 ± 5.1	(n = 68) 16.74 ± 5.27 p > 0.2	(n = 32) 15.03 ± 4.97

Table 4: *Duration of labour (DOL) in two groups, and subgroups of primiparous and multiparous women.*

Mode of Delivery

There were 80 spontaneous vaginal deliveries (80%) in Group A and 68(68%) in Group B, the total number of women being 100 in each group. The incidence of spontaneous vaginal deliveries, instrumental deliveries and caesarean section has not been found statistically significant for p > 0.05 (Table 5).

Mode of delivery	Group A		Group B		p value
	No. of women	%	No. of women	%	
Spontaneous vaginal delivery	80	80	68	68	> 0.05
Outlet forceps delivery	4	4	16	16	> 0.05
Ventouse delivery	4	4	8	8	> 0.05
Caesarean delivery	12	12	8	8	> 0.05
Total	100	100	100	100	

Table 5: *Distribution of women according to mode of delivery.*

Apgar score of baby

As singleton pregnancies with viable fetus were included in the study, 100 healthy babies were born to women both in Group A and Group B. The mean Apgar score of Group A at 1 minute is higher than Group B but is not statistically significant for p > 0.2. The mean Apgar score at 5 minutes was also comparable and is not statistically significant for p > 0.3. There were only 4 newborns in the study with Apgar score < 7 at 1 minute of life (Table 6). There was no admission of the neonates to special care units and they were all discharged in healthy condition.

	1 minute		5 minutes	
Group A	7.96 ± 0.84	p > 0.2	9.36 ± 0.51	p > 0.3
Group B	7.84 ± 0.55		9.44 ± 0.58	

Table 6: *APGAR scores at 1 minute and 5 minutes in newborns in group a and group B.*

Incidence of complications and side effects

There were four women in Group A, who have hypertonic uterine contractions Gastrointestinal irritation was seen in 12 women (12%) in Group A. All 12 had nausea and vomiting and only 4 of these 12 women had diarrhea and abdominal cramps. In Group B there were 8 women (8%) who had nausea and vomiting. The difference in incidence of gastrointestinal irritation is not statistically significant for >

0.05. Fetal distress was seen in 20 women (20%) in Group A out of the 12 had fetal bradycardia and 8 had meconium stained liquor. In Group B fetal distress was seen in 24 women (24%) out of which 8 had fetal bradycardia and 16 had meconium stained liquor. The incidence of fetal distress in Group A and Group B is statistically not significant for $p > 0.05$. There were no other complications like hyperpyrexia, postpartum hemorrhage, perinatal injuries, or hypersensitivity to cerviprime and oxytocin was seen (Table 7).

Complications and side effects	Group A		Group B		p value
	No. of women	%	No. of women	%	
Hypertonic uterine contractions	4	4	0	0	p > 0.05
Nausea and vomiting	12	12	8	8	p > 0.05
Diarrhea	4	4	0	0	p > 0.05
Fetal distress:					
- Bradycardia	12	12	8	8	p > 0.05
- Meconium Stained liquor	8	8	16	16	p > 0.05
Others	0	0	0	0	--

Table 7: *Incidence of complications and other side effects.*

Discussion

As intra cervical application of PGE2 gel is emerging as most efficacious and safe means of Induction of labor, a randomized prospective observational study comprises of two groups (group A and B), had been initiated to compare the efficacy and safety of intracervical PGE2 as compared to I.V. oxytocin for induction of labor.

The mean change in Bishop score in group A, after 12 hours of strict intra-cervical application of PGE2 gel was 6.92 as compared to 2.92 in group B ($p < 0.005$). The change is higher than what has been observed by Noah., *et al*. [16] which was 5.2 after 12 hours of application of PGE2 even though the women with Bishop score ≤ 5 were included in the study. Wiqvist., *et al*. [12] included women with Bishop score ≤ 4 and found mean change to be 4.4, and after excluding women who went into labor, i.e. Bishop score corrected for labor, was 3.5. The greater change in Bishop score can be explained by the high percentage of women who were in active labor at the time of assessment of 12 hours Bishop score. The change of Bishop scores in primiparous women though statistically not significant is marginally more than in multiparous women with cerviprime instillation. Cruz., *et al*. [13] reported mean change of Bishop score as 6 in primiparous as well as multiparous women while considering women with Bishop score ≤ 5. In group B the higher change in Bishop score in multiparous women is explained by the higher efficacy of I.V. oxytocin infusion in multiparous women as shown by Anderson., *et al*. [15].

The mean duration of labor of 8.99 hours in group A is less than group B which is 16.22 hours. Multiparous women showed shorter duration of labor compared to primiparous women in group A and B, but this did not prove significant on statistical analysis for $p > 0.4$ and $p > 0.2$ respectively. Cruz., *et al*. [13] showed a mean induction delivery interval of 11.83 hours and 7.83 hours for primiparous and multiparous women after giving 0.5 mg PGE2gel intracervically. In general, the results comparing primiparous and multiparous women have not been very conclusive and mostly comparable except for the number of women who went into labor with ripening doses of cerviprime, which was disproportionately high in primiparous women.

There were 12 emergency caesarean sections (12%) in group A and 8 in group B which were statistically insignificant ($P > 0.05$). Spontaneous vaginal delivery was observed in 80% and 68% respectively and rests were instrumental delivery.

Trofatter., *et al*. [14] reported 9 (31.03%)and 8 (26.67%) caesarean sections in control and PGE2 gel groups of 29 and 30 women respectively, the indications for which have not been mentioned. Spontaneous vaginal deliveries were 12 (41.38%) and 16 (53.3%) in each group respectively and rest were forceps deliveries. The higher incidence of operative delivery cannot be explained because of non – availability of data regarding their indications.

The neonatal outcome of the present study was similar in group A and B. The mean Apgar scores 1 minute and 5 minutes of 7.96 minutes versus 7.84 minutes, and 9.36 minutes versus 9.44 minutes in group A and B are statistically comparable for $p > 0.2$ and $p > 0.3$ respectively. Only one instance of Apgar score < 7 at one minute was noted in PGE2 gel group and none in Group B. Baveja., *et al*. [17] have noted 1 case of asphyxia and 1 respiratory distress in 221 neonates in gel group and in 224 neonates of control group, there were 2 cases of asphyxia and 1 case each of jaundice, meconium aspiration, hypoglycemia, and septicemia.

In group A 4% women had hypertonic uterine action whereas no woman of group B had experienced it. Trofatter., *et al*. [14] also reported one case of hypertonicity in 30 women receiving PGE2 gel. There is a definite risk of hypertonic uterine action probably in women who have accidental extra-amniotic instillation or due to heightened sensitivity to PGE2. This can be decreased by the strict intracervical application which is expected to improve with increased experience and limiting its use to women with unfavorable cervix only.

Nausea and vomiting was seen in 12 women and 4 had diarrhea in group A. Only 8 women had nausea and vomiting in group B. The difference was not statistically significant ($p > 0.5$) in the present study. Noah., *et al*. [16] had shown 7.7% incidence of gastrointestinal upset compared to 3% control group. Baveja., *et al*. [17] had given 9% incidence but he had included women who had the fever along with women having nausea and vomiting.

Fetal distress was recorded in 20% women in group A and 24% in group B. The difference in both the groups did not prove to be statistically significant ($p > 0.05$). Baveja., *et al*. [17] found 12.2% incidence of fetal distress inPGE2 gel group and 8.5% in the placebo group with severe birth asphyxia noted in 2 babies in each group of 221 and 224 women respectively. Noah., *et al*. [16] found the incidence of fetal distress to be 13% and 11.6% in gel group and placebo group. The high incidence of fetal distress compared to other studies in both groups can be explained by the fact that the subjects included were at high risk for fetal distress in this study.

Other complications like hyperpyrexia, postpartum hemorrhage, perineal injuries, hypersensitivity to cerviprime or oxytocin were not observed in this study. The sample size being small, these complications, which as such have the low incidence in modern obstetrics, could not be studied. Multicentric studies with a bigger sample size are best suited to study the safety in terms of the relatively rare complications listed above.

Conclusion

The comparative study of safety and efficacy of intra cervical PGE2 gel with intravenous oxytocin for induction of labor conducted in Civil Hospital, Aizawl; indicates that intra cervical application of 0.5mg of PGE2 gel (Cerviprime) is an effective primary agent, it induces labor in significant number of women and is recommended in women with unfavorable cervix who require induction of labor. It reduces the duration of labor significantly and it is safe for parturient and the fetus. The benefits to the mother in terms of being ambulatory, no requirement or decreased the duration of intravenous therapy, short labor and stay in hospital resulting in less mental and emotional strain is worth mentioning.

This study proved PGE2 gel (0.5 mg) to be an efficacious and safe agent for cervical ripening and also induction of labour in a significant number of women by I.V Oxytocin infusion and this needs to be explored in the further study.

Acknowledgment

None.

Conflict of Interest

None.

Ethical Approval

Institutional Ethical Committee and the Scientific Committee of Civil Hospital Aizawl Mizoram, India.

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