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Original Research Article

A study to evaluate the efficacy of combined prostaglandins and vaginal estradiol compared to prostaglandin alone in labor induction

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ABSTRACT

Background: Induction of labor (IOL) is a process where labor is initiated artificially before its spontaneous onset for the delivery of fetoplacental unit by mechanical or pharmacologic methods.

Methods: The present Hospital based prospective randomized comparative study was conducted in the department of obstetrics and gynecology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi during the period of January 2015 to December 2015. The selected women were randomized into two groups by simple randomization using an opaque sealed envelope, into either without vaginal estradiol Group A: Group PGE2 - Prostaglandin E2 gel intracervical alone group or Group B: PGE2 + E (Estradiol) - combined Prostaglandin E2 gel intracervical and 50 µg of estradiol tablet intravaginal group.

Results: In the present study 65% of the women in group PGE2 required three doses of prostaglandins compared to 23.33% in group PGE2 and estradiol for the cervix to become favorable. In this study there is significantly longer mean interval time noted for induction to cervical ripening (12.88 ± 4.91 versus 8.92 ± 5.07 ; $p < 0.001$), induction to active labor (16.97 ± 4.93 versus 11.02 ± 4.72 ; $p < 0.001$) and induction to delivery time (21.97 ± 3.83 versus 13.14 ± 4.98 ; $p < 0.001$) in group PGE2 compared to combined PGE2 and estradiol group.

Conclusions: Thus, vaginal estradiol along with prostaglandins has the potential in cervical ripening and induce labor and in an efficacious way. There is beneficial fetal outcome when combined vaginal estradiol along with intracervical prostaglandin E2 was used.

Keywords: Estradiol, Fetal, Induction, Labour, Prostaglandin

INTRODUCTION

The aim of obstetrics is a pregnancy that results in a healthy infant and a healthy mother. Usually in majority of the women labour starts spontaneously and it results in vaginal delivery at or when the term is near. Induction of labour for cervical ripening is necessary if there are any medical or obstetric complications of pregnancy. Induction of labor is necessary when the benefits of delivery to either the mother or fetus outweigh than those who plan to continue their pregnancy.¹

Induction of labour (IOL) is a process where labour is initiated artificially before its spontaneous onset for the delivery of fetoplacental unit by mechanical or pharmacologic methods.² Though there are medical or obstetrical complications of pregnancy warranting inductions for non-medical or social reasons, induction of labour is like a rapier or a double edged sword wherein one edge of the blade is always towards the user's neck. In other words, the more interference with the normal spontaneous onset of labour the higher chances that they may land up having risks like increased caesarean

sections, fetal distress, more instrumental deliveries, chorioamnionitis, psychological disturbances.^{3,4} Numerous techniques have been attempted for induction of labour to ripen the unfavourable cervix and enhance the changes necessary for labour in the lower uterine segment like intravenous infusion of oxytocin, intravaginal or intracervical administration of prostaglandins and intracervical Foley's balloon catheter insertion.⁵

Success of labour induction largely depends on cervical status; cervix that is unripe conveys a lower likelihood of vaginal delivery.⁶ When pregnant women of gestational age more than 41 weeks is induced, it is associated with a small reduction in perinatal deaths and meconium aspiration syndrome (MAS).⁷ Induction following PROM shows reduction in chorioamnionitis, endometritis, and neonatal ICU (NICU) admissions.⁸

As the pregnancy reaches term, there is increasing concentrations of estrogen in the maternal circulation, the idea that if addition of estrogen to the prostaglandins could potentiate spontaneous onset of labor has led to this study in exploring the role and efficacy of vaginal estradiol with PGE2 combination for induction of labour in unfavourable cervix and to assess the safety of the fetal outcome. Also, there is not enough literature to show the true effect of efficacy of vaginal estrogen along with prostaglandins for cervical ripening and labour induction.

Objective of this study was to evaluate the efficacy of combined prostaglandins and vaginal estradiol compared to prostaglandin alone in labour induction.

METHODS

The present Hospital based prospective randomized comparative study was conducted in the department of obstetrics and gynecology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi during the period of January 2015 to December 2015.

The sample size was calculated by considering type I error rate $\alpha = 0.05$ and type error $\beta = 0.02$ and power of 10% sample size was 120. A total of 120 pregnant women with singleton pregnancy having ≥ 36 weeks of gestation, cephalic presentation, Bishop's score ≤ 4 , intact membrane, history of no previous Cesarean section eligible for my study for induction of labour were randomized into two groups of 60 each and studied. Singleton pregnant women ≥ 36 weeks admitted in labour room at KLES Dr. Prabhakar Kore Charitable Hospital fulfilling inclusion criteria for induction of labour under the department of obstetrics and gynecology, KLES Dr. Prabhakar Kore Charitable Hospital, Belagavi were involved.

Inclusion criteria

- Gestational age ≥ 36 weeks.

- Singleton pregnancy
- Cephalic presentation
- Bishop's score less than or equal to 4
- With intact membrane.

Exclusion criteria

- Pregnant women with previous LSCS or any scar on uterus
- Pregnant women with PROM/ PPRM
- Pregnant women with placenta previa.

The selected women were randomized into two groups by simple randomization using an opaque sealed envelope, into either without vaginal estradiol Group A: Group PGE2 - Prostaglandin E2 gel intracervically alone group or Group B: PGE2 + E (Estradiol) - Combined Prostaglandin E2 gel intracervically and 50 μg of estradiol tablet intravaginal group. Patients were interviewed for demographic characteristics and obstetric history. Data regarding age, obstetric history and period of gestation were noted. These women were evaluated for pre-induction cervical status based on modified Bishop's Score. If pre-induction Bishop's Score ≤ 4 , they were included for the study and the findings were recorded on a predesigned and pretested preform.

Group PGE2

In this group pregnant women underwent induction of labour using intracervical prostaglandin E2 gel only, every sixth hourly for a maximum of three doses of prostaglandin till cervical ripening is achieved.

Group PGE2 and estradiol (PGE2+ E)

In this group pregnant women underwent induction of labour using vaginal estradiol tablet 50 μg with intracervical prostaglandin E2 gel in the first dose followed by prostaglandin E2 gel intracervically alone in the subsequent next two doses each dose after six hours apart, thereby maximum of total three doses till cervical ripening is achieved.

Induction of labor was performed by the treating obstetrician. Pre-induction Bishop's score was assessed and women who had Bishop's score ≤ 4 were included. Non-stress test was taken for at least 20 minutes before and 30 minutes after the induction. After randomization, they were either induced using group A protocol of prostaglandin gel (dinoprostone) alone, 0.5mg intracervically every sixth hourly of maximum three doses till cervical ripening was achieved or, group B protocol was followed using combined prostaglandin gel 0.5mg intracervically and estradiol 50 μg tablet vaginally inserted in the posterior fornix in the first dose followed by prostaglandin gel 0.5 mg intracervically in the subsequent next two doses every sixth hourly for total of maximum three doses till cervical ripening was

achieved. Women were advised to be at bed for at least half an hour after induction.

Statistical analysis

Data obtained was coded and entered into the Microsoft Excel Spreadsheet. The data was analyzed using statistical software SPSS 20. The categorical data was expressed in terms of frequencies and percentages while continuous data was expressed as mean±standard deviation (SD). The two groups were compared using either chi-square test or Fishers exact test for categorical data and independent sample's 't' test was used to compare the means of different parameters. A 'p' value of less

than or equal to 0.05 at 95 Confidence intervals was considered as statistically significant.

RESULTS

These women were randomized into two groups of 60 each, as Group PGE2 (induction with intracervical prostaglandin E2 gel only every 6th hourly of maximum three doses) and Group PGE2 and vaginal estradiol (induction with 50 µg estradiol tablet vaginally with intracervical prostaglandin E2 gel in the first dose followed by prostaglandin E2 gel intracervically alone in further next two doses, sixth hourly interval of maximum three doses in total till cervical ripening is achieved).

Table 1: Distribution of social and pregnancy profile in both the groups.

		Group PGE2 (n = 60)		Group PGE2+E (n = 60)		p value
		Number	%	Number	%	
Age group	20 or less	10	16.67	13	21.67	0.438
	21 to 25	35	58.33	27	45.00	
	26 to 30	13	21.67	15	25.00	
	30 or more	2	3.33	5	8.33	
Antenatal care	Unregistered	26	43.33	37	61.67	0.577
	Registered	34	56.67	23	38.33	
Gravida	Primi	41	68.33	32	53.33	0.210
	2	12	20.00	11	18.33	
	3	5	8.33	10	16.67	
	4	1	1.67	5	8.33	
	5	1	1.67	1	1.67	
	6	0	0.00	1	1.67	
Parity	Primigravida	41	68.33	32	53.33	0.092
	Multigravida	19	31.66	28	46.66	
Gestational weeks	36+1 to 36+6	3	5.00	3	5.00	0.659
	37+1 to 37+6	12	20.00	6	10.00	
	38+1 to 38+6	10	16.67	9	15.00	
	39+1 to 39+6	9	15.00	13	21.67	
	40+1 to 40+6	17	28.33	19	31.67	
	41+1 to 41+6	9	13.33	10	11.67	

In the present study most of the women were aged between 21 to 25 years in group in PGE2 (58.33%) as well as in group PGE2 and estradiol (45%). However, the age distribution in group PGE2 and group PGE2 and estradiol was comparable ($p = 0.438$). The mean age in group PGE2 was 23.67 ± 3.05 years compared to 24.53 ± 3.98 years in group PGE2 and estradiol. In the present study 56.67% of the women in group PGE2 and 38.33% in group PGE2 and estradiol was registered case for antenatal care. However, both the groups were comparable in terms of antenatal care ($p = 0.577$). In the present study most of the women in group PGE2 (68.33%) as well as PGE2 and estradiol (63.33%) were primigravida ($p = 0.210$) and hence comparable. In this study 28.33% of the women from group PGE2 and

31.67% from group PGE2 and estradiol had gestational age between 40 ± 1 to 40 ± 6 weeks ($p = 0.659$) and hence were comparable. In this study the mean period of gestation in group PGE2 was 39.24 ± 1.47 weeks compared to 39.54 ± 1.51 weeks in group PGE2 and estradiol but the difference observed was statistically not significant ($p = 0.252$) (Table 1).

In the present study the commonest indication for induction of labor was postdatism in group PGE2 (21.67%) as well as group PGE2 and estradiol (26.67%).

In the present study pre induction Bishop's Score of 3 and 4 were noted maximum in both the groups i.e., 28.33% and 20% respectively in PGE2 group and in

PGE2 and estradiol group as 26.67% and 28.33%. Pre induction Bishop's Score of 2 were similar in both study groups to be 20%. Pre induction Bishop's Score of 1 was 16.67% in PGE2 group and 13.33% in combined group. Pre induction Bishop's Score of zero were least in both study groups as 15% and 11.67% in combined study group. However, the distribution of women based on pre induction Bishop's Scores was almost equal and was not significant ($p = 0.850$). In this study the mean pre induction Bishop's score in group PGE2 was 2.19 ± 1.37 compared to 2.45 ± 1.35 in group PGE2 and estradiol (Table 2).

In the present study 65% of the women in group PGE2 required three doses of prostaglandins compared to 23.33% in group PGE2 and estradiol for the cervix to become favourable. In this study the mean number of doses administered were significantly higher in PGE2 group (2.62 ± 0.59) compared to that of combined PGE2 and estradiol group (1.86 ± 0.76) which was statically significant. In the present study the significantly higher number of women had successful cervical ripening in group PGE2 and estradiol (83.33%) compared to group

PGE2 (61.67%). 38.33% (30/120) of women in both the groups had failed cervical ripening ($p = 0.001$). 7 failed to achieve active labour in PGE2 group and 2 failed to achieve establishment of active labour in combined group. In the present study higher number of vaginal deliveries were noted in PGE2 and vaginal group significantly compared to PGE2 alone group (80% versus 51.67%) and hence was statistically significant ($p = 0.001$) (Table 3).

Table 2: Pre-induction Bishop's score.

Score	Group PGE2 (n = 60)		Group PGE2 +E (n = 60)	
	Number	%	Number	%
0	9	15.00	7	11.67
1	10	16.67	8	13.33
2	12	20.00	12	20.00
3	17	28.33	16	26.67
4	12	20.00	17	28.33
Total	60	100.00	60	100.00

Chi square = 1.365 $p = 0.850$.

Table 3: Comparison of labor parameters among study subjects in both the groups.

		Group PGE2 (n = 60)		Group PGE2 +E (n = 60)		p value
		Number	%	Number	%	
Doses	1	3	5.00	21	35.00	$x^2 = 26.432$ $p < 0.001$
	2	18	30.00	25	41.67	
	3	39	65.00	14	23.33	
Successful cervical ripening	Yes	37	61.67	53	88.33	$x^2 = 11.378$ $p = 0.001$
	No	23	38.33	7	11.67	
Establishment of active labour	Yes	53	88.33	58	96.67	$x^2 = 3.0$ $p = 0.083$
	Failed	7	11.67	2	3.33	
Mode of delivery	Vaginal	33	55.00	49	81.67	$x^2 = 12.1$ $p = 0.001$
	LSCS	27	45.00	9	15.00	
Fetal outcome	Alive	60	100.00	56	93.33	$p = 0.042$
	MSB (macerated still birth)	0	0.00	4	6.67	

Table 4: Mean time interval for induction of labour.

Variables	Group PGE2 (n = 60)		Group PGE2+E (n = 60)		p value
	Mean	SD	Mean	SD	
Induction to cervical ripening interval (hours)	12.88	4.91	8.92	5.07	< 0.001
Induction to active labour interval (hours)	16.97	4.93	11.02	4.72	< 0.001
Time for from induction to delivery (hours)	21.97	3.83	13.14	4.98	< 0.001

In this study there is significantly longer mean interval time noted for induction to cervical ripening (12.88 ± 4.91 versus 8.92 ± 5.07 ; $p < 0.001$), induction to active labour (16.97 ± 4.93 versus 11.02 ± 4.72 ; $p < 0.001$) and induction to delivery time (21.97 ± 3.83 versus 13.14 ± 4.98 ; $p < 0.001$) in group PGE2 compared to combined PGE2 and

estradiol group. Hence, they were statistically significant in each time interval.

DISCUSSION

The incidence of labour induction has increased over the last decade. Labour induction may be indicated by

medical or obstetrical complications of pregnancy or may be requested or chosen for non-medical or social reasons. Around 20% of all deliveries are preceded by labor induction. In the last 50-60 years, prolonged pregnancy and maternal hypertensive disorders were the major indications.

In a prospective double-blind study by Dasgupta E and Singh G, the mean maternal age was 21.67 ± 1.15 years in women who underwent induction of labour with misoprostol compared to women who underwent induction of labour with misoprostol + estradiol had mean age of 22.33 ± 2.58 years ($p = 0.121$).⁹ The mean maternal age observed in the present study was slightly higher in both the groups compared to the study by Dasgupta E and Singh G but was comparable in both the groups.⁹

The mean number of doses of prostaglandins administered were significantly higher in PGE2 only group compared to PGE2 and estradiol combined group (2.62 ± 0.59 versus 1.86 ± 0.75 ; $p < 0.001$). These findings suggest that, induction of labour with intracervical prostaglandin E2 gel requires significantly higher number of doses compared to combined intravaginal estradiol tablet and prostaglandin E2 gel. On an average, 4-5 doses of misoprostol were required in a study by Dasgupta E and Singh G, for cervical ripening or initiation of active labor which is similar to other studies also, however dose required in combined group was significantly less ($p = 0.017$).⁹ In study by Dasgupta E and Singh G, in misoprostol only group, duration of interval between induction initiation to cervical ripening, induction initiation to active labor and initiation and induction initiation to delivery were 12.67 ± 2.21 , 15.33 ± 3.76 and 18.25 ± 6.13 hours, respectively.^{9,10}

According to Raksha M and Rao A study, when vaginal misoprostol was combined with vaginal estradiol the mean time interval from induction to cervical ripening had shown to be 7.62 hours which is in slightly similar to our study, it took 8.92 hours for combined prostaglandins and vaginal estradiol group for cervix to ripen after initial induction.¹⁰ In Crane JMC, Butler B a systemic review study, there was a higher rate of vaginal deliveries with misoprostol compared to PGE2 (RR = 1.22, 95% CI = 0.96-1.55) and lower rate of oxytocin administered in misoprostol group when compared to PGE2 group (46.4% versus 62.4%). Various studies have found induction delivery interval with vaginal misoprostol in Dasgupta E and Singh G to be 16-20 hours, which is in agreement with our study (16.97 ± 4.93).⁹ In Dasgupta E and Singh G study and Raksha M and Rao A study, combined misoprostol and vaginal estradiol the induction to delivery duration interval were reduced to 12.07 hours while in present study it took 13.14 hours in combined group as compared to prostaglandin alone group which was much more i.e., 21.97 hours.^{9,10}

Some studies have shown effect on cesarean section rate with misoprostol as in Raksha M and Rao A study, they had 29 caesareans with misoprostol group and 10 with misoprostol and estradiol group.¹⁰ In the present study significantly higher number of vaginal deliveries were noted in group PGE2 and estradiol compared to group PGE2. However, no such difference was found in Dasgupta E and Singh G study.⁹

CONCLUSION

Based on the findings of this study it may be concluded that, induction of labor with combined vaginal estradiol along with intracervical prostaglandin E2 gel requires significantly lower number of doses of prostaglandin E2 gel for cervical ripening, yields higher success rate of cervical ripening with lesser duration interval for establishment of active labor and induction to delivery time and is more effective than of intracervical prostaglandin E2 gel alone. Thus, vaginal estradiol along with prostaglandins has the potential in cervical ripening and induce labor and in an efficacious way. There is beneficial fetal outcome when combined vaginal estradiol along with intracervical prostaglandin E2 was used.

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