A Prospective Clinical Study to Compare Intracervical Dinoprostone Gel with Vaginal Misoprostol for Induction of Labour

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ABSTRACT

Introduction: Induction of labor (IOL) is an increasingly common obstetric procedure. Methods for labor induction include both mechanical and pharmacological options.The only definitive treatment is delivery and it can be achieved by various methods ranging from induction of labour (with inducing agents) to operative vaginal delivery and abdominal surgery. This study was undertaken to compare the efficacy and safety of induction of labour with two inducing agents – intracervical dinoprostone gel and vaginal misoprostol tablet, in women with hypertensive disorders of pregnancy.

Material and methods: A comparative study between intracervical dinoprostone gel and vaginal misoprostol for induction of labour in women with hypertensive disorders of pregnancy was performed in the Department of Obstetrics and Gynecology at RMSPH, VIMS, Kolkata. Study includes 100 number of cases for the above study. It was a prospective clinical study. The cases were randomly allocated in two groups; one group received intracervical dinoprostone gel (0.5 mg, 6 hrs interval for maximum 4 doses) and another group vaginal misoprostol (25 µg, 6 hrs interval for maximum 4 doses).

Results: The mean induction to vaginal delivery interval was 22.12±2.768 hours in dinoprostone gel group (p=0.000) and 21.92±3.228 hours in misoprostol group (p=0.000). Study shows 75% subjects delivered by vaginal route <=24 Hrs, whereas only 25% subjects delivered after 24 Hrs.

Conclusion: Intravaginal misoprostol appears to be more efficient for labor induction than intracervical dinoprostone; however, dinoprostone has been demonstrated to be safer because of the lower incidence of uterine hyperstimulation and tachysystole. The incidence of vaginal deliveries was higher in vaginal misoprostol group compared to dinoprostone gel group. There was no significant difference in respect to the mean induction vaginal delivery interval between the two groups.

Keywords: Induction of labour, Dinoprostone Gel, Misoprostol, Hypertensive Disorders of Pregnancy, Vaginal Delivery, LSCS

INTRODUCTION

Induction of labor is defined as the process of artificially stimulating the uterus to start labor.[1] WHO defines IOL as the initiation of labour by artificial means prior to its spontaneous onset at a viable gestational age, with the aim of achieving vaginal delivery in a pregnant woman with intact membranes. In developed countries, IOL accounts for about 25% of all deliveries. In developing countries, the rates vary.[2] Labor induction may be indicated by medical or obstetrical complications of pregnancy or may be requested or chosen for non-medical or social reasons. When a woman and her care provider decide that labor induction is desired, they must next choose a method of induction. Several factors may influence the choice of method for induction of labour including cervical and membrane status, parity, and patient and provider preference.[3, 4]

Indications for labor induction include both maternal and fetal conditions. Induction may be advocated to reduce fetal or neonatal morbidity and mortality as with post-term pregnancy, oligohydramnios, suspected intrauterine growth restriction (IUGR) and fetal gastroschisis, to minimise maternal morbidity, as with maternal cardiac disease and pre-eclampsia/eclampsia, or to benefit both mother and fetus as with prelabour rupture of membranes (PROM) at term and fetal macrosomia.[5, 6]

Prostaglandins have evolved as the most popular and frequently used pharmacologic agents for IOL, owing to their dual action of cervical ripening and uterine contraction inducing effect. Prostaglandin E_2 (cerviprime gel), a registered inducing agent in many countries is expensive and needs to be refrigerated due to its sensitivity to temperature changes. It is instilled intracervically or placed high in the posterior fornix of the vagina and may need to be re-instilled after 6 h if required. Another alternative is misoprostol

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(15-deoxy-16-hydroxy-16-methyl prostoglandin E1) which is used in various dosages. It is stable at room temperature, comparatively cheaper and can be given via several routes (oral, vaginal, sublingual, buccal and rectal).[7]

This study was undertaken to compare the efficacy and safety of induction of labour with two inducing agents – intracervical dinoprostone gel and vaginal misoprostol tablet, in women with hypertensive disorders of pregnancy.

MATERIAL AND METHODS

It was a prospective randomized clinical study to compare the efficacy and safety of intracervical dinoprostone gel (0.5mg) with the vaginal misoprostol (25 µg) for induction of labour in women with hypertensive disorders of pregnancy. The study was undertaken in the department of Obstetrics & Gynaecology at Ramakrishna Mission Seva Pratishthan Hospital & Vivekananda Institute of Medical Sciences, Kolkata between 1st February to 31st January 2009. Total sample size was 100. The women with hypertensive disorders of pregnancy requiring induction of labour were included in the study population who satisfying the following criteria's: single live fetus, cephalic presentation, intact membranes and reactive cardiotocography. Patient's were excluded with malpresentation, past history of cesarean section or any scar on uterus; any contraindications to PGs, including bronchial asthma, glaucoma and cardiac diseases. Subjects with pre-labour rupture of the membranes, antepartum hemorrhage, fetal compromise (intra uterine growth restriction), oligohydramnios and high risk pregnancy like eclampsia was also excluded. Demography of the study population (age, parity, duration of pregnancy in weeks, weight, height, education, residence, occupation and income etc.) were noted. Success rate for induction of labour in each group was measured in terms of:

1. Maximum number of doses required for induction
2. Need for augmentation with oxytocin/ARM/ARM+ oxytocin
3. Induction to vaginal delivery interval
4. Number of vaginal delivery
5. Number of cesarean section and its indications

Study Tools: Induction agents [dinoprostone gel 0.5 mg/ misoprostol tablet and to record cardiotocograph Philips Series 50 CTG machine was used.

Study Techniques

Permission was obtained from the Institutional Ethics Committee. Written informed consent was obtained from all the women who participated in the study. Women with hypertensive disorders of pregnancy were selected as per inclusion and exclusion criteria. Two identical packets contained either dinoprostone gel (0.5 mg) or tablet misoprostol (25 µgm) were offered to each patient by our nursing staffs. Patients were allowed to choose one of the packets in between the two. Accordingly, the selected patients were randomized and allocated into two groups. Each group contained 50 cases. One group was named dinoprostone gel group (PGE2 group or Group I) and another group was named misoprostol group (PGE1 group or Group II). Demographic details in terms of age, parity, weight, height, residence, educational qualification, monthly income and gestational age in weeks were noted. A thorough general and systemic examination was done. Abdominal examination was performed to confirm the fetal presentation and rule out any uterine activity. Fetal heart rate pattern was assessed by cardiotocography. Vaginal examination was done to ascertain the modified Bishop score. (table1)

Group I (50 cases): Received (0.5 mg) intracervical dinoprostone gel every 6 hours for a maximum of 4 doses (PGE2 group)

Group II (50 cases): Received vaginal misorprostol (25 mcg) tablet every 6 hrs for a maximum of 4 doses (PGE1 group)

The timing of first dose was noted and considered as zero hour. One hr after the application of 1st dose of inducing agent, uterine contraction and fetal heart rate pattern were monitored by CTG. Cases were assessed after 6 hrs of the first dose of inducing agent and uterine activity, fetal heart rate pattern and cervical assessment for modified Bishop scores were recorded. Next dose of inducing agent was repeated. This protocol was follow at 6 hr interval. Subsequent dose/ doses were withheld if the women was in active phase of labour (uterine contraction >3/10 min and persist for >40 sec); non reassuring fetal heart rate pattern and abnormal uterine activity and rupture of membranes.

RESULTS

One hundred women with hypertensive disorders of pregnancy required induction of labour were recruited, 50 received intracervical dinoprostone gel (PGE2 group or group 1) and 50 received vaginal misoprostol tablet (PGE1 group or Group II).

Table 2 shows mean age in PGE1 and PGE2 groups 27.22 and 26.28 respectively. The two groups are similar in respect to the distribution of mean age.

Distribution of parity in PGE1 group consisting of 72% primipara and 28% multipara (p=0.005). Distribution of parity in PGE2 group consisting of 70% primipara and 30% multipara (p=0.005) [Table 3].

The other demographic characteristics of the women like parity, education, occupation, religion, residence, income, average weight and height were similar in both the groups [Table 4]. In PGE1 50% required augmentation and PGE2 group 56% was required augmentation. In PGE1 group 72% was delivered by vaginal delivery whereas PGE2 group 66% subjects delivered by vaginal route. The incidence of cesarean section was 17 (34%) and 14 (28%) in PGE2 group and PGE1 group respectively.

Table 5 shows mean induction to vaginal delivery in both PGE1 and PGE2 groups (p=0.000). The mean induction to vaginal delivery interval was 22.12±2.768 hours in dinoprostone gel group (p=0.000) and 21.92±3.228 hours in misoprostol group (p=0.000).

Table 6 shows 75% subjects delivered by vaginal route <=24 Hrs, whereas only 25% subjects delivered after 24 Hrs [Table 6]. There were 8% cases in each group where labour could not be induced and LSCS done due to failed induction

of labour.

Table 7 is showing the indications of LSCS. Importantly only one subject experienced uterine hyperstimulation in in PGE1 and PGE2 groups. The incidence of caesarean section due to fetal distress (non-reactive CTG) was 8 (16%) in dinoprostone gel group and 6 (12%) in misoprostol group. The incidence of caesarean section due to hyper stimulation was 1 (2%) in each group. Only one case 2% was undergo caesarean due to meconium stained amniotic fluid in misoprostol group. No such incidence was noted in dinoprostone gel group.

In dinoprostone gel group, maximum 4 doses required in 24 (48%) cases, out of which 18 (36%) achieved vaginal delivery. In misoprostol group, maximum 4 doses required in 30 (60%) cases, out of which 22 (44%) cases undergo vaginal delivery. Three doses required in 14 (28%) cases in dinoprostone gel group, out of which 10 (20%) achieved vaginal delivery but 6 (12%) patients undergo LSCS (p=o.121). On the other hand, in the misoprostol group 10 (20%) case required 3 doses and all the case 20% undergo successful vaginal delivery (p=0.011) [Table 8].

Table 9 shows 34 cases vaginal delivery achieved with clear liquor in PGE1 group but 2 cases it was meconium stained. In PGE2 group 32 cases vaginal delivery achieved with

	0	1	2	3
Dilatation of OS (cm)	<1	1-2	2-4	>4
Effacement (cm)	>4	2-4	1-2	<1
Station	-3	-2	-1/0	+1/+2
Position of the cervix	Posterior	Mid/Anterior		
Consistency of the cervix	Firm	Average	Soft	
Total score=13, favorable score=6-13, unfavorable score=0-5				

Table-1: Modified Bishop Score8

Age/ PGE1 [N=50]	Statistics	Age/ PGE2 [N=50]	Statistics
Mean	27.22	Mean	26.28
Std. Deviation	3.877	Std. Deviation	4.554
Minimum	19	Minimum	18
Maximum	36	Maximum	38

Table 2: Age distribution in PGE1 and PGE2 groups

Parity	Frequency [PGE1]	Percentage	Frequency [PGE2]	Percentage
Primi	36	72	35	70
Multi	14	28	15	30
Total	50	100	50	100

Table-3: Parity in PGE1 and PGE2 groups

Parameter		PGE1 Percentage	PGE2 Percentage
Education	Primary/HS Graduate & Above	31 (62%) 19 (38%)	28 (56%) 22 (44%)
Occupation	House wife Service Teacher	39 (78%) 7 (14%) 4 (8%)	36 (72%) 8 (16%) 6 (12%)
Religion	Hindu Muslim	42 (84%) 8 (16%)	41 (82%) 9 (18%)
Residence	Urban Rural	38 (76%) 12 (24%)	36 (72%) 14 (28%)
Income (Avg.)	Rs 14380	-	Rs 14280
Weight (Kg)	53.14	-	57.90
Height (Inch)	63.14	-	63.48

Table-4: Demographic parameters in PGE1 and PGE2 groups

Number	Minimum	Maximum	Mean	SD
PGE1	I-D Interval			
36	13	27	21.92	3.228
PGE2				
33	15	27	22.12	2.768

Table-5: Mean induction to vaginal delivery (I-D Interval) in PGE1 and PGE2 groups

	Frequency	Percent	Frequency	Percent
Time of VD <=24 Hrs	27	75	25	75.75
Time of VD >24 Hrs	9	25	8	24.24
Total	36	100	33	100

Table-6: Time of vaginal delivery [VD] in PGE1 and PGE2 groups

	Frequency [PGE1]	Percent	Frequency [PGE2]	Percent
FOI	4	8	4	8
SUS-CTG	6	12	8	16
NPOL	2	4	4	8
HYPER S	1	2	1	2
MECO	1	2	-	-
Total	14	28	17	34

Table-7: Indication of LSCS in PGE1 and PGE2 groups

Max. Dose req. PGE1	Mode of delivery		Total
	VD	LSCS	
Max. Dose 2	4	6	10
Req. GG			
3	10	0	10
4	22	8	30
Total	36	14	50
Max. Dose req. PGE 2			
Max. Dose 2	5	7	12
Req. GG			
3	10	4	14
4	18	6	24
Total	33	17	50

Table-8: Shows requirement of maximum number of doses to achieve vaginal delivery in PGE1/PGE2 groups

Nature of liquor PGE1	Mode of delivery		Total
	VD	LSCS	
Nature of liquor			
Clear	34	8	42
Meconium stained	2	6	8
Total	36	14	50
Nature of liquor PGE2			
Nature of liquor			
Clear	32	10	42
Meconium stained	1	7	8
Total	33	17	50

Table-9: Shows vaginal delivery achieved with clear and or meconium stained

Nature of liquor PGE1	Mode of delivery		Total
	VD	LSCS	
Need for NICU			
No	34	7	41
Yes	2	7	9
Total	36	14	50
Nature of liquor PGE2			
Nature of liquor			
Clear	32	10	42
Meconium stained	1	7	8
Total	33	17	50

Table-10: Neonates required NICU admission delivered by vaginal route

clear liquor but 1 case it was meconium stained. There was no significant statistical difference between the two groups regarding the incidence of meconium stained liquor to achieve vaginal delivery.

Table 10 shows only 2 neonates required NICU admission in PGE1 group whereas only one in PGE2 group, delivered by vaginal route [p=0.000]. In this respect two groups were similar.

DISCUSSION

There have been an increasing number of published reports of misoprostol use for induction of labour with varying regimens and doses. Higher incidence of tachysystole was reported with repeated doses. Maydanil et al[9] have concluded that 25 µgm vaginal misoprostol could be effective for labor induction. So in our study we decided to 25 µgm misoprostol vaginally at 6 hours interval and compared this with intracervical dinoprostone gel, which was also repeated at 6 hours interval for induction of labour in women with hypertensive disorders of pregnancy.

Initiation of Uterine Contraction

Onset of initiation of contraction was similar in two groups. In the PGE2 group it was 17.0921±2.92442 hr (p=0.000) and in PGE1 group 17.4722±3.13948 hr (p=0.000). This finding was supported by similar study done by Agarwal N et al in 2003.[10]

Need for Augmentation of Labour

In the dinoprostone gel group, labour augmentation was required in 28 (56%) [p=0.032] and in misoprostol group it was 25 (50%) [p=0.000]. Although statistically not significant, need for augmentation of labour was less in vaginal misoprostol group compared to dinoprostone gel group. The same trend was reported in the previous studies also, 33.8% in misoprostol group versus 63.74% in dinoprostone group, when 50 µgm misoprostol 3 hrly was used[11], 21% versus 47% when 50 µgm misoprostol 4 hrly was used[12]. Even with 25 µgm misoprostol 2 hr interval oxytocin requirement was less for misoprostol than dinoprostone, 44.4% versus 87.9%.[13] The reduced need for oxytocin by two-third was reported after 50 µgm misoprostol 8 hrly

versus dinoprostone 8 hrly.[14]

Mode of Delivery

In our study, the incidence of vaginal delivery was higher in the misoprostol group than the dinoprostone group. The incidence of vaginal delivery was 36 (72%) in misoprotol group (p=0.002) and 33 (66%) in dinoprostone group (p=0.024). It was reflected in other studies also.[15, 16]

Induction Vaginal Delivery Interval

The study show there was no significant difference in respect to the mean induction vaginal delivery interval. The mean induction to vaginal delivery interval was 22.12±2.768 hrs in dinoprostone gel group (p=0.000) and 21.92±3.228 hrs in misoprostol group (p=0.000). It was supported by a study done by EJ Langenegger et al in 2005.[17] It was a randomized controlled trial found both misoprostol and dinoprostone gel to be equally effective. In a randomized trial, Alexandro Megalo et al in 2004[18], found that misoprostol effectively shorten the induction to vaginal delivery interval. Recently, even reduction of upto 12 hr was reported with 50 µgm vaginal misoprostol.[19] Thus, about 30-40% reduction in time was seen in misoprostol group as compared to dinoprostone gel.[17] In our study misoprotol failed to reduce the mean induction induction delivery interval may be due to the lower initial Bishop score or inadequate dose of misoprostol.

Out of 33% vaginal deliveries 25 (75.76%) delivered <= 24 hr in PGE2 group. Out of 36 patients, 27 (75%) delivered <=24 in PGE1 group. There was no significant difference between the two groups. The vaginal misoprostol was as effective as intracervical dinoprostone gel for vaginal delivery within 24 hr of initiation of IOL. It was supported by another study.[20]

Cesarean Section and Its Indication

The incidence of cesarean section was lesser in misoprostol group in this study. It was 14 (28%) in misoprostol group and 17 (34%) in dinoprostone group. Incidence of cesarean section due to fetal distress (nonreactive CTG) was 8 (16%) in dinoprostone gel group (p=0.000) and 6 (12%) in misoprostol group (p=0.000). The incidence of LSCS due to failed induction of labour was similar, 8 (16%) in two groups. These results were supported by another randomized controlled trial done by M Elhassen[21], Frank Chuk and Huffaker[22] have compared 50 µm vaginal misoprostol with intracervical dinoprostone gel every 4 hrs for labour induction and have reported similar results.

In our study, intracervical dinoprostone gel and vaginal misoprostol was equally effective in regards of improvement in modified Bishop score, need for augmentation of labour and reduction in mean induction delivery time. On the other hand, some studies[23] showed that misoprostol was more effective than dinoprostone gel. In these studies misoprostol was use in higher dose and also used in frequent intervals. Incidence of hyperstimulation 7-8% with 50 µgm vaginal misoprostol at 3-4 hrs intervals was reported.[24] Report with 50µgm vaginal misoprostol at 6 hr interval has demonstrated hyperstimulation 5.8%-26.5%.[26] In contrast, we had only one case (2%) of hyperstimulation in each group. Le Roux et al[15] has reported an increased incidence of caesarean section for fetal distress and hyperstimulation with 50µgm vaginal misoprostol when compared to dinoprostone gel. In our study, the incidence of fetal distress was comparatively less in misoprostol group 6 (12%) than dinoprostone gel group 8 (16%). Hence, in our study efficacy was not sacrificed and complication was significantly reduced. So, vaginal misoprostol 25µgm, 6 hr interval appears to better choice than early repeated doses.

Veena B et al study revealed the proportion of women who had normal vaginal delivery was significantly high in PGE1 group (76.8 and 61.1%), and notably less proportion underwent LSCS (15.8 vs 32.6%).[27] This observation contradicts few other existing evidences in which misoprostol was shown to increase the rate of caesarean section when oral misoprostol was compared to PGE2 (28 vs 24%).[28] Hofmeyr JG et al[28] systematic review showed 22 trials with 5,229 participants compared vaginal misoprostol with other vaginal prostaglandins for the outcome of vaginal deliveries within 24 hours. Women receiving misoprostol were less likely to not be delivered within 24 hours (22 trials 5229 participants, 920/2550 versus 1179/2679, RR 0.77, 95% CI 0.66 to 0.89, NNT = 10) and were less likely to require oxytocin augmentation (38 trials, 7022 participants, 1355/3465 versus 1794/3557, RR 0.68, 95% CI 0.61 to 0.76, NNT= 7). Meconium-stained amniotic fluid was more common among subjects receiving misoprostol (18 trials, 3991 women, 246/1909 versus 190/2082, RR 1.35, 95% CI 1.13 to 1.61, NNH = 32). Misoprostol increased uterine hyperstimulation without FHR changes (26 trials 4804 women 381/2311 versus 199/2493, RR 1.99, 95% CI 1.41 to 2.79, NNH = 13), although hyperstimulation with FHR changes did not differ (31 trials 5830 women). Vaginal misoprostol reduced the need for oxytocin augmentation (38 trials, 7022 women, 1355/3465 versus 1794/3557, RR 0.68, 95% CI 0.61 to 0.76, NNT = 7) and epidural anesthesia (8 trials, 2141 women, 469/1063 versus 516/1078, RR 0.92 95% CI 0.85 to 0.99, NNH = 27). Caesarean section rates were not significantly different.[28]

Mozurkewich E et al study compared with cervical PGE2, vaginal misoprostol reduced failure to achieve vaginal delivery within 24 hours (13 trials, 1627 women, 253/814 versus 402/813, RR 0.63, 95% CI 0.56 to 0.71, NNT = 6). Oxytocin augmentation was required less often with misoprostol based on 20 trials including 2316 women, (411/1177 versus 727/1139, RR 0.55, 95% CI, 0.48 to 0.64 NNT = 4) and women receiving misoprostol were less likely to have a cervix unfavorable for induction after 12-24 hours (1 trial, 155 women, 38/76 versus 58/79, RR 0.68, 95% CI 0.52 to0.88, NNT = 5).[4]

Limitation of the Study

The study unable to find out an ideal dosing schedule which would be very logical from pharmacological point of view, though the both groups showed successful vaginal delivery at 3 doses, increment/decrement of dose causing increase incidence of LSCS due to side effect from drug. In our study maximum 3 doses seems to be better dosing schedule for

vaginal delivery outcome. This point should be clarified by further researches. In our study relatively less augmentation was required for subjects receiving PGE1 tab, compare to the PGE2 group. This may favor the misoprostol to be given for better vaginal delivery outcome in appropriate situation. This is very interesting but our study was unable to furnish reason for the same. This points highlights for further study.

CONCLUSION

Vaginal misoprostol was as effective and more cost effective agent for induction of labour in women with hypertensive disorders of pregnancy as compared to intracervical dinoprostone gel with no increase in maternal or neonatal morbidity. The incidence of vaginal deliveries was higher in vaginal misoprostol group compared to dinoprostone gel group. There was no significant difference in respect to the mean induction vaginal delivery interval between the two groups. The incidence of cesarean section was less in vaginal misoprostol group than dinoprostone gel group. There was no increased incidence of caesarean section due to fetal distress in vaginal misoprostol group. Neonatal outcomes in vaginal misoprostol group were as good as dinoprostone gel group. There was no statistical significant difference between the two groups regarding the side effects, with special reference to the uterine hyperstimulation. Vaginal misoprostol was cost effective and patient's compliance was much better in vaginal misoprostol group than dinoprostone gel group.

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