

Comparitive Study of Efficacy of Intravaginal Isosorbide Dinitrate with Dinoprostone Gel on Cervical Ripening Prior To Induction of Labor

Dr Neeraj Sharma¹, Dr Anubha Jain Singhal², Dr Dolly Chawla³,
Dr Priya Shukla⁴, Dr Neeru Malik⁵

¹specialist, Obs and gynae, Dr Baba Saheb Ambedkar Hospital

²senior resident, Obs and gynae, Dr Baba Saheb Ambedkar Hospital

³senior specialist & Head of the department, Obs and Gynae, Dr Baba Saheb Ambedkar Hospital

⁴dnb, wObs and Gynae, Dr Baba Saheb Ambedkar Hospital

⁵senior medical officer, Obs and Gynae, Dr Baba Saheb Ambedkar Hospital

Abstract: Labor is defined as the process of regular uterine contraction leading to progressive effacement and dilatation of the cervix and birth of the baby. Induction of labor is an intervention designed to artificially initiate labor. Induction should only be considered when it is felt that the benefits of the delivery outweigh the potential maternal and fetal risks of awaiting spontaneous labor. Several methods are available for cervical ripening like prostaglandins, misoprostol, oxytocin, nitric oxide donors, mechanical methods like hygroscopic cervical dilators and amniotomy. The ideal agent is yet to be found. This is a prospective randomized controlled study conducted in the department of OBS and GYNAE in BABA SAHEB AMBEDKAR HOSPITAL. 100 women were admitted in the labor ward for induction of labor, who were more than 40 weeks of gestation and divided into 2 groups. Group 1 was given intravaginal isosorbide dinitrate and Group 2 was given intracervical dinoprostone gel respectively after taking baseline Bishops score and then results compared at 6 hours and 12 hours respectively for cervical ripening. The median of modified Bishop score in group 1, 12 hours and 18 hours after the medication was 1(0-7) and 3 (0-10) respectively ($p=0.001$) while in group 2, 12 hours and 18 hours after the medication was 1(0-7) and 3 (0-10) respectively ($p=0.001$). Thus the above study showed that PGE₂ gel is more effective in cervical ripening than isosorbide dinitrate.

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I. Introduction

Labor is defined as the process of regular uterine contraction leading to progressive effacement and dilatation of the cervix and birth of the baby. Induction of labor is an intervention designed to artificially initiate labor. Induction should only be considered when it is felt that the benefits of the delivery outweigh the potential maternal and fetal risks of awaiting spontaneous labor. Induction of labor often is undertaken with an unfavourable and an unripe cervix. A considerable amount of research has been directed towards various methods to prepare or ripen the cervix before the induction of labor. These methods have attracted interest because cervical ripening is a reasonable predictor of a likelihood of a successful induction terminating in vaginal delivery. The goal of cervical ripening is to facilitate the process of cervical softening, thinning and dilatation with resultant reduction in the rate of failed induction and induction to delivery time. A number of scoring systems to characterize the cervix has been developed and the BISHOP SCORE is the most widely used scoring system. If the cervix is unfavourable (BISHOP SCORE < 6), cervical ripening is warranted prior to induction of labor. Several methods are available for cervical ripening like pharmacological agents which include prostaglandins preparations in form of intracervical PGE₂ gel, intravaginal PGE₂ gel, controlled – release PGE₂, misoprosrol, oxytocin, nitric oxide donors; mechanical methods like hygroscopic cervical dilators and transcervical dilators , and surgical methods like membranes stripping and amniotomy. Other methods are like herbal supplements, castor oil, hot baths and enemas, sexual intercourse, breast stimulation, acupuncture and transcutaneous nerve stimulation but at present evidence are lacking to support these as viable methods for cervical ripening. Steiner and Creasy in 1983 described the “ideal agent” for cervical ripening: it should cause cervical change in a physiological manner that is similar to the natural ripening process and exclusively effect in cervical changes, without uterine contractions or hyperstimulation⁵.

II. Aims

- To compare the effect of intravaginal isosorbide dinitrate on cervical ripening prior to induction of labor with that of intracervical dinoprostone gel
- To evaluate the safety of repeat dose of isosorbide dinitrate

III. Material And Methods

It was a prospective randomized controlled study, conducted in the department of OBS and GYNAE of BABA SAHEB AMBEDKAR HOSPITAL, DELHI, from a period of 2 years after taking clearance by the ethical committee of the hospital.

STUDY DESIGN: Prospective randomized controlled study.

SAMPLE SIZE: 100 pregnant women.

PROCEEDURE AND METHODOLOGY: One hundred pregnant women with more than 40 weeks period of gestation who were admitted in labor ward for induction of labor were included in the study for preinduction cervical ripening as per inclusion criteria which were singleton pregnancy, nulliparity, cephalic presentation, more than 40 weeks of gestation and unfavorable cervix with modified Bishops score less than 6. Before the drug administration a well written and informed consent was taken, general and systemic examination was done, fetal heart rate, pelvic examination and BISHOP scoring was recorded at the start of induction. Hemoglobin estimation, blood grouping, urine routine and microscopic examination and ultrasonography was also done. All participants were fully informed and counseled about the nature and scope as well as about the potential risks of the study and side effects like nausea, vomiting ,pain abdomen, diarrhea, headache, hot flushes, palpitation, giddiness, before the first application of PGE₂ gel or isosorbide dinitrate. Subjects were allotted to 2 groups through randomization by computer .Group 1 was administered 40 mg isosorbide dinitrate tablet in the posterior fornix of vagina, while in group 2, patients were administered dinoprostone gel 0.5 mg in gel form in 3mg base intracervically. Modified bishop score in both groups was reassessed at 6 and 12 hours after administration of first dose. If the modified bishops score remained less than or equal to “6” after 12 hours, second dose was given. Reassessment was done 18 hours after first dose and then oxytocin was given, if required. Induction Delivery interval was measured as the time interval between the initiation of the drug administration and delivery. Mode of delivery whether vaginal or ceasarian was noted along with its indication. Patients were monitored for pulse rate, blood pressure, temperature, fetal heart rate was also recorded and any side effects like headache, hot flushes, palpitation, nausea, vomiting, giddiness was observed.

Statistical analysis

Data was analyzed using SPSS-15 software. Chi square test / fishers exact test was applied to compare two groups in case of categorical data. In analysis of quantitative variables independent t test and Mann-Whitney U test was applied as per the requirement of the data to obtain significance between the groups. “p-Value” of <0.05 was taken as significant.

IV. Observation And Results

The subjects in the groups were clinically similar and there were no significant differences in the baseline characteristic like, age, parity, socioeconomic status, gestational age and baseline modified bishop score as depicted in Table 1.

Table no 1: Characteristics of subjects in 2 groups

	GROUP 1 (isosorbide dinitrate)	GROUP 2 (Dinoprostone gel)	*p value
Age (in years) mean± SD	22.65±2.1	22.46±2.14	*0.451
Socioeconomic status (lower class)	33(66%)	31 (62%)	0.563
Parity (nulliparous)	50	50	-
Period of gestation (in weeks) mean ± SD	40.30± 0.14	40.30± 0.15	0.893
Bishop score at admission MEDIAN (min – max)	1(0-3)	0 (0-3)	** 0.852

*independent t test

**Mann Whitney U test

Table no 2 shows that there is significant difference in improvement in the modified bishop score. It was more in group 2 than in group 1. The median of modified bishops score 6 hours after the administration of drug was 1(0-3) in group 1 and 1(0-9) in group 2. The **p value was 0.001**, which was statistically significant. After 12 hours it was 1(0-7) in group 1 and 3(0-10) in group 2 ; and that after 18 hour was 3(0-10) in group 1 and 4(1-10) in group 2 . The **p value** after 12 and 18 hours after administration of drug was **0.001** and **0.004** respectively which was statistically significant.

Table no 2: Comparison of changes in modified Bishops score

	GROUP 1 (isosorbide dinitrate)	GROUP 2 (dinoprostone gel)	*p value
BISHOPS SCORE at admission	1(0-3)	0(0-3)	*0.852
6 hours after 1 st dose	1(0-3)	1(0-9)	0.001
12 hours after first dose / time of second dose	1(0-7)	3(0-10)	0.001
18 hours after first dose	3(0-10)	4(1-10)	0.004

* *Mann Whitney U test/ Wilcoxon rank- sum test*

Table no 3 depicts the percentage of the subjects requiring the second dose of medication and oxytocin. It recorded that 96% of women in group 1 required second dose of the medication while only 56 % in group 2 required it. The *p value was 0.001* and was statistically significant. The use of oxytocin was also more in group 1 than in group 2 , 96% and 78% respectively and was statistically significant with *p value= 0.015*

Table no 3: Showing requirement of second dose and use of oxytocin

	GROUP 1	GROUP 2	*p value
REQUIREMENT OF SECOND DOSE	48 (96%)	28(56%)	0.001
USE OF OXYTOCIN	48(96%)	39(76%)	0.015

**Fisher's test*

Table no 4 demonstrates that the median induction to delivery interval in group 1 was 34.8(5.6 – 52.7) hours which was statistically longer than that in group 2,18.85 (5.5-48.5) hours. The *p value calculated was 0.001*, which was statistically significant

Table no 4: Comparing induction delivery interval

	GROUP 1	GROUP 2	*p value
INDUCTION- DELIVERY INTERVAL (IN HOURS) MEDIAN (min – max)	34.8(5.6-52.7)	18.85(5.5-48.5)	0.001

* *Mann Whitney U test/ Wilcoxon rank- sum test*

Table no 5 records that the cesarian section were more in group 1 (52%) while the vaginal deliveries were more in group 2 (74%). There were 13 subjects who underwent cesarean section in group 2. It was found to be statistically significant as *p value= 0.013*.

Table no 5: mode of delivery

Mode of delivery	GROUP 1	GROUP 2	*p value
Vaginal	26(56%)	37(74%)	0.013
caesarian	24(48%)	13(%)	

**Pearson chi-square test*

Amongst the sideeffects, headache was present in 56% of women in group 1. Nausea and vomiting were present in 12% and 18% of women in group 2. The side effects like hot flushes and giddiness were not found in any of the groups.

V. Discussion

The ideal agent for induction of labor would achieve cervical ripening followed by ‘spontaneous’ onset of labor without causing uterine hyper stimulation (Calder 1998)¹¹⁶. Cervical ripening prior to induction of labor is a common indication for PGE₂ gel. However in the last few years there has been a considerable interest in NO donors in cervical ripening. Previous studies in both, animals and humans, have shown that NO donors can induce cervical ripening after their local application^{87,88}

Thompson et al (1998)¹⁰¹ and Fecchinetti et al (2000)¹⁰² were the pioneer in this area and studied about a preparation of NO donors, sodium nitroprusside given intracervically before suction evacuation. They found that the intra cervical nitroprusside was effective in reducing cervical resistance and softening the cervix.

The present study compared the effectiveness of intravaginal isosorbide dinitrate (group 1) on cervical ripening prior to induction of labor with that of dinoprostone gel (group 2). The median of modified Bishop score in group 1, 12 hours after the medication was 1(0-7) and in group2 was 3 (0-10). The difference was statistically significant as the *p value=0.00*). The primary factor responsible for improvement in modified Bishop Score was change in cervical consistency. The vaginally applied isosorbide mononitrate increases the expression of cyclooxygenase-2 in the cervix of the pregnant women in first trimester. Therefore it can be suggested that the change in the cervical consistency may be due to the stimulation of the local prostaglandins synthesis. Though isosorbide dinitrate have an considerable effect on cervical ripening however, PGE₂ gel was more effective than that in inducing changes in modified Bishop score. The improvement in modified Bishop

score in isosorbide dinitrate group were less than PGE₂ gel after 12 hours and 18 hours of the medication. The median of modified Bishop score in group 1, 12 hours and 18 hours after the medication was 1(0-7) and 3 (0-10) respectively ($p=0.001$) and in group 2 value was 3(0-10) and 4(1-10) after 12 hours and 18 hours respectively with ($p=0.004$). These results were comparable to those found in the study done by Chanrachakul et al (2000) in which he compared 500 mcg glyceryl trinitrate (n= 54) with 3 mg of PgE2 gel (n=56) women for cervical ripening at term⁹. The increase in median of Bishop score was 2 unit in the glyceryl trinitrate group and 3 units in the PGE2 group⁷. The results were also comparable to those of Osman et al (2005) who found that the mean change over baseline modified bishop score was significantly greater at both 16 and 24 hours for the PGE2 group¹⁰. At 16 hours the main change was 1.36, for isosorbide mononitrate and 2.29 for PGE₂ . Mean difference 0.94; 95% CI, 0.60-1.28; P<0.0001.

Wolfer et al (2006) compared the efficacy of isosorbide mononitrate given simultaneously with dinoprostone with that of dinoprostone alone in promoting delivery in 120 nulliparous women at term¹¹² and concluded that vaginally administered isosorbide mononitrate does not play a role in promoting delivery in term pregnancy if given at the same time of dinoprostone gel.

There is increasing interest in out patient cervical ripening treatment, leading to shorter admission to delivery times and thus reduced health care costs. It has been proved by previous studies that NO donors can do that, though less effectively than prostaglandins, but without causing uterine contractions., thus NO donors may be appropriate to use on OPD basis. To conclude this Bulbero et al (2007) randomly selected 200 at 42 weeks of gestation with unripe cervix to receive vaginally either 40 mg isosorbide mono nitrate or placebo tablets on OPD basis¹¹³. He justified that use of NO donors seems to be an effective, safe and well tolerated procedure¹⁰⁸ when used on opd basis. In the same thought Habib et al (2008) conducted a RCT of 102 women and found that 37.25 % women had bishop score more than 6 and went in to labor within 36 hours of starting medication as compare to the placebo group.

It has been well demonstrated in the study that PGE₂ gel is more effective in reducing the induction-delivery interval than isosorbide dinitrate. That study has same results as that of Chanrachakul et al (2000), who reported 26.3 in GTN group and 21.8 in PGE₂ group ($p=0.01$)⁹ . Osman et al (2005) also reported the same finding of significant difference in the induction delivery interval of 26.9 in PGE2 group and 39.7 in isosorbide mononitrate group. The interval was shorter in the group using PGE₂ gel.

The present study also demonstrated that second dose was required in 96% patients in group 1 as compared to 56 % in group 2. It is comparable to Osman et al, 111/99 women in isosorbide group where as only 55/199 in PGE2 group. The need of oxytocin was also greater in group1 (96%) than in group 2 (78%). The result is in agreement with that of Chanrachakul et al where oxytocin was needed in 42 out of 54 women (78%) in the glyceryl trinitrate group and 24 out of 56 subject (43%) in the PGE₂ group ($p< 0.001$)⁹ Bollapragada et al (2009) reported that oxytocin was required in 63% women in isosorbide group than in 59% women in PGE2 group , thus comparable to our study

In our study maximum number of patient who delivered vaginally were from GROUP 2 (60%), while more caesarians were required in GROUP 1 . The total number of women who delivered vaginally in GROUP 1 were 26 (52%) as compared to 37 (74%) women in GROUP 2. The results were comparable to those found by Wolfler et al (2006). He reported that 72.7 % women delivered vaginally in placebo group while only 58.2 % delivered vaginally in isosorbide mononitrate group¹¹².

There were no statistically significant differences in fetal apgar scores at 1 and 5 min. this is in agreement with the results of previous studies.^{9,11,12,110,111,112,113,115}

The main side effects reported after intravaginal administration of isosorbide dinitrate was headache, which was significant .Though women has satisfactory relief with paracetamol. It is well known that these most common side effects are due to the vasodialatory action on NO. Previous studies have similar findings.^{9,11,12,108,110,114,115}

VI. Conclusion

The present prospective study suggests that intravaginal isosorbide dinitrate is effective in cervical ripening prior to induction of labor . However intracervical PGE₂ gel was more effective as bishop score was more favorable with it at 12 and 18 hours respectively.

Isosorbide dinitrate was less effective than dinoprostone gel as it has a longer induction – delivery interval than dinoprostone gel. The number of patients delivering vaginally was more when PGE2gel was administered.

The second dose of 40 mg isosorbide dinitrate is safe to use and no clinically significant side effects were reported. Also isosorbide dintrate is inexpensive and stable at room temperature.

Isosorbide dintrate can be administered at an outpatient basis as they induce cervical ripening without causing uterine contractions. They do not require fetal heart rate monitoring. They have no adverse effects of clinical importance during the ripening process.

Its use on an out patient would lead to shorter admission to delivery interval thus reducing hospital stay and work load on labor and delivery units and reduced health care costs.

Further studies are necessary to identify the ideal formulation, dose, frequency of administration of NO donors, as well as to confirm the safety of the procedure when repeatedly administered.

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