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**Original Research Article**

# Randomized control trial of low dose oral misoprostol compared with intracervical dinoprostone gel for cervical ripening

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## ABSTRACT

**Background:** Induction of labour is a therapeutic option when the benefits of delivery outweigh risks of continuing pregnancy. There are several agents for induction of labour to achieve better outcome of labour. Acceptable methods for induction are oxytocin infusion, dinoprostone gel, misoprostol and mechanical cervical dilators. Prostaglandins are the preferred choice in unripened cervix. Objective of this study was to compare efficacy, safety of low dose oral misoprostol compared with intracervical dinoprostone gel for cervical ripening.
**Methods:** One hundred women with single live fetus, term gestation, cephalic presentation, reactive fetal heart pattern and Bishops score <6 were included in the study. They were randomized to receive either 6 doses of 25ug oral misoprostol every 3rd hourly or 0.5ug intracervical dinoprostone every 6th hourly for a maximum of 3 doses.
**Results:** Bishops score improvement after 6,12,18 hours in both the groups was statistically insignificant. Induction delivery interval was11.96±5.88 for misoprostol and 10.95±4.58 in dinoprostone group with P value 0.341 which was statistically insignificant. Need for oxytocin augmentation was less (18%) in misoprostol group as compared to dinoprostone group (44%). Caesarean section rate was slightly higher in misoprostol group (26% vs 24%). Meconium stained amniotic fluid was high in misoprostol group (16%) compared to dinoprostone group (8%). Maternal complications were minimal and neonatal outcome was good in both the groups.
**Conclusions:** Compared to dinoprostone; misoprostol is easy to store, cost effective, stable at room temperature, can be easily administered and had better patient compliance and acceptability. It was found to be a better cervical ripening agent with similar maternal and fetal safety profile.

**Keywords:** Bishops score, Dinoprostone, Induction delivery interval, Misoprostol

## INTRODUCTION

Induction of labour is a therapeutic option when the benefits of delivery outweigh risks of continuing pregnancy. Inadequate cervical ripening is a known obstacle to successful labour induction and delivery. There are several agents for induction of labour to achieve better outcome of labour. Acceptable methods for induction are oxytocin infusion, dinoprostone gel, misoprostol and mechanical cervical dilators. Oxytocin is more effective on ripened cervix. Prostaglandins are the preferred choice in unripened cervix.

Dinoprostone (PGE2) gel requires an intracervical application, needs refrigeration and expensive. The PGE2 preparation for cervical ripening and induction of labour contains Dinoprostone as the naturally occurring form of PGE2 and are used locally either intravaginally or intracervically and has lesser side effects

PGE2 increases the activity of the collagenase which reaches a maximum activity at 2 hours after application in patients of multiparity and 4 hours after application in patients of nulliparity (Witter FR).[1]

The optimal intracervical dosage of dinoprostone is 0.5mg. Dinoprostone contains 0.5mg dinoprostone (PGE2) gel packaged in a syringe with two 10mm and 20mm catheters. Before administration, the gel must be kept refrigerated and then brought to room temperature just before administration. It is recommended that after dinoprostone gel administration, the patient should remain in a supine position for at least 15-30 minutes to minimize leakage from the cervical canal. If there is no cervical response after the starting dose, a repeat dose of 0.5mg dinoprostone should be administered after 6 hours. The maximum recommended cumulative dose for a 24-hour period is 1.5mg of dinoprostone.

Hyperstimulation rates are minimal. Data regarding long term safety for foetuses exposed to PGE2 for cervical ripening are scant. No adverse events with neonatal outcome.

Misoprostol (Cytotec Searle, Chicago, IL) is a synthetic PGE1 analogue. The FDA recognizes that in certain circumstances off-label uses of approved products like misoprostol are appropriate, rational and accepted medical practice. After oral administration, misoprostol is rapidly absorbed and converted to its pharmacological active metabolite, misoprostol acid. Plasma concentration of misoprostol acid peak in approximately 30 minutes and decline rapidly thereafter. Orally administered misoprostol is rapidly absorbed and becomes intensively bound to plasma proteins, when administered vaginally peak plasma level are reached more slowly (80±27) minutes than with oral administration (34±17) minutes and are sustained up to 4 hours. Intrauterine pressure began to increase on an average of 8 minutes after oral administration and 25 minutes after vaginal administration and was maximal 25 minutes after oral administration and 46 minutes after vaginal administration (Goldberg B.A et al).[2] Uterine contractility initially increased and then plateaued 1 hour after oral administration, whereas uterine contractility increased continuously for 4 hours after vaginal administration. Maximal uterine contractility was significantly higher after vaginal administration. This difference in oral and vaginal misoprostol activity is because of the obligatory hepatic pass that occurs with oral but not with vaginal route. This effect is also reflected on uterine contractility.

Misoprostol use is associated with a higher incidence of uterine hyperstimulation and thick meconium. For this reason, patient receiving misoprostol should be continuously monitored for uterine activity and foetal heart rate. Low dose misoprostol regimen will probably reduce the incidence of uterine hyperstimulation and subsequent abnormal foetal heart rate pattern and further reduce the potential need for caesarean delivery.

It appears that misoprostol can be easily administered and when compared to dinoprostone, is cost effective, with similar safety and efficacy. Hence, misoprostol received increased attention as a highly effective cervical ripening agent. This medication has the advantage of being inexpensive, easy to store, and stable at room temperature, whereas PGE2 gel is an unstable compound that must be refrigerated to preserve its potency.

## METHODS

A randomized control trial was done on women of reproductive age group attending labour room at KIMS Hospital and research centre, Bangalore. The study period included was from January 2015 to June 2016. The study population included 100 randomly selected women in labour.

Patients with singleton pregnancy between 37 to 42 weeks with cephalic presentation and a reactive nonstress test, cephalic presentation with Bishop score <6 were included.

Patients having complications like placenta previa, oligihydramnios, severe intrauterine growth restriction, parity >5, previous uterine surgery, cephalopelvic disproportion, renal or hepatic dysfunction, hypersensitivity to prostaglandins, premature rupture of membranes and malpresentation were excluded.

Among the indicated 100 cases, 50 were given oral misoprostol and 50 intracervical dinoprostone gel. The random numbers were generated for the 100 cases, and subjects were allocated randomly. Women admitted for induction of labour with Bishop's score<6 were included in the study and informed written consent was obtained.

After routine investigations and special investigations like Nonstress test and ultrasonogram, pelvic examination for initial bishop score assessment was done before induction of labour.

50 cases received 25ug of oral misoprostol every 3$^{rd}$ hourly for maximum of 6 doses. Remaining 50 cases received 0.5mg intracervical dinoprostone gel every 6-hourly maximum of 3 doses and bishop score was assessed every 6th hourly or if the cases get good contractions, until the cervix is favourable for amniotomy or the patient will go into active labour. oxytocin was commenced if contractions become inadequate or if the woman had received all doses.

Partogram was obtained to assess the progress of laour. All patients were monitored half hourly for uterine contractions both for frequency and duration, and to look for hypertonus, tachysystole or hyperstimulation and maternal vital signs. Continuous/intermittent fetal monitoring to assess for fetal wellbeing.

## RESULTS

Mean age in Group I was 23.70±3.40 and in Group II was 23.52±3.47. The cases in both the groups were age matched and the P value 0.794 was not significant.

**Table 1: Patient characteristics.**

| | | Group I | | Group II | |
|---|---|---|---|---|---|
| | | No. | % | No. | % |
| Parity | Primi | 32 | 64 | 30 | 60 |
| | Multi | 18 | 36 | 20 | 40 |
| Gestational age (weeks) | 37-40 | 15 | 30 | 18 | 36 |
| | 40+1-42 | 35 | 70 | 32 | 64 |

Parity wise and the P =0.680 was not significant.

Gestational age in both the groups were matched and the P =0.680 was not significant.

Indication for induction was postdatism in 70% and 64% cases of Group I and Group II in both the groups. Gestational hypertension and GDM was indication of induction in 12% each in group I and 14% each in group II. Decreased fetal movements indication for induction in 6% and 8% of cases in group I and group II respectively.

**Table 2: Comparison of Bishops score.**

| Bishop score | Group I | Group II | P value |
|---|---|---|---|
| Initial | 3.46±1.23 | 3.36±1.10 | 0.670 |
| 6 hrs | 5.67±2.20 | 5.66±1.91 | 0.985 |
| 12 hrs | 5.94±1.95 | 6.53±2.15 | 0.406 |
| 18 hrs | 6.25±1.91 | 5.20±0.84 | 0.275 |

30% (n=15) cases in Group I and 38% (19) cases in Group II Bishop score prior to induction was 4.P value was 0.933, 0.640 and 0.932 at 6, 12 and 18 hrs respectively which was not statistically significant.

**Table 3: Total number of doses distribution in two groups.**

| No. of doses | Group I | | Group II | |
|---|---|---|---|---|
| | No | % | No | % |
| 1 | 14 | 28.0 | 33 | 66.0 |
| 2 | 18 | 36.0 | 12 | 24.0 |
| 3 | 6 | 12.0 | 5 | 10.0 |
| 4 | 4 | 8.0 | 0 | 0.0 |
| 5 | 2 | 4.0 | 0 | 0.0 |
| 6 | 6 | 12.0 | 0 | 0.0 |
| Total | 50 | 100.0 | 50 | 100.0 |

P<0.001, significant, Fisher Exact test

In group A it was observed that majority of cases i.e.; 36% (n=18) cases required 2 doses of PGE1.In group B it was observed that majority of cases i.e.; 66% (n=33) required 1 dose of PGE2 gel.

Pelvic examination to see for improvement in Bishops score was done for 14 patients In Group I at 3 hours as they were getting 2-3contractions lasting for 30-35 seconds in 10 minutes. In these cases, further doses of misoprostol were withheld as Bishops score was favourable among which 9 were primigravida and 5 multigravida.

**Table 4: Delivery details.**

| Delivery details | | Group I (n=50) | | Group II (n=50) | |
|---|---|---|---|---|---|
| | | No | % | No | % |
| Augmentation with oxytocin | | 9 | 18.0 | 22 | 44.0 |
| Mode of delivery | Vaginal | 37 | 74 | 38 | 76 |
| | LSCS | 13 | 26 | 12 | 24 |
| Liquor colour | Clear | 42 | 84 | 46 | 92 |
| | Meconium | 8 | 16 | 4 | 8 |

In Group II pelvic examination was done for 12 patients to note improvement in Bishops score before 6 hours as patients had 2-3contractions lasting for 30-35 seconds in 10 minutes. All patients had favourable Bishops score among which 3 were primigravida and 9 were multigravida.

In group I, 18% (n=9) cases and in group II 44% (n=22) cases required augmentation with oxytocin and P =0.005**which was statistically significant.

In Group I, 26% (n=13) and in Group II 24% (n=12) cases underwent LSCS and P=0.817 which was not statistically significant.

In Group I 16% (n=8) and in Group II 8% (n=4) cases had meconium stained amniotic fluid and P value was not statistically significant

Fetal distress was the most common indication for LSCS in both the groups ie.in Group I 69.2% (n=9) and in Group B 66.7% (n=8) cases.

**Table 6: Induction delivery interval in two groups.**

| IDI in hrs | Group I | | Group II | |
|---|---|---|---|---|
| | No | % | No | % |
| <10 | 26 | 52.0 | 23 | 46.0 |
| 10-20 | 19 | 38.0 | 24 | 48.0 |
| >20 | 5 | 10.0 | 3 | 6.0 |
| Total | 50 | 100.0 | 50 | 100.0 |
| Mean±SD | 11.96±5.88 | | 10.95±5.88 | |

P=0.341, not significant, Chi-Square test

P=0.341 and induction delivery interval was not statistically significant in two groups

As P=1 complications during labour is not statistically significant in both the groups.

Most common reason for NICU admission was Meconium aspiration syndrome. 28.57% (n=2) in Group A and 42.85% (n=3) in Group B.

**Table 7: Complications during labour.**

| Complications | Group A | Group B | Total |
|---|---|---|---|
| Postpartum hemorrhage | 6 (33.3%) | 5 (38.5%) | 11 (35.4%) |
| Pyrexia | 6 (33.3%) | 5 (38.5%) | 11 (35.4%) |
| Vomiting | 5 (27.8%) | 3 (23.1%) | 8 (25.8%) |
| Hypertonus | 0 (0%) | 0 (0%) | 0 (0%) |
| Tachysystole | 1 (5.6%) | 0 (0%) | 1 (3.22%) |
| Total | 18 (100%) | 13 (100%) | 31 (100%) |

P=1.000, Not significant, Fisher Exact test

**Table 8: Reasons for NICU admission.**

| Reasons for NICU Admission | Group A | Group B | Total |
|---|---|---|---|
| Meconium aspiration syndrome | 2 (28.57%) | 3 (42.85%) | 5 (35.71%) |
| For observation | 1 (14.28%) | 1 (14.28%) | 2 (14.28%) |
| Transient tachypnea | 1 (14.28%) | 2 (28.57%) | 3 (21.42%) |
| Gestational diabetes mellitus | 2 (28.57%) | 1 (14.28%) | 3 (21.42%) |
| Respiratory distress | 1 (14.28%) | 0 (0%) | 1 (7.14%) |
| Total | 7 (100%) | 7 (100%) | 14 (100%) |

P=1.000, Not significant, Fisher Exact test

## DISCUSSION

In present study the mean age in both the groups was 23.70±3.40 and 23.52±3.47 respectively and difference in age was not statistically significant. Similarly, in study done by Bartha et al the mean age in both the groups is 28.31±5.09 and 28.12±4.66 and in Kulshreshtha S et al study the mean age is 20±3.75 and 25.35±3.31 in two groups respectively and the distribution in age in two groups was not statistically significant.[3,4] In a similar study by Kamal P et al the mean age in both the groups was 23.38 and 23.36 respectively.[5]

In our study postdatism was the most common indication for induction, 70% and 64% in Group I and Group II respectively. Parmar M et al study showed 40% and 36% cases, Greagsons et al study 95% and 94%, Sheela CN et al study 36% and 32%cases induced for postdatism in Group I and Group II respectively.[6,7,8]

In study done by Kulshreshtha S et al the mean pre-induction Bishops score was 4.45±1.77 in PGE1 and 4.25±1.89 in PGE2 group and in our present study the mean pre-induction Bishops score was 3.46±1.23 in PGE1 and 3.36±1.1 in PGE2 group.[5]

In studies done by Bartha et al, Patil Kamal P et al, Kulshreshtha S et al the IDI in Group I was 14.02 (8.4212.54±7.73-27.61), 11.68±4.49, 6.92±4.01 and in Group II the IDI was 20.23 (16.67-32.75), 14.83±7.08, 12.54±7.73 respectively.[3-5] In all these studies IDI was shorter in misoprostol group compared to dinoprostone group. In present study the IDI in Group I and Group II are 11.96±5.88 and 10.95±4.58 and was shorter in dinoprostone group but it was not statistically significant.

Present study has shown requirement of oxytocin was high in PGE2 group compared to PGE1 group. It was favoured by studies of Parmar M et al, Patil P et al, Greaves NR et al, Bartha et al.[3,6,9,10]

Incidence of caesarean sections was high in PGE2 group compared to PGE1 group in studies done by Bartha L et al, Patil Kamal P et al, Kulshreshtha S et al.[3,4,9] Present study showed high caesarean section rate in PGE1 group compared to PGE2 group in accordance with study done by Parmar M et al, but it was not statistically significant.[6]

Liquor colour at delivery was meconium stained in 12% in PGE1 group and 6% in PGE2 group in study done by Patil P et al10.In our study it was 16% in PGE1 and 8% in PGE2 group which was comparable.

## CONCLUSION

Prostaglandins provide an effective method for achieving cervical ripening. On the basis of our study, misoprostol appears to be an effective agent for cervical ripening. The results of labour outcome convincingly prove that in the patients treated with misoprostol, induction delivery interval, incidence of caesarean section, neonatal outcome in terms of APGAR score were almost same compared to dinoprostone. Misoprostol is easy to store, cost effective, stable at room temperature, can be easily administered and had better patient compliance and acceptability. So, low dose oral misoprostol is an effective, economical convenient option for cervical ripening.

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