A Randomised Controlled Trial Comparing Intravaginal Misoprostol and Intracervical Dinoprostone in Pre Induction Cervical Ripening

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Abstract

Objective: To compare the efficacy and safety of intravaginal misoprostol with intracervical dinoprostone for preinduction cervical ripening. **Material &Methods:** It was a randomized controlled trial conducted at department of obstetrics and gynecology, JIPMER, Puducherry. Three hundred women with Bishop score of <6, were assigned randomly to receive either intravaginal misoprostol 25 µg every four hours for four doses, and intracervical dinoprostone gel 0.5 mg every eight hours for two doses. (one hundred women in each group). Oxytocin was initiated as per standardized protocol, if the cervix was favourable. If the cervical ripening was unsuccessful (Bishop score < 6) after the maximum doses of drugs in both the groups, then further treatment was individualized. Efficacy and cost of the drugs were compared in both groups. **Results:** Primary outcome measure was change in Bishop score. Mean Bishop score change at the end of 16 hours was significantly higher in the misoprostol group, (2.57±0.59) compared to dinoprostone group (2.17±0.10, p=0.016). This finding was inspite of the fact that the dinoprostone group had higher Bishop score prior to the ripening.(3.55±0.56 vs 3.28±0.77, p=0.006). Secondary outcome measures such as mean intervention-delivery interval, oxytocin requirement, mode of delivery, maternal and neonatal outcomes were similar in both the groups. Overall mean cost of ripening agent per patient was significantly less in the misoprostol group, (22.56±93.16 rupees) compared to dinoprostone group (493.89±173.99 rupees, p<0.0001).**Conclusion:** Low dose misoprostol is as effective as dinoprostone in cervical ripening and demonstrates similar fetal and maternal safety profile.

Keywords: Misoprostol, Dinoprostone, Pre induction cervical ripening, Bishop score.

1. Introduction

From time immemorial, the process of childbirth has been regarded as a natural outcome of pregnancy. In certain situations, continuation of pregnancy to term or beyond term may inadvertently be detrimental to the health of both the mother and the fetus. Hence an attempt is made by the obstetrician to artificially initiate the process of labour which is known as "induction of labour". Recently, elective inductions of labour have increased dramatically. The condition of cervix is important for the success of labour induction, which is evaluated by Bishop score. Score of ≥ 6 predicts the likelihood of successful induction. Bishop score of ≤ 4 identifies an unfavourable cervix and is an indication for cervical ripening. Several methods have been used to ripen the cervix prior to induction of labour. Wide variety of prostaglandins, dosages, dosing intervals, routes of administration are available for this purpose. Among them, dinoprostone gel is one of the commonly used methods. Though the

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efficacy and safety of intracervical dinoprostone, a prostaglandin E2 analogue, is well established, it is expensive, needs to be refrigerated and requires skill for intracervical application. Misoprostol, the methyl ester of PGE_1, is inexpensive, can be stored at room temperature, and is easy to administer .Misoprostol can thus be considered as an alternative to dinoprostone for preinduction cervical ripening. A large number of trials exist on misoprostol use in cervical ripening. Though FDA has not approved the use of misoprostol in pregnancy, . misoprostol for pre-induction cervical ripening is considered as a safe and effective "OFF-LABEL"use by the ACOG.It recommends the use of 25 mcg of intravaginal misoprostol every 3 to 6 hours. The purpose of this study was to compare the efficacy and safety of intravaginal misoprostol and intracervical dinoprostone for preinduction cervical ripening.

2. Material and Methods

This study was conducted in Department of Obstetrics and Gynaecology, JIPMER hospital, Puducherry from September 2009 to June 2011.The objective was to compare the safety and efficacy of intravaginal misoprostol with intracervical dinoprostone in preinduction cervical ripening. The study was approved by local institutional ethical committee. Women with medical and obstetrical indications for induction of labour were enrolled for the study. Inclusion criteria were singleton pregnancy,gestational age ≥ 37 completed weeks,cephalic presentation, live fetus. Exclusion criteria were H/O previous caesarean or any uterine scar,multiple pregnancy, cephalopelvic disproportion or estimated fetal weight ≥ 4kg, grand multipara,Bishop score > 6, eclampsia,antepartum, haemorrhage, active genital infection, contraindication for the use of prostaglandins(H/O asthma, glaucoma, cardiac disease), suspected chorioamnionitis, renal or hepatic dysfunction.

All women had undergone a routine transabdominal ultrasound, non stress test, haemoglobin and routine urine examination. Prior to induction, vaginal examination was done to assess the Bishop score. After written and informed consent, women were randomised into two groups. Randomization was done using a table of random numbers.

Group I - Intravaginal misoprostol group:Women in this group received 25 µg of intravaginal misoprostol tablet every 4 hours for maximum of four doses.

Group II- Intracervical dinoprostone group:Women in this group received 0.5 mg of dinoprostone gel intracervically, every 8 hours, for maximum of two doses. Patient was asked to stay in the bed for 30 minute after the administration of drugs.. Bishop score was evaluated after administration of each dose of drug in both the groups. Subjects under study did not receive the further doses of drug when the Bishop score was ≥6, uterine contractions occurred (≥ 3 in 10 min , lasting for 45 seconds), signs of fetal distress developed or cervical dilatation was ≥3 cm.

In either case, oxytocin infusion or artificial rupture of membranes was done if the cervix was favourable. If the cervical ripening was unsuccessful (Bishop score < 6) after the maximum doses of drugs in both the groups, then further treatment was individualized.

Regular fetal heart rate monitoring was done. Progress of labour was monitored carefully.

Cervical ripening was considered successful if a Bishop score of ≥6 was achieved or the women went into spontaneous labour. Primary outcome measure was Change in Bishop score. Secondary outcome measures included mean Induction- delivery interval, time to active labour, no of women who had spontaneous onset of labour, oxytocin requirement (no of women requiring oxytocin, duration of oxytocin administered) ,mode of delivery, uterine hypersystole/tachysystole/hyperstimulation, no of doses of dugs used, costs of drugs, maternal adverse effects such as pyrexia, vomiting, diarrhoea, shivering ,antepartum / post partum haemorrhage, maternal injuries and fetal adverse effects such as meconium stained amniotic fluid or fetal heart rate abnormalities. Neonatal outcome variables included term / preterm/ post term APGAR at 5 min,neonatal intensive care unit admission,duration of NICU stay , intrapartum death and birth trauma.

The data so obtained was analysed stastically using Mann Whitney U test for parameters following nonnominal distribution (Bishop score, APGAR score), Chisquare test for binominal variables (time to active labour, spontaneous onset of labour, oxytocin augmentation and induction and mode of delivery, maternal or fetal adverse effects, neonatal outcome,), unpaired t test for continuous variables (age, parity, gestational age, cost of drug). $P < 0.05$ is considered statistically significant.

3. Results

300 women were recruited in the study, of whom 150 received intracervical dinoprostone and 150 received intravaginal misoprostol. There were no women withdrew from trial. Age, period of gestation and parity were comparable in both the groups. Both the groups had almost an equal proportion of nulliparas and multiparas. The indications for induction were almost similar in both the groups except for the hypertensive disorders of pregnancy, which was significantly more in the misoprostol group,(22% vs 12.66%) ,and PROM, which was more common in the dinoprostone group (22.66% vs 5.3%). The common indication for induction in both groups was prolonged pregnancy (Table 1)

Mean pre ripening Bishop score was 3.28±0.77 in the misoprostol group and in the dinoprostone group, it was 3.55±0.56 (p=0.006) and thus, dinoprostone group had a slightly more ripe or favourable cervix than the misoprostol group at the time woman were recruited for the study. The mean Bishop score at the end of 8 hours and 16 hours of cervical ripening was almost similar in both the groups. Though the women in the dinoprostone group had more favourable cervix than misoprostol group before ripening, the mean Bishop score at 8 and 16 hours were not different from the misoprostol group. However, The mean change in Bishop score was higher in the second eight hours in the misoprostol p value = 0.016. (Table 2)

Successful cervical ripening included women who had Bishop score of ≥ 6 and those women who had spontaneous onset of labor. Successful cervical ripening was observed in 98% of patients in misoprostol group and 92.66% of dinoprostone group. The

number of women who achieved successful ripening at eight and sixteen hours were not different in both the groups. Of the 3 patients who had failed ripening in the misoprostol group, further attempts were made to ripen the cervix with Foley's catheter or dinoprostone gel followed by oxytocin infusion. Caesarean section was done in two patients for failed induction and one patient delivered vaginally .Of the 11 women in the dinoprostone group where ripening was considered as failure, misoprostol was used in a further attempt to ripen the cervix. One patient had one dose of misoprostol, four had two doses and six had four doses. Eight of these women delivered vaginally with oxytocin and three underwent caesarean section, done for failed induction (Table 3).

Table 4 shows various intrapartum variables in both groups.

Labour onset was spontaneous in more patients in the dinoprostone group (59%), compared to misoprosotol group (57%). Among these, oxytocin for augmentation was required by 29.76% patients in the misoprostol group and 44% patients in the dinoprostone group.

Labour onset, oxytocin induction, augmentation and duration of oxytocin use were similar in both the groups. The mean intervention to delivery interval was similar in both the groups (18.67±10.22 hrs v/s 18.02±0.62 hrs). However, the mean duration of labour, both spontaneous and induced, was shorter in the dinoprostone group. (7.03±6.7 hrs v/s 5.59±3.97 hrs.) (p=0.024) (Table 4)

The mode of delivery was similar in both the misoprostol and dinoprostone groups with caesarean section rates of 9% and 7.79% and instrumental delivery rates of 9.33% and 8% respectively. The indications for caesarean section and operative vaginal delivery was almost similar among the two groups. Fetal distress was the commonest indication for cesarean section followed by non progress of labour. (Table 5)

Perinatal outcome was similar in both the groups. Nine babies in the misoprostol group and 7 babies in the dinoprostone group required NICU admission for various reasons like, respiratory distress, birth asphyxia. There were no no neonatal or stillbirths noted in either group. (Table 6)

Side sffects were minimal in both the misoprostol and dinoprostone groups. Most common complication observed was meconium stained liquor in both the groups (11% in misoprosol group vs 7% in dinoprostone group), followed by abnormal fetal heart rate patterns (4% in misoprosol group vs 7% in dinoprostone group). (Table 7)

The mean cost of misoprostol or dinoprostone was caluculated by finding out the number of doses of either drug needed by all the women who had successful ripening or spontaneous onset of labour and the average cost worked out. The average cost of misoprostol per cervical rpening is 22.56±93.16 rupees and that of dinoprostone is 493.89±173.99 rupees. (p=<0.0001). Hence misoprostol is twenty times cheaper than dinoprostone. (Table 7).

Table 1: Maternal Demographic Characteristics

Variables	Misoprostol (n=150)	Dinoprostone (n=150)	p
Mean Age (years) [a] 0.14	23.38±3.04	23.93±3.42	0.14
Parity[a] – Nulliparas n(%)	87(58)	92(61.33)	>0.99
Multiparas n (%)	63(42)	58(38.66)	>0.99
Mean gestational age (weeks) [a]	40	30	>0.99
Indications for labour induction,n(%)[b]			
past dates	55(36.66)	40(26.66)	0.08
hypertensive disorders of prgnancy	33(22)	19(12.66)	**0.047**
PROM	8(5.3)	34(22.66)	**<0.001**
oligohydramnios	25(16.6)	30(20)	0.55
GDM	1(0.66)	2(1.33)	0.56
Rh negative pregnancy	9(6)	5(3.33)	0.41
Multiple indications	19(12.66)	20(13.33)	0.86

a-unpaired t test, data represented as mean±SD, or n (%), b-chi square test

Table 2: Mean Bishop Score and mean change in Bishop Score

Mean Bishop score[c]	Misoprostol	Dinoprostone	p value
Pre ripening[c]	3.28±0.77(n=150)	3.55±0.56(n=150)	**0.006#**
At 8 hours[c]	7.48±3.77 (n=147)*	7.81±3.73 (n=150)	0.569
At 16 hours[c]	10.05±3.18 (n=85)	9.98±3.63	0.874
Mean change in 8-0 hrs.	4.2±3.00(n=147)*	4.26±3.17(n=150)	0.386
Mean change in 16-8 hrs.	2.57±0.59 (n=85)	2.17±0.10 (n=80)	**0.016**

c-Mann whitney U test. #-significant*In the misoprostol group, three women underwent cesarean section for fetal distress after second and third doses of misoprostol- before the full duration -planned, and the cervix was still unfavourable in all the three patients and hence they were excluded from the analysis regarding cervical ripening

Table 3: Outcome of Cervical Ripening

Outcome	Misoprostol n=147	Dinoprostone n=150	p value
Total no. of successful ripening [b]	n=144(98%)	n=139(92.66%)	0.06
After 8 hrs	62 (42.17%)	70 (46.6%)	0.508
After 16hrs	82(55.78%)	69(46%)	0.116
Failed ripening	3(2%)	11(7.34%)	0.56
outcome: vaginal delivery	1	8	0.56
Cesarean section	2	3	

b-chi square test

Table 4:Intrapartum Variables

Outcome	**Misoprostol (n=147)**	**Dinoprostone (n=150)**	**p**
Occurrence of spontaneous onset labour [b]	84(57.14%)	89(59.33%)	0.791
No of doses among women with spontaneous labour [b] 1 2 3 4	 7(8.33%) 36(42.85%) 22(26.19%) 19(22.61%)	 50(56.17%) 39(43.82%%)	 0.61 0.61
Oxytocin use Induction Augmentation Duration(min)[b]	 60(n=147) 25(n=84) 723.54±3.75	 50(n=150) 40(n=89) 647.23±2.85	 0.224 0.057 0.2
Mean induction-vaginal delivery interval(hours) Mean duration of labour(hours)[a]	18.67±10.22 (n=134) 7.03±6.71(n=138)	18.02±0.62 (n=134) 5.59±3.97	0.43 **0.024#**

a- unpaired t test, b- chi suare test, #-significant

Table 5: Outcome of Labour

Mode of delivery[b]	**Misoprostol (n=150)**	**Dinoprostone (n=150)**	**p value**
SVD	123 (82.6%)	126 (84%)	0.75
Vacuum	6 (4%)	4(2.66%)	0.74
Forceps	8 (5.33%)	8(5.33%)	1.0
Cesarean section	13 (9%)	12(7.79 %)	0.8
Indications for cesarean section Fetal distress	7(53.84%)	7 (58.33%)	
CPD	1 (7.69%)	-	
Failure of induction	1 (7.69%)	3 (25%)	
Failure of ripening	1 (7.69%)	-	
Non progress of labour	3(23%)	2(16.66%)	

b- chi square test

Table6: Perinatal Outcome

Neonatal parameter	Misoprostol n=150	Dinoprostone n=150	p value
Mean birth weight (kgs)[a]	2.94±0.36	2.90±0.44	0.376
Mean APGAR at 1 minute [c]	7.84±0.61	7.79±0.82	0.549
Mean APGAR at minute At 5 minutes[c]	8.88±0.44	8.83±0.69	0.454
NICU ADMISSION[b]	9(6%)	7(4.6%)	0.81
Respiratory distress[b]	6(4%)	4(2.6%)	0.76
Birth asphyxia[b]	3(3%)	3(2%)	1.0

a- unpaired t test, b- chi square test, c- Mann-Whitney test

Table 7: Side effects and cost of Drugs

Side effects [b]	Misoprostol (n=150)	Dinoprostone (n=150)	p value
MSL	17(11.33%)	10(6.66%)	0.22 (NS)
Abnormal FHR	7(4.66%)	11(7.33%)	0.46 (NS)
Uterine Hyperstimulation	3(2%)	1(0.66%)	0.62(NS)
PPH	2(1.32%)	2(1.32%)	1.0 (NS)
APH	1(0.66%)	1(0.66%)	1.0 (NS)
Nausea and vomiting	1(0.66%)	1(0.66%)	1.0 (NS)
Mean cost of drugs (Rs)[a]	22.56±93.16	493.89±173.99	<0.0001#

a- unpaired t test , b-chi square test #(Significant)

4.Discussion

There are several studies comparing misoprostol and dinoprostone as cervical ripening and labour induction agents and have used different formulations like gel, tablets,inserts, pessaries and different routes of administration like intravaginal, intracervical, oral and sublingual , in different doses. The present study was designed to compare and evaluate the efficacy of intravaginal misoprostol (25µg tablet) and intracervical dinoprostone (0.5mg gel) in cervical ripening.

In our study, there were more hypertensives in the misoprostol group and more PROM in the dinoprostone group.

Our finding of mean change after 16 hours of 2.57±0.59 was less than that in Ramsay *et al* study in the misoprostol group [1].In our study, though the difference between the misoprostol group and the dinoprostone group was smaller, it was significant, like in their study, the change in Bishop score after 16 hours in the misoprostol group (2.57±0.59) being higher than the change in Bishop score after 16 hours in

dinoprostone group (2.17±0.10) (p=0.016). This finding is inspite of the fact that the dinoprostone group had a higher Bishop score in the beginning in our study.Even though, the initial Bishop score was significantly higher in the dinoprostone group, the change in the Bishop score was significantly higher in the misoprostol group. Hence it may be said that, misoprostol is better ripening agent compared to dinoprostone. Some studies used 50 µg of vaginal misoprostol every 6 hours for 12 hours [1].While some used 50 µg of intravaginal misoprostol every 4 hours till active labour [2, 3].

Though all the studies used 0.5 mg of intracervical dinoprostone, the frequency varied from every 4 hours to every 12 hours [2].

We have defined successful ripening as achieving a Bishop score of ≥ 6 or spontaneous onset of labour. In our study we have assessed the cervical status at 8 hours and 16 hours after the initial dose of ripening agents.

Chuck and Huffaker [3] reported higher number of vaginal deliveries within 24 hours of induction in the misoprostol group, compared to dinoprostone group. (100% (39/39) in the misoprostol group vs 68 % (27/39) in the dinoprostone group). This was significant (p=0.001). In contrast Meyer *et al*, reported 93 % deliveries within 24 hours in the misoprostol group, compared to 81%in deliveries the dinoprostone group [4]. This was not significant (p=0.19). They have also reported 5 % failure rates in the dinoprostone group and none in the misoprostol group (failed induction was when cervical change with uterine contraction was not achieved and patient was delivered by caesarean section with failed induction as the sole indication).

Ramsey *et al* defined successful induction as delivery within 24 hours of treatment initiation. They observed 60.5% success rate in the misoprostol group, compared to 40 % in the dinoprostone group, which was not significant [1]. (p=0.1)

Wing *et al*, defined successful induction as vaginal delivery occurring within 24 hours of administration of first dose of the drug [5]. Accordingly, they achieved 65.5% success rate in the misoprostol group compared to 41.4% in the dinoprostone group. (p<0.001). The high failure rates in the study by Wing et al, 34.5% in the misoprostol group and 59.1% in the dinoprostone group are difficult to explain. This happened in spite of the fact that they used more doses and more frequently (25µg misoprostol 3 hourly for 24 hours and 0.5mg dinoprostone 6 hourly for 18 hours)

In our study, successful cervical ripening was observed in 98% of the patients in the misoprostol group and 92.66% of the dinoprostone group, but the difference was not statistically significant (p=0.0604). The number of successful ripening at eight as well as sixteen hours also did not differ between these two groups in our study. In the Chuck et al3 study, significantly more women in the misoprostol group (36 out of 39 patients) had spontaneous labour, compared to dinoprostone group (28 out of 40) (p=0.025). The studies by Ramsey *et al* and Meyer *et al* also had more spontaneous onset of labour in the misoprostol group, which was also significant (p <0.05 and p= 0.002).Our study showed more number of women in the dinoprostone group having spontaneous onset of labour, though this difference was not statistically

significant (p=0.79).The reason for this may be these workers used different doses of misoprostol with different frequencies for different length of time [1,4].

In all studies, more oxytocin induction was needed in the dinoprostone group, when compared to the misoprostol group. In contrast, in our study oxytocin induction was similar between both the groups. In our study, number of women requiring oxytocin was similar in both the groups, for induction as well as augmentation of labour. The caesarean section rates were higher in the studies by Chuck and Huffaker 20% in the misoprostol group and 20% in the dinoprostone group, and Meyer *et al* 21% in the misoprostol group and 19% in the dinoprostone group [3,4]. In our study, it was almost similar in both the groups, 9% in the misoprostol group and 8% in the dinoprostone group. We had about 9% instrumental deliveries in the misoprostol group and 8% in the dinoprostone group. In all studies, the most common indication was fetal distress .The side effects included fever, nausea and vomiting. Meconium stained liquor, abnormal fetal heart rate patterns, uterine hyperstimulation, antepartum and postpartum haemorrhage were the obstetric problems observed.In our study, complications were minimal and similar in both the groups. In the misoprosol group, only 2% had uterine hyperstimulation, 4.66% had abnormal heart rate patterns and meconium passage was seen in 11.33% patients. In the dinoprostone group, 0.66% had uterine hyperstimulation, 7.33% had abnormal heart rate patterns and meconium passage was seen in 6.66 % patients. This difference was not statistically significant. Efficiency of the ripening agent will also be reflected on the intervention delivery interval and duration of labour.our study showed no difference in mean intervention-delivery interval between both the groups (p=0.43). Mean duration of labour was not studied in Chuck and Wing et al studies. Mean duration of labour was significantly shorter in the dinoprostone group in our study (5.59±3.97 in the dinoprostone group, compared to 7.03±6.71 in the misoprostol group, p=0.024). This finding is in agreement with Ramsey et al 1(5±0.6 in the dinoprostone group, compared to 6.4±0.8 in the misoprostol group, p=0.05). None of the above studies, including our study reported any significant differences in Apgar score, NICU admission, or other neonatal adverse effects between both the groups. Mean APGAR at both 1 and 5 minutes were slightly lower in our study compared to Ramsey *et al* study in both the groups[1]. In contrast, our study reported slightly higher NICU admission rates in the misoprostol group (6%), compared to dinoprostone group (4.6%). Birth asphyxia was noted in 2%, in each group).Mean cost of misoprostol per cervical ripening in our study was 22.56±93.16 rs, significantly lower than that of dinoprostone (493.89±173.99, p<0.0001). it is slightly higher compared to study by Neelu and Pooja, cost of misoprostol was 9.25 rupees and that of dinoprostone was 352.80 rupees[2]. Though, other authors have not caluculated the cost per induction, they have stated that misoprostol is cheaper than dinoprostone.

Conclusions

The results of the present study show that both misoprostol and dinoprostone are equally effective in pre-induction cervical ripening. Low dose intravaginal misoprostol is safe and maternal and

neonatal complications are similar to intracervical dinoprostone for cervical ripening. Misoprostol is much more economical compared to dinoprostone.

Conflict of interest statement: We declare that we have no conflict of interest.

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