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Comparison of Misoprostol versus Dinoprostone for pre-induction cervical ripening at-term

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ABSTRACT

Background: The purpose of this study was to compare the efficacy and safety of 25µg Misoprostol vs. 0.5mg Dinoprostone for pre-labour ripening of the cervix at-term.

Methods: Nullipara or Para one women with unfavourable cervices after 37 completed weeks with live foetuses were randomized to received either 25µg intravaginal Misoprostol or 0.5mg intracervical Dinoprostone. The doses were repeated after 6 hrs if the Bishop Score was less than 6. In cases, in which cervical ripening was not reached even after two doses of ripening agents, oxytocin induction was started at least 6 hours apart. Insertion delivery interval (IDI), complications and pregnancy outcome associated with the use of drugs were compared.

Results: Two hundred women - 100 in each group were evaluated. Comparatively more women (62% vs. 58%) in the Misoprostol group achieved cervical ripening (BS≥6) after one dose. The mean IDI was significantly shorter (3.91 hrs) in the Misoprostol group. The difference was marked more among the multipara at 5.72 hrs, mean difference (p=0.045). In the Misoprostol group 76.92% delivered within 24 hrs whereas, only 70.4% in the Dinoprostone group. Vaginal deliveries were achieved more in the Misoprostol group (78% vs. 71%). No significant differences found in terms of intrapartum complications and foetal outcome. Meconium stained liquor was found more in the Dinoprostone group (23% vs. 32%).

Conclusions: A 25µg dose of Misoprostol is superior in promoting cervical ripening, significantly shortened the insertion delivery interval. It is safe and effective for cervical ripening when applied in the hospital setting with close monitoring.

Keywords: dinoprostone, induction, labour, misoprostol.

INTRODUCTION

Labour begins naturally for most women, but in approximately 5% of the pregnancies the cervix does not ripen normally and 10% to 11% of pregnancies, labour must be induced for medical or obstetric reasons.[1] Induction of labour in patients with an unfavorable cervix may result in prolonged, tedious labour and eventually increases operative deliveries. A failed induction in the presence of an unfavorable cervix is found in approximately 15% of the cases.[2] Misoprostol (PGE_1) and Dinoprostone (PGE_2) show safety and efficacy in the management of labour in unfavorable cervices. PGE_2 is approved by Food and Drug Administration (FDA), USA for cervical ripening and labour induction, but this preparation is expensive, limitation in availability and needs refrigerator for storage. However, Misoprostol has the advantages of being inexpensive, easy to store and stable at room temperature. The ideal induction agent should be safe, practical, efficacious, inexpensive, and that which, closely simulates the natural labour process. The aim of this study is to assess the effectiveness of Misoprostol 25µg administered vaginally for pre-labour ripening of cervix at term.

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METHODS

This is a hospital based, non-blinded randomized controlled trial comparing 25µg vaginal Misoprostol with 0.5mg intracervical Dinoprostone. The study was carried out in the Maternity Hospital, Thapathali, Kathmandu during a period of four months from January 14, 2006 to May 13, 2006. This is a tertiary and referral level hospital with 330 beds including 48 service beds.

The study was carried out among 200 pregnant. 100 women received 25µg Misoprostol and 100 women received 0.5mg Dinoprostone gel. Enrollment was carried out from the admission room, OPD and from the ward. Inclusion criteria were: Nullipara or Para one women, admitted for the induction of labour after 37 completed weeks with live foetus, singleton pregnancy with cephalic presentation, Bishop Score (BS) ≤5. Exclusion criteria were: abnormal foetal heart rate pattern, cephalo-pelvic disproportion, ante partum hemorrhage, women with previous uterine surgery, premature rupture of membrane, maternal diseases like - heart disease, asthma, glaucoma, known sensitivity to prostaglandin, foetal anomaly. The study received approval from Institutional Research Board (IRB).

Orientation and information about the study was given to the medical and paramedical staffs also. Before the drug instillation, written consent was obtained from the woman herself. Detailed systemic and clinical examination was done and initial BS was established. For the women who were selected for Dinoprostone gel instillation, were asked to lie on the dorsal position and the cervix was exposed using a bivalve (Cusco's) speculum. Gel was instilled intracervical from pre-filled syringe. For the women in Misoprostol group, 100µg Misoprostol tablets were stabilized between gloved fingers and broken into four. Fragments were inspected visually by two persons, and only the fragments that were not shattered were accepted for use. 25µg Misoprostol tablet (1/4 tablet) was inserted into the posterior vaginal fornix. Then patients were advised to lie on the left lateral position for half an hour in both the study groups. Uterine contraction and foetal heart sound (FHS) were monitored regularly every 30 minutes. If there were any side effects, on duty registrar or consultant were informed immediately and managed accordingly and in such cases further ripening agents were not given. Women were re-examined after 6 hrs of the first dose of insertion of the ripening agents and BS was again evaluated. The treatment was repeated if the BS was less than 6. Maximum of two doses of ripening agents were given.

In cases, in which cervical ripening was not reached even after two doses of ripening agents, oxytocin induction according to the hospital protocol was started on the next day or at least 6 hrs apart. Woman who failed to initiate the labour after this regimen, were taken as a case of failed induction. Progress of labour was monitored according to hospital protocol. Decisions requiring amniotomy, analgesics, oxytocin augmentation were made by on duty registrar, if necessary. All babies and mothers were followed up till discharge.

Data analysis was done manually as well as with the help of computer. Chi square test was applied for testing the significance. The resultant P value was considered significant, if less than 0.05. SPSS version 10 was used for calculation and tabulation of the data. The result obtained was presented in tables for easier interpretation.

RESULTS

Total numbers of admissions during the study were 6046 and total deliveries were 5499. Altogether 358 women underwent induction of labour. General induction rate over this period was 6.51%. During the study period, 20 to 24 years age group found more. As seen in (Table 1), there were no significant differences in gravidity, gestational age and pre-induction cervical score between the two groups.

Table 1. Characteristics of the study groups.

Indicators	PGE1 (n=100)	PGE2 (n=100)
	Mean ± SD	Mean ± SD
Maternal age (Years)	22.81 ± 2.95	23.92 ± 3.41
Gest age by date (Weeks)	41.40 ± 1.05	41.29 ± 1.14
Gest age by USG (Weeks)	39.09 ± 1.52	39.15 ± 1.60
Pre-induction cervical score	3.36 ± 1.13	3.42 ± 1.12
Hospital stay	4.02 ± 2.70	4.21 ± 2.83

Induction of labour was performed more in nullipara. Among 200 women, 146 women were nullipara. Comparatively more women (62% vs. 58%) in the Misoprostol group achieved cervical ripening (BS≥6) after one dose of ripening agent (Among nullipara 59.74% in PGE_1 verses 56.57% in PGE_2 and among multiparas 69.6% in PGE_1 verses 61.29% in PGE_2) (Table 2).

Table 2. Change in Bishop Score to ≥ 6 after 6 hours of initial dose.

Nullipara (146)		Multi (54)	
PGE1 (n=77)	PGE2 (n=69)	PGE1 (n=23)	PGE2 (n=31)
46 (59.74%)	39 (56.52%)	16 (69.56%)	19 (61.29%)

The use of oxytocin was comparatively more in the Dinoprostone group in the present study, but statistically

not significant (among nulliparas 51.9% in PGE_1 vs. 59.4% in PGE_2 and among multiparas 30.4% in PGE_1 vs. 38.7% in PGE_2).

Failed induction recorded 13.0% in PGE_1 vs. 11.6% in PGE_2 in nullipara, whereas among multipara none in PGE_1 vs. 9.7% in PGE_2 (Table 3).

Table 3. Outcome of induction.

Indicators	Nullipara (146)		P Value	Multi (54)		P Value
	PGE1 (n=77)	PGE2 (n=69)		PGE1 (n=23)	PGE2 (n=31)	
Oxytocin given	40 (51.9%)	41 (59.4%)	0.364	7 (30.4%)	12 (38.7%)	0.529
Failed Induction	10 (13.0%)	8 (11.6%)	0.798	0	3 (9.7%)	0.253

In present study, the mean induction delivery interval (IDI) was shown to be shorter in the Misoprostol group (18.42 hrs in PGE_1 vs. 22.33 hrs in PGE_2) (Table 4). There was significantly shorter IDI when compared separately in between multipara (14.46 hrs in PGE_1 vs. 20.18 hrs in PGE_2, P=0.045) (Table 5). Out of 100 women in the Misoprostol group 78 delivered vaginally and among them 60 women i.e.76.92% delivered within 24 hrs. In the Dinoprostone group, 71 women had vaginal delivery and 50 women i.e 70.4% of them delivered within 24 hours (Table 4).

There were no any statistically significant differences found regarding spontaneous vaginal delivery (64 in PGE_2 vs70 in PGE_1) and instrumental deliveries (7in PGE_2 vs8 in PGE_1). The rate of lower segment cesarean section (LSCS) in the present study was also found to be less in the Misoprostol group (22 vs. 29), however the difference is not significant.

There were no any statistically significant differences found regarding post partum hemorrhage (PPH), intra and post operative complications. There were altogether 16 cases of PPH found in both the groups during 4 months period (9 in the Misoprostol and 7 in the Dinoprostone group). During the study period, cervical tear and vaginal hematoma was found in one / one woman and one maternal death occured in the Misoprostol group due to spinal anesthetics leading to irreversible hypovolemic shock when performing LSCS. Spontanious vaginal delivery with third degree tear, wound Dehiscence, retained Placenta and extended vaginal wall tear were found in one / one woman in the Dinoprostone group. There were 2 cases of chorioamnionitis in the Misoprostol group and one in the Dinoprostone group. There was 1/1 case of tachysystole (>5 contractions in 10 mins) in each group. Three patients experienced vomiting in the Dinoprostone group, whereas none in the Misoprostol group. One patient had diarrhoea after 24 hrs of Misoprostol insertion.

Meconium stained liquor was found more in the Dinoproatone group (23.0% vs. 32%) but the difference was not statistically significant. There were no any statistically significant differences found in neonatal outcome regarding Apgar Scores in 1 and 5 minutes, NICU admission and mean birth weight between the two study groups (Table 6).

Table 4. Interval from induction to delivery in total patients.

Indicators	PGE1 (n=78)	PGE2 (n=71)	P Value
< 12 hrs	27 (34.6%)	22 (31.0%)	0.753
12 - 24 hrs	33 (42.3%)	28 (39.4%)	0.307
> 24 hrs	18 (23.1%)	21 (29.6%)	0.181
Mean IDI in hrs	18.42 ± 10.769	22.33 ± 18.860	0.119

Table 5. Insertion Delivery Interval (IDI) in hours.

Indicators	Nullipara (146)		P Value	Multi (54)		P Value
	PGE1 (n=77)	PGE2 (n=69)		PGE1 (n=23)	PGE2 (n=31)	
Interval from induction to vaginal delivery in hours						
Mean hours	19.88 hrs	23.81hrs	0.264	14.46 hrs	20.18 hrs	0.045
<12 hrs	18 (31.6%)	10 (23.8%)	0.679	9 (42.9%)	12 (41.4%)	
12-24 hrs	23 (40.4%)	18 (42.9%)		10 (47.6%)	10 (34.5%)	0.372
>24 hrs	16 (28.1%)	14 (33.3%)		2 (9.5%)	7 (24.1%)	
Total	57	42		21	29	

Table 6. Neonatal Outcome.

Indicators	PGE1 (n=100)	PGE2 (n=100)	P Value
Mean Apgar Score of total deliveries			
A.S. at 1 minute	5.66	5.67	0.953
A.S. at 5 minutes	7.57	7.70	0.392
Mean birth weight in grams	2.99 ± 0.46	3.07±0.43	0.22
NICU admission	22	22	1.0
Intrapartum SB		1	
Meconium stained liquor	23	32	0.141

DISCUSSION

Induction of labour at full term pregnancy is performed for a wide range of maternal and foetal indications. Nowadays Misoprostol has received increased attention as a highly effective cervical ripening agent. It can be administered per oral, vaginal, sublingual, buccal and rectal routes. Vaginal administration generally allows more effective cervical ripening for induction of labour. The WHO expert committee included 25µg intravaginal Misoprostol in the complementary list of the Model List for the induction of labour at-term.[3] FIGO also recently recommended intravaginal dosages of Misoprostol 25µg 4 hourly for maximum six disages for induction of labour at term.[4] So Misoprostol could be proved to be such an agent with the advantages of cost and convenience, although it is not FDA-labelled for this purpose.

Varaklis K and his colleagues reported that Misoprostol experienced a significantly reduced mean time from drug administration to onset of three contractions in 10 min (p=0.007), mean time to rupture of membrane (p=0.01) and mean time to delivery (p=0.006) was also shorter in the Misoprostol group.[7] Similarly Wing DA,[5] McKenna DS,[6] Sanchez-Ramos L et al.[8] Dan Sunkel[9] and Gupta N[10] also reported shorter IDI in Misoprostol group than in Dinoprostine group. In most of the above studies Misoprostol was applied very frequently 2 to 3 hours apart and more than two doses. Michael L et al., reported even a single dose of 25µg intravaginal Misoprostol shown the time from initial dose to delivery was significantly shorter in the Misoprostol group, the majority of patients entered in active labour within 48 hrs and no other adverse effects were noted.[11] In present study we have used only two doses of ripening agents - six hours apart and which also shown shorter the IDI in the Misoprostol group (18.42 hrs vs. 22.33 hrs) (Table 4). There was significantly shorter IDI when compared separately in between multipara (14.46 hrs vs. 20.18 hrs, P=0.045) (Table 5).

The most common recorded side effects of Misoprostol are nausea, vomiting, diarrhea, abdominal pain, chills, shivering and fever. Prostaglandins such as PGE_2 and PGF_2 can cause myocardial infarction and bronchospasm, but Misoprostol does not.[12] Side effects of Misoprostol are directly related with dose and interval between the doses, lowering the doses can lessen the side effects. Hofmeyr GJ, reviewing 26 trials reported that, uterine hyperstimulation was more common with PGE_1 than with PGE_2. Uterine hyperstimulation is less in lower doses of Misoprostol compared to higher doses[13] and in Cochrane review he reported that vaginal Misoprostol in doses above 25µg four-hourly was more effective than conventional methods of labour induction, but associated with more uterine hyperstimulation.[14] American family physician, analysing Cochrane review reported that uterine hyperstimulations were fewer in the lower doses group compared with higher doses of intravaginal Misoprostol.[15] Blanchard K et al. recommended a vaginal dose of 25µg Misoprostol for induction of labour, as it is associated with a lower incidence of uterine hyperstimulation. Using higher doses of Misoprostol may increase its efficacy, however, uterine hyperstimulation and other asverse maternal and fetal outcomes were associated with higher doses (>25µg) or more frequent dosing intervals < every 3 to 6 hours.[16]

Marjorie Meyer neither found patient with hyperstimulation nor one requiring cesarean delivery for nonreassuring foetal assessmentduring the ripening period.[17] They used only ond dose of 25µg intravaginal vs. 0.5mg intracervical Dinoprostone, the evening before oxytocin induction. Sanchez-Ramos L et al., found Misoprostol was associated with a higher rate in tachysystole 20.1% vs. 8.2% in control group and hyperstimulation 5.8% vs. 3.4% in control.[8] Dan Sunkel reported when larger oral doses such as 200µg were compared to 25µg or 50µg vaginal doses, the oral route resulted in increased uterine tachysystole and hyperstimulation. Uterine rupture rates in patients undergoing a trial of labour after cesarean section were reported as 5.6% for PGE_1 and 2.9% for PGE_2, 0.7% for oxytocin, compared to 0.45% for spontaneous labour.[9] Varaklis K also found Misoprostol assssociated with hypertonus, they have used 25µg intravaginal Misoprostol 2 hourly.[7] Gupta N found that Uterine contraction abnormalities were more in Misoprostol group than intracervical Dinoprostone (12% vs. 4%; p>0.10).[10] He used 25µg intravaginal Misoprostol 6 hourly for 5 doses.

In the present study we have found no any statistically significant differences regarding intra and post operative complications.

Weaver SP[15] shown that Misoprostol has an increased rate of vaginal delivery within 24 hrs without significant differences in LSCS rates or operative vaginal delivery and foetal outcomes compared with other cervical ripening methods.Dan Sunkel,[9] and Wing DA[5] also reported higher rate of vaginal delivery within 24 hrs in Misoprostol group. Most of the studies[8,9,13] found significantly less LSCS rate in the Misoprostol group than other methods. Marjorie Meyer[17] and Gupta N[10] (12% in PGE_1 vs. 26% in PGE_2, p>0.05) found no significant difference in LSCS rate.[10] The present study also shown 25µg Misoprostol is effective than 0.5mg Dinoprostone, in achieving delivery vaginally within 24 hrs (Table 4) and having less LSCS rate (22 vs. 29) although the result was statistically not significant. In contrast, study[7] found significantly more women delivering by LSCS in the Misoprostol group. They have studied 25µg Misoprostol

very frequently, 2 hourly and 0.5mg Dinoprostone 6hours apart. Higher and more frequent doses of Misoprostol increases cesarean section rate.

Hofmeyr GJ[13] reported, use of Misoprostol was associated with increased cervical ripening and reduced need for oxytocin. Lower doses of Misoprostol compared to higher doses did not show significant differences except for more need for oxytocin augmentation. Others[5,7,9] found significant more women in the Dinoprostone group needing oxytocin augmentation. Oxytocin augmentation was used more often in the 25µg dose group than higher dose.[15]

Marjorie Meyer found that even a single dose of 25µg Misoprostol more effective in achieving cervical ripening than 0.5mg intracervical Dinoprostone and significantly decrease the cumulative dose of oxytocin. Out of 41, 19 patients went into spontaneous labour in the Misoprostol group and 6 of 42 in the Dinoprostone group (p=0.002).[17] Frohn WE[18] also found significantly less women requiring a second dose of Misoprostol. But they have studied in women with premature rupture of membrane (PROM) after 34 weeks gestation. It is clear to us that PROM itself causes release of endogenous prostaglandins. Marjorie Meyer[17] noted induction failure in equal number of patients in both the groups. Gupta N reported more failure of induction in the Dinoprostone group (2% and 8% in PGE_1 and PGE_2 respectively (p>0.10).[10] Change in favourable BS is associated with higher and more frequent dose of Misoprostol. In this study we have used a very small dose (25µg of Misoprostol) only. Even this small dose of Misoprostol proved to be better than Dinoprostone gel in attending favourable Bishop Score. Comparatively more women (62% vs. 58%) in the Misoprostol group achieved cervical ripening (BS≥6) after one dose of ripening agent. (Among nullipara 59.74% in PGE_1 verses 56.57% in PGE_2 and among multiparas 69.6% in PGE_1 verses 61.29% in PGE_2) (Table 2). The use of oxytocin was also comparatively less in Misoprostol group (among nulliparas, 51.9% in PGE_1 vs. 59.4% in PGE_2 and among multiparas, 30.4% in PGE_1 vs. 38.7% in PGE_2) (Table 3)

Hofmeyr GJ,[13] found meconium stained liquor were more common with PGE_1 than with PGE_2. Wing DA[5] found similarity in the two groups, whereas others found more meconium passes in the Misoprostol group but lower dose did not show significant differences. Others[5,8,10,15,17] also found no statistically significant differences regarding neonatal adverse outcomes. Most of the studies also showed that although the use of Misoprostol increases passes of meconium in the foetus, neonatal adverse effect is less even in higher doses. Neonatal intensive care unit admissions were fewer in the lower doses group compared with higher doses of intravaginal Misoprostol.[15] Meconium stained liquor was seen more frequently in higher than 25µg dose of Misoprostol and in more frequent use (<6 hrs apart). There is an association of passing of meconium in foetuses with increasing doses of Misoprostol. In the present study meconium stained liquor was found more in the Dinoproatone group (23.0% vs. 32%) (Table 6). A 25µg intravaginal Misoprostol reduces passes of Meconium in foetuses, and is safe.

CONCLUSIONS

A 25µg dose of Misoprostol is superior in promoting cervical ripening, significantly shorter induction to delivery interval and more vaginal deliveries within 24 hrs compared with 0.5mg intracervical prostaglandin gel. Misoprostol use resulted in less need for oxytocin use, decrease in LSCS rate and fewer prevalence of Meconium passes. A 25µg intravaginal Misoprostol is more effective than 0.5mg intracervical Dinoprostone. It is easy to use and cheap drug for cervical ripening when applied in hospital setting with close monitoring.

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