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Intracervical dinoprostone versus sublingual misoprostol for preinduction ripening of cervix

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Abstract

Objective: To compare the efficacy of intracervical dinoprostone and sublingual misoprostol in preinduction cervical ripening.

Study design: This prospective observational study was performed on 410 women with medical or obstetrical indications for labour induction. On an alternative basis, women were selected for intracervical dinoprostone and sublingual misoprostol for pre-induction cervical ripening. 0.5 milligram of dinoprostone was placed intracervically every 6-12 hours for a maximum of three doses in one group and 25 microgram of misoprostol was given sublingually, every 4 hours for a maximum of five doses in the other group. Mean number of doses required, induction to active phase interval, induction to delivery interval, need for oxytocin augmentation, mean cost and neonatal outcomes were analyzed. Statistical analysis was done using SPSS 17 version software. Statistical significance was considered as 0.05 level (P value).

Results: There was no significant difference in the mean number of doses required with regard to Bishop's score when misoprostol was used, but significant difference was there when dinoprostone was used. There was no statistically significant difference in induction to active phase interval, induction to delivery interval and neonatal outcomes between the two groups. There was significantly higher failed induction in dinoprostone group. There was significantly lesser oxytocin requirement in misoprostol group. Mean cost was 37.75 times greater in dinoprostone group.

Conclusion: 25 microgram of sublingual misoprostol provides a cheaper alternative method to intracervical dinoprostone for induction of labour.

Introduction

Induction of labour is the artificial initiation of uterine contractions prior to their spontaneous onset leading on to progressive effacement and dilatation of cervix and delivery of the baby. It is indicated when there is risk of continuation of pregnancy either to the mother or the foetus. Labour is commonly induced in response to a number of fetal and maternal indications, including post-term pregnancy, preeclampsia and premature rupture of the membranes without the onset of spontaneous contractions within the next 24 hours. Prostaglandin E2 (PGE2) dinoprostone, the most commonly used agent for induction of labour is unstable at room temperature and also requires refrigeration. Misoprostol, the prostaglandin E1 (PGE1) analogue is being increasingly used as an alternative as it is easier to store due to its stability at room temperature. It is also significantly cheaper when compared to dinoprostone.

In 2011, WHO issued guidelines on induction of labour,[(1)] which included the use of oral and vaginal misoprostol for induction of labour. Trials with doses ranging from 25 to 100 micrograms indicate that vaginal administration of the lowest of these doses at interval of 3–6 hours might be optimal.[(2)] Nowadays misoprostol has received increased attention as a cervical ripening agent. It can be administered by various routes like oral, vaginal, sublingual, buccal and rectal routes. There has been interest in the sublingual route for labour induction, on the assumption that avoidance of the first pass hepatic circulation would yield bioavailability similar to that achieved with the vaginal route. An additional possible advantage is that avoidance of direct cervical effects might reduce the risk of uterine hyperstimulation.[(3)]

Dinoprostone has been the agent of choice for preinduction cervical ripening for several decades. In the present study we compare the efficacy of intracervical dinoprostone and sublingual misoprostol in labour induction.

Materials and Methods

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology, Sri Ramachandra Medical College between August 2012 and July 2014. The study was approved by the Institutional Ethics Committee, Sri Ramachandra Medical College with reference number CSP-MED/13/JUN/O7/22. Using n-master software with power of 80% and alpha error 5% sample size was calculated as 205 for each study group.

After proper counselling, an informed consent was taken and patients were assigned to two groups. They were alternatively assigned to receive either intracervical dinoprostone gel or sublingual misoprostol with 205 pregnant women in each group. Demographic details like age and parity were noted. Gestational age was confirmed with previous scan reports. Vital signs were checked. Abdominal examination was done to confirm the gestational age, presentation, liquor volume and foetal heart rate.

Sonography was done to confirm the presentation, estimated foetal weight and amniotic fluid index. Vaginal examination was done to ascertain the bishop's

score and NST was done to confirm the foetal well-being.

Inclusion criteria

- Parity less than 5
- Singleton term and post-term pregnancies.
- Live fetus –Cephalic presentation.
- Reassuring fetal heart rate tracing.
- Bishop score of 6 or less.

Exclusion criteria

- Previous uterine scars.
- Estimated fetal weight on scan greater than 3.75kg
- Amniotic fluid Index less than 5 cm.
- Foetal malformations.
- Any contraindication to vaginal delivery like placenta previa, abruption placenta or unexplained vaginal bleeding.
- Significant foetal or maternal comorbidities like severe pre-eclampsia or early onset IUGR
- History of bronchial asthma, glaucoma, serious cardiovascular disorders, renal diseases or allergy to misoprostol

Administration of Drug

- An intracervical application of Dinoprostone gel 0.5mg was done. This was repeated every 6 to 12 hours until (a) 3 or more uterine contractions lasting for 40 seconds at 10 minutes interval was established or (b) maximum of 3 doses was given or (c) cervical dilatation more than or equal to 4 cms was reached. Bishops score was assessed at each induction with PGE2 gel.
- 25mcg misoprostol was administered sublingually. The dose was repeated every 4 hours .The criteria to discontinue further doses were when (a) more than 3 uterine contractions lasting for 40 seconds at 10 minutes interval was established or (b) maximum of 5 doses given or (c) cervical dilatation more than or equal to 4 cms was reached. A vaginal examination was repeated after the third dose or when adequate uterine contractions were established. Fetal heart rate and uterine activity were monitored during induction with each dose.
- Spontaneous rupture of membranes was not an indication to stop further doses.
- Oxytocin drip if required was started 6 hrs after the last dose of induction for both the drugs. ARM was done prior to oxytocin augmentation to note the amount and colour of liquor.
- Failed induction was defined as a) if the woman did not get into active labour 6 hours after administration of the last dose of the drug and b) Caesarean section or an alternative method of induction was decided as per the discretion of the consultant
- Primary outcome measures assessed were (a) time taken from induction to onset of active phase, (b) induction to delivery interval and (c) need for oxytocin augmentation.
- Secondary outcome measures assessed were (a) mode of delivery , (b) number of caesarean sections for failed induction and (c) side effects noted for mother and foetus especially tachysystole, uterine hyper stimulation, meconium stained liqour and d) neonatal outcomes with reference to apgar at 1minute and 5 minutes baby weight and NICU admissions. Also mean cost of induction was analysed for both the drugs.

All the patients were monitored closely throughout the course of labour. Progress of labour was charted on a partogram in active labour. Intermittent auscultation or continuous cardiotocography was used as the case indicated.

Uterine tachysystole was defined as more than five contractions per 10 minutes, uterine hypertonus as when one contraction lasted more than 2 minutes and hyperstimulation syndrome as the presence of non-reassuring FHR tracing combined with either tachysystole or hypertonus. Non-reassuring FHR patterns were defined as persistent or recurring episodes of severe variable decelerations, late decelerations, prolonged fetal bradycardia or a combination of decreased beat-to-beat variability and a decelerative pattern.[4]

Results

90% of woman in both the groups were between 21 to 35 years of age. Mean age at induction with dinoprostone was 25.61 ± 3.431. Mean age at induction with misoprostol was 25.03 ± 3.290. More than 60% of woman were primigravidae. 75% of woman were between 37 to 40 weeks of gestation. Mean gestational age at induction with dinoprostone was 39 weeks and 2 days ± 1.10925. Mean gestational age at induction with misoprostol was 39 weeks and one day ± 1.09675.

Mean Bishop's score at induction with dinoprostone was 4.46 ± 1.270.

Mean Bishop's score at induction with misoprostol was 4.50 ± 1.286.

Thus both the groups were matched for age, parity, gestational age and modified Bishop's score(Table 1). The indication for induction was almost similar in both the groups, most common indication being post-dated pregnancy.

Table 1: Demographic Details

Demographic Details	Dinoprostone		Misoprostol		p Value
	Number	Percentage	Number	Percentage	
Age					
≤20 Years	18	8.8%	15	7.3%	0.586
21-35 Years	187	91.2%	190	92.7%	
Gravida					
Primigravida	135	65.9%	131	63.9%	0.679
Multigravida	70	34.1%	74	36.1%	
Gestational Age					
≤ 40 Weeks	159	77.6%	169	82.4%	0.217
> 40 Weeks	46	22.4%	36	17.6%	
Modified Bishop's Score					
≤ 4	93	45.4%	89	43.4%	0.691
>4	112	54.6%	116	56.6%	
Indications for Induction					
Post-Datism	74	36.1%	59	28.8%	-
Premature Rupture of Membranes	41	20%	30	14.6%	-

Of the 205 women recruited in each group, 81% (n=167) in the dinoprostone group and 87% (n=179) in the misoprostol group went into active phase of labour. 11%(n=24) women in the dinoprostone group and 5% (n=10) women in the misoprostol group had failed induction. 14 women (8%) in the dinoprostone group and 16 women (8%) in the misoprostol group were taken up for emergency LSCS even before they reached the active phase of labour due to pathological CTG or meconium stained liquor recognized during spontaneous rupture of membranes.

There was a statistically significant difference between the mean number of doses required for those with MBS≤4 and MBS>4 when dinoprostone was used. There was no statistical significant difference between the mean number of doses required for those with MBS≤4 and MBS>4 when misoprostol was used.(Table 2) Mean number of doses required with dinoprostone was 1.89 ± 0.836. Mean number of doses required with misoprostol was 2.72 ± 1.387.

Table 2: Mean number of doses

Dinoprostone		Mean Number of Doses	Standard Deviation	p Value
	MBS≤4 N=87	2.20	0.775	0.000
	MBS>4 N=104	1.63	0.801	
Misoprostol				
	MBS≤4 N=79	2.71	1.397	0.893
	MBS>4 N=110	2.74	1.386	

Only 167 women in the dinoprostone group and 179 women in the misoprostol group entered active phase of labour. 34 women(24 women in the dinoprostone group and 10 women in the misoprostol group) had failed induction of labour and hence underwent Caesarean Section. This difference was statistically significant (p=0.0167). Mean induction to active phase interval with Dinoprostone was 11.8 hours ± 5.855. Mean induction to active phase interval with misoprostol was 11.97 hours ± 6.459.(Table 3)

68.6% of women induced with dinoprostone needed oxytocin augmentation. Only 51.9% of women induced with misoprostol needed oxytocin augmentation. Hence there was statistical significance(p=0.001) between those who required oxytocin augmentation in the two groups.(Table 3)

Table 3: Characteristics and outcomes of labour

Characteristics	Dinoprostone N(%)	Misoprostol N(%)	P Value
Vaginal Delivery	133(64.9)	151(72.7)	0.285
Vaginal Delivery within 24 Hours	90.2%	88.8%	0.380
Caesarean Section	72(35.1)	54(26.3)	0.109
Indication for Caesarean Section			
a. Foetal Distress	27(37.5)	19(35.2)	0.238
b. Failed Induction	24(33.3)	10(18.5)	0.016
c. Arrest of Descent/Dilatation	11(15.3)	11(20.4)	-
d. Others	10(13.9)	14(25.9)	-
Oxytocin Requirement	131(68.6)	98(51.9)	0.001
Mean Induction to Active Phase Interval (Mean ±S.D)	11.8±5.855	11.97±6.459	0.142
Mean Induction to Delivery Interval (Mean ±S.D)	14.73±7.022	14.42±7.182	0.145
Abnormal Cardiotocogram	48(23.4)	47(22.9)	0.918

Most common indication for Caesarean Section was foetal distress in both the groups and the difference was not statistically significant(p=0.238). Failed induction was higher in the dinoprostone group(p=0.0016). 4 women in the misoprostol group delivered vaginally after one additional dose of dinoprostone gel.

Mean induction to delivery interval with Dinoprostone was 14.73 hours ± 7.022. Mean induction to delivery interval with Misoprostol was 14.42 hours ± 7.182. Thus the mean induction delivery interval was similar in both groups. Both groups had similar incidence of abnormal fetal heart tracings(23.4% vs 22.9%). Hence the drugs used did not significantly alter the CTG. (Table 3)

Secondary outcome measures analysed were PPH, uterine activity abnormalities like hyperstimulation, tachysystole, vomiting, diarrhea and hyperthermia. There was no statistically significant difference with regard to the secondary outcome measures between the two drugs.(Table 4)

Table 4: Secondary outcomes including side effects

Secondary Outcomes	Dinoprostone		Misoprostol		p Value
	Number	Percentage	Number	Percentage	
Atonic PPH	7	3.4%	8	3.9%	0.793
Traumatic PPH	8	3.9%	10	4.9%	0.630
Tachysystole	0	0%	1	0.5%	0.317
Hyperstimulation	0	0%	3	1.5%	0.082
Vomiting	6	2.9%	8	3.9%	0.587
Diarrhoea	6	2.9%	7	3.4%	0.778
Hyperthermia	2	1%	2	1%	1.000

There was no statistically significant difference between the two groups with regard to neonatal outcomes like birth weight, Apgar at 1 and 5 minutes, meconium passage and NICU admissions.(Table 5)

Table 5: Neonatal outcomes

Neonatal Outcomes	Dinoprostone		Misoprostol		p Value
	Number	Percentage	Number	Percentage	
B.WT <=3Kg	106	51.7%	125	61%	0.058
B.WT >3Kg	99	48.3%	80	39%	
1 Min APGAR <=7	16	7.8%	18	8.8%	0.720
5 Min APGAR <=7	3	1.5%	5	2.4%	0.475
Meconium Passage	18	8.8%	19	9.3%	0.863
NICU Admission	17	8.3%	21	9.8%	0.183

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Abnormal Cardiotocogram	48(23.4)	47(22.9)	0.918

Cost of one dose of dinoprostone gel was Rs 240. Cost of one dose of misoprostol was Rs 4 and 60 paise.Mean cost of induction with Dinoprostone was Rs.453/-.

Mean cost of induction with Misoprostol was Rs.12/-.

There was statistical significance for the mean cost of induction between the two drugs(p=0.000). The mean cost of induction with Dinoprostone was 37.75 times greater compared to misoprostol.

Discussion

The study by Patil Kamal P et al[5] 2004 showed a statistically significant difference between the induction to active phase interval probably due to the higher dose of oral misoprostol (200mcg as a single dose).The number of doses of dinoprostone was similar to our study. Manjunath et al,[6] S Gregson et al[7] showed requirement of oxytocin for augmentation was lesser in misoprostol group than dinoprostone and was also statistically significant. Oxytocin requirement was significantly higher with misoprostol (45% vs 58%) in trial by N Van Gemund et al[8] which is in contrast to our study. Since N Van Gemund et al[8] had used pulverised misoprostol with cellulose it is possible that the efficacy of misoprostol have been reduced.

There was no statistically significant difference in failed induction between the two drugs in trial by Manjunath AP et al[6] possibly because he used only three doses of 25 mcg misoprostol unlike our study where five doses were used. In Papanikolaou et al[9] study higher dose for both drugs were used (50 mcg vaginal misoprostol and 3 mg dinoprostone) probably accounting for lower failure rates compared to our study and also number of study population was less and mean gestational age was higher.

In most of the studies induction delivery interval was significantly lesser(Rozenberg et al[10] 2004, P Rozenberg et al[11] 2001, Papanikolaou et al[9] 2004, Patil Kamal et al[5] 2004, Pandis et al[12] 2001) in all the women when misoprostol was used as the method of induction. However our study showed the induction delivery interval was similar in both groups. N Van Gemund et al[8] 2004 proved that induction to delivery interval was more in misoprostol group probably as he used a maximum of three doses per day and restarted the next day. Also pulverised misoprostol was used. Vaginal delivery was significantly shorter (within 24 hours) in misoprostol group in most of the

studies[10,11,9,12] probably due to the higher dose of misoprostol used (50 mcg vs. 25 mcg) compared to our study.

In trial by Rozenberg et al 2004[10] though tachysystole, hyperstimulation and PPH were more frequent with a 50 mcg dose of misoprostol than with dinoprostone vaginal insert, it was not statistically significant.

Papanikolaou et al[9] study showed higher incidence of tachysystole, hyperstimulation and abnormal CTG in misoprostol group which is explained by the higher dosage of 50 mcg used and a higher mean gestational age at induction. But only occurrence of tachysystole was statistically significant. Neonatal outcomes like meconium passage, Apgar at 5 minutes and neonatal intensive care unit admissions were not significantly different between the two groups in study by Manjunath et al,[6] N Gemund et al,[8] S Gregson et al[7] and Pandis et al[12] and these findings matched with our study. Though high risk pregnancies were included in trial by Rozenberg et al[10] 2004 neonatal outcomes like meconium passage and Apgar at 5 minutes had no significant difference similar to our study. In trial by Rozenberg et al[11] 2001 meconium passage was significantly higher in misoprostol group (2.4% vs 11.7%, 4.86[1.11-21.3]). The difference in meconium stained amniotic fluid rates could be due to chance, although this increase in the prevalence of antenatal meconium excretion has also been reported previously. It may indicate fetal compromise or reflect the direct effect of misoprostol on foetal intestinal motility.[13,14] Drug costs were £81 and £0.3, respectively in trial by P Rozenberg et al[11] 2001. This was equal to Rs.6885 and Rs.25.5 respectively. Thus a lower cost of misoprostol provided a cheaper drug for labour induction and this finding matched with our study.

Conclusion

25 microgram of sublingual misoprostol provides a cheaper alternative method to intracervical dinoprostone for induction of labour.

Limitations of our Study

The study was not blinded because two different routes for both the drugs enabled both the participant and the administrator to know the drug administered. The interval between the doses of dinoprostone varied from 6 hours to 12 hours.

References

1. WHO recommendations for induction of labour. Geneva: World Health Organization, 2011.
2. ACOG. Induction of Labour. Washington, DC, USA: The American College of Obstetricians and Gynecologists, ACOG Practice Bulletin Number 10. 1999.
3. Shetty A, Mackie L, Danielian P, Rice P, Templeton A. Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *BJOG: an international journal of obstetrics and gynaecology* 2002;**109**:645–50.
4. American College of Obstetricians and Gynecologists: Fetal heart rate patterns: monitoring, interpretation, and management. ACOG Practice Bulletin no.207 Washington, DC: American College of Obstetricians and Gynecologists; 1995.
5. Patil Kamal P, Swamy MK, Rao Radhika K. Oral misoprostol vs intra-cervical dinoprostone for cervical ripening and labour induction. The Journal of Obstetrics and Gynecology of India. 2005;55:128-131.
6. Girija Shivarudraiah, Manjunath Attibele Palaksha. A randomised controlled trial comparing low dose vaginal misoprostol and dinoprostone gel for labor induction. The Journal of Obstetrics and Gynecology of India. 2011;153-160.
7. Sarah Gregson, Mark Waterstone, Ian Norman, Trevor Murrellsrandomised controlled trial comparing low dose vaginal misoprostol and dinoprostone vaginal gel for inducing labour at term BJOG: an International Journal of Obstetrics and Gynaecology April 2005, Vol. 112, pp. 438–444.
8. N.van Gemund, S. Scherjon, S.le Cessie, J.H Schagen van Leeuwen, J. Van Roosmalen, H.H.H Kanhai. A randomised trial comparing low dose vaginal misoprostol and dinoprostone for labour induction. International journal of Obstetrics and Gynaecology. 2004;111:42-49.
9. Evangelos G Papanikolaou, Nikos Plachouras, Aikaterini Drougia, Styliani Andronikou, Christina Vlachou, Theodoros Stefos, Evangelos Paraskevaidis and Konstantinos Zikopoulos Comparison of Misoprostol and Dinoprostone for elective induction of labour in nulliparous women at full term: A randomized prospective study *Reproductive Biology and Endocrinology* 2004,2:70.
10. Patrick Rozenberg, Sylvie Chevret, Marie Victoire Senat, Florence Bretelle, Anee Paule Bonnal, Sage Femme, Yves Ville. A randomised trial that compared intravaginal misoprostol and dinoprostone vaginal insert in pregnancies at high risk of fetal distress. American Journal of Obstetrics and Gynecology. 2004;191:247-253.
11. Patrick Rozenberg, Sylvie Chevret, Franc¸ois Goffinet, Isabelle Durand-Zaleski, Y. Ville, Christophe Vayssie`re, Aline Roberto, Zouhair Lahna, Israel Nisana, Caroline Fisch, Philippe Chaumet-Riffaud, Claud Chastang Induction of labour with a viable infant: a randomised clinical trial comparing intravaginal misoprostol and intravaginal dinoprostone British Journal of Obstetrics and Gynaecology December 2001, Vol. 108, pp. 1255–1262.
12. G. K. Pandis, A. T. Papageorghiou, C. M. Otigbah, R. J. Howard and K. H. Nicolaides Randomized study of vaginal misoprostol (PGE1) and dinoprostone gel (PGE2) for induction of labor at term *Ultrasound Obstet Gynecol* 2001;18:629–635.
13. Wing DA, Jones MM, Rahall A, Goodwin TM, Paul RH. A comparison of misoprostol and prostaglandin E2 gel for pre-induction cervical ripening and labor induction. Am J Obstet Gynecol 1995;172:1804 -1810.
14. Hofmeyr GJ, Gu¨lmezoglu AM, Alfirevic Z. Misoprostol for induction of labour: a systematic review. Br J Obstet Gynaecol 1999;106:798–803.