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Original Research Article

Mifepristone: an alternate to dinoprostone in induction of labour

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ABSTRACT

Background: To assess and compare the efficacy, safety and fetomaternal outcome of mifepristone versus dinoprostone in priming the cervix and in inducing labour in pregnant women at term.
Methods: This is a prospective comparative study done in Chettinad health and research institute, over a period of one year from October 2015 to October 2016. 50 pregnant women (Group 1) in 3rd trimester with unfavorable cervix were given 200mcg of mifepristone orally. If labour did not start or if the Bishop score remained poor at the end of 24hrs, induction was continued with 0.5mg of dinoprostone gel at a maximum of 3 gels at 6th hourly interval. Another 50 pregnant women (Group2) in 3rd trimester underwent induction according to the routine dinoprostone gel regimen of maximum 3 gels at intervals of 6hrs.
Results: Improvement in Bishop score was significant with mifepristone by the end of 24hrs.But, in comparison, there was statistically significant improvement in Bishop score in favour of dinoprostone (Mean 4.7) than mifepristone (Mean 4.0). Also, the induction delivery interval was significantly less (Mean 11.5 hrs) with dinoprostone than mifepristone (Mean 20.3 hrs). Number of cases undergoing LSCS for failed induction was less in mifepristone group (4%). The rate of vaginal delivery, Caesarean sections, instrumental delivery and overall fetal outcome was comparable in both groups.
Conclusions: Mifepristone is a safe, effective and suitable alternate agent for cervical ripening and initiation of labour when given 24 h before onset of labour.

Keywords: Bishop score, Dinoprostone, Induction of labour, Mifepristone

INTRODUCTION

The history of labour induction dates back to Hippocrates original description of mammary stimulation and mechanical dilatation of cervical canal. The availability of newer oxytocics and induction techniques which are now effective as well as more predictable have significantly modified our traditionally conservative attitude towards induction of labour, which was once regarded as "meddlesome midwifery".[1] Nevertheless even today none of the methods of induction are both absolutely safe and certain.

Karim et al were the first to report use of prostaglandins for labour induction.[2] Dinoprostone is a naturally occurring prostaglandin (PGE2) and is commonly used for induction of labour. The role of mifepristone (RU-486), a progesterone antagonist, in labor induction is not as well established as it is for therapeutic abortions. As a fall in level of progesterone is considered one of the important events in the onset of spontaneous labour, the anti- progesterone mifepristone was used in several trials to induce labour at term. Mifepristone (RU-486) is a 19non steroid that binds strongly to progesterone receptors and inhibits the activity of progesterone at cellular level. It has minimal effects on uterine

contractility as it ripens the cervix, making it an option for use in induction and enhance the rates of spontaneous labour. However, in late pregnancy, the uterus is sensitized by mifepristone to prostaglandins and promotes cervical dilatation which induces labour. Hence the sequential use of mifepristone followed by dinoprostone is more effective in induction of labour with less chances of failed induction and thereby decreasing the Caesarean rates. There are no apparent maternal or neonatal side effects.[3] The pharmacokinetics of mifepristone is characterized by rapid absorption and a long half-life of 25-30 h.[4]

Various trials employing 200mg of mifepristone resulted in shorter interval to the onset of labour and less oxytocin was required for those achieving vaginal delivery. More recently Elliot and colleagues compared the effects of 50mg and 200mg of oral mifepristone with placebo on cervical ripening and labour induction at term in primigravid women with unfavourable cervices.[5] At a dose of 200mg, mifepristone resulted in a favourable cervix or spontaneous labour more often than did placebo.

METHODS

Objectives

1. To comparatively study the efficacy of Mifepristone and Dinoprostone as a cervical ripening and priming agent for induction of labour.
2. To study safety and fetomaternal outcomes after the use of mifepristone versus dinoprostone.

This is a prospective comparative study done in Chettinad Health and Research Institute, a tertiary care hospital in Chennai for a period of 1 year from October 2015 to October 2016.A total of 100 pregnant women, 50 women in mifepristone group and 50 in the dinoprostone group, scheduled for induction of labour were selected for the study by consecutive sampling method.

Inclusion criteria

1. Singleton pregnancy with cephalic presentation and intact membranes if labour induction was indicated and delivery could be postponed for 24 hrs.
2. Women with unfavorable cervix (Bishop score less than 5).
3. Antenatal patients in third trimester (28-41 wks).
4. Patients with reactive NST.
5. Pregnancy induced hypertension.
6. Gestational Diabetes Mellitus.
7. Post dated pregnancy.
8. Intrauterine fetal death.
9. Mild IUGR, mild oligohydramnios, polyhydramnios, fetal congenital malformations.

Exclusion criteria

1. Parity more than 4.
2. Previous Caesarean section.
3. Major cephalopelvic disproportion, macrosomia.
4. Malpresentation.
5. Known hypersensitivity to prostaglandins or mifepristone.
6. Medical problems like impaired renal, hepatic or adrenal function.
7. Antenatal hemorrhage.
8. Premature rupture of membrane.

Outcome variables

Labour progression (Bishop score, induction delivery interval, number of dinoprostone gels required, syntocinon augmentation), maternal outcome (mode of delivery, indications for Caesarean section, number of failed inductions, incidence of hyper stimulation), fetal outcome (healthy baby, fetal distress, APGAR scores, NICU admission, perinatal death).

After detailed history, examination, conformation of diagnosis, investigations and after informed consent, women were allocated into two groups by consecutive sampling method. The participant who received mifepristone was assigned to study group 1(n=50) and who received dinoprostone gel was assigned to study group 2 (n=50) .1 tablet of 200mg mifepristone was given orally for those in group1 and were assessed after 24 hours or with onset of labour, whichever was earlier. If Bishop score was ≥8, patient was transferred to labour room and syntocinon started. Even after 24hrs, if Bishop score was ≤8, dinoprostone gel was administered vaginally every 6th hourly to a maximum of 3 doses. If after 3 doses of dinoprostone gel Bishop score was not changed, the induction attempt was categorized as failed.

In Group 2, women were induced with intracervical dinoprostone gel, which is repeated at 6th hrly intervals, upto maximum of 3 gels till Bishop score became ≥8. If Bishop score is ≥ 8, oxytocin was started after 6hrs of last dose of dinoprostone gel. If cervix remains unfavorable even after 6hrs of 3rd attempt with gel, induction was categorized as failed.

If at any time, in either of the groups, progress of labour was unsatisfactory or variable fetal heart pattern was observed, the participants underwent Caesarean section. The efficacy of mifepristone was assessed on the basis of improvement in Bishop's score, induction to delivery interval, necessity of augmentation of labour with oxytocin, mode of delivery, number of cases with failed induction, maternal and fetal outcome.

Statistical analysis

The data was analyzed with SPSS-IBM (Version 21.0). Mean and proportions were calculated. Chi-square test and independent t test were applied. P value of < 0.05 was considered to be significant.

RESULTS

Baseline characteristics like parity, period of gestation, indication for induction were comparable in both groups (Table 1).

Table 1: Baseline characteristics of study population (n=100).

Parameter	Group I n (%)	Group II n (%)	P value
(a) Parity			0.373
Primi	34 (68)	38 (76)	
Multi	16 (32)	12 (24)	
(b) Period of gestation			0.713
< 37 weeks	3 (6)	5 (10)	
37-40 weeks	33 (66)	30 (60)	
>40 weeks	14 (28)	15 (30)	
(c) Indication for * Induction			
GDM	7 (14)	12 (24)	
PIH	11 (22)	9 (18)	
IUGR	2 (4)	4 (8)	
Oligohydramnios	16 (32)	9 (18)	
Polyhydramnios	01 (2)	2 (4)	
Post dated	14 (28)	13 (26)	
Others	4 (8)	4 (8)	

* Multiple response, Others (BOH, intrahepatic cholestasis, congenital anomalies)

Table 2 shows labour outcome based on the improvement in Bishop score and induction delivery interval. The improvement in Bishop score was better in dinoprostone group [mean 4.7(±1.49)] when compared to mifepristone group [mean 4.0(±1.48)] which was statistically significant (p value 0.042). It has to be noted that, this result could not be achieved in dinoprostone group with one gel alone. 20 women needed 2 dinoprostone gels and 11 women needed 3 gels to improve the Bishop score. Whereas in mifepristone group, Bishop score was assessed after one dose of mifepristone (200 mg).

Table 2: Efficacy of mifepristone and dinoprostone among the study population (n=100).

Parameters	Mean (SD)	Mean difference	95% CI	t value	p value
Bishop's score improvement					
Group I	4.0 (±1.48)	0.707	0.09-1.40	2.020	0.042
Group II	4.7 (±1.49)				
Induction Delivery Interval (hrs)					
Group I	20.3 (±15)	8.72	3.843 -13.6	3.546	0.001
Group II	11.5 (±8.7)				

Independent t test applied, P< 0.05 significant

Mean induction delivery interval was more [20.3 h (±15)] in mifepristone group while it was lesser [11.5 h (±8.7)] in dinoprostone group, which was again statistically significant (p value 0.001).4 cases in mifepristone group and 6 cases in dinoprostone group delivered within 6 hrs of induction. 2 participants developed hyper stimulation in both the groups of which 1 neonate in dinoprostone group needed NICU admission for fetal distress.

Table 3: Maternal outcomes among the study population (n=100).

Parameter	Group I n (%)	Group II n (%)	P value
Mode of Delivery:			
Vaginal Delivery	38 (76)	38 (76)	-
LSCS	12 (24)	12 (24)	-
Indication for LSCS (n=12):			
Failed Induction	2 (16.67)	5 (41.67)	0.251
Fetal distress	9 (75)	5 (41.67)	
Cephalo Pelvic Disproportion	1 (8.33)	2 (16.67)	
Synto augmentation:			
Not required	38 (76)	31 (62)	0.130
Required	12 (24)	19 (38)	

Table 3 shows parameters of maternal outcome among the study population. Number of women who had vaginal delivery and Caesarean sections were the same in both the group 5 (41.67%) women in group 11 had to undergo Caesarean section for failed induction whereas only 2 (16.67%) in group 1 underwent Caesarean section for the same indication. Thus showing that chances of failure of induction was lesser with mifepristone than dinoprostone. 9 (75%) out of 12 cases of Caesarean section in mifepristone group was done for fetal distress (Non-reactive NST). But none of these neonates had poor APGAR score nor did they need NICU admission.5(41.67 %) in dinoprostone group underwent Caesarean section for fetal distress and 2 neonates out of these 5 needed NICU admission. Thus showing that mifepristone does not increase the incidence of fetal distress. The requirement of syntocinon augmentation was less with mifepristone (24%) when compared to dinoprostone (38%).Difference was not statistically significant.

Table 4 and 5 shows parameters of fetal outcome. The groups had comparable fetal outcomes. Though 1 and 5 minute APGAR scores were better in group 1, there was no statistically significant difference.

Table 4: Fetal outcome among study population (n=100).

Parameter	Group I n (%)	Group II n (%)
Perinatal death	0	0
Healthy baby	46 (92)	46 (92)
Fetal distress	9 (18)	7 (14)
NICU admission	4 (8)	4 (8)

Table 5: Differences in APGAR Scores of study population (n=100).

Parameter	Mean (SD)	Mean difference	95% CI	t value	p value
APGAR 1					
Group I	7.87 (±0.71)	0.600	0.078-1.278	1.757	0.082
Group II	7.84 (±0.84)				
APGAR 5					
Group I	9.04 (±0.41)	0.440	0.193-1.073	1.379	0.171
Group II	8.9 (±0.42)				

Independent t test applied, p <0.05 is significant

DISCUSSION

Studies by Frydman et al were the earliest on the use of mifepristone for induction of labour.[6] Many studies have reported that mifepristone is better than a placebo in ripening the cervix and in reducing the incidence of Caesarean section rates. This study was to see if mifepristone was as safe or better than dinoprostone in achieving the same result. The age, parity, period of gestation was comparable in both groups of our study. Oligohydramnios was the commonest indication for Caesarean section in mifepristone group, whereas postdatism was the commonest indication in dinoprostone group.

Improvement in mean Bishop's score was significant with mifepristone by the end of 24 hours. Wing et al, Athawale et al, Fathima et al also noted significant change in Bishop score with use of oral mifepristone.[7-9] Hapangama and Neilson reported that there is insufficient evidence to support a particular dose, but a single dose of 200 mg of mifepristone appears to be the lowest effective dose for cervical ripening (RR 2.13, 95% CI 1.15-3.97).[10] In our study the improvement in Bishop score was significantly better with dinoprostone when compared with mifepristone. This was contrary to the study by Gaikwad et al.[11] This is probably because in our study we used more than one gel in 31 cases to achieve improvement in Bishop score in group two, whereas Gaikward et al used only one dinoprostone gel, to assess the improvement in Bishop score.

The mean induction delivery interval in mifepristone group was 20.3 hrs and in dinoprostone group it was 11.5 hrs. The difference was statistically significant (p value 0.001) in favor of dinoprostone. But there was not much difference in the time from prostaglandin administration to vaginal delivery between the subgroup of women who required dinoprostone gel following priming with mifepristone, and dinoprostone group. The induction delivery interval in group1 is more, as it takes about 24-48 hrs for the drug to have priming effect on the cervix. Hapangama and Neilson reported that mifepristone treated women were more likely to be in labour or to have a favourable cervix at 48 hrs (RR 2.41, 95% CI, 1.70-3.42) and this effect persists at 96 hrs(RR 3.40, 95% CI 1.96-5.92).[10]

Main advantage of mifepristone is that it can be given on outpatient basis and the patient is asked to report after 24hrs or with onset of labour whichever is earlier. Whereas with dinoprostone, patient must be hospitalized on induction with first gel of dinoprostone itself. Thus the total duration of hospital stay in mifepristone group is much lesser than in dinoprostone group. Hapangama and Neilson reported that mifepristone treated women were more likely to be in labour or to have a favourable cervix at 48 hrs (RR 2.41, 95% CI, 1.70-3.42) and this effect persists at 96 hrs (RR 3.40, 95% CI 1.96-5.92).[10]

In the present study, 20 (40%) women in mifepristone group went into labour and delivered vaginally without need of dinoprostone. Of which 15 (30%) women delivered within 24 hrs. In Yellikar et al study, 8 (16%) women in study group went into labour and delivered vaginally without any need of prostaglandins within 24 hr of ingestion of mifepristone.[12] Frydman et al reported 3% of women going into labour within 24 hrs of ingestion of mifepristone.[6]

Totally 30 women in group1 needed dinoprostone gel in addition to mifepristone to prime the cervix of which 21 women needed 1 gel, 6 needed 2 gels and 3 needed 3 gels to improve the Bishop score. The number of gels needed following mifepristone, when mifepristone alone was not sufficient for cervical priming was significantly lesser (42) than the total number of gels needed in dinoprostone group (92).

The need for augmentation with syntocinon was less in mifepristone group than dinoprostone group, though it was not statistically significant. Hapangama and Neilson also reported that there was less likely need for augmentation with oxytocin (RR0.80,95% CI 0.66 to 0.97).[10] The number of Caesarean sections, vaginal delivery and perinatal outcome was comparable in both groups. 2 women needed to undergo Caesarean section for failed induction of labor in mifepristone group whereas 5 had to undergo Caesarean section for the same indication in dinoprostone group. This was comparable to Hapangama and Neilson study who reported that mifepristone treated women were less likely to undergo Caesarean section as a result of failure of induction (RR 1.43,95% CI 0.20-0.80).[10] Thus showing that chances of failure of induction of labour was less with mifepristone.

Though abnormal fetal heart rate pattern (NRNST) were more common in mifepristone group, the 5'APGAR scoring after delivery in these neonates was good and also there was no evidence of differences in admission to NICU. The same was reported by Hapangama and Neilson (RR1.11,95% CI 0.72 -1.71).[10]

CONCLUSION

Mifepristone is a safe and effective induction agent for cervical ripening and initiation of labour, when given at least 24 hrs prior in third trimester pregnancies whenever induction of labour is indicated. Even though mifepristone is expensive, as it can be administered on outpatient basis, there might be overall savings in this group. Mifepristone and cerviprime are comparable in feto-maternal outcome. Thus, mifepristone can be a safe alternate to dinoprostone in induction of labour, especially when prostaglandins are contraindicated.

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