ORIGINAL RESEARCH

Cervical Ripening Using Mifepristone before Induction of Labor in Term Pregnancy: Prospective Randomized Comparative Study

Nikita Sharma[1], Seetesh Ghose[2], Setu Rathod[3]

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Abstract

Background: Mifepristone is a pharmacological agent (antiprogestin). When used in late pregnancy as an inducing agent, it antagonizes the action of progesterone at the cellular level and promotes cervical ripening. This study aims to compare the efficacy of mifepristone and prostaglandin (PGE_2) gel for cervical ripening.

Methodology: Women fulfilling inclusion criteria were enrolled either into the study group (mifepristone) or the control group (PGE_2 gel). After assessment of the initial Bishop's score in both the groups, the study group was administered mifepristone 200 mg orally once and the control group was administered intracervical PGE_2 gel at intervals of 6 hours for a maximum of three doses. Subsequent Bishop's score was assessed at 6, 12, 18, and 24 hours in both groups. An artificial rupture of membrane (ARM) with oxytocin augmentation was done when required. Parameters measured were the demographic profile of patients, Bishop's score, the requirement of misoprostol and augmentation with oxytocin, mode of delivery, induction delivery interval, outcome (successful/failed induction), appearance, pulse, grimace, activity, and respiration. (APGAR) score at 1 minute, and 5 minutes, neonatal intensive care unit (NICU) admission above 24 hours.

Result: Improvement of Bishop's score was significantly higher in the control group at 6, 12, and 18 hours as compared to the study group. A total of 94% of patients required misoprostol only in the study group. Augmentation with oxytocin rate was higher in the control group (73%) as compared to the study group (71.1%). The induction delivery interval was significantly shorter in the control group with a $p < 0.001$. The vaginal delivery rate was higher in the study group. No significant difference was noted in neonatal outcomes in both groups.

Conclusion: Mifepristone is not a better primary ripening agent than PGE_2 gel.

Keywords: Labor induction and augmentation, Labor management, Neonatology.

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Introduction

Labor, initiation of uterine contraction, is induced with the aim of vaginal delivery after the period of viability. This is achieved by any method, that is, medical, surgical, or combined. This is done to reduce the risk of continuation of pregnancy either to the mother or to the fetus. Although the incidence of induction of labor varies worldwide, in developed countries, it is over 10–20%.[1,2] The success of induction of labor relies upon the status of the cervix prior to it. Cervical ripening is defined as a series of complex biochemical changes within the cervix, which makes the cervix soft, relaxed, and open in response to the contraction of the uterus.[1] So, many times, induction fails when it is tried before the ripening of the cervix. So, the ripening of the cervix prior to induction is essential for the successful induction of labor.

Cervical ripening is assessed using Bishop's score and if the score is less than 6, the mechanical method (Foley's catheter) or medical method (PGE_2 gel) is used to achieve it. This is followed by initiation of labor with prostaglandin tablets (PGE_1), orally or vaginally, or with oxytocin infusion.[3,4] Use of prostaglandins or oxytocin for induction of labor is associated with an untoward effect on the mother and perinatal outcome. The maternal effect includes hyperstimulated uterine contraction, while perinatal outcomes include fetal distress, meconium-stained liquor, meconium aspiration syndrome, and hyperbilirubinemia of the neonate. These untoward maternal and neonatal outcome leads to increased operative interference and increased NICU admission. So, the efforts are on to reduce the use of uterotonics, which can be achieved with the use of PGE_2 gel or mifepristone (RU486) for ripening of the cervix prior to induction of labor.

Mifepristone has been developed to block the action of progesterone at the cellular level, this help to initiate the process of labor. It is being used for early trimester termination of pregnancy. However, its use as a cervical ripening agent prior to induction of labor in term pregnancy is not practiced routinely because of the conflicting result.

[1–3]Department of Obstetrics and Gynaecology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India

Corresponding Author: Seetesh Ghose, Department of Obstetrics and Gynaecology, Mahatma Gandhi Medical College and Research Institute, Sri Balaji Vidyapeeth, Puducherry, India, Phone: +91 9443244630, e-mail: seetesh@mgmcri.ac.in

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So, this study was planned to compare the cervical ripening effect of mifepristone with that of commonly used PGE_2 gel prior to induction of labor.

The aim of this study was to compare the effectiveness of mifepristone (RU486) and prostaglandin (PGE_2) for the ripening of the cervix.

Objectives

- To study the effectiveness of mifepristone(RU486) in comparison to prostaglandin gel (PGE_2) for improvement of Bishop's score.
- To compare the requirement of additional uterotonics following PGE_2 administration for induction of labor.
- To compare mode of delivery, induction delivery interval, and perinatal outcome following PGE_2 administration for induction of labor.

Methodology

This randomized comparative study was conducted in the labor room of the department of obstetrics and gynecology, Mahatma Gandhi Medical College and Research Institute, a tertiary care hospital in Puducherry, India after obtaining Institutional Human Ethical Committee clearance. The total study period was 18 months from January 2017 to June 2018. All primigravida who required induction of labor and fulfilled the inclusion criteria were enrolled and written consent was obtained. Primigravida with singleton pregnancy in cephalic presentation with maternal age 18–35 years cases with gestational age after 37 weeks, intact membrane, reactive FHR, and Bishop's score less than 6 were included in the study. Pregnant women with medical complications, previously scarred uterus, antepartum hemorrhage, and estimated fetal weight less than 2000 gm and above 4000 gm were excluded. Mifepristone and prostaglandin gel was allocated using a computer-generated random number. On the scheduled day of induction, after an initial assessment of Bishop's score, one group received mifepristone 200 mg orally once only and the other group received PGE_2 gel at 0, 6, and 12 hours. Subsequent Bishop's score was assessed at 6, 12, 18, and 24 hours for both groups. Misoprostol 25 µg was administered vaginally, after 24 hours, fourth hourly for a maximum of six doses, or the women entered into active labor, whichever was earlier. Artificial rupture of the membrane was done and oxytocin infusion was started, if required, once the women entered into active labor. Partograph was used to monitor the progress of labor. The mode of delivery, vaginal or lower segment cesarean section (LSCS), was decided based on the progress of labor and FHR pattern. The parameters studied were mean maternal age, mean gestational age, Bishop's score, the requirement of augmentation, number of misoprostol tablets used, mode of delivery, an indication of LSCS, induction to delivery interval, APGAR score (1 and 5 minutes) and more than 24-hours NICU admission. All data were analyzed using SPSS, version 24.0, a *t*-test was used for the numerical variable and a Chi-square test was used for the categorical variable; $p < 0.05$ was considered significant.

Results

The difference in the demographic profile of both groups, mifepristone, and PGE_2, that is, maternal age and mean gestational age are not significant (Table 1).

In the mifepristone and PGE_2 gel groups, prolonged pregnancy was the main indication, at 87 and 90%, respectively. This was followed by oligohydramnios at 13 and 7%, respectively.

Although the difference ($p = 0.16$) of mean Bishop's score between both the groups at 0 hour was not significant, it was significant at 6, 12, and 18 hours with $p < 0.001$. In the PGE_2 group, all women entered into the active phase of labor within 24 hours whereas only three patients in the mifepristone group entered into the active phase of labor, and three patients were taken for LSCS in view of meconium-stained liquor. Bishop's score improvement was better in PGE_2 when compared to the mifepristone group as shown in Table 2 and Figure 1.

Although the augmentation rate was 71.1% in mifepristone and 73% in the PGE_2 group, the difference was not significant statistically as shown in Table 3. Vaginal deliveries were 63 and 48% in the mifepristone and the PGE_2 groups, respectively. So, caesarean sections, for various indications, were 37 and 52% in the mifepristone and the PGE_2 group, respectively. This difference was significant statistically with $p = 0.03$. The interval between induction to delivery was shorter in the PGE_2 group in comparison to the mifepristone group; $p = 0.001$ was considered statistically significant (Table 3).

Table 1: Comparison of demographic profile of patients

		Study group (n = 100)	*Control group (n = 100)*	
S.No.	*Characteristics*	*Mean ± SD*	*Mean ± SD*	*p-value*
1	Maternal age (years)	23.8 ± 2.7	23.5± 2.8	0.72 (NS)
2	Gestational age (weeks)	40.3 ± 1.6	40.3 ± 1.1	0.99 (NS)

NS, non-significant; SD, standard deviation

Table 2: Comparison of Bishop's score at various time points

	Bishop's score at various time points (hours)	*Study group*		*Control group*		
S.No.		*Number recorded n = 100*	*Mean ± SD*	*Number recorded n = 100*	*Mean ± SD*	*p-value*
1	0	100	3.1 ± 1.5	100	3.0 ± 1.3	0.16
2	6	100	4.1 ± 1.6	83	3.5 ± 1.0	<0.001*
3	12	98	4.2 ± 1.9	63	4.5 ± 1.2	<0.001*
4	18	97	4.3 ± 1.7	31	5.5 ± 1.7	<0.001*
5	24	94	4.4 ± 2.3	0	–	–

*$p < 0.05$ is significant; SD, standard deviation.

Fetal distress was the most common indication of LSCS in the mifepristone and PGE_2 groups, being 28 (75.6%) and 31 (59.6%), respectively. Other indications in the mifepristone group were cephalopelvic disproportion 7 (18.9%), arrest of dilation 1 (2.7%) and nonprogress of labor 1 (2.7%). In the PGE_2 group, other indications were cephalopelvic disproportion 14 (26.9%) and arrest of dilation 4 (7.8%), and non-progress of labor 3 (5.7%) (Table 3).

There was no case of failed induction in either group.

The difference in neonatal outcomes in terms of APGAR score at 1 minute, and 5 minutes, and NICU admission above 24 hours in both groups (Table 4).

Discussion

The studies conducted by Yelikar et al.,[3] Archana et al.,[5] Mandade and Bangal,[6] Ramesh et al.,[7] Arumugaselvi et al.,[8] and Sah and Padhye[9] showed satisfactory improvement in Bishop's score after 24 hours ranging from 3 to 8 in the mifepristone group. However, this change was not significant in our study. This is because our study is only about primigravida. However, the majority of other studies include both primigravida and multigravida.

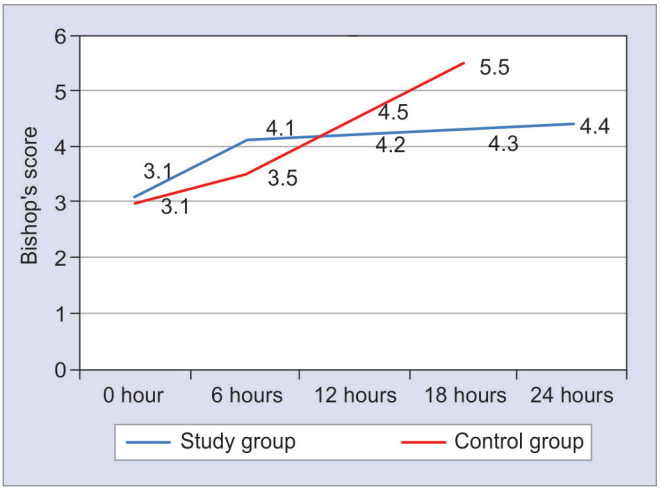

Fig. 1: Bishop's score at various time points

In the studies by Archana et al.,[5] Mandade and Bangal,[6] and Wing et al.[10] misoprostol requirement was 68, 54, and 67% in the mifepristone group respectively. In our study, it was 94%, which was higher when compared to other studies. This may be due to no significant improvement in Bishop's score.

The need for augmentation rate varied from 20% to 66% in studies done by Wing et al.,[10] Athawale et al.,[11] Gaikwad et al.,[4] Yelikar et al.,[3] and Arumugaselvi et al.[8] in mifepristone group, whereas it was 71.1% in our mifepristone group. This was significantly higher when compared to the majority of studies. This is because our study population includes only primigravida.

Vaginal delivery rate varies from 43% to 96% in studies done by Wing et al.,[10] Athawale et al.,[11] Gaikwad et al.,[4] Yelikar et al.,[3] Archana et al.,[5] Mandade and Bangal,[6] Ramesh et al.,[7] Arumugaselvi et al.,[8] and Sah and Padhye.[9] However, vagianal delivery in our mifepristone group was 63%.

Induction delivery interval varies from 9.34 ± 2.81 hours to 36 ± 11.6 hours in studies by Wing et al., Archana et al.,[5] Mandade and Bangal[6], Gaikwad et al.,[4] Yelikar et al.,[3] and Ramesh et al.[7] In our study, induction delivery interval was 40.6 ± 8.9 hours. This is because, our study included only primigravida, whereas the majority of the other studies have included multiparity.

In the mifepristone group, fetal distress was the most common indication for LSCS noted by Archana et al.,[5] Gaikwad et al.,[4] Sah and Padhye,[9] ranging 8–38%. This was also noticed in our study. In fact, it was 75.6% and which was significantly higher compared to above-mentioned studies. This may be due to over-diagnosis of meconium-stained liquor as fetal distress.

The mean APGAR score at 1 minute was 6.86 ± 0.49 and 7.78 ± 0.67 at 5 minutes in the study by Sah and Padhye[9] whereas in our study, the mean APGAR score at 1 minute was 7.9 ± 0.2 and 9 ± 0.1 at 5 minutes. The NICU admission rate was 10% in the study by Sah and Padhye[9] whereas in our study, there was no NICU admission. The neonatal outcome in terms of APGAR score and NICU admission was not different between our mifepristone group and Sah and Padhye, and Garg et al., studies.[9–12]

Table 3: Maternal outcome

Study group (Mifepristone) (n = 97) and %		*Control group (PGE_2 gel) (n = 100) and %*	*p-value*
Requirement of augmentation	69 (71.1%)	73 (73%)	0.77
Mode of delivery			
LSCS	37 (37%)	52 (52%)	0.03*
SVD	63 (63%)	48 (48%)	
Induction delivery Interval in hours	*Mean ± SD*	*Mean ± SD*	<0.001*
	40.6 ± 8.9	15.1 ± 1.2	
Indication of LSCS			
Fetal distress	28 (75.6%)	31 (59.6%)	
Cephalopelvic disproportion	7 (18.9%)	14 (26.9%)	
Arrest of dilation	1 (2.7%)	4 (7.8%)	
Non-progress of labor	1 (2.7%)	3 (5.7%)	
Total	37 (100%)	52 (100%)	

*$p < 0.05$ is significant; SD, standard deviation

Table 4: Neonatal outcome

Characteristics	*Study group (n = 100) Mean ± SD*	*Control group (n = 100) Mean ± SD*	*p-value*
APGAR score			
1 minute	7.9 ± 0.2	7.9 ± 0.4	0.33
5 minutes	9 ± 0.1	8.9 ± 0.2	0.31
NICU admission	0	2	0.15 (NS)
>24 hour	100	98	–

NS, non-significant; SD, standard deviation

The limitations of our study were interobserver bias in recording Bishop's score and interobserver decision making for LSCS, which can be improved with a single investigator, assessor, and decision maker.

Although the incidence of successful vaginal delivery was higher with optimal neonatal outcomes in this study, the use of mifepristone as a primary cervical ripening agent may not be recommended. This is because the mean induction delivery interval, requirement of tablet misoprostol and augmentation with oxytocin were more with mifepristone.

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