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Research Article

A comparative study of mifepristone with dinoprostone for induction of labor in third trimester

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Abstract: ***Background***: In modern obstetrics, labour induction is considered a way to improve maternal and foetal outcomes. In this regard, an increase in the frequency of induced labour has been noted worldwide. However, some evidence suggests that elective labour induction prolongs hospital stay and may increase costs and resource utilisation. Considering these provisions, and also the fact that some women prefer to be at home as long as possible before delivery, outpatient cervical ripening could be a reasonable alternative. ***Material and methods***: This study was open-label randomized controlled trial conducted in the Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow, over a time period of 1 year from August 2018 to August 2019 enrolled women who were admitted to the labor room at term with indications of induction of labor, willing to participate in the trial. ***Result***: The age of the patients ranged from 18 to 33 years. The mean age in the Mifepristone group was 25.10±3.50 years, and in the Dinoprostone group, it was 24.80±3.40 years (p=0.685). In the Mifepristone group, 30 (55%) were primigravida, and 25 (45%) were multigravida, while in the Dinoprostone group, 31 (57%) were primigravida, and 23 (43%) were multigravida (p=0.710). ***Conclusion***: Misoprostol an analogue of PGE1 appear to be perfect substitute for induction of labour. Its use was found to be associated with reduced time to delivery and high rate of vaginal delivery within 12 and 24 hours of induction. The requirement for oxytocin in augmentation was substantially reduced.

Keywords: Intrauterine Foetal Death, Prostaglandin, Mifepristone, Induction Delivery Interval.

INTRODUCTION

In modern obstetrics, labour induction is considered a way to improve maternal and foetal outcomes [1]. In this regard, an increase in the frequency of induced labour has been noted worldwide.[2] However, some evidence suggests that elective labour induction prolongs hospital stay and may increase costs and resource utilisation.[3] Considering these provisions, and also the fact that some women prefer to be at home as long as possible before delivery, outpatient cervical ripening could be a reasonable alternative.

It is well known that a "ripe" cervix is the most important predictor of success of labour induction. The use of pharmacological agents or mechanical methods to promote cervical ripening before the initiation of the induction process, known as preinduction, is important for successful induction. The preinduction and induction of labour are essentially linked in the same chain; however, they are different. Preinduction is aimed at ripening of the cervix (softening,[4] shortening, and initial dilatation) and consists predominantly of remodelling the connective tissue that constitutes the bulk of the uterine cervix. Induction is the process of stimulating the uterine muscle fibres to initiate contractions.[5] As in the setting of an unfavourable cervix, preinduction requires more time than induction, and it may be beneficial to perform it on an outpatient basis.[6] Mechanical methods (balloons or dilators) provide dilatation of the cervix; that is, they are preinduction methods. Pharmacological agents, such as prostaglandins and oxytocin, activate the contractile activity of the uterus; therefore, they should be considered as methods of labour induction.[7]

Mifepristone, a 19-norsteroid compound, counteracts progesterone at the receptor level and eliminates its inhibitory effect on uterine tissue, increases the synthesis of prostaglandins, and inhibits the action of prostaglandin dehydrogenase [8]. The antiprogestogenic effect of mifepristone promotes cervical ripening by increasing cervical collagenase and prostaglandin synthesis, and enhancing the expression of the extracellular matrix-degrading protease stromelysin-1 [9]. To achieve the effect of cervical ripening, a sufficiently long period is required, usually 24–72 h. Given that the action of mifepristone is mainly aimed at ripening the cervix and not stimulating uterine contractions, its use should be considered as a preinduction method.[10].

The efficacy and safety of mifepristone for the preinduction/induction of labour have been confirmed in observational and randomised trials[11]

Considering that mifepristone is a means of preinduction, and does not directly induce labour, and that it takes up to 24–72 h to achieve the effect, it seems appropriate and convenient to use it on an outpatient basis. However, there are currently no studies comparing the efficacy and safety of mifepristone preinduction of labour on an inpatient and outpatient basis.[12]

This study aimed to evaluate whether the outpatient use of mifepristone for cervical ripening before the induction of labour at term is efficient and safe

MATERIALS AND METHODS

This study was open-label randomized controlled trial conducted in the Department of Obstetrics and Gynaecology, King George's Medical University, Lucknow, over a time period of 1 year from August 2018 to August 2019 enrolled women who were admitted to the labor room at term with indications of induction of labor, willing to participate in the trial. The study was approved by Institutional Ethics Committee KGMU Lucknow (Vide letter Ref No.262/Ethics/R. Cel-16, Ref. code:90th ECM II B-Thesis/P35 dated 15-08-2018) and had been performed in accordance with the ethical standards described in an appropriate version of the 1975 Declaration of Helsinki, as revised in 2000

The inclusion criteria were singleton gestation, cephalic presentation, Bishops score ≤ 5, and reactive nonstress test pattern. The exclusion criteria were premature rupture of membrane, previous history of cesarean section or uterine surgery, intrauterine death, any hypersensitivity and contraindication to PGE2 gel such as asthma, glaucoma, and any preexisting cardiovascular diseases, multiple pregnancy, chorioamnionitis, and any febrile morbidity and any contraindication to the induction of labor.

During the study period, a total of 460 pregnant women were admitted for the induction of labor. Out of 460 women, 225 women were excluded who did not met the inclusion criteria and who denied of participating in the study. One hundred and ninety-one women who fulfilled the inclusion criteria were enrolled in the study after written informed consent and were randomized by the simple computer-generated random number table into group A (mifepristone) and group B (Dinoprostone gel). Allocation concealment was done by the distribution of drugs by sequentially numbered opaque sealed envelopes (SNOSE). Group A had 94 women in which six women discontinued the intervention as they denied further induction, and Group B had 97 women in which five women discontinued the intervention as they denied further induction So Group A had 88 women, and Group B had 92 women

All enrolled women were subjected to detailed history; per abdominal and per vaginal examination, including Bishop's score; and relevant investigations, which include complete blood count, ABO-RH, viral markers, Diabetes in pregnancy study groups in India (DIPSI), urine routine, and microscopy, Serum thyrotropin hormone (S.TSH) (if previously not done), and further specific investigations were done according to other risk factors.

Labor and delivery details were noted, and outcome was measured: Primary outcomes were change in bishops score and induction to the onset of contractions, and secondary outcomes were induction to delivery interval, mode of delivery, cesarean for failed induction, any adverse events, and fetal outcome

Statistical Analysis

The results were analyzed using descriptive statistics and making comparisons among the various groups. Discrete (categorical) data were summarized as in proportions and percentages (%), while continuous in mean and SD. The chi-square test, arithmetic mean, standard deviation, unpaired t-test, and odds ratio were done using SPSS 23.

RESULTS

The age of the patients ranged from 18 to 33 years. The mean age in the Mifepristone group was 25.10±3.50 years, and in the Dinoprostone group, it was 24.80±3.40 years (p=0.685). In the Mifepristone group, 30 (55%) were primigravida, and 25 (45%) were multigravida, while in the Dinoprostone group, 31 (57%) were primigravida, and 23 (43%) were multigravida (p=0.710).

A total of 35 (65%) patients in both groups were at a gestational age of more than 40 weeks. About 12 (22%) patients in the Mifepristone group and 10 (19%) in the Dinoprostone group were at 37–40 weeks, whereas 7 (13%) in the Mifepristone group and 8 (15%) in the Dinoprostone group were at less than 37 weeks of gestation (p=0.930).

The most common indication for induction was prolonged pregnancy (65%), followed by hypertensive disorders (23%) and gestational diabetes mellitus (12%) in both groups (p=1.000). Patients in both groups were comparable, with no significant statistical differences in demographic parameters.

Table 1: Demographic Characteristics of Both Groups (n=460)

Demographic Parameter	Group A (Mifepristone) (n=88)	Group B (Dinoprostone) (n=92)	P Value (Chi-Square)
Age (18-33 years)			
Mean Age (years)	23.90 ± 3.30	23.44 ± 3.35	0.711
Gravida			
Primigravida	47 (53%)	51 (55%)	0.687
Multigravida	41 (47%)	41 (45%)	
Gestational			0.946

Age (weeks)			
<37 weeks	14 (16%)	17 (18%)	
37-40 weeks	18 (20%)	17 (18%)	
>40 weeks	56 (64%)	58 (64%)	
Indication for Induction			1.000
Prolonged Pregnancy	56 (64%)	58 (64%)	
Hypertensive Disorders (HDP)	21 (24%)	22 (24%)	
Gestational Diabetes Mellitus (GDM)	11 (12%)	12 (12%)	

Table 2: Bishop's Score Before and After 24 Hours

Bishop's Score	Mifepristone Group (A) (n=88)	Dinoprostone Group (B) (n=92)	P-value (Chi-square)
Preinduction Bishop's Score			0.966
0	4 (5%)	3 (3%)	
1	9 (10%)	11 (12%)	
2	15 (17%)	14 (15%)	
3	12 (14%)	13 (14%)	
4	48 (54%)	51 (56%)	
Bishop's Score After 24 Hours			0.36
>6	70 (80%)	68 (74%)	

Most of the patients in both groups had pre-induction Bishop's score of 2 to 4. After 24 hours, 78% patients in Mifepristone group and 70% patients in Dinoprostone group had Bishops's score >6 (Table 3). Comparing the mean gain in Bishop's score after 24 hours, Mifepristone group had better gain (4.45±1.35) as compared to patients in Dinoprostone group ((4.07±1.34) with p value of 0.159 (Table 3). However, the difference was not statistically significant. The mean duration of labor was longer in Dinoprostone group as compared to Mifepristone group (p=0.247). However, the induction delivery interval (IDI) was lesser in Dinoprostone group (12.28±6.75) as compared to Mifepristone group (14.00±7.00) (Table 4). Half of the patients in group A (48%) and two-third of the patients in group B (70%) required oxytocin for labor induction or augmentation. The mean dose of oxytocin (units) required was higher in Dinoprostone group (2.26±0.17) and lesser in Mifepristone group (3.29±1.35) with p-value of 0.001. This difference was highly significant statistically.

Table 3: Gain in Bishop's Score over Time

Time Point	Group A (Mean ± SD)	Group B (Mean ± SD)	P-value
Pre-induction Bishop's score	2.79 ± 1.29	2.65 ± 1.30	0.588
Bishop's score after 12 hours	4.25 ± 1.81	4.95 ± 1.39	0.243
Bishop's score after 24 hours	7.23 ± 2.03	6.71 ± 1.76	0.174
Difference in Bishop's score	4.45 ± 1.35	4.07 ± 1.34	0.159

Table 4: Duration of Different Stages of Labor

Labor Stage	Group A (n=88) Mean ± SD	Group B (n=92) Mean ± SD	P-value
Stage I (hours)	4.91 ± 1.78	5.48 ± 2.33	0.216
Stage II (minutes)	20.87 ± 6.24	24.32 ± 6.28	0.017 *
Stage III (minutes)	4.16 ± 1.21	4.83 ± 1.94	0.067
Induction to Delivery Interval (IDI) (hours)	14.01 ± 7.01	12.29 ± 6.74	0.274

Table 5: Requirement of Oxytocin for Augmentation

Oxytocin Requirement	Group A (n=88) (%)	Group B (n=92) (%)	P-value
Yes	42 (47.7)	64 (69.6)	0.025 *
No	46 (52.3)	28 (30.4)	
Dosage of Oxytocin (units) (Mean ± SD)	2.26 ± 0.17	3.29 ± 1.35	0.001 #

Table 6: Maternal and fetal complications

Complications	Group A (n=88)	Group B (n=92)	Statistical Analysis (Chi-square test)
Maternal complications			
Fever	0.0455 (4)	0.0435 (4)	P = 0.570
GI symptoms	0.0114 (1)	0.0326 (3)	
Abdominal cramps	0.0227 (2)	0.0217 (2)	
Hypertonic uterine contractions	0.0114 (1)	0.0000 (0)	
PPH	0.0000 (0)	0.0109 (1)	
Fetal complications			
Birth asphyxia	0.0114 (1)	0.0109 (1)	P = 0.328
MSL	0.0227 (2)	0.0652 (6)	
Transient tachypnoea of newborn (TTN)	0.0114 (1)	0.0217 (2)	
NICU admission	0.0909 (8)	0.1413 (13)	
APGAR <7 at 5 minutes	0.0909 (8)	0.1087 (10)	

DISCUSSION

There are various methods of induction of labor available but none of them is ideal. Various studies have been done to evaluate the role of mifepristone at term. So, the purpose of our study was to compare the efficacy of mifepristone with that of PGE2 gel. The rationale behind this study was to utilize the antiprogestrogenic activity of mifepristone at term and to find out whether it is a suitable and effective labor-inducing agent. In our study, baseline characteristics like age, booking status, socioeconomic status, education, parity, period of gestation, indication for the induction of labor, and Bishops score were comparable in both groups.[13]

In the present study we assessed the age distribution of the study subjects. We observed that majority of the study subjects belonged to the age group of 26 to 35 years (55% and 50% in either group), followed by more than 36 years (37.5% and 40% resp). Wing et al11 in Southern California, Los Angels, conducted a randomized controlled trial in which 88 percent of the patients were in the age bracket of 21-30 years. Kanan Yelikar et al12 in their study observed that the mean age of the study subjects is 22.98 years. If we compare parity in both groups, the groups were comparable (p = 0.310). Similarly in studies done by Yellikar ET al12, mean parity was 1.48 ± 0.44 and 1.62 ± 0.44 (p= 0.659). Gupta et al.13 also compared the effectiveness of mifepristone, and the groups were comparable (p <0.0310). In our study, the mean gestation age was comparable (p= 0.239). In a similar study, Sah and Padhye discovered that there was no statistically significant difference in gestational age between the two groups.[14]

In this study we assessed the gravida status among the study subjects. We observed that majority were primigravida (72.5% and 62.5 resp).In this aspect our study correlates with studies done by Giacalone et al Department of Obstetrics and Gynaecology, Hospital Arnaud de Villeneuve, University of Montepetlier.[15] Similar to the Wing DA et al, Elliot et al study and Kanan Yelikar these trials compared mifepristone to placebo, whereas herePGE2 gel was used.

In the present study we assessed the Bishops score at the start. We observed that majority of the subjects had score of 3 (70% and 62.5% resp), followed by score 2 (25% and 30% resp). Our findings are similar to those of Elliot et al15, Department of Obstetrics and Gynecology, University of Edinburgh, United Kingdom, 1998, who included Bishop's score of 4 or less in the research group. The mean Bishop's score at the start of our study was 2.72, which is comparable to the mean Bishop's score at the start of Kanan Yelikar's study, which was 2.02.[16] Yellikar ET al12. And Gupta et al13 compared oral mifepristone versus placebo and found that preinduction Bishop score in both groups was 2.02 ± 0.749 and 2.79 ± 1.29, respectively. In contrast toour study, Sailatha et al16. found that the mean increase in post-induction Bishops score at 24 hours was 4 ± 1.48 in mifepristone group and 4.7 ± 1.49 in PGE2 gel group, and this was statistically significant (p = 0.042).[17]

The literature data indicate that misoprostol does not increase maternal and fetal morbidity. Our findings, on the other hand, indicate an increased rate of cesarean section with repeated use of vaginal misoprostol 50 µg. It is reasonable to think that a lower dose of misoprostol (25 µg versus 50 µg) may reduce tachysystole or hypertonia (as shown in a literature review37) and thereby reduce the rate of cesarean section due to fetal heart rate abnormalities observed in our study. Oral administration may reduce abnormal fetal heart rate.[18]

In the present study we assessed the mean blood loss among the study subjects. We observed that mean blood loss in Mifepristone group was 187.6 ml, whereas in dinorpstone group was comparatively greater 232.8 ml. The difference was found to be statistially significant (p value: <0.0001). In the present study we assessed the neonatal complications among the study subjects. We observed that Respiratory distress, Meconium aspiration, TTN, NICU admission were comparatively found to be lesser in mifepristone group as compared to dinoprostone group.[19] NICU admission were required more in dinoprostone group (10%), as comapred to mifepristone group (7.5%). Wing DA et al11 discovered that there was no statistically significant difference in neonatal outcome between the mifepristone-treated and control groups. Our findings are similar to those of Kanan Yelikar, who found no statistically significant differences in perinatal outcomes between two groups. Sandhya Kumari et al24 in their study observed that the NNU admission was less in mifepristone group 9 (10.2%) as compared to PGE2 group 15 (16.3%) and the proportion of NNU admission in group B was relatively more than the group A but no statistically significant difference was noted (p = 0.231).[21] Three babies in each group had an Apgar score of 6 at 5 minutes in their study, and there was no statistically significant difference between them (p= 0.956). Gaikwad et al.23 found that 6 and 14 percent of new-borns in the mifepristone and dinoprostone groups, respectively, required NICU admission, which was similar to our findings. Among the babies, 36% required baby unit admission in mifepristone. In contrast to our findings, Sah and Padhye discovered that in the mifepristone group 5 (10%) neonates required NICU admission while in the dinoprostone group, 1 (2%) babies required NICU admission.[22].

CONCLUSION

Misoprostol an analogue of PGE1 appear to be perfect substitute for induction of labour. Its use was found to be associated with reduced time to delivery and high rate of vaginal delivery within 12 and 24 hours of induction. The requirement for oxytocin in augmentation was substantially reduced

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