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COMPARATIVE STUDY OF ORAL MIFEPRISTONE VERSUS ORAL MISOPROSTOL SOLUTION (FIXED DOSE) FOR CERVICAL RIPENING IN ANTENATAL WOMAN

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ABSTRACT

Introduction: Cervical ripening or cervical softening is a process that is necessary for both spontaneous labor and labor induction. Prior to initiating induction, cervical ripening should be considered if bishop score of cervix is 6 or less than 6. Varying drugs and dosage are used for the same.

Aim: The role of mifepristone for cervical ripening prior to labor induction and oral misoprostol solution (fixed dose) for labour induction are two such regimen studied and analysed in our study.

Methods: A cross- sectional comparative study involving 100 patients (50 mifepristone, 50 misoprostol group) was done at a tertiary care hospital over a period of one year.

Two groups were made-

Group 1 patients were subjected to tab mifepristone 200 mg orally stat followed by another dose of 200mg after 24 hours.

Group 2 were given oral misoprostol solution (fixed dose) for 24 hours. Bishop score on admission and after 12 hour and after 24 hour is calculated and compared in both groups.

Results: The data analyzed as per protocol analysis, increase in bishop score was seen in both groups after 12 and 24 hours, but in group 1 patients only 50% patients developed cervical ripening in 1st 12 hour whereas in group2, 84% patients had ripened cervix within first 12 hours of study. At the end 66% patients in group 1 and 72% patients in group 2 delivered vaginally. Uterine hyperstimulation and meconium passage and aspiration are the seen more with group2 patients. No major side effects were observed in both groups. 4 patients were lost to follow up in mifepristone group.

Conclusion: Tablet mifepristone is as effective as misoprostol solution for cervical ripening and induction of labor and with less side effects but more time interval between induction and ripening.

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Keywords: mifepristone, cervical ripening, misoprostol

1. INTRODUCTION

Cervical ripening or "cervix softening" is a process that is necessary for both spontaneous labour and labour induction. Nonetheless, for women undergoing induction, the cervical ripening process must frequently be triggered iatrogenically.

In the United States, around four million women give birth each year.[1] More than 20% of these women will receive labour induction, and at least 50% are candidates for cervical ripening.[1]

The ground substance of cervix consists of proteoglycans (which reinforce the cervix), glycosaminoglycans (which soften the cervix), fibrillary collagen, and matricellular proteins. The cellular components of the cervix consist of fibroblasts and mast cells. Within the cervix, there is little smooth muscle. Numerous cervical maturation processes include the disintegration or reorganisation of these cervical components.

In 1964, Dr. Edward Bishop created the Bishop score. The Bishop score evaluates cervical dilatation, effacement, position, consistency, and foetal head position. Prior to initiating oxytocin, cervical ripening should be considered if the Bishop score is six. For women with a Bishop score more than 8, the chance of vaginal birth following induction is comparable to that of spontaneous labour. [2]

Chemical approaches such as oxytocin, prostaglandins, and NO donors; mechanical procedures such as extra amniotic saline infusion (EASI) and hygroscopic agents; have been employed for cervix ripening. However, these treatments are not risk-free. In cases of vaginal birth after caesarean section (VBAC) chemical techniques may increase the risk of uterine rupture thus the most appropriate way should be adopted to minimise bad effects based on the status of the mother and foetus. The mechanical approaches are safer but possibly somewhat less effective than prostaglandins.[3]

Mifepristone (Antiprogestin), which was discovered in 1981 by Philibert et al 24) are routinely used and licenced for early pregnancy termination, cervical dilatation prior to abortion, and labour induction following foetal death in utero. [4] Few studies have been undertaken on the effects of mifepristone on cervical ripening and labour induction in full-term, viable pregnancies.

In the absence of progesterone's inhibitory impact, there is an increase in prostaglandin synthesis and inhibition of prostaglandin dehydrogenase activity. After mifepristone, the sensitivity of the myometrium to the contraction-inducing activity of prostaglandins increases dramatically [5], and labour typically begins without further inductors.

These characteristics of mifepristone defined its usage for cervical ripening and pregnancy termination preparation.

In obstetrics, the most common approved indications for mifepristone include early pregnancy termination, cervical dilatation prior to surgical abortion, and labour induction in the event of foetal death in utero. Fewer research has been undertaken on the effects of mifepristone on cervical ripening and labour induction in full-term, viable pregnancies.

Due to its uterotonic and cervical-ripening properties, Misoprostol has also become an essential medication in Obstetrics and Gynaecology. Misoprostol is used for medical abortion, cervical ripening prior to surgical abortion, uterine evacuation in cases of embryonic or foetal demise, and labour induction. Additionally, the medication may be used to manage and even prevent postpartum haemorrhage.

Misoprostol can be given orally, vaginally, sublingually and rectally. Misoprostol is a safe drug but serious complications and teratogenicity can occur with unsupervised use.

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Use of mifepristone for induction of labour is still under investigation. It is not an oxytocic so it is not associated with over or hyperstimulation of uterus and there is no increase in the incidence of rupture of uterus or any other side effects such as those of misoprostol.
Because of above stated benefit of mifepristone, we compared the efficacy of oral mifepristone against oral misoprostol solution (fixed doses) for cervical ripening and labour induction in live pregnancies.

2. MATERIAL AND METHODS

This is a cross sectional comparative study conducted Nehru Hospital Medical collage Gorakhpur in Emergency or outdoor department of OBS & Gynae. The study was conducted over a period of 1 year (1 August 2021 to 31 July 2022) with approval from institute from ethics Committee.
Antenatal women having singleton pregnancy between 28 to 42 weeks gestational age were included in this study.
A total of 100 patients (50 mifepristone, 50 misoprostol) were taken after taking informed consent.

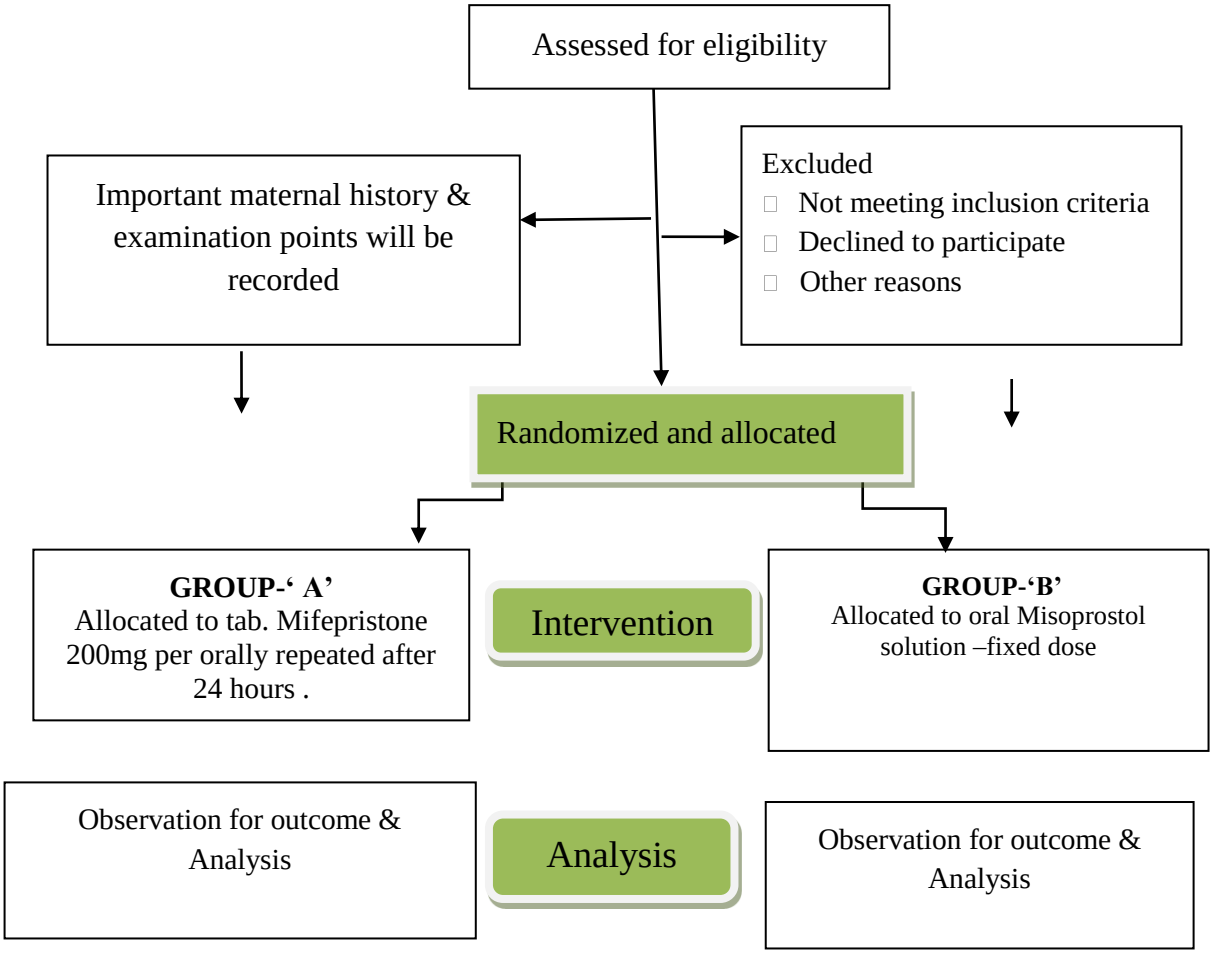
Eligibility Criteria

Inclusion criteria- Age between 18-45 years, singleton live cephalic pregnancy of >28-week gestation with unripe uterine cervix (bishop score<6) and intact membranes and with no contraindications for vaginal delivery and labour induction.

Exclusion criteria- Myoma/uterine anomaly, impaired renal, adrenal, or hepatic function, breech presentation, any concerns about the well-being of the fetus, any medical indication for scheduled cesarean delivery.

Randomization

Allocation of study participants in two groups-



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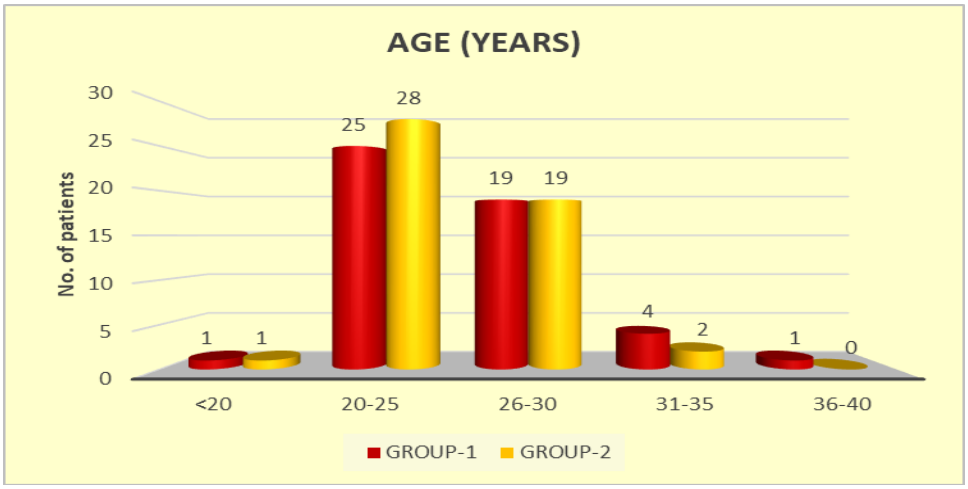
After intervention in group 1 and group 2 following points were recorded from the patients-

1. Bishop's score before and after mifepristone and misoprostol.
2. Induction to active labour interval.
3. Outcome of induction of labour on both groups
   -vaginal delivery/ caesarean section
   -Augmentation required – Methods of augmentation required
   1) Oxytocin injection
   2) Artificial rupture of membranes.

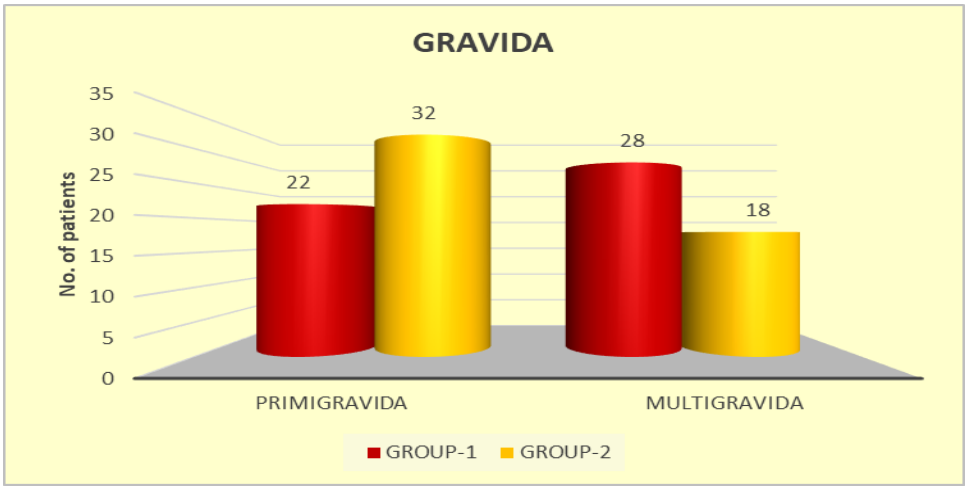
5. Number of doses of Mifepristone, number of doses of misoprostol required for induction of labour.
6. Maternal complications like- Post partum haemorrhage, Retained Placenta, Rupture uterus, chorioamnionitis etc.

3. RESULTS



In our study, that maximum patients of Group 1 and Group 2 belonged to the age group of 20 to 25 years (50% and 56% respectively) , followed by 26 to 30 years (38%) in each group. With respect to age both groups were similar also.

Parity distributions of participants in both the groups were similar ,maximum patients in group 1 and group 2 were primigravida (44% and 60% respectively).



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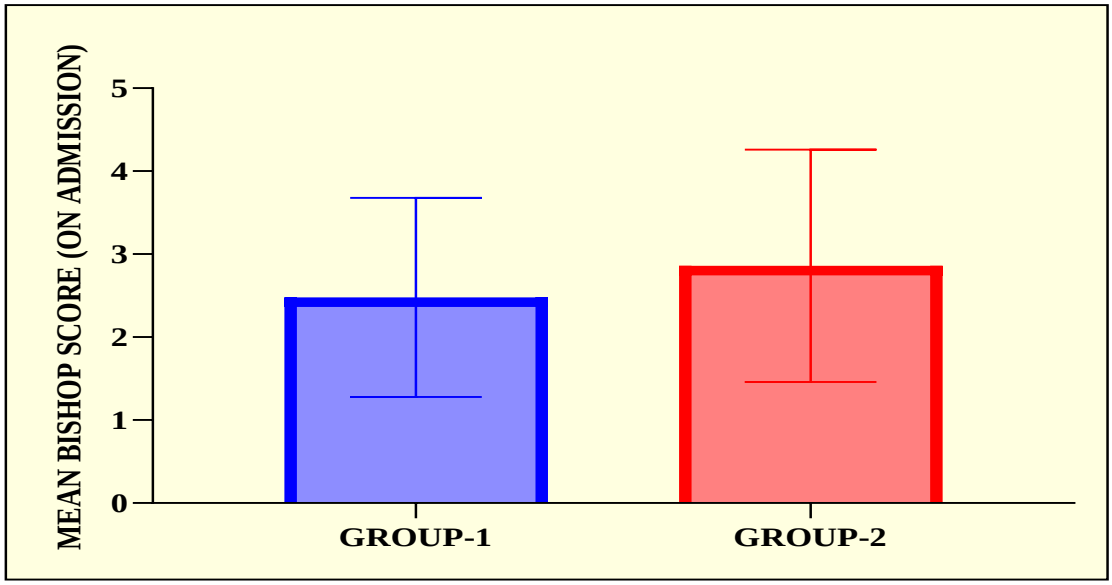
Maximum patients belong to lower middle and upper lower socio-economic status in both the groups and the socioeconomic status was the same.
66% patients in group 1 and 72% patients in Group 2 were literate.
Gestational age at the time of Induction for maximum patients was between 37- 40 weeks.
- Bishop score on admission

BISHOP SCORE	**GROUP-1 [n=50]**		**GROUP-2 [n=50]**		**P-VALUE**
	N	**%**	**N**	**%**	
0-2	26	52.00%	23	46.00%	X=0.3601 p=0.5484
3-5	24	48.00%	27	54.00%	

On Admission	Group 1	Group 2	P- value
Mean Bishop score	2.48+- 1.20	2.86 +- 1.40	t- 1.588 p- 0.1147

Bishop score on admission has no association with the groups for deciding the method of cervical ripening.
Mean Bishop score on admission was (2.48+1.20 versus 2.86+1.40 for Group 1 and group 2 respectively) with p- value > 0.05.



Bishop Score after 12 hours

BISHOP SCORE	**GROUP-1 [n=50]**		**GROUP-2 [n=50]**		**P-VALUE**
	N	**%**	**N**	**%**	
0-4	20	40.00%	5	10.00%	X=22.38 **p<0.0001***
5-8	26	52.00%	23	46.00%	
>8	0	0.00%	6	12.00%	
Already delivered/LSCS	4	8.00%	16	32.00%	

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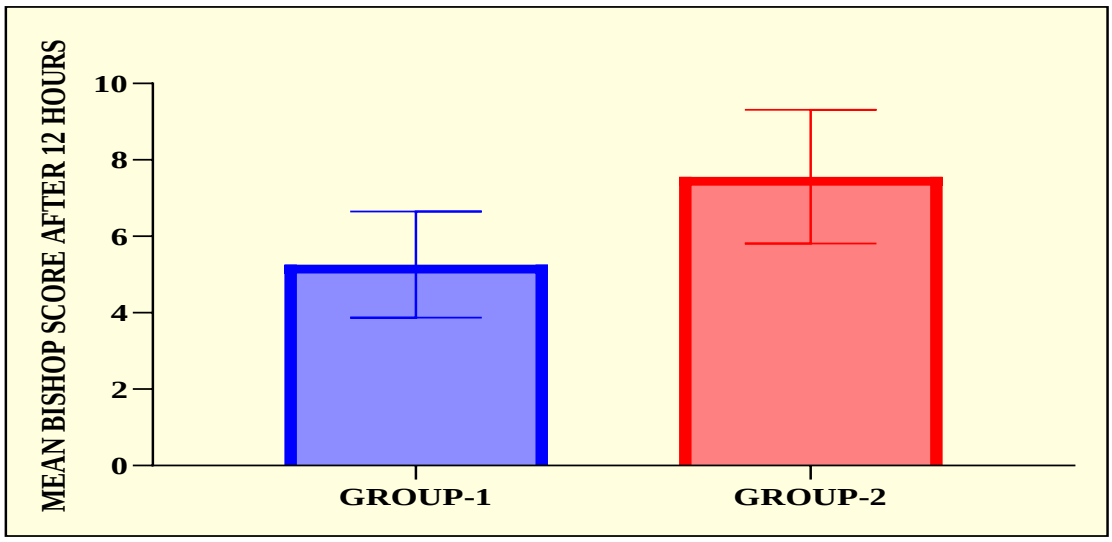
After 12 hours	Group 1	Group 2	P- value
Mean Bishop score	5.26+- 1.39	7.56+- 1.75	t- 7.867 p < 0.0001

There was significant improvement in mean Bishop score after 12 hours in both the groups. Improvement in mean bishop score was more in group 2 as compared to group 1.More number of patients(32%) were already delivered before 12 hour in group 2 as compared to group 1 (8%).



Bishop Score after 24 Hours

BISHOP SCORE	**GROUP-1 [n=50]**		**GROUP-2 [n=50]**		**P-VALUE**
	N	**%**	**N**	**%**	
0-4	0	0.00%	0	0.00%	X=4.827 **p=0.0280***
5-8	34	68.00%	2	4.00%	
>8	7	14.00%	3	6.00%	
Already delivered/LSCS	5	10.00 %	29	58.00%	

After 24 hours	Group 1	Group 2	P- value
Mean Bishop score	7.63+- 1.59	9.80 +- 2.04	t- 6.401 p< 0.0001

After next 12 hours i.e. after 24 hours of Induction, total 68% patients in group 1 developed cervical ripening whereas 14% patients had bishop score of >8. In Group 2, most of the patients either had ripen cervix before 24 hours or delivered/managed before 24 hour. Only few of the remaining patients developed cervical ripening in 24hours.
5 patients (10%) delivered in group 1 and 29 (58%) in group 2 within 24 hours.

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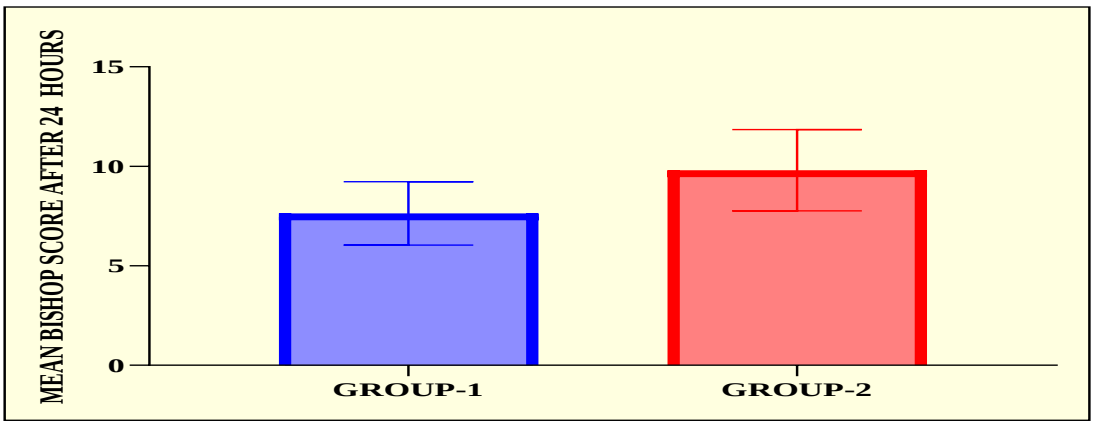

Comparative table for mean Bishop score in both the Groups.

	GROUP-1 [n=50]		GROUP-2 [n=50]		P-VALUE
	MEAN	**SD**	**MEAN**	**SD**	
ON ADMISSION	2.48	1.20	2.86	1.40	t=1.588 p=0.1146
AFTER 12 HOURS	5.26	1.39	7.56	1.75	t=7.867 **p<0.0001***
AFTER 24 HOURS	7.63	1.59	9.80	2.04	t=6.401 **p<0.0001***
AFTER 48 HOURS	10.57	1.92			
P-VALUE	F=247.1 **p<0.0001***		F=151.3 **p<0.0001***		

The above table shows the comparative study of mean Bishop score at admission, after 12 hours and after 24 hours of induction for cervical ripening in both the groups.
The comparison between both the groups was statistically significant with p- value< 0.05.
Time Interval between Induction to cervical ripening (>6 bishop score) comparison between both groups.

Time Interval (hours)	GROUP-1 [n=50]		GROUP-2 [n=50]		P-VALUE
	N	**%**	**N**	**%**	
0-12	25	50.00%	42	84.00%	**X=12.3947**
13-24	19	38.00%	5	10.00%	**p =0.0004**

50% of the patients in group 1 had cervical ripening cervix within 12 hours of tab mifepristone whereas 38% ripened in next 12 hours. Some of the patients took 48 hours to ripen the cervix whereas few left unripen.
In group 2, 84% of the patients had cervical ripening or delivered within 12 hours of 1st dose of misoprost solution. Rest 10 % of the patients in group 2 had ripening in the next 12 hours.
Failed induction is seen in 8% patients of Group 1 whereas only in 2% patients in group 2.

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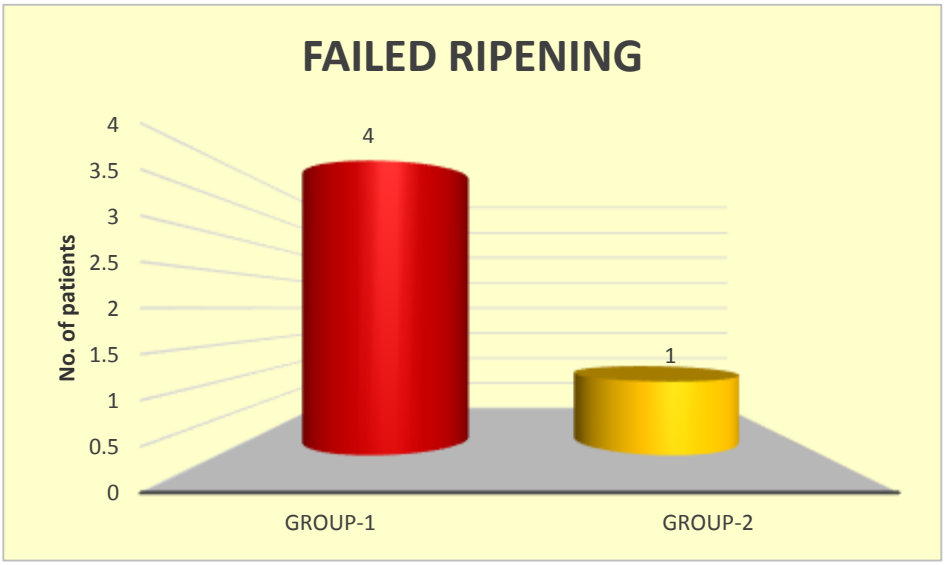
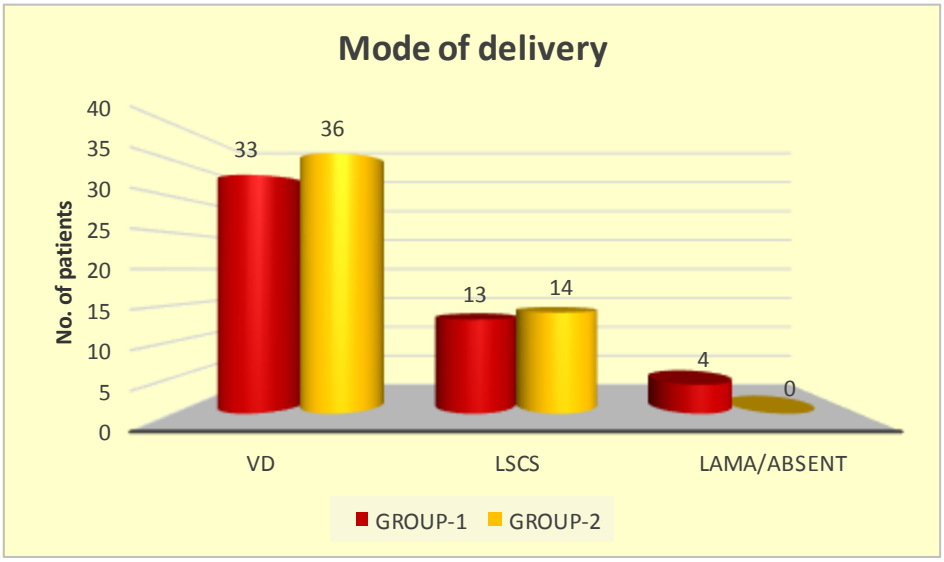


Maximum patients in both Group 1and Group 2 delivered with requirement of augmentation either by oxytocin or ARM or both.



On the basis of mode of delivery maximum patients in Group 1 and Group 2 (66% and 72% respectively) delivered by vaginal route where as 26% in group 1 and 28% in group 2 had caesarean sections.

4 patients in group 1, left went LAMA or ABSCONDED due to prolonged latency period between induction and ripening of cervix so we were not able to follow up for mode of delivery.

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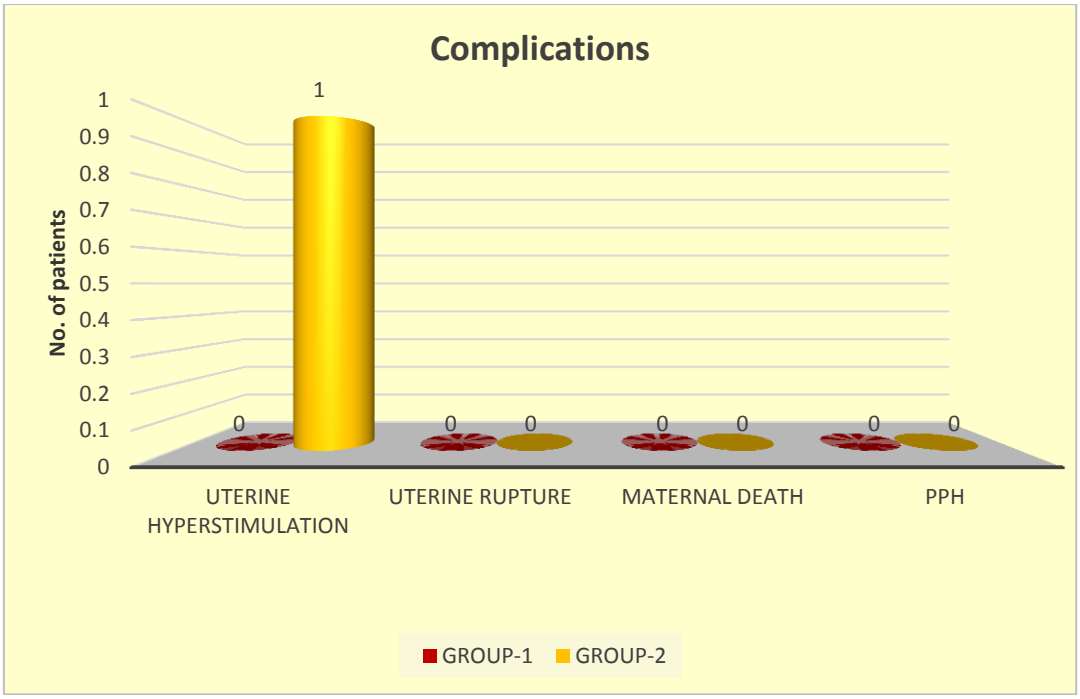

No significant side effects and complications were noted in both the groups but slightly higher chances of uterine hyperstimulation noted in group 2.
In our study, most of the patients delivered live births in both the groups with lesser NICU admissions.

4. DISCUSSION

For Patients desiring spontaneous labour or vaginal delivery research continues to invent and modify new drugs and methods for induction of labour. Induction of labour has two important components - i.e. cervical ripening and stimulation of uterine contractions to achieve dilatation of cervix and delivery of foetus.
Various studies have been conducted on mifepristone and misoprostol for cervical ripening and labour induction.
The mean bishop score after 12 hours were (5.26 + - 1.36)versus (7.56 + - 1.75) with p value < 0.05 which is statistically significant i.e. there was significant improvement in the mean bishop score after 12 hours in both the groups which was comparable to the study of **A. Ghimire et al (2020)** [6] with mean bishop score of (2.94 versus 3.24) and kenan yelikar et al(2018) with mean bishop score of (2.02+- 0.749) versus (2.16+-0.77) and C. Lelaidier et al(1992) (mifepristone versus placebo) with mean bishop score (1.48 versus 1.12). Similar study on Titrated misoprostol versus oral conventional misoprostol solution done by **A. Thaisomboon et al (2012)** [7] with (10.8+-6.9) versus (9.9+-7.1) with p>0.05 and a meta-analysis of misoprostol for cervical ripening and labour induction done by **L Sanchez-Ramos et al (1997).** [8]
In our study, Improvement in mean bishop score is more for group 2 as compared to group 1.
In both the groups a few numbers of the patients were already delivered within 12 hours of first study dose.
Significant improvement in bishop score is seen in next 12 hours in group 1 i.e. (68% patients had 5 - 8 bishop score) whereas in group 2 maximum patients had cervical ripening within the first 12 hours of misoprost solution and rest of the patient developed cervical ripening in next 12 hours. Similar results of improvement in bishop score were also noted by A

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randomised study on cervical ripening with mifepristone before labour induction (80% versus 50% in mifepristone versus placebo study) by **P L Giacalone et al (1998).**[9]
Few of the remaining patient in group 1 needed second dose of mifepristone after 24 hour for cervical ripening and induction.
Thus 50% of the patients in group 1 developed bishop score of > 6 within the first 12 hours of study period whereas 19% in next 12 hours. some of the patient took 48 hours and some left unripen, whereas in group 2, 84% of the patients had ripen cervix (> 6 bishop score) within the first 12 hours and 10% in next 12 hours.
In the present study, 66% patients of group 1 and 72% of the patients in group 2 delivered vaginally whereas 26% of the patients of group 1 and 28% of group 2 underwent cesarean section which was comparable to the study by **Kenan yelikar et al (2018)** [10] 84% versus 74% patients delivered vaginally where as 12% Vs 16% had caesarean section. **In Sharma C, et al (2016)** [11] 73.6% versus 82.4% had vaginal delivery.
The common reason for cesarean section in both the groups was fetal distress and non-progression of labour.
The incidence of meconium aspiration and fetal distress or uterine hyperstimulation is found more in oral misoprost solution group (group 2). Uterine tachysystole as a secondary outcome was also seen in study done by **A. Thaisomboon et al (2012).**[7]
2 patients in group 1 absconded and 2 patients in group 1 went LAMA due to noncompliance to mifepristone and increased interval of drug doses, that is why they could not be followed for their mode of delivery.
Failed induction is seen in 8% of patients of group 1 and 2% of patients in group 2.
Side effect profile of both the groups were minimal with lesser side effects.

5. CONCLUSION

Both the groups were comparable to each other with respect to age, parity, socioeconomic status, literacy rate and gestational age at the time of induction.
In our study change in the bishop score after 12 hour and 24 hour was statistically significant between both the groups.
Improvement in mean bishop score is more for group 2 as compared to group 1, Also the time taken for cervical ripening was found more in group 1 patients.
Maximum number of the patients in both the groups delivered vaginally.
The common reason for caesarean section in both the groups was fetal distress and non - progression of labour.
The incidence of meconium aspiration and fetal distress and uterine hyperstimulation is found more among oral misoprost solution group.
Hence, we concluded that tab mifepristone is as effective as misoprostol solution for cervical ripening and induction of labour and with less side effects but more time interval between induction and ripening.

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