ORIGINAL RESEARCH PAPER

Obstetrics & Gynaecology

COMPARATIVE ANALYSIS OF SAFETY, EFFICACY AND FETOMATERNAL OUTCOME OF INDUCTION OF LABOUR WITH MIFEPRISTONE VERSUS INTRACERVICAL DINOPROSTONE GEL.

KEY WORDS: Mifepristone, Dinoprostone, Induction of labour.

Raji Chinniah Associate Professor of Obstetrics and Gynaecology,Thanjavur Medical College, Thanjavur, Tamilnadu.

Saranya Arumugam* Post graduate in Dept of obstetrics and Gynaecology,Thanjavur Medical college *Corresponding Author

ABSTRACT

Objective: This study compares the efficacy of Mifepristone and Dinoprostone gel as a cervical ripening agent for induction of labour and to assess fetomaternal outcome.

Methods: It is a single blind prospective randomized comparative study.200 women with 41 weeks of gestation were selected. 100 women received 200mg oral mifepristone and 100 women received 0.5mg dinoprostone gel intracervically . Pre induction and Post induction Bishop's score 6 hours after dinoprostone and 24 hours after mifepristone or with onset of labour, whichever was earlier was assessed. When score was favourable oxytocin augmentation was started. Maternal and Neonatal outcome were observed

Results: Vaginal delivery occurred in 82% with Mifepristone and 73% with Dinoprostone. After induction with Mifepristone 71% women had cervical ripening as compared to 62% with Dinoprostone. NICU admissions were low with mifepristone.

Conclusion: Favourable bishops score occurred in mifepristone group

INTRODUCTION

Induction of labour is indicated when the benefits of early delivery are greater than the risks of continuing the pregnancy (1). There are several methods of labour induction, including administration of prostaglandins, oxytocin or mechanical methods (2). A successful induction is primarily depends on the pre-induction Bishop's scoring of the cervix. When the cervix is favourable the usual method of induction is amniotomy and oxytocin, whereas with an unfavourable cervix intracervical prostaglandins are commonly used (3).Dinoprostone is a synthetic analogue of ProstaglandinE2 (PGE2). It acts mainly on the cervix due to its collagenolytic property and stimulates labour and delivery. Mifepristone is also called as RU (RousselUclaf) - 486.It is 19 norsteroid with potent competitive anti progesterone activity, results in softening of cervix and increase the senstivity to prostaglandins (4).Various studies conducted on induction of labour in live term pregnancies with mifepristone in doses of 200-400 mg has shown to improve cervical ripening and rates of spontaneous labour with no apparent maternal or fetal side effects(5). Induction of labour is one of the most common interventions practiced in modern obstetrics. Overall, throughout the world, up to 20 per cent of women have labour induced by one method or the other [6]. Augmentation is the process of stimulation of uterine contractions that are already present but found to be inadequate [7].

Aims and objectives:

To compare the efficacy of Mifepristone and Dinoprostone as a cervical ripening agent for induction of labour, To study improvement in Bishop's score, Need for oxytocin in augmentation of labour or not, To study induction delivery interval, modes of delivery and Neonatal Intensive Care Unit admissions (NICU).

Materials and methods :

The study was conducted in the Department of OG Thanjavur Medical College Hospital, during the period of August 2016 to July 2017. 200 women with uncomplicated prolonged pregnancies admitted in labour ward or through antenatal OPD were selected for study

Inclusion criteria:

- Uncomplicated prolonged pregnancies (41 completed weeks) with
- Adequate liquor
- Reactive NST
- No cephalopelvic Disproportion
- Pre induction Bishop"s score <4

Exclusion criteria:

- Previous caesarean section,
- Malpresentation,
- Cephalopelvic disproportion,
- Premature rupture of membranes (PROM),
- Severe oligohydramnios,
- Intra Uterine Fetal Death,
- Intrauterine Growth Restriction
- Gestational Hypertension, Gestational Diabetes and other medical complications

It is a prospective randomized comparative Study.

After proper counselling and taking informed consent, detailed history and clinical examination was performed. The two groups were matched according to age, gravida, parity and gestational age. 200 women were divided into two groups, 100 women in group A received 200mg Mifepristone and 100 women in group B received 0.5 mg of intra cervical Dinoprostone gel. Pre induction Bishop's score was assessed . Post induction Bishop's score was assessed after 6 hours in dinoprostone group and after 24 hours in mifepristone group or with onset of labour, whichever was earlier. Oxytocin augmentation was started with unsatisfactory progress of labour. If cervix remains unfavourable , Dinoprostone gel was repeated at the interval of 6 hours for maximum of 3 doses. Caeserean section was done for unsatisfactory progress or fetal distress.

The efficacy was assessed by the following criteria:

Favourability of Bishop score at 24 hours
Duration of I, II, III stage of labour and blood loss
Drug administration to delivery interval
Mode of delivery
APGAR at 5 minute,
Neonatal complications and neonatal mortality
Maternal complications

Criteria for Success of Induction:

Patients who delivered vaginally including operative vaginal delivery

Criteria for Failure of induction:

Who has not entered active phase of labour or underwent caesarean section

Results:

Table 1: Baseline demographic characteristics of the subjects

S. No	Parameter	PGE2 group	Mifepristone Group	P value
1	Number (n)	100	100	
2	Age in years (Mean ± SD)	24.11± 3.16	24.1± 3.05	0.9 (NS)
3	Socioeconomic status n(%)			
	Class III	11 (11%)	6 (6%)	0.31 (NS)
	Class IV	69 (69%)	82 (82%)	0.047
	Class V	20 (%)	12 (12%)	0.176 (NS)
4	Primigravida/ Multigravida	70/30	70/30	0.999(NS)

Table 2: Age and parity distribution. between the PGE2 and mifepristone group

S. No	Age in years	PGE_2 group		Mifepristone Group	
		Primi	Multi	Primi	Multi
1	≤ 20	9 (9%)	1 (1%)	7 (7%)	1 (1%)
2	21 to 29	59 (59%)	26 (26%)	61 (61%)	24 (24%)
3	≥ 30	2 (2%)	3 (3%)	2 (2%)	5 (5%)
4	Total	70	30	70	30

Table 3: Preinduction Bishop score between PGE2 and Mifepristone groups

S. No	Bishop Score	PGE_2 group		Mifepristone Group	
		Primi	Multi	Primi	Multi
1	2	14 (14%)	19 (19%)	16 (16%)	18 (18%)
2	3	53 (53%)	8 (8%)	51(51%)	9(9%)
3	4	3(3%)	3(3%)	3 (3%)	3 (3%)

Bishop score < 4 in all women

Table 4: Favorability of Bishop score between PGE2 and Mifepristone groups.

S. No	Bishop Score	PGE_2 group		Mifepristone Group	
		Primi	Multi	Primi	Multi
1	<6	33 (33%)	5 (5%)	26 (26%)	3 (3%)
2	≥ 6	37 (37%)	25 (25%)	44 (44%)	27 (27%)

Table 5: Comparison of Bishop Score between the PGE2 and Mifepristone group at various time points

S. No	Bishop Score	PGE2 group	Mifepristone Group	P value
1	Bishop score at start	2.73 ± 0.56	2.72 ± 0.75	0.9 (NS)
2	Bishop score at augmentation	5.37 ± 1.21	5.68 ± 1.23	0.082 (NS)
3	Bishop score difference from start to augmentation time	3 ± 1.03	3.1 ± 1.05	0.4 (NS)

p-value were not significant

Table 6: Augmentation with oxytocin between PGE2 and Mifepristone group.

S. No	Augmentation with oxytocin	PGE2 group		Mifepristone Group	
		Primi	Multi	Primi	Multi
1	Required	56 (56%)	27 (27%)	68 (68%)	22 (22%)
2	Not required	14 (14%)	3 (3%)	2 (2%)	8 (8%)

Table 7: Comparison of duration of labour between the PGE2 and Mifepristone group at various stages

S. No	Duration of Labour	PGE2 group (n=100)	Mifepristone Group (n=100)	P value
1	Stage 1 (in hours)	10.26 ± 2.9	13.8 ± 3.9	<0.0001*
2	Stage 2 (in minutes)	24.33 ± 8.03	23.3± 8.5	0.312 (NS)
3	Stage 3 (in minutes)	5.48 ± 2.67	4.08 ± 1.27	0.006*
4	ID interval (in hours)	16.48 ± 5.8	21.33 ± 4.5	<0.0001*

Duration of II and III stage of labour were shorter in mifepristone. Induction to delivery interval shorter with PGE2 gel.

Table 8: Comparison of duration of labour between the PGE2 and Mifepristone group at various stages in primigravida

S. No	Duration of Labour	PGE2 group	Mifepristone Group	P value
1	Stage 1 (in hours)	10.84 ± 2.99 (n=47)	14.97 ± 3.56 (n=55)	<0.0001*
2	Stage 2 (in minutes)	26.38 ± 8.23 (n=47)	25.76 ± 8.85 (n=55)	0.717 (NS)
3	Stage 3 (in minutes)	5.5 ± 2.7 (n=60)	4.07 ± 1.32 (n=54)	0.0004*
4	ID interval (in hours)	17.24 ± 6.28 (n=47)	22.6 ± 4.14 (n=55)	<0.0001*

Primigravida and multipara both required oxytocin for vaginal delivery but more in Mifepristone group and in primigravida.

Table 9: Comparison of duration of labour between the PGE2 and Mifepristone group at various stages in Multigravida.

S. No	Duration of Labour	PGE_2 group	Mifepristone Group	P value
1	Stage 1 (in hours)	9.23 ± 2.51 (n=26)	11.63 ± 3.94 (n=27)	0.011*
2	Stage 2 (in minutes)	20.62 ± 6.15 (n=26)	18.48 ± 5.31 (n=27)	0.18 (NS)
3	Stage 3 (in minutes)	5.43 ± 2.65 (n=24)	4.09 ± 1.2 (n=26)	0.02*
4	ID interval (in hours)	15.12 ± 2.15 (n=26)	18.74 ± 4.3 (n=27)	0.005*

Total duration is more in Mifepristone group

Table 10: Mode of delivery between PGE2 and Mifepristone groups.

S. No	Mode of delivery	PGE_2 group (n=100)		Mifepristone Group (n=100)	
		Primi	Multi	Primi	Multi
1	Labour naturale	44 (44%)	26 (26%)	53 (53%)	27 (27%)
2	Instrumental delivery	3(3%)		2(2%)	
3	LSCS (Fetal Distress)	12 (12%)	2 (2%)	7 (7%)	1 (1%)
4	LSCS (Failed Induction)	11(11%)	2 (2%)	8 (8%)	2 (2%)

Vaginal delivery is more in Mifepristone group.

Table 11. Comparison of blood loss between the PGE2 and mifepristone groups

S. No	Group name	Mean	Standard deviation	SEM	P value
1	PGE2 group (in ml)	268.5	201.7	20.17	0.0006 (Mann Whitney Test)
2	Mifepristone group (in ml)	198.5	153.1	15.31	

P value:0.0006(significant), Mean blood loss in mifepristone group was less

Table 12.Comparison of neonatal complications between PGE2 and mifepristone group.

S. No	Complication/ Indicators	PGE_2 group (n=100)		Mifepristone Group (n=100)	
		Primi	Multi	Primi	Multi
1	Respiratory distress	8 (8%)	2 (2%)	5(5%)	1 (1%)
2	Meconium aspiration syndrome	6(6%)	1(1%)	4(4%)	1(1%)
3	Transient tachypnea of newborn	2 (2%)	0	0	0
4	Average Apgar at 1 minute	4.41 ± 0.82	4.8 ± 0.61	4.8 ± 0.69	4.76 ± 0.7

5	Average apgar at 5 minutes	6.67 ± 0.51	6.9 ± 0.30	6.97 ± 0.53	7.1 ± 0.54
6	NICU admission	19/70 (27.14%)	3/30 (10%)	9/70 (12.85%)	3/30 (10%)

NICU admission was more in PGE2 gel than in mifepristone group.

But there was no neonatal mortality in both groups. APGAR score at 1minute and 5 minute were similar in both groups

Discussion:

Baseline characteristics like age, parity, period of gestation, indication for induction were comparable in both groups.

1.AGE:

In this study,61(61%) primi and 24(24%) multigravida were between the age group of 21-29years in mifepristone group; 59(59%)primi and 26(26%)multigravida were between the age group of 21-29years in PGE2 gel group accounting for 85% in the age group of 21-29years in both groups . This study correlates with randomized controlled trial conducted by Wing et al (8)of Southern California, Los Angels, Oct 2000 in which 88% of the patients were in the age group of 21-30years.

In this study the mean age in mifepristone group is 24.1years which is also comparable with Kanan Yelikar study(9),J obstet gynaecol India.2015, where the mean age in study group is 22.98years.

2.GRAVIDITY:

Both primi(70%) and multigravida(30%) were included in the study. In this aspect our study correlates with studies done by Giacalone et al(10), Department of Obstetrics and Gynaecology, Hospital Arnaud de Villeneuve, University of Montepetlier,Oct 1998.

3.TREATMENT SCHEDULE:

In this study mifepristone given as 200mg single dose orally and observation period of 24 hours similar to the Wing DA et al(8) , Elliot et al(11) study and Kanan Yelikar(9) in which mifepristone were compared with placebo whereas PGE2 gel in this study.

4.Preinduction Bishop"s score:

In our study, Pre induction Bishop"s score was less than 4 in both groups which is comparable with study done by Elliot et al(11) in which Bishops score of less than 4 were included. In our study, mean Pre induction Bishop"s score was 2.72 which is comparable with Kanan Yelikar study(9), where mean bishop"s score was 2.02.

5.FAVOURABILITY OF BISHOP'S SCORE AT AUGMENTATION:

In our study, favourable Bishop score of 6 or more at augmentation was seen in 62% in primigravida and 90% in multigravida which was consistent with Frydman et al (4) study, Giacalone et al (10)study, Wing DA et al (8)study and Elliot et al study(11).

In our study the mean Bishop's score at the end of 24 hours in mifepristone group is 5.68 which is comparable with Kanan Yelikar study(9) where it is 5.04.

6.OXYTOCIN AUGMENTATION:

In our study,in the mifepristone group among 68 primigravida who required oxytocin, 53 delivered by labour natural. In PGE2 gel group 56 primigravida required oxytocin, 44 delivered by labour natural . In mifepristone group, 8 multipara not required oxytocin, 6 delivered by labour natural, in PGE2 gel, 3 multipara not required oxytocin, 3 delivered by labour natural. In this aspect, our study correlates with the study done by Wing DA et al (8),2002 in which patient who delivers vaginally needed oxytocin for augmentation when mifepristone had been given.

7.DURATION OF FIRST AND SECOND STAGE OF LABOUR:

In this study, the mean duration of first stage and second stage in primi was 10.84 hours &26.38minutes in PGE2 gel and 14.97 hours &25.76 minutes in Mifepristone group repectively.In multipara, the mean duration of first stage and second stage is 9.23 hours &20.62 minutes in PGE2 gel and 11.63 hours & 18.48 minutes in mifepristone group repectively.These results are consistent with the normal WHO STANDARDS.

8.INDUCTION AND DELIVERY INTERVAL:

In this study, mean induction delivery interval in primi and muti in PGE2 gel was17.24 hours and 15.12 hours respectively, in mifepristone group,in primi and multi was 22.6 hours and 18.74hours.
Parity influenced the likelihood of vaginal delivery.

In this study the mean induction delivery interval in Mifepristone group was 21.33 +/- 4 hours which is comparatively less than the the randomized controlled trial conducted by Wing et al, in which mean induction delivery interval was 26.8+/-11 hours.

In this study 60 (60%) women 37% primigravida and 23% multigravida delivered vaginally within 24 hours and totally 82 (28%) women 55% primigravida and 27% multigravida delivered vaginally within 48 hours which was consistent with Wing DA et al (8) study.

9.MODE OF DELIVERY:

In this study vaginal delivery rate was 82% in Mifepristone group (55% primigravida and 27% multigraavida) the results were consistent with studies by Giacalone et al (10) and Wing DA et al except Suh et al (12) study where the vaginal delivery is only 22.58%.

10.OUTCOME OF INDUCTION:

In this study, successful vaginal delivery occured in 82% of Mifepristone group which was consistent with 87.5 % success rate in Wing DA et al (8) study and 80.5% in Giacalone et al (10) study.

LSCS rate was 18% with mifepristone group among which 8% is for Fetal distress and in this aspect our study is consistent with Wing DA et al (8) study.

Our study is comparable with James P Neilson study(Cochrane Database Syst Rev 2009) (15) which concluded that Mifepristone treated women were less likely to undergo cesarean section.

In a study conducted by VidyaGaikwad et al (13) rate of successful IOL or vaginal delivery was 84% with mifepristone and 56% with dinoprostone.In their study ShanithaFathima et al (14)demonstrated significant efficacy of mifepristone for cervical ripening and induction of spontaneous labor after drug administration as more women had favorable Bishop's scores at the end of 48hr.

11.INTRAPARTUM COMPLICATIONS:

In this study intrapartum complications like hypertonus, tachysystole or hyperstimulation were not encountered, which was consistent with Wing DA et al (8) study.

This is in contrast to study conducted by Giacalone et al (10), Department of Obstetrics and Gynaecology, University of Montpellier, July 2001 in which Mifepristone treated group had higher rates of uterine hyperstimulation and tachysystole.

A total of 11% that is 9% primigravida and 2%multigravida had FHR abnormalities in our study which is consistent with study conducted by Wing et al (8) in which abnormal FHR pattern were found in 18% of the study group.

12.MATERNAL COMPLICATIONS:

In this study,none of our study population had major

complications

A total of 10% study population had minor complications like nausea,vomiting, abdominal cramps in mifepristone group which is consistent with the study conducted by Stenlund et al, Karolinska Hospital, Stocholm, Oct 1999.

13.NEONATAL COMPLICATIONS:

Meconium passage was encountered in 4% and NICU admission was 22.85% in mifepristone group & meconium passage was 7% and NICU admission was 33.74% in PGE2gel group.. APGAR score at 1minute & 5 minute were similar in both groups. But there was no neonatal mortality in both groups.

Conclusion:

This study reveals that oral mifepristone is very safe and an effective drug for preinduction cervical ripening. It has an added advantage of ease of administration, better patient compliance and acceptance, shorter duration of II, III stages of labour, less blood loss with an overall success rate of 82%. The drug has no untoward side effects on uterine contraction and no major maternal complications. This drug has safe neonatal outcome.

ACKNOWLEDGEMENT

I gratefully acknowledge and express my sincere thanks to the Dean ,TMCH, Thanjavur for allowing me to do this study and utilize the institutional facilities . I would like to thank all medical and para medical staff who has helped me in completing this study. A special thanks to all patients who willingly co-operated and participated in this study. Thanks to all my colleagues and friends who gave constant encouragement . My co-author Dr.A.Saranya read and approved the final manuscript.

Funding-No Funding Sources
Conflict Of Interest-None Declared
Ethical Approval-The Study Was Approved By The Institutional Ethics Committee.

REFERENCES

[1]. Arulkumaran S. Induction of labour. In: Arjun G,Penna L.The Management of Labour. 3rd ed:University Press,2011.p 368
[2]. S Petrou, SE Taher, G Abangma, O Eddama, P Bennett. Cost- effectiveness analysis of prostaglandin E2 gel for the induction of labour at term. BJOG 2011; 118: 726-734.
[3]. 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. 2001; 629-635.
[4]. FrydmanR,Lelaidier C, Baton-Saint-Mleux C, Fernandez H, Vial M,Bourget P. Labor induction in women at term with mifepristone (RU 486): a double-blind, randomized, placebo-controlled study. Obstet Gynecol. 1992 Dec; 80(6):972-5.
[5]. Clark K., Ji, H., Feltovich, H., Janowski, J., Carroll, C., Chien, E.K., Am J ObstetGynecol 2006, 194, 1391-1398
[6] The Management of Labour, 3rd edition, Chapter 23. Induction of labour; P.368.
[7] DC Dutta. Text book of Obstetrics.6th edition. New Delhi: New Central Book Agency; 2000. P.98.
(8). Wing DA et al, Mifepristione for pre induction cervical ripening beyond 41 weeks gestation: a randomized controlled trial, Obstet Gynecol 200 Oct;96 (4) : 543 – 8.
(9). Yellikar K, Deshpande S, Deshpande R, Lone D. Safety and efficacy of oral mifepristone in preinduction cervical ripening and induction of labor in prolonged pregnancy. J ObstetGynecol India. 2015; 65(4):221-5.
(10). Giacalone PL et al, Cervical ripening with Mifepristone before labour induction: a randomized study, Obstet Gynecol 1998 oct;92 4pt 1;487- 92.
(11). Elliot et al, The effects of Mifepristone on cervical ripening and labour induction in primigravida, Obtet Gynecol 1998 Nov; 92 (5) : 804 – 9.
(12).SuH etal, Mifepristone for induction of labour, Zhonghua Fu Chan Ke Za Zhe 1996 Nov;31 (11) : 676 – 80.
[13]. GaikwadVidya, Mittal Bilsi, MangalPuri. Comparative Analysis of Safety,Efficacy and FetomaternalOutcome ofInduction of Labour with Mifepristone versus IntracervicalDinoprostone Gel.RJPBCS.2014; 5(2):611.
[14]. FathimaShanitha, Nayak S.R, RaoBharathi, Praveena Gandhi, ShameemV.P.A. Mifepristone in the induction of labour at term.Int J Pharm Biomed Res 2013, 4(3), 164-166. [
(15). Cochrane library, category 7.1.2 mifepristone obstetrics and gynaecology mifepristone for induction of labour 5.8.2009.