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RESEARCH ARTICLE

A STUDY ON EFFICACY AND SAFETY OF ORAL MEFIPROSTONE FOR CERVICAL RIPENING AND INDUCTION OF LABOUR AND ITS OUTCOME IN PRIMIGRAVIDA

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Abstract

Cervical ripening is important prerequisite for induction of labour, induction is indicated when it is advantageous to mother and fetus. Successful induction of labour decreases caesarean rate. Induction of labor is a most common obstetric intervention. Commonly used drugs for induction of labor are prostaglandin analogues such as dinoprostone (PGE2) and misoprostol. Mifepristone/RU (486), a new class of drug is used for inducing labour in late pregnancy by antagonizing progesterone, thus increasing uterine contractility and by increasing the sensitivity of the uterus to the actions of prostaglandins.
OBJECTIVES:- To study the efficacy of Mifepristone in priming the cervix or inducing labor in 24 hours in term pregnancy in primigravida.To study the improvement in bishop score.To study maternal and foetal outcome.
METHODOLOGY:- Total 50 women at term pregnancy, where pregnancy can be continued for another 24 hours with bishop score 3 or less were selected.Tablet Mifepristone 200 mg was given orally at admission after assessing BISHOP score and monitored. Bishop score was assessed at 24 hours. In women who did not enter labor spontaneously other modes of induction was done.
RESULTS:- There is significant and progressive improvement in bishop score at 24hr, the Mean bishop score at 24 hr is 7.04.Pre induction cervical ripening increases rate of vaginal delivery in mifepristone administered group by 64%, significant increase in spontaneous delivery rate 24%, seen among mifepristone administered group and decrease •in caesarean section rate seen in mifepristone administered group. Mean induction to delivery interval was significantly decreased after cervical ripening with mifepristone.There was no significant adverse effect seen on mother and newborn compared to control group.
INTERPRETATION AND CONCLUSION: Cervicalripening with mifeprist one prior to induction of labour at term improves bishop score and decreases rate of failed induction and cesarean section rate, with good neonatal outcome.

Introduction:-

Induction of labour is an important process in which labour process is induced in order to reduce the risk to mother or fetus. The primary aim is to achieve effective and safe method of delivery with good fetal and maternal outcome. Effective methods of Induction was introduced into obstetric practice in 1780, initially it was practiced for only high risk cases, since 20th century induction began to be used in low risk cases[1]

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Labour induction in unfavorable cervix is a difficult and lengthy procedure, causing trouble for both mother and obstetrician. So when labour induction is performed "favourable cervix is fundamental to a good outcome". Many studies on induction of labour have revealed that unfavourable cervix leads to failed induction and hence increase in caesarean section rate,when termination of pregnancy is necessary and cervical ripening has not occurred, this natural process has to be accelerated. Successful cervical ripening prior to labour induction continues to remain a challenge for obstetricians, Research in pre induction cervical ripening helped in the development of various methods to ripen the cervix prior to induction[2]

The primary methods of induction of labour are mechanical and pharmacological. Cervical ripening agents are utilized primarily when the Bishop score is unfavourable. Pharmacological forms of IOL include synthetic prostaglandins and synthetic oxytocin. Prostaglandins are used for cervical ripening. Misoprostol, prostaglandin El (PGEI), and dinoprostone, prostaglandin E2 (PGE2), are used in various doses and routes of administration[3]

Prostaglandin analogues have several disadvantages, Misoprostol has the disadvantage of hyperstimulation, meconium stained liquor, fetal distress, increase chance of uterine rupture and more admission to NICU unit and Dinoprostone also has disadvantages like the need for refrigeration and higher cost, these disadvantages have put us in the search for newer methods of Pre induction cervical ripening[4].

Fall in progesterone levels in term is an important factor responsible for spontaneous onset of labour hence antiprogesterone discovery have made labour induction much easier, Mifepristone RU486 is a steroid compound that binds to progesterone receptor and it antagonizes progesterone activity leading to onset of labour,Mifepristone increases the sensitivity of myometrium to uterotonics . It blocks the progesterone receptors present in decidua and it stimulates prostaglandin release, it stimulates the release of nitric oxide by the expression of nitric oxide synthase in cervical cells of women. This is one of the mechanisms by which mifepristone initiates cervical ripening[5]

The number of studies have demonstrated efficacy of mifepristone for cervical ripening, and its beneficial outcome on fetus and mother and decrease in need of other uterotonics for labour induction and augmentation[6]

Study done by Oleg R Baev et al. shown that mifepristone was efficient cervical ripening agent and labour inducing agent in full term pregnancy and there were no significant difference in maternal and neonatal outcome. another study by Hampangana et al in 2009 have shown that Mifepristone significantly improves the cervical ripening and increases sensitivity of the uterus to prostaglandins and initiates the labour and significantly decreases the requirement of oxytocin for augmentation of labour and prostaglandins for labour induction . In this context the present study is undertaken to demonstrate the safety and efficacy of oral mifepristone on cervical ripening prior to induction of labour at term pregnancy and its safety of fetal and maternal outcome[7]

Methodology:-

Source of data: Pregnant women with singleton term pregnancy, with cephalic presentation with gestational age between 37-42 week, admitted to the antenatal ward in department of Obstetrics and Gynaecology, Basaveshwar Teaching and General Hospital and Sangameshwar Teaching and General Hospital. Kalaburagi in whom pregnancy can be prolonged up to 24 hours,after an approval from the institution ethical committee and written informed consent from the pregnant women

1. Study design: A prospective interventional study.
2. Study setting: The study was conducted in Department of Obstetrics andGynecology, Basaveshwar Teaching and General Hospital and Sangameshwar Teaching and General Hospital. Kalaburagi.
3. Study period: 18 months (1 March 2021 till August 31 2022)
4. Inclusion criteria:

• Singleton pregnancy with cephalic presentation with no contraindications for vaginal delivery
• Gestational age of 37 weeks to 42 completed weeks, having term scan
• BISHOP SCORE</-5
• Intrauterine fetal demise
• Mild pregnancy induced hypertension
• Mild intrauterine growth restriction
• Mild oligohy dramnios Post dated pregnancy

5. EXCLUSION CRITERIA:

• Previous scar on uterus
• Patients with gestational diabetes, antepartum heamorrhage, coagulopathy, cardiac disease, anemia
• Premature rupture of membranes
• polyhy dramnios

Method of Data Collection

The study was approved by Ethics committee of MRMC, Pregnant women with term pregnancy admitted in Antenatal ward at Basaveshwara hospital and Sangameshwara hospital are the main study subjects and were enrolled for the study after they gave informed consent for the procedure ,case record is used to record maternal age, socioeconomic status, gestational age at admission, obstetric history, past history, personal and family history is taken, General physical examination was done , per abdomen examination was done , Per vaginal examination was done to assess bishop score and pelvic adequacy.

INVESTIGATION Complete haemogram

Urine routinue

• Blood grouping and Rh typing

• Non Stress Test

Obstetrics scan with BPP

• Serology

• Blood sugars

• Bleeding time and clotting time

• After examination and Analysing investigations ,case is subjected to study by giving Tablet Mifepristone 200mg orally ,0 ' hour is the time, when women were administered tablet mifepristone, and reassessed BISHOP score at 24 hours

MONITORING:

• Monitoring was done for maternal vitals, uterine contraction and fetal heart sounds every 2nd hourly, NST for fetal well being every 4th hourly and bleeding per vagina or leak per vagina is monitored , patient is shifted them to labor room and Bishop score was reassessed at 24 hr ,ifbishop score is less than 6 they were induced with PGE2 gel and augmentation with oxytocin was done if required, if signs of fetal distress , those women were taken for emergency caesarean section. If patients gets adequate contractions within 24 hours then those patients are shifted to labor room and bishop score is assessed anytime, if BISHOP score is favorable with labour is augmented with oxytocin as required.

• PGE2 GEL was used as mode of induction of labour depending on bishop score, oxytocin is used for labour augmentation if required, and Partogram was maintained for all women and used to record all the clinical events during the course of labour

The Safety and Efficacy was assessed by the following criteria:

• Favorability of Bishop score at 24 hrs

• Au Duration of induction to delivery interval

• Mode of delivery

• Rate of failed induction

• Indication for caesarean section

• Apgar score at 0 and 5 min

• Neonatal complication and nicu admission

• Maternal complication,

• Adverse effect of drug augmentation with oxytocin

Statistical analysis: Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions.

Chi-square test or Fischer's exact test (for 2x2 tables only) was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two quantitative variables Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs

P value (Probability that the result is true) of <0.05 was considered statistical tests.

TABLES:

Table l : Distribution of cases according to gestational age (n=50)

Gestational age	Number of patients	Percentage
37+ to 38 + weeks	□10	20%
39 to 40 weeks	□16	32%
40+ to 42 weeks	24	□48%

Table 1 showing 48% of patients are of with 40 to 42 weeks gestational age , 32 % with 39 to 40 weeks gestational age and 20 % that is 10 patients of 37 + to 38+ weeks gestational age

Table 2: Distribution of cases according to bishop score at admission (0 hrs) with respect to gestational age and mean (n=50)

Gestational age	BISHOP SCORE AT O hours		Mean
	0-3	4-5	
37+ to 38 + weeks	05□5		3.80
39 to 40 weeks	13□3		3.06
40+ to 42 weeks	19□5		3.17

Table 2 : Describing out of 50 patients 19 patients with gestational age 40 to 42 weeks was having 0 to 3 bishop score with mean3.17.13 patients of 39 to 40 weeks of gestational age was having mean value of 3.06 and 5 patients with 37 to 38 weeks gestational age was having mean value of 3.80

Table 3 : Distribution of cases according to bishop score at 12 hrs with respect to gestational age (n=12)

Gestational age	BISHOP SCORE AT 12 hours		Mean
	<10	>10	
37+ to 38 + weeks	1	2	3.0
39 to 40 weeks	0	2	1.0
40+ to 42 weeks	4	3	5.43

Table 3 showing bishop score less than 10 and more than 10 at 12 hours in that 37 + to 38+ weeks gestational age is 1 and 2 patients with mean value 3.0 and 4 and 3 patients with gestational age of 40+ to 42 weeks with mean value 5.43

Table 4 : Distribution of cases according bishop score at 24 hrs with respect to gestational age (n=38)

Gestational age	BISHOP SCORE AT 12 hours			Mean
	<6	7-9	>10	
37+ to 38 + weeks	3	2	2	8.29
39 to 40 weeks	3	8	3	5.86
40+ to 42 weeks	6	11	0	7.59

This table is explaining about the bishop score at 24 hours that is 37 + to 38+ weeks gestational age was having less than 6 in 3 patients 7 to 9 score in 2 patients and more than 10 in 2 patients with mean value 8.29. 40 to 42 weeks gestational age with bishop score 6 , 11 , 0 with mean value of 7.59 .

Table 5: Distribution of cases according to BISHOP score at 0 hour and Outcome (n= 50)

BISHOP SCORE 0 HOUR	TYPE OF DELIVERY		TOTAL	FISHER EXACT (p value)
	NVD	LSCS		
0-3	1 33.33%	2 66.66%	3 100%	0.34
4-5	29 61.70%	18 38.30%	47 100%	0.69

Table 5 showing 1 NVD and 2 LSCS with bishop score 0-3 with p value of 0.34 and with 4 -5 bishop score 29 patient delivered normally and 18 patients underwent LSCS with p value of 0.69.

Table 6: Distribution of cases according to BISHOP score at 24 hour and outcome (n=38)

BISHOP SCORE 24 HOUR	TYPE OF DELIVERY		TOTAL	CHI SQUARE VALUE
	NVD	LSCS		
<6	4 33.33%	8 36.66%	12 100%	3.81 (0.14)
7-8	6 50%	6 50%	12 100%	
>9	10 71.42%	4 28.57%	14 100%	

In this table total 12 patients was having bishop score of less than 6 in that 4 delivered normally and 8 underwent LSCS with CHI SQUARE value of 3.81 . total 12 patients were having bishop score 7 to 8 , 6 delivered normally and 6 underwent section and 14 patients had bishop score more than 9 in that 10 NVD and 4 underwent LSCS .

Table 7: Distribution of cases according to APGAR score among neonates admission (n= 50)

APGAR SCORE AMONG NEONATES	NICU ADMISSION		TOTAL	CHI SQUARE VALUE
	YES	NO		
AT 1 MIN(<5)	4 36.33%	7 63.66%	11 100%	0.0002 (>0.99)
AT 5 MIN(<9)	4 28.57%	10 71.42%	14 100%	

Table 7 describing apgar score among neonates total 11 neonate had less than 5 at 1 minute in which 4 admitted in NICU , total 14 neonate had less than 9 Apgar score at 5 min in which 4 admitted in NICU (CHI SQUARE value >0.99)

Table8: Distribution of cases according to induction to delivery interval

induction delivery interval	Number of deliveries	Mean
12-24 hrs	12	16.4
24-36 hrs	20	23.16

12 patients induction and delivery interval was 12 – 24 hours with mean value of 16.4 and 20 patients delivered with 24 – 36 hours with mean value 23.16

Table 9: Distribution of cases according to induction to delivery interval and its outcome

PGE2GEL	induction delivery interval		Outcome		
	12-24 hrs	24-36 hrs	VD	LSCS	VACUUM ASSISTED DELIVERY
YES	0	6	4	2	0
NO	12	16	28	0	3
FISHER EXACT VALUE (P VALUE)	0.271		Not estimatable		>0.999

In this table 6 patients delivered with interval of 24 to 36 hours in that 4 NVD and 2 LSCS , 12 patient with 12-24 hours and 16 was having 24 to 36 hours induction and delivery interval in which 28 patients delivered normally (3 vaccume assisted delivery)

Table 10: Distribution of cases according to NICU admission and their indication

Gestational age	NICU ADMISSION		MSAF	
	YES	NO	YES	NO
37+ to 38 + weeks	0	10	3	7
39 to 40 weeks	3	13	7	9
40+ to 42 weeks	1	23	5	19
FISHER EXACT VALUE (P VALUE)	0.236		0.316	

Table 10 showing distribution of cases according to nicu admission , in this gestational age of 39 + to 40 weeks was having 7 MSAF in which 3 neonates admitted in nicu .

Results:-

There is significant and progressive improvement in bishop score at 24hr, the Mean bishop score at 24 hr is 7.04.
Preinduction cervical ripening increases rate of vaginal delivery in mifepristone administered group by 64%, significant increase in spontaneous delivery rate 24%, seen among mifepristone administered group and decrease in caeserean section rate seen in mifepristone administered group. Mean induction to delivery interval was significantly decreased after cervical ripening with mifepristone.There was no significant adverse effect seen on mother and newborn compared to control group.

Discussion:-

The commencement of labour is still a mysterious process is well known,that progesterone is necessary for the maintenance and continuation of pregnancy, fall in progesterone causes various mechanisms to initiate labour , an antiprogesterone blocks the progesterone receptor and initiates the labour ,Mifepristone a progesterone antagonist is a steroid compound which causes cervical ripening and sensitise uterine myometrium to prostaglandins .
Initially this medication has been used along with misoprostol for elective abortions and medical termination of pregnancy during the first trimester, later many studies found its significant beneficial effect on term pregnancy, Results of these studies have demonstrated that mifepristone improves bishop score, helps in successful induction.
In our study we included 50 women who are fulfilling the inclusion criteria

Improvement In Bishop Score

In our study we assess BISHOP score at 24 hours after giving tablet Mifepristone 200mg orally.
We found that there is significant and progressive improvement in bishop score at 24hr, the Mean bishop score at 24 hr is 7.04.

Table 11

Studies	Improvement in BISHOP score
Uma H Chourasia et al	96%
HampanganaD,NeiIson J et al	92%
Oleg et al	92%
Present study	97&

The present study is significantly comparable with Uma H Chourasia et al study and Hampangana D, Neilson JP et al study, that there is significant improvement in Bishop score at 24 hours,
In our study there were mean improvement in bishop score and spontaneous onset of labour within 24 hours among 12 patients.
This result is comparable with Oleg et al in 2017 demonstrated that more mifepristone treated women had labour within 24 , 48 and 72hr from enrolment.

Vaginal Delivery
Our study demonstrated that about 64% (32) women had full term vaginal delivery , P Value 0.17, The difference was not statistically significant ,mifepristone as pre induction cervical ripening agent decreases the rate of failed induction and increases the vaginal delivery rate .
• Spontaneous labour
Our study demonstrated significant number of women entered spontaneous labour within 24 hours with only 25%(3)cases requiring augmentation with oxytocin, delivered without any maternal complicatons.

The resent study is comparable with following studies

Study	Percentage
liott CL et al	12 %
Uma Chourasia et al	10%
Oleg et al	16%
Present study	25%

These studies require reference number
CAESAREAN DELIVERY
In Our study 36% (18)women underwent caeserean section for various indications . Outcome is not statistically significant

Indication For Caesarean Delivery
In our study 36% (18)women had caeserean section for Various reasons like , In 830/0(15) women the indication was fetal distress ,
16.5%(1) had Non reassuring fetal heart rate after induction with PGE2gel after 24 hours of oral Mifepristone 200 mg, these indications caserean section was done.

Mode Of Induction
In our study we used PGE2 (dinoprostone) gel for induction ,study demonstrated about 12%(6) women required PGE2gel for induction 28(87.5%) patients did not need induction with PGE2gel , among them 12(37%) patient progressed within 24 hours. Pre induction cervical ripening with mifepristone decreases need ofprostaglandin use for induction.
Our study results in delivery outcome were comparable with study done by,
• Yelikar et aldemonstrated that less requirement of prostaglandins requirement for induction of labour in mifepristone treated group compared to placebo.
• RuthujaAthawale et al demonstrated that less requirement of misoprostol in mifepristone group compared to placebo .

Study	Percentage
Yelikar et al	12 %
RuthujaAthawale et al	14%
Present study	12%

Augmentation With Oxytocin
Our study demonstrated that 18% (9) cases require augunentation with oxytocin, This shows that use of mifepristone for preinduction cervical ripening decreases the need of oxytocin for augmentation but p value is not statistically significant.
Our study results are similar to study done by

• HanpanagoudaD,Neilson JP 7 (May 2009) in their study of Inifepristone for induction of labor compared to placebo , demonstrated less need of augmentation with oxytocin in mifepristone treated women compared to placebo.
• Uma H Chourasia et al in 2019 demonstrated that oral tablet mifepristone 200mg at term pregnancy for cervical ripening demonstrated significant reduction in the need of augmentation with oxytocin in study group (51 %) compared to control group (76%).

Study	Percentage
HanpanagoudaD,Neilson JP et al	8
Uma Chourasia et al	16
RuthujaAthawale et al	14
Present study	18

Mean Induction To Delivery Interval
The mean induction to delivery was 23.4 hours
Preinduction cervical ripening using mifepristone prior to induction significantly decreases induction to delivery interval
• Uma Chourasia et al demonstrated that shorter Mean induction delivery interval was noticed in study group compared in control group mefiprostone decreases the mean induction to delivery interval
• Oleg r et al demonstrated that induction to delivery interval was shorter in mefiprostone group.

Study	need for induction
Uma Chourasia et al	Reduced
Oleg et al	Reduced
Wing D et al	Reduced
Present study	Reduced

Fetal Outcome
Apgar Score
Our study shows there was no statistically significant difference found with respect to APGAR score, About 36.6% had bishop score less than 7 at I min .p value is >0.99 , hence there is no statistical significant difference found with respect to APGAR score .
Nicu Admission
Study demonstrated 8.% (4) had NICU admission with indications being respiratory distress secondary to meconium aspiration(2) and birth asphyxia (2).
Maternal complications
In our study there were no maternal complications among study cases.

Conclusion:-

Ripening the cervix prior to induction ,leads to successful induction, Based on preceding research , oral mifepristone is very safe ,effective, and simple method of cervical ripening ,it also has the added advantage of ease of administration.
Our study demonstrates that mifepristone is more effective in improving the bishop score at 24 hr i, reducing the risk of caesarean section being performed for failed induction, allowing us to avoid unnecessary caesarean sections and decreases the maternal morbidity associated with it. Also Pre induction cervical ripening with mifepristone decreases the requirement of prostaglandins and oxytocin for labour induction and augmentation respectively.
There was no significant adverse effect to the mother and the newborn, Majority of women who received mifepristone RU- 486, have improvement in cervical scoring and spontaneous labour and lesser operative delivery , however a large multicentric trial may be required to ensure the safety of mifepristone on the preinduction cervical scoring improvement .

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