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Role of Mifepristone in Induction of Labor and Effect on Fetomaternal Outcome in Term Pregnancy

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Abstract: ***Background: Mifepristone is a steroidal compound that has antiglucocorticoid and antiprogesterone properties. It increases uterine activity, causes cervical effacement and dilatation, needed for the delivery. An attempt is made in the present study to assess the efficacy of single dose of oral mifepristone in third trimester as cervical ripening for induction of labor, fetomaternal outcome in term pregnancy and to know the side-effects of oral mifepristone. Method: 100 women with term pregnancy (37-40 weeks) and Bishop score <6 were recruited, and allocated into two groups. Women who received Tab. Mifepristone 200 mg orally were assigned in Study Group (n = 50) and who received placebo orally were assigned in Control Group (n = 50) At the end of 24 h, change in the Bishop's score was assessed and Tab. Misoprostol 25 µg was administered intravaginally every 4 h, maximum 6 doses for induction/augmentation of labor. Analysis regarding safety and efficacy of the drug was done with regards to maternal and perinatal outcome. Result: 64% of the patients were observed with improved Bishop's score. Induction delivery interval was shorter in the study group and noteworthy feature is 46% patients did not require even a single dose of Misoprostol after cervical ripening with Mifepristone suggesting that only Mifepristone may be only drug required in future for induction. Among the babies, 12% in the control group required baby unit admission as compared to 04% in the study group. Conclusion : In the present study, the women who were induced with mifepristone 200 mg per orally showed drastic improvement in cervical score within 24-48 hours and decreased the cesarean rate in the study group and amount of dose requirement of augmentation of labor with Misoprostol or Oxytocin, lesser NICU admission and maternal complication.***

Keywords: Mifepristone, Induction of labor, Bishop' score

1. Introduction

Induction of labor is the non-spontaneous initiation of uterine contractions, prior to their spontaneous onset leading to progressive effacement and dilatation of cervix and delivery of the baby [1]. Sometimes it is essential to induce labor when the risk to the mother or fetus with pregnancy continuation outweighs the risk that is involved with intervention [2].

According to ACOG 2009- Goal of Induction of labor is to achieve vaginal delivery by stimulating uterine contraction before spontaneous onset of labor [3]. A ripe or favorable cervix is a prerequisite for successful vaginal birth. So, cervical ripening should be assessed before any regimen is selected.

Tablet Mifepristone is also called as RU (Roussel Uclaf) - 486.It is 19 – nor steroid with potent competitive anti-progesterone and significant anti-glucocorticoid activity. Mifepristone is used as a pretreatment to prime the cervix adequately.

Mifepristone produced a modification in the consistency of the cervix with a statistical improvement in cervical calibration. Mifepristone causes blockage of progesterone receptors and inhibits the activity of progesterone at cellular level with potent antiprogestogenic, antiglucocorticoid and a weak anti androgenic action and causes cervical ripening effect.

Mifepristone has minimal effects on uterine contractility and increase the sensitivity to prostaglandins and convert the quiet pregnant uterus into organ of spontaneous activity. Hapangama and Neilson [4] in Cochrane collaboration published in 2009 are of the opinion that there is insufficient information available from clinical trials to support the use of mifepristone to induce labor.

Aim

Effect of mifepristone in cervical ripening for induction of labor

Objectives:

1) To study the effectiveness and safety of mifepristone in cervical ripening for induction of labor in term pregnancy with good maternal and fetal outcome that favor in reduce rate of cesarean section.
2) To study the effect of mifepristone on fetomaternal outcome in study group and compare it with a control group of same size.
3) To observe the improvement in cervical score in study group and compare it with the control group
4) Necessity for augmentation of labor.

2. Materials and Methods

It is a hospital based prospective randomized comparative study conducted on 100 Women who met the inclusion criteria were enrolled in study & done in the department of obstetrics and gynecology of Nalanda Medical College and

Hospital from JAN 2019 to november2020. Written informed consent taken from patients.

Inclusion Criteria

1) Term (37-40wks) pregnancy
2) Cephalic presentation
3) Intact membrane
4) Adequate pelvis

Exclusion Criteria

1) Previous Lower Segment Cesarean Section (LSCS).
2) Intra Uterine Growth Restriction (IUGR).
3) Oligohydramnios.
4) Malpresentation.
5) Associated medical disorder (hypertension, diabetes mellitus, heart disease, anemia, thyroid, epilepsy, asthma).
6) Premature Rupture of Membrane (PROM).
7) Hypersensitivity to Prostaglandins & Mifepristone.
8) Placental insufficiency.
9) Cephalo Pelvic Disproportion.

At admission, a detailed history was taken regarding relevant medical, surgical and obstetrical information. Gestational age was evaluated by last menstrual period and with ultrasound.

- Informed consent was obtained; Obstetric examination was done to reassure lie, gestation age, and fetal heart rate. Per vaginal examination was done to assess Bishop's score and to assess pelvis.
- The participant who received Tab. mifepristone 200 mg was assigned in Study Group (n = 50) and who received placebo were assigned in Control Group (n = 50).
- In all women, at the end of 24 h, Bishop's score was assessed and if it was <6 than Tab. Misoprostol 25 µg was administered vaginally every 4 h, (maximum 6 doses—150 µg) till the Bishop score became ≥6 or the women entered in active labor.
- When the women entered in active labor, ARM was done and if required Oxytocin drip was started for augmentation of labor, but not earlier than 4 h after the last dose of Misoprostol.
- If fetal heart rate pattern remained normal with satisfactory progress of labor, these women were kept for vaginal delivery.
- If progress was unsatisfactory or variable fetal heart pattern, these women underwent cesarean section. The efficacy of mifepristone was assessed on the basis of improvement in Bishop's Score, mean dose of Misoprostol required, and duration of induction to active phase of labor.
- The results observed were subjected to statistical analysis by appropriate test and a 'p'value of < 0.05 was considered as significant

3. Observation

The detailed analysis was carried out for both the groups regarding the.

1) Efficacy of drugs in terms of:
   - Change in Bishop's score.
   - No. of doses of T. Misoprostol required.
   - Number of failure of induction of labor.
2) Maternal outcome studied in terms of:
   - Mode of delivery.
   - Incidence of cesarean delivery.
   - Adverse effect of drug after intake.
3) Fetal outcome studied in terms of:
   - APGAR score.
   - Needed admission in neonatal intensive care unit (NICU)

Table 1: Modified Bishop's score.

	0	1	2	3
Dilatation(cm)	1	1-2	2-4	>4
Effacement(cm)	4	2-4	1-2	>1
Station(cm)	3	-2	-1/0	+1/+2
Consistency	Firm	Average	Soft	
Position	Posterior	Central	Anterior	

4. Result

Table 2: Distribution of cases according to age

Age Groups (in years)	No. of cases in Control Group		No. of cases in Study Group	
	N=50	%	N=50	%
<20	2	4%	3	6%
21-25	35	70%	32	64%
26-30	8	16%	9	18%
31-35	3	6%	4	8%
>35	2	4%	2	4%
Mean age with SD	24.5±4.13		24.78±3.92	

Majority of women enrolled in both the group were from same age group (21-25); only up to 8% of patients were elderly (>30yrs) in both the groups.

Table 3: Distribution of patients according to gestational age in weeks

Gestational Age in weeks Percentage	Control Group		Study Group	
	N=50	%	N=50	%
37-38	16	32%	18	36%
39-40	32	64%	30	60%
>40	02	04%	02	04%

Majority of the patients were between 39-40 wks (64% in control group and 60% in study group) which shows almost equal distribution in both the group.

Table 4: Bishop's score in both the groups

Bishop Score	Control Group		Study Group	
	N=50	%	N=50	%
≤3	17	34%	21	42%
≥3	33	66%	29	58%
Mean Bishop Score	4.02±1.09		3.84±1.03	
After 24 hours				
≤3	21	42%	01	02%
4-8	24	48%	17	34%
≥8	05	10%	32	64%
Mean dose required	3.84±1.03		8.54±2.06	

It was observed that there was significant improvement in the Bishop's score after administrating Mifepristone to the patients; mean Bishop's score 24hrs after mifepristone were 8.54±2.06. This improvement was even proven statistically significant with p value = <0.0001

Table 5: Subsequent dosages of Misoprostol in both the groups

Dose of Misoprostol	Control Group (Group 1)		Study Group (Group 2)	
	N=50	%	N=50	%
0	0	0	23	46%
1	7	14%	19	38%
2	29	58%	05	10%
3	14	28%	03	06%
Mean dose required	2.14±0.63		1.4±0.8	

Repeated dose of Misoprostol required in control grp was observed to be higher than study group as shown in table. Association between requirement of subsequent dose of Misoprostol in both the groups proven statistically significant with p value= <0.0001.

Noteworthy feature is 46% patients did not require even a single dose of Misoprostol after cervical ripening with Mifepristone suggesting that only Mifepristone may be only drug required in future for induction

Table 6: Mode of delivery in both the groups

Mode of delivery	control Group		Study Group	
	N=50	Percentage	N=50	Percentage
VD	39	78%	43	86%
LSCS	08	16%	06	12%
Instrumental VD	03	06%	01	02%

Most of the pts delivered vaginaly (78%) in Group 1 and (86%) Group 2. It was observed that there is 4% reduction in LSCS in combination group, but is not significant statistically.

Table 7: apgar score and NICU admission in relation to study and control group

Apgar Score <7	Control Group		Study Group	
	≤ 7	≥7	≤7	≥7
1 minute	17(34%)	33(66%)	08(16%)	42(84%)
5 minute	44(88%)	44(88%)	02(04%)	48(96%)
Admission to NICU				
Yes	06(12%)		02(04%)	
No	44(88%)		48(96%)	
Total	50(100%)		50(100%)	

Out of all neonates born, 66% of the neonates had Apgar score ≥7 at 1 min in control Group & 84% in study Group. Only 12% neonate had APGAR <7 at 5 min in control Group and 4% in study Group which is statistically insignificant.

Maternal complications in relation to study and control group. Cases of failed induction were omitted in calculation of complications. The majority did not have any major complications in either of the group like sepsis, pyrexia and PPH. Just few minor genital tract injuries but the difference was not significant statistically in the study group.

5. Discussion

Research continues to invent and modify doses of different drugs for induction of labor. The female sex hormone, progesterone stops the uterus contracting during pregnancy. Drugs such as mifepristone have been used to stop the action of this hormone, either to induce labor or to allow the pregnancy to be terminated.

In this present study we found significant improvement in Bishops score in study group. This suggests that tab. Mifepristone has got dual role as cervical ripening agent and also as labor inducing agent.

Byrne [5] demonstrated that mifepristone exposure and induced labor were associated with increase in cortisol levels and significant elevation in cortisol levels was observed within 18 h of exposure to mifepristone.

Wing DA et al [7] studied showed induction–delivery interval less with use of T. Mifepristone than in placebo subjects.

Dharani K Hapangama, James P Neilson in (2009) [6] studied for Mifepristone for induction of labor. To determine the effects of mifepristone for third trimester cervical ripening or induction of labor. Women receiving mifepristone were less likely to undergo a caesarean section as a result of failure to induce labor (RR 0.40, 95% CI 0.20 to 0.80). There is insufficient evidence to support a particular dose but a single dose of 200 mg mifepristone appears to be the lowest effective dose for cervical ripening (increased likelihood of cervical ripening at 72 hours (RR 2.13, 95% CI 1.15 to 3.97)

Rutuja Athawale, Neema Acharya, S. Samal, C. Hariharan (2013)[8] studied to portrait the beneficial of mifepristone induction of labor. 100 patients (term) were included, after their informed consent. Patients were categorized by BISHOP SCORE at the beginning of induction for comparison of BS, mode of delivery, induction delivery interval (IDI). After induction with mifepristone for cervical ripening in study group 76% patient who had cervical score 8 within 24 hours, whereas in control group 2% female's cervical score was>8. Among the babies, 44% in the control group required baby unit admission as compared to 36% in the study group

Kanan Avinash Yelikar, Sonali Deshpande, Rinku Deshpande, Dipak Lone (2015)[11]studied Safety and Efficacy of Oral Mifepristone in Pre-induction Cervical Ripening and Induction of Labor in Prolonged Pregnancy. This is a single blind randomized control trial. 100 women with prolonged pregnancy beyond 40 weeks and Bishop Score <6 were recruited, and randomly allocated into two groups. . Mean induction to delivery interval was 1,907 ± 368.4 min for Study Group versus 2,079 ± 231.6 min for Control Group. The improvement in mean Bishop Score was 5.0408 ± 1.90 for Study Group compared with 3.26 ± 1.15 was for Control Group after 24 h. Mean dose of Misoprostol in Study Group was 40 ± 27.2, while the same in Control Group was 52 ± 19.46. Eight (16 %) women in Study Group and two (4 %) women in Control Group delivered vaginally within 24 h without any need of augmentation.

Oleg R Baev, Valentina P Rumyantseva (2017) studied to evaluate efficacy and safety of mifepristone use for cervical ripening and induction of labor versus expectant management in full-term pregnancy. : After 48h from

enrollment mean gain in Bishop score was 2.58±1.33 in the induction group and 1.15±0.97 in the expectant group (<0.001). Failed management rate was 5.41% and 2.67%, respectively. Significantly more mifepristone treated women had labor within 24, 48 and 72h from enrollment (RR 15.20 CI 95% 2.06-112.18; RR 6.08 CI 95% 2.73-13.57; RR 2.14 CI 95% 1.04-4.42) (p<0.05). Enrollment-induction to delivery interval was significantly shorter in mifepristone group: 2.69±2.06 vs. 3.77±1.86days (p<0.001).

Lata G., Rana N., Mittal R., Kumar S. (2018) studied Mifepristone for cervical ripening and induction of labor. The study was aimed to evaluate the efficacy of Mifepristone for induction of labor and in improving the Bishop score at term. The study also aimed to assess induction delivery interval and maternal and fetal outcomes with Mifepristone.

6. Conclusion

From my study I conclude Mifepristone (RU 486) is a safe and efficient agent for cervical ripening and for initiation of labor when given 24h before labor induction.

It appears to reduce the need for augmentation with Misoprostol.

Mifepristone provides an interesting new alternative for induction of labor at term and can be considered by the obstetricians as a simple and safe method of labor induction.

Mifepristone, a progesterone antagonist, is known to cause softening and dilation of the human pregnant cervix and increase in uterine activity. Mifepristone combined with or without augmentation is a safe, efficient, economical and convenient induction agent for initiation of labor in women at term with no increase in adverse events on the fetus or mother.

7. Ethical Approval

The study was approved by the Institutional ethics committee

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