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Obstetrics

Study of Use of Single Dose of Oral Mifepristone in Induction of Labour

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Abstract: Mifepristone is a steroidal compound that has antiglucocorticoid and antiprogesterone properties. It increases uterine activity, causes cervical effacement and dilatation, needed for the delivery. The objectives of this study were to know the efficacy of single dose of oral mifepristone in third trimester cervical ripening for induction of labour and to know the side-effects of oral mifepristone. Sample size of 100 was divided into two groups of 50 each, cases and control. Pre induction Bishop's score was evaluated. 50 patients in the cases group were given a single dose of tablet mifepristone 200 mg orally and were reviewed after 24 hours for cervical changes and Bishop's score was calculated. Control group was not given any drug. Final outcome was evaluated. It was found that in the cases group, 32 patients had preinduction Bishop's score of <4, 14 patients had a score between 4 to 7 and 4 patients had a score of >7. The corresponding values in the control group were, 24, 19 and 07, respectively. Postinduction calculation of Bishop's score revealed that, in the cases group, 17 patients had a score of <4, 21 patients had a score between 4 to 7 and 12 patients had a score of >7, whereas in the control group, the corresponding number of patients in each group were 22, 20 and 8, respectively. The mean induction-delivery interval was 33 hours in the cases group and 41 hours in the control group. 15 patients out of 50 in the cases group and 27 patients out of 50 in the control group needed additional induction for the delivery**.** Mifepristone is an effective induction agent for cervical ripening and initiation of labor when given 24 hours prior with reduced need for prostaglandins and can be administered safely with no increase in adverse effects on the fetus or mother.
Keywords: Bishop's score, Induction of labor, Mifepristone, Single dose.

INTRODUCTION

One of the most common indications for labour induction is prolonged pregnancy as it is associated with the increased risk to the fetus, including increased perinatal mortality rate, low 5-min Apgar scores, dysmaturity syndrome, and increased risk of death within the first year of life. A ripe or favorable cervix is a prerequisite for successful vaginal birth. So, cervical ripening should be assessed before any regimen is selected. Successful labor induction is clearly related to the state of the cervix. Women with an unfavorable cervix, who have not experienced cervical ripening phase before labor, present the greatest challenge with regard to labor induction [1]. Induction of labour is carried out in over 20% of pregnancies on an average in developed countries [2]. It is indicated to be advantageous for both the mother & baby and decreases perinatal morbidity and mortality [3, 4].

Methods of Induction of Labour

- Medical: Use of Mifepristone[5], Prostaglandin[6], Synthetic oxytocin preparations, natural induction, Relaxin[7]
- Mechanical: 'Membrane sweep'/ 'stretch and sweep'
- Surgical: Artificial rupture of the membranes.

A new class of pharmacological agents (antiprogestins) has been developed to antagonize the action of progesterone. Of these, mifepristone (also called RU 486) is best known. It is a 19 nor-steroid which has greater affinity for progesterone receptors than does progesterone itself. It blocks the action of progesterone at the cellular level. Key metabolites also have high affinity to progesterone receptors. Mifepristone has a potential, as a method of inducing labour in late pregnancy through its actions in antagonizing progesterone, thus increasing uterine contractility and by increasing the sensitivity of the uterus to the actions of prostaglandins [8].

Mifepristone is a steroidal compound that has anti glucocorticoid and anti progesterone properties. It increases uterine activity and causes cervical effacement and dilatation. The pharmacokinetics of mifepristone is characterized by rapid absorption and a long half-life of 25–30 hours [9]. Mifepristone as an anti progesterone agent used orally for induction of labour (IOL) is still under investigations. According to Cochrane systematic review use of mifepristone for IOL has limited evidence in support but it is better than placebo to reduce CS rates. Mifepristone is not an oxytocic so it is not associated with over/hyper stimulation of uterus hence there is not increase the incidence of rupture uterus [10].

Mifepristone now has an established role in termination of pregnancy during the early first, and the second trimesters [11]. Animal studies have suggested that mifepristone may also have a role in inducing labor in late pregnancy. Hapangama and Neilson, in Cochrane collaboration published in 2009, concluded that there is insufficient information available from clinical trials to support the use of mifepristone to induce labor. Keeping this in mind, the present study was undertaken to find out the safety and efficacy of mifepristone for pre-induction cervical ripening and labor induction in women with prolonged pregnancy [12]. Various studies conducted on induction of labor in live term pregnancies with mifepristone in doses of 200-400 mg have shown an improvement in cervical ripeness and increased rates of spontaneous labor with no serious maternal or fetal side effects [13].

AIMS AND OBJECTIVES

The aim of the study was to know the efficacy and safety of single dose of oral mifepristone in third trimester cervical ripening for induction of labour.

The objectives were-

- To study the effect of mifepristone in study group and control group.
- To observe the improvement in cervical score as compared to control group.
- To view the final outcome of the study group and compare it with the control group.
- To study the occurrence of maternal and neonatal complications in study and compare it to control group.

MATERIALS AND METHODS

This was a prospective interventional study carried out in DVVPF's Medical college and Hospital, Ahmednagar, over a period of six months i.e. from September, 2017 to February, 2018, after getting ethical clearance. 100 patients were admitted for induction of labor and randomly divided into two groups of 50 each, cases and control. Pre induction modified Bishop's score was evaluated. 50 patients in the cases group were given a single dose of tablet mifepristone 200 mg orally and were reviewed after 24 hours for cervical changes and Bishop's score was calculated. Control group was not given any drug. Final outcome was evaluated.

Inclusion criteria

- Term gestation (>37 weeks)
- Prolonged pregnancy
- Oligohydramnios
- Singleton gestation
- Cephalic presentation
- Reactive FHR pattern
- Intact membranes
- Intrauterine foetal death

Exclusion criteria

- Foetal distress
- Antepartum hemorrhage
- Previous cesarean section

RESULTS

Total of 100 patients were selected for the study who were admitted for induction of labor. It was found that the mean age in the cases group was 22.5 and in the control group were 24.5. The mean parity in the cases group and control group were para 2 and the mean gestational age in the cases group was 38 weeks and in the control group was 37 weeks. (Table no 1)

Tabl-1: Distribution according to mean age, parity and gestatational age

CHARACTERISTICS	CASE	CONTROL	STATISTICAL ANALYSIS
Mean age	22.5 years	24.5 years	NS
Mean parity	Para 2	Para 2	NS
Mean gestational age	37 weeks	38 weeks	NS

The preinduction and postinduction Bishop's score was evaluated. It was found that in the cases group, 32 patients had preinduction Bishop's score of <4 14 patients had a score between 4 to 7 and 4 patients had a score of >7. The corresponding values in the control group were, 24, 19 and 07, respectively. (Table no 2)

Table-2: Distribution according to preinduction Bishop's score

PREINDUCTION BISHOPS SCORE	CASE	CONTROL
<4	32	24
4-7	14	19
>7	04	07

Postinduction calculation of Bishop's score revealed that, in the cases group, 17 patients had a score of <4, 21 patients had a score between 4 to 7 and 12 patients had a score of >7, whereas in the control group, the corresponding number of patients in each group were 22, 20 and 8, respectively. (Table no 3)

Table-3: Distribution according to postinduction Bishop's score

POSTINDUCTION BISHOPS SCORE	CASE	CONTROL
<4	17	22
4-7	21	20
>7	12	08

The mean preinduction Bishop's score and postinduction Bishop's score in the cases group was 2.76 +/- 0.15 and 6.13 +/- 0.71, respectively. In the control group, the mean preinduction Bishop's score and postinduction Bishop's score was 3.14 +/-0.27 and 3.42 +/- 0.52, respectively. (Table no 4)

Table-4: Distribution according to mean Bishop's score

MEAN BISHOPS SCORE	CASE	CONTROL	STATISTICAL ANALYSIS
Preinduction	2.76 +/- 0.15	3.14 +/- 0.27	0.350
Postinduction	6.13 +/- 0.71	3.42 +/- 0.52	0.001
Mean Rise in Bishop's score	3.37 +/- 0.56	0.28+/- 0.25	-

In the cases group, 9 patients out of 50 required LSCS whereas 41 patients delivered vaginally, of which 7 delivered within 24 hours of induction and 34 delivered after 24 hours.

In the control group, 29 patients out of 50 required LSCS whereas 21 patients delivered vaginally, of which 3 delivered within 24 hours of induction and 18 delivered after 24 hours. (Table no 5)

Table-5: Distribution according to the mode of delivery

MODE OF DELIVERY		CASE	CONTROL	STATISTICAL ANALYSIS
LSCS		09	29	0.62
Vaginal	<24 Hours	07	03	0.05
	>24 Hours	34	18	0.74

In the cases group, additional augmentation was needed in the form of Dinoprostone gel or oxytocin in 15 cases, whereas augmentation was needed in 27 patients in control group. Uterine hyperstimulation was not observed in any of the patients. (Table no 6)

Table-6: Distribution according to maternal complications

MATERNAL COMPLICATIONS	CASE	CONTROL
Need for augmentation	15	27
Uterine Hyperstimulation	00	00

Meconium stained liquor was present in 8 patients in the casesgroup and 10 patients in the control group. APGAR score of the baby was low in 6 patients in the cases group and 7 patients of the control group. Also, it was observed that 3 babies in the cases group and 5 babies in the control group needed NICU admission. Stillbirth or neonatal death was not observed in any of the patients (Table no 7).

Table-7: Distribution according to neonatal outcome

NEONATAL OUTCOME	CASE	CONTROL
Meconium Stained Liquor	08	10
Low APGAR Score	06	07
NICU Admission	03	05
Neonatal Mortality	00	00

The mean induction-delivery interval was 33 hours in the cases group and 41 hours in the control group. 15 patients out of 50 in the cases group and 27 patients out of 50 in the control group needed additional induction for the delivery. (Table no 8)

Table-8: Distribution according to the final outcome

FINAL OUTCOME	CASE	CONTROL
Mean Induction-Delivery Interval	33 Hours	41 Hours
Need for additional induction	15	27

DISCUSSION

Hapangama D, Neilson JP [14], in their study of 'Mifepristone for induction of labour' found that mifepristone treated women were more likely to have a favourable cervix at the end of 48 hours. There was less need of augmentation with oxytocin, less chance to undergo caesarean section or have failure of induction. Abnormal fetal heart rate patterns were not common. The above mentioned points were observed in our study also.

Li L, Gao W, Chen S in their study at Beijing Tian Tan Hospital, Capital University of Medicine, on labour induction in women at term with mifepristone and misoprostol observed that, in women who were given mifepristone, the cervical length was 1-3 cm shorter and Bishop's score was 4-5 higher than that before treatment [15]. Similar findings were present in our study also.

In our study 100 patients were included who were admitted for induction of labor. It was found that in the cases group, 32 patients had preinduction Bishop's score of <4, 14 patients had a score between 4 to 7 and 4 patients had a score of >7. The corresponding values in the control group were, 24, 19 and 07, respectively. (Table no 2) Postinduction calculation of Bishop's score revealed that, in the cases group, 17 patients had a score of <4, 21 patients had a score between 4 to 7 and 12 patients had a score of >7, whereas in the control group, the corresponding number of patients in each group were 22, 20 and 8, respectively. (Table no 3). In the cases group, 9 patients out of 50 required LSCS whereas 41 patients delivered vaginally. The mean induction-delivery interval was 33 hours in the cases group and 41 hours in the control group. 15 patients out of 50 in the cases group and 27 patients out of 50 in the control group needed additional induction for the delivery. (Table no 8).

The need of oxytocin requirement for augmentation of labour is very minimum so there is very less chances of scar dehiscence and rupture uterus [16]. Mifepristone initiate the labour naturally, causes cervical ripening by releasing NO, and promotes uterine contractions by forming gap junctions and increasing influx of calcium. It also increases the prostaglandins release without acting as a direct uterotonic[17].

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

Hapangama and Neilson[19] reported that 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, i.e. increased likelihood of cervical ripening at 72 hours. In our study statistically significant improvement was observed in mean Bishop's score in cases group at the end of 24 hours. This improvement in score indirectly indicates the withdrawal of progesterone support.

Wing *et al*. [20] demonstrated more women had favorable Bishop's score after 24 hours of mifepristone than placebo and Atawale *et al*. [21] and Fathima *et al*. [22] also noted the significant change in Bishop's score with the use of oral mifepristone. Wing *et al*. also reported the reduced need of prostaglandin/oxytocin in mifepristone group.

In our study also, there was a significant change in the Bishop's score after 24 hours. Hapangama and Neilson reported that there was no difference in the neonatal outcome [24]. Similar findings were seen in our study as well.

CONCLUSION

Mifepristone, a progesterone antagonist, is known to cause softening and dilatation of the human pregnant cervix and an increase in uterine activity. It is theoretically attractive for use as an adjunct in cervical priming and labour induction. Mifepristone is associated with an increase in the chance of vaginal delivery within 24-48 hours with decreasing incidence of LSCS. Hence mifepristone combined with or without augmentation is a safe, efficient, economical and convenient induction agent for initiation of labor in women at term. Therefore, this may justify future trials comparing mifepristone with the routine cervical ripening agents currently in use. Blood transfusion requirement is also minimum and anaesthesia related complications are avoided very effectively, as overall rates of LSCS are less.

Mifepristone is an effective induction agent for cervical ripening and initiation of labor when given

24 hours prior in prolonged pregnancy with reduced need for prostaglandins and can be administered safely with no increase in adverse effects on the fetus or mother. It has an added advantage of ease of administration, better patient compliance and acceptance, reduced oxytocin requirement, shorter duration of 2nd and less blood loss with an overall good success rate. The drug has no untoward side effects on uterine contraction and no major maternal complications.

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