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Original Research Article

Efficacy and safety of oral mifepristone on preinduction cervical ripening at term pregnancy prospective randomized control study

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ABSTRACT

Background: 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. Beyond term pregnancy there will be placental insufficiency, it leads to complications such as oligohydramnios thereby cord compression, birth asphyxia, increased incidence of operative delivery. Induction at term pregnancy has the potential to improve the neonatal outcomes. Aim was to study the efficacy and safety of oral mifepristone on cervical ripening prior to induction of labor at term pregnancy and to compare the feto maternal outcome with control group.
Methods: Total 112 pregnant women at term pregnancy, where pregnancy can be continued for another 48 hours with bishop score 4 or less were selected. Sample was equally divided into study group (56 women) to receive 200mg mifepristone and control Group group (56 women) to receive placebo orally. Bishop score was assessed at 24hours and 48hours. In women who did not enter labor spontaneously other modes of induction was done.
Results: There is significant improvement in bishop score at 24 hr and 48hr in study group p value 0.001, 80.35% women in study group and 50 % women in control group delivered vaginally. 33.9% women of study group and 10.7% women of control group delivered spontaneously. Requirement of PGE2 gel and oxytocin was significantly lesser in study group, there was no significant adverse effect seen on mother and newborn compared to control group.
Conclusions: Cervical ripening with mifepristone prior to induction of labour at term improves bishop score and decreases rate of failed induction and cesarean section rate, with good neonatal outcome.

Keywords: Bishop score, Favourable cervix, Mifepristone

INTRODUCTION

The desire to relieve mother from life threatening complications by continuing pregnancy made Induction of labour an important milestone in obstetrics. 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] There are various effective indications for inducing labour in present obstetrics, prolonged pregnancy is one of the common indication for induction of labour.

Around 20-30% women require induction of labour for some maternal or fetal indication and it is also true that induction fails in 20% of induced pregnancies.[2] Labour induction in unfavourable 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.[3]

Studies demonstrated that prostaglandin analogues such as dinoprostone gel and misoprostol are commonly used for

cervical ripening, but many of them demonstrated that 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 gel also has disadvantages like the need for refrigeration and higher cost.[4,5] These disadvantages have put us in the search for newer methods of Pre induction cervical ripening. One of the important events in spontaneous onset of labor is fall in level of progesterone at term, antiprogesterone discovery have made labor induction much easier.

Mifepristone RU486 is a steroid compound that binds to progesterone receptor and it antagonizes progesterone activity 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.[6]

This antiprogestin has been studied extensively for preinduction cervical ripening at term pregnancy and many studies have proven its efficacy and safety to onset of labour and it increases the sensitivity of myometrium to uterotonics.[7-10]

Aims were to study the efficacy and safety of oral mifepristone on cervical ripening prior to induction of labour at term pregnancies, to observe the improvement in Bishop score in study group compared to control group and to compare the fetal and maternal outcome in study group and control group.

METHODS

It is prospective randomized control study. Pregnant women with singleton term pregnancy with gestational age between 37-42 weeks, admitted to the antenatal ward in Department of Obstetrics and Gynecology, Cheluvamba Hospital attached to MMCRI, Mysore from January 2020 to June 2021.

Our study comprises total 112 pregnant women equally distributed in study 56 women group A treated with mifepristone 200mg orally and control group 56 women group B treated with placebo orally, then the women were reviewed for bishop score at 24hr and 48hr, and induction and augmentation of labour was done based upon improvement in bishop score.

Inclusion criteria

Inclusion criteria were the age group between 18-35 year, gestational age between 37-42 week, women willing to give informed consent, singleton live pregnancy with cephalic presentation, Bishop score 4 or less, and intact membrane with reassuring non stress test and in whom the labour induction was indicated and could be postponed for 48hrs included in the study. .

Exclusion criteria

Exclusion criteria were maternal factors including all patients with medical disorders complicating pregnancy, lower genital tract infection, hypersensitivity to prostaglandins, anaemia in pregnancy, uterine malformation, hepatic and adrenal dysfunction, renal desease, women with parity more than 4, and previous lscs. Fetal factors including appreciable macrosomia, low estimated fetal weight, IUGR, and malpresentation were excluded from this study.

RESULTS

Both mifepristone and placebo groups were comparable regarding maternal age, gestational age, parity and BMI. Figure 1 shows in study group there is progressive, significant improvement in bishop score at 24hr, 48hr.

Table 1: Improvement in bishop score after preinduction cervical ripening at 24hr and 48hr.

Time	Groups	Mean	SD	P value
0hrs	Study	2.23	0.914	0.174
	Control	1.96	1.144	
24hrs	Study	5.14	2.040	<0.001
	Control	3.70	2.272	
48hrs	Study	7.22	2.151	<0.001
	Control	4.58	2.398	

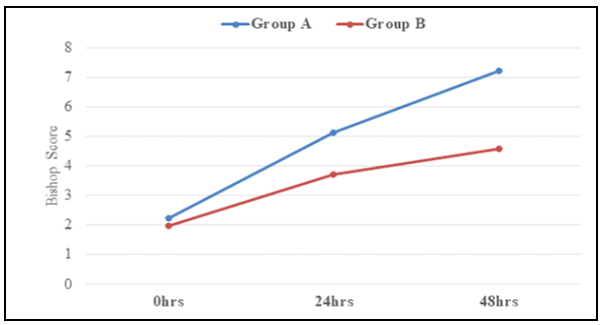

Figure 1: Comparison of mean bishop score at 0hr, 24hr, 48hr among two groups.

There was no statistically significant difference found between two groups with respect to mean Bishop score at 0hrs P value 0.174. There was a statistically significant difference found between two groups with respect to mean Bishop score at 24hrs and 48hrs, P value <0.001 (Table 1).

The 44.64% (25 women) in study group did not require induction compared to 25% (14 women) in control group, and the P value 0.010 there was statistically significant difference found between two groups with respect to mode of induction (Table 2).

Total 45 women in study group and 28 women in control group had FTVD, 9 women in study group and 26 women in control group had caesarean delivery , 2 women in each

group had vaccum assisted vaginal delivery, P value 0.002, there was statistically significant difference found between two groups with respect to mode of delivery. The number of caesarean section significantly reduced after cervical ripening by tablet mifepristone 200mg (Table 3).

Table 2: Distribution of subjects according to mode of induction among two groups.

Mode of induction	Study group	Control group
PGE2 GEL	19	35
	33.92%	62.5%
ARM	12	7
	21.42%	12.5%
No Induction	25	14
	44.64%	25%

Table 3: Mode of delivery in study and control group.

Mode of delivery	Study group	Control group
FTVD	45	28
	80.35%	50%
LSCS	9	26
	16.07%	46.42%
VAVD	2	2
	3.5%	3.5%

Table 4: Fetomaternal outcome.

NICU admission	Study group	Control group
No	51	47
	91.1%	83.9%
Yes	5	9
	8.9%	16.1%
Total	56	56

The 8.9% (5 babies) in study group and 16.1% (9 babies) in control group had NICU admission. There was no statistically significant difference found between two groups with respect to NICU admission, P value 0.620 (Table 4).

DISCUSSION

The commencement of labour is still a mysterious process it is well known ,that progesterone is necessary for the maintenance and continuation of pregnancy, fall in progesterone causes various mechanism to initiate labour, an anti-progesterone block progesterone receptor and initiates labour, mifepristone a progesterone antagonist ,a steroid compound which causes cervical ripening and sensitise uterine myometrium to prostaglandins. Initially this medication has been used along with misoprostol for elective abortion, but many studies found its significant beneficial effect on term pregnancy, results of these studies have demonstrated that mifepristone improves bishop score and helps in successful induction.

In our study, study population comprised of 112 pregnant women with equal number of women in the study Group (Group A) and control group (Group B). There were no significant statistical differences between Group A and Group B in demographics or medical or obstetrics history.

The mean Bishop score at time of inclusion (0 hr) in Group A is 2.25 and in Group B is 1.96 with no significant difference found between 2 groups, P value is 0.174. Hence both groups were comparable.

We found that there is significant and progressive improvement in bishop score, the mean bishop score at 24 hr, in Group A is 5.14 and 3.70 in group B with p value <0.001. We found that there is significant improvement in Bishop score at 48hr, the mean bishop score in Group A is 7.22 and 4.58 in Group B, there is 2.64 mean Bishop score improvement in Group A compared to Group B, with p value <0.001. Majority of studies too demonstrated significant improvement in bishop score.

Chourasia et al in 2019 in their study of 'mifepristone for preinduction cervical ripening compared to placebo demonstrated that oral tablet mifepristone 200mg was found to be an effective agent for cervical ripening prior to induction in women at term compared to placebo.[11] Successful ripening was more frequent in the study group (96%) as compared to control group (81%) .

Gill et al in 2007, in their study reported sufficient cervical ripening with 400mg of mifepristone within 48 hrs.[12]

Giacalone et al from France in May 2001, they used single dose of 400mg of mifepristone in 42 patients with 48hrs of observation period proved that mifepristone is effective for cervical ripening.[13]

This study demonstrated that there is significant improvement in spontaneous delivery rate in study group without any need of induction and augmentation, 19 women in Group A had spontaneous vaginal delivery compared to only 6 women in Group B with p value 0.003 and about 80.35% (45) women in study group and 50% (28) women in control group had full term vaginal delivery. P Value 0.002, there is gain of about 30.35% in vaginal delivery rate in Group A, faled induction rate was significantly less in study group. Mifepristone as pre induction cervical ripening agent decreases the rate of failed induction and increases the vaginal delivery rate.

In this study, 16.07% (9) women in Group A and 46.42% (26) women in Group B underwent caeserean section for various indications.

In this study, failed induction was one of the common indication for caeserean section due to failed induction. Only 3.6% (2) women underwent caeserean delivery in

study group, where as 23.2% (13) women in control group had caeserean delivery due to failed induction. This signifies mifepristone significantly decreases the rate of failed induction and decreases the caeserean delivery rate.

Hampangama D, Neilson JP (May 2009) in their study of mifepristone for induction of labour compared to placebo, demonstrated that mifepristone treated women were less likely to undergo caesarean section or failure of induction compared to placebo.[14]

Prospective study done by Mcgill et al United Kingdom showed that the rate of caesarean section was significantly lower among women induced with mifepristone alone compared to control group.[12]

The amount of PGE2 gel and oxytocin for induction and augmentation of labour is significantly reduced in mifepristone treated group. Our study demonstrated that 73.2% (41) women Group A and 39.3% (22) women in Group B did not require augmentation with oxytocin, 33.92% (19) women in Group A and 62.5% (35) women in Group B required PGE2 gel for induction. The need of PGE2 induction is significantly decreased in mifepristone treated group compared to placebo by 28.58%. Many studies have demonstrated ripening the cervix with mifepristone prior to induction decreases the need of prostaglandin agent for induction.[15-17]

The mean induction to delivery interval in Group A is 16.65hrs and in Group B is 19.72hrs. Mifepristone treated women induction to delivery interval is less compared to placebo by 3.07hrs (mean IDI), p value 0.017, which is statistically significant. Many studies demonstrated ripening cervix with mifepristone decreases mean induction to delivery interval.[10,18]

There was no statistically significant difference seen in fetal and maternal complications seen among 2 groups. Many studies have shown that mifepristone have no significant adverse effect on mother and newborn.[11,12]

Very few adverse effect such as meconium stained liquor, tachysystole and hyperstimulation syndrome was seen, there is no statistically significant difference found between two groups with respect to adverse effects in both groups, p value is 0.932.

CONCLUSION

Planned induction of labor plays a vital role in modern obstetrics. Over the years there is increase in caesarean section rates, one of the common indication is failed induction. 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 and 48hr, reducing the rate of caesarean delivery being performed for failed induction, allowing us to avoid unnecessary caesarean delivery 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 significant improvement in Bishop score 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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