

# EFFICACY STUDY OF MIFEPRISTONE IN PRE-INDUCTION CERVICAL RIPENING AND INDUCTION OF LABOUR

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## ABSTRACT

This study was carried out to see the safety and efficacy of mifepristone as pre-induction cervical ripening agent along with misoprostol in induction of labour. It was a study done from January to June 2020 in Department of Obstetrics and Gynecology, Nepal Medical College Teaching Hospital. Total 120 patients were included in this study. Out of which, 60 women were kept in test group who were induced by mifepristone and misoprostol and 60 women were kept in control group induced by misoprostol only. Patient characteristics, improvement of bishop score, maternal and neonatal outcome was recorded. Chi-square and T-Test were used to compare the result. Patient characteristics and the Bishop score at zero-hour of both the groups were similar. The mean bishop score 48 hours after use of mifepristone in test group was significantly increased in test group vs control group ( $P < 0.0001$ ). There were total 12(20%) patient who went in to labour with mifepristone only without the use of misoprostol. Total number of normal delivery was more ( $p$  value=0.003) and cesarean was less ( $p=0.013$ ) in test group than in control group. The instrumental delivery in both test and control group were same. The adverse effect and neonatal outcome was similar in both the regime. Thus mifepristone as pre-induction cervical ripening agent is a safe and efficient drug.

## KEYWORDS

Induction labour, mifepristone, misoprostol

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## INTRODUCTION

Induction of labour is initiation of labour by surgical or medical methods which aims at delivery of the baby. Its indications are post term pregnancy, intrauterine growth retardation, medical disorder such as diabetes, hypertensive disorder, premature rupture of membrane etc. It is carried out in over 20% of pregnancy on an average.<sup>1</sup> It is beneficial for both mother and baby when indicated. It reduce perinatal morbidity and mortality.<sup>2,3</sup> Methods of induction of labour are use of mifepristone,<sup>4</sup> prostaglandin,<sup>5,6</sup> oxytocin infusion,<sup>7</sup> mechanical, membrane sweeping and artificial rupture of membrane.

Mifepristone antagonize the action of progesterone at cellular level. It is characterized by rapid absorption, long half life of 25 to 30 hours.<sup>8</sup> At term pregnancy it increases the sensitivity of uterus to action of prostaglandin and produce cervical ripening. Mifepristone was approved by Food and Drug Administration in USA in 2002. Since then it had been use along with misoprostol for early pregnancy termination of pregnancy. It is also being used for induction of labour due its anti-progesterone effect.

Although mifepristone was being used as labour inducing agent, Hapangama and Neilson<sup>9</sup> in Cochrane collaboration published an article in 2009, saying that there is insufficient information available from clinical trials to support the use of mifepristone to induce labour. Since then, many studies have been done which confirms the efficacy and safety of mifepristone in pre-induction cervical ripening and induction of labour. Gaikward and her team<sup>10</sup> in 2014 conducted the study of use of mifepristone or dinoprostone for induction of labour. They found the rate successful induction of labour was 84% with mifepristone and 56% with dinoprostone. Yelikear and his group<sup>11</sup> also studied safety and efficacy of oral mifepristone in pre-induction cervical ripening and induction of labour in prolong pregnancy. They found that mifepristone had modest effect on cervical ripening when given 24 hours prior to labour induction and reduce the need for misoprostol.<sup>11</sup> Similar findings were found in many other studies.<sup>12-15</sup> It increases the sensitivity of the uterus to prostaglandins and facilitates labour.<sup>16</sup>

Misoprostol is a very effective drug for induction of labour but it is associated with hyper-stimulation of the uterus and fetal heart sound abnormalities which is dose related.<sup>17</sup> It is associated with complications such as uterine

rupture, fetal distress and intra uterine fetal death. Mifepristone when used for induction of labour at term produce little uterine contraction. This allows longer time of cervical maturation without altering maternal tolerance or fetal well being.<sup>17</sup> This study was carried out to see the safety and efficacy of mifepristone for cervical ripening and induction of labour.

## MATERIALS AND METHODS

This study was carried out from January to June 2020 at Department of Obstetrics and Gynecology, Nepal Medical College Teaching Hospital, Attarkehl, Gokarneswor-8, Kathmandu, Nepal. Total of 120 women were included in the study, of them 60 women were kept in test group in whom labor was induced by mifepristone and misoprostol and 60 women were kept in control group induced by misoprostol only.

The inclusion criteria were single term pregnancy (after 37 complete weeks till 41 weeks plus 6 days), both primigravida and multigravida of 18 to 40 years which require induction of labour such as prolong pregnancy, preeclampsia, intrauterine growth retardation, diabetes mellitus, gestational diabetes mellitus, cases with reassuring non stress test, intact membrane and bishop score less than 6. While, women with any contraindication to induction of labour and vaginal delivery such as twin pregnancy, premature rupture of labour, previous caesarean, antepartum hemorrhage, abnormal doppler study, estimated fetal weight more than 4 kg and patient requiring immediate delivery were excluded from the study.

The cases meeting inclusion criteria were explained about the study, and the need of admission 48 hours before the induction. Only those cases who willingly decided to be part of the research, were enrolled in the study. Prior to admission, informed written consent was taken from all the patients. Patients were given serial numbers. All odd number were placed in test group (mifepristone and misoprostol group) and all even number were be placed in control group (misoprostol group). The resident doctor was allowed to give the medication in view of safety of the patient. Sixty patients were given 200mg of mifepristone orally and 60 patients were given placebo. After 48 hours, all the patient underwent pelvic examination to see Bishop's score and induction or augmentation of labour was done according to Bishop's score. Modified Bishop's score was used for assessing the ripening of cervix. Induction of labour was done by 25mcg of misoprostol. Maximum of 2

doses was given 6 hours apart. Oxytocin drip was started after 24 hours of last misoprostol according to Bishop's score. Regular artificial rupture of membrane was carried out after 3 cm of cervical dilatation. The efficacy of mifepristone was assessed on the basis of improvement of Bishop's score, number of patient going to labour with mifepristone alone or with further use of misoprostol and oxytocin and duration of labour. Side effects to mifepristone and misoprostol were also noted. All the data was collected using a proforma, data entry and statistic analysis was done using SPSS version-16. Chi-square and T test was used for statistic analysis. P value <0.05 was taken as significant.

## RESULTS

Total 60 patients received mifepristone and misoprostol (test group) and 60 patients received placebo and misoprostol (control group) for induction of labour. Patient characteristics are given in Table 1. We can see

both the groups had similar characteristics. Mean age was (test group 25.83 years ±4.81) and (control group 25.70 years ±5.19) p=0.884. Mean gestation was 40.13±0.77 weeks in test group and 40.40±0.98weeks in control group p=0.100. Parity were also comparable in both groups with p=0.302. The maternal outcome is given in Table 2. We can see the Bishop's score at 0 hour of both the group is similar which is statistically not significant (P=0.448). The mean bishop score 48 hours after use of mifepristone in test group was significantly increased in test group vs control group. (4.80±1.35 vs 2.58±1.05) (P<0.0001). There were total 12 (20.0%) patient who went in to labour with mifepristone only without the use of misoprostol. As regard to maternal outcome total number of normal delivery was 43 (71.66%) in test group and 27 (45.0%) in control group with p value= 0.003 which is significantly more than control. The instrumental delivery in both test and control group were same. 3.33% vs 8.33% (p=0.436). Cesarean was significantly less in test group 25.00% vs 46.67% (p=0.013).

**Table 1: Patient characteristics**

Characteristics		Test (n=60)	Control (n=60)	t/z value	p- value
Age	Mean	25.83±4.81	25.70±5.19	0.146	0.884*
Gestation	Mean	40.13±0.77	40.40±0.98	1.66	0.100 *
Parity	Primi	35(58.33%)	38(63.33%)	3.059	0.302**
	Gravida 2	20(33.33%)	21(35.00%)		
	Gravida 3 or more	5(8.34%)	1(1.67%)		

\*Independent T- Test, \*\*Chi-Square Test

**Table 2: Maternal outcome**

Variables	Test (n=60)	Control (n=60)	t/z value	P value
Mean Bishop score in 0 hour	2.30±0.56	2.40±0.85	0.762	0.448
Mean Bishop score after 48 hours	4.80±1.35	2.58±1.05	10.051	>0.0001*
Normal delivery with mifepristone only	12 (10%)	0 (0.00)	11.204	0.001**
Total Normal Delivery	43 (71.66%)	27 (45.00%)	8.777	0.003**
Instrumental delivery	2 (1.7%)	5 (4.20%)	0.607	0.436**
Cesarean Section	15 (12.5%)	28 (23.30%)	6.125	0.013

\*Independent T- Test, \*\*Chi-Square Test

**Table 3: Safety of the drug regime**

Variables	Test	control	t/z value	P value
Adverse effect				
Meconium stain liquor	9 (15%)	16 (26.67%)	2.476	0.116**
Hyperstimulation	2 (3.33%)	5 (8.33%)	0.607	0.436**
Tachysystole	2 (3.33%)	5 (8.33%)	0.607	0.436**

\*Mann-Whitney U test, \*\*Chi -Square test

Table 4: Neonatal outcome

	Test (n=60)	Control (n=60)	Z value	P value
Healthy baby	52 (86.67%)	53 (88.33%)	0.076	0.783
Death	1 (1.67%)	4 (6.67%)	1.878	0.171
NICU admission	9 (15.00%)	9 (15%)	0.000	1.00

The adverse effects are given in Table 3 where both the regimes had similar outcome. Meconium stain liquor was similar in both the groups (P= 0.116). Also the cases of hyperstimulation was 3.33% vs 8.33% with p=0.436. There were 3.33% of tachysytole in test group and 8.33% in control group with p=0.436. The perinatal outcomes of both the groups were similar which is given in Table 4. The healthy babies in test and control group were 86.67% vs 88.33% with p=0.783, the neonatal intensive care unit (NICU) admission were equal 15.00% in both groups and neonatal death was more in control group although it was not statistically significant (1.67%) in test group and 4(6.67%) in control group (P=1.00). Among the neonatal death one baby in test group was due to congenital pneumonia and in control group 3 neonatal death was due to meconium aspiration syndrome and one was due to birth apnoea.

## DISCUSSION

Mifepristone (RU486) has specific high affinity to the progesterone receptor and thus compete with progesterone at level of their respective binding site.<sup>18</sup> As the result of the withdrawal of inhibitory effect of progesterone there is an increase in the synthesis of prostaglandins.<sup>19</sup> Sensitivity of myometrium to the contraction inducing activity of prostaglandins markedly increase after mifepristone administration<sup>20</sup> and labour often starts without additional inductors.

In this study, the efficacy of mifepristone as pre-induction cervical ripening agent was studied as compare with placebo. The Bishop's score of the mifepristone group was significantly improved after 48 hours as compare to control group with p<0.0001. Stenlund *et al*<sup>21</sup> also have reported ripened cervix in 79.2% women at the end of 48 hours with mifepristone as compared to 16% of women who received placebo. Yeliker *et al*,<sup>11</sup> Atawale *et al*<sup>12</sup> and Fathima *et al*<sup>22</sup> also noted significant improvement after the use of mifepristone. Whereas, Wing *et al*<sup>23</sup> demonstrated improve Bishop's score after 24 hours after the use of mifepristone, but it was not statistically significant. The number of normal delivery within 48 hours without use of

misoprostol was 12 (20.00%). This shows that it is an efficient agent for inducing labour. This finding was similar to the study done by Yeliker and her team.<sup>11</sup> In their study, 8 (16.00%) had normal delivery without use of misoprostol in test group as compare to 2 (4.00%) in control group (p=0.05). The number of normal deliveries (71.66% vs 45.00%, p=0.003) were more and number of cesarean (12.50% vs 23.30%, p=0.013) were less in mifepristone group in our study. There many studies done where they found that, with the use of mifepristone the operative deliveries were significantly decreased. Ghimire *et al*<sup>24</sup> in their study found that vaginal delivery was 66.0% in test group and 42.0% in control group. Whereas cesarean was 58.0% vs 34.0% in test and control group with p value 0.01. Athawale *et al*<sup>12</sup> also had 76.0% vaginal delivery in test group and 24.0% in control group. Contrary to present study, Archana *et al*<sup>25</sup> showed more number of vaginal delivery in misoprostol group (90.0%) than mifepristone group (60.0%).

The number of instrumental delivery was 3.33% and 8.33% respectively in test and control group p=0.436 in our study. This finding was similar to study done by Fathema *et al*.<sup>22</sup> They found that mifepristone group had less cesarean rate, more normal delivery and less instrumental delivery as compare to control group. On the other hand the adverse effect of the drug regime and neonatal outcome was almost similar in mifepristone group and control group in our study (Table 3 and Table 4) Mane *et al*<sup>14</sup> also found the rate of NICU admission and meconium stain liquor were same in mifepristone and control group. Similarly, Hapagama and Neilson<sup>9</sup> in their study also found less common abnormal fetal heart pattern in mifepristone group.

Although mifepristone is a somewhat expensive medicine as compare to misoprostol and the need to admit the patient 48 hours earlier, it improves the Bishop's score significantly and decreases the rate of operative delivery. Therefore, if mifepristone is used for pre-induction cervical ripening in induction of labour, the procedure become safer, and associated with less health hazard.

In conclusion, mifepristone as preinduction cervical ripening agent is an efficient agent. It is safe drugs which can be used with misoprostol to decrease reduce number of operative delivery.

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