Effectiveness of Mifepristone plus Misoprostol and Misoprostol alone in Cervical Ripening and Induction of Labour in Postdated Pregnancy

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ABSTRACT

Aims: To compare the effectiveness of mifepristone plus misoprostol in pre-induction cervical ripening and induction of labour in uncomplicated post-dated primigravidae.

Methods: It is a hospital based prospective comparative study enrolling 50 uncomplicated post-dated pregnancies in each group to determine the efficacy and safety of mifepristone and misoprostol with misoprostol alone for induction. It was conducted in Institute of Medicine. Computer software SPSS 20 was used for processing and analysis of the data. Chi-square test and paired sample t-test was used.

Results: Comparing change in Bishops score among the two groups, no any statistically significant difference was seen. Sixty-six percent delivered vaginally in mifepristone group as compared to 42% in misoprostol group ($p \leq 0.01$). Rest delivered by caesarean section. No significant maternal side effects and complications were seen. Twenty-six percent in mifepristone group and 50% babies in misoprostol group developed fetal side effects ($p=0.01$).

Conclusions: Mifepristone and misoprostol both bring favourable change in the Bishop's score. Regarding success rate and fetal complications mifepristone seems to be effective and safe.

Keywords: induction of labour, mifepristone, misoprostol, post-dated pregnancy

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INTRODUCTION

The reported incidence of post-dated pregnancy is 5-10%.[1] Post-dated pregnancies result in various feto-maternal complications. So, for the safety of mother and fetus we need to deliver the fetus in right time and one of the methods is by inducing labour. 10-30% of the world total deliveries involved labour induction, lowest in Niger being 1.4% and highest in Sri Lanka being 35.5%.[2] To increase the success of a vaginal delivery with an unfavourable cervix, several effective cervical ripening methods can be applied that include non-pharmacological and pharmacological options.[3] Cervical ripening is one of the most important factors for successful induction of labour (IOL). Mifepristone provides an interesting new alternative to classic uterotonics agents for IOL. Unlike Prostaglandins, mifepristone has minimal effects on uterine contractility as it induces labour mainly by cervical ripening and it is associated with lesser maternal and fetal complications. Mifepristone (RU-486) is a 19-Norsteroid that binds strongly to progesterone receptor and inhibits the activity of progesterone at cellular level with potent anti-progestogenic, anti-glucocorticoid and a weak anti androgenic actions.[4,5] It is also on the WHO model list of essential medicine.[6] Ten trials, that recruited 1108 women, were included in Cochrane study. There is evidence, from the trials, that mifepristone does induce both ripening of the cervix, and labour.[7]

The incidence of cesarean section is increasing all over the globe including Nepal. One of the reasons is

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lack of cervical ripening. So drugs like mifepristone and misoprostol have been used to favour cervical ripening. In Nepal, regarding this only few studies have been conducted. So this study might prove to be a helpful contribution.

Hence this study aims to find out the effectiveness of mifepristone-misoprostol over misoprostol in inducing labour and if mifepristone proves to be an effective and safe inducing agent then it can be used as a safe and effective method for IOL.

METHODS

This is a hospital-based prospective comparative study undertaken from 13th April 2016 to 12th April 2017. It was conducted in the labour room and maternity ward of Institute of Medicine (IOM) in order to determine the efficacy and effectiveness of mifepristone and misoprostol for induction of labour in uncomplicated primigravidae with postdated pregnancy. Ethical approval was taken from Institutional review board of IOM and consent from each patient was taken.

Primigravidae with post-dated pregnancy confirmed by Last menstrual period (LMP) or first trimester USG if LMP was not sure or cycles were irregular, with cephalic presentation, no any contraindication for vaginal delivery, delivery was expected within 48 hours and the cervical bishop score was <6 prior to induction were included. Scarred uterus, cephalopelvic disproportion, medical problems like impaired renal, hepatic or adrenal function, nonreactive NST (non-stress test), antepartum haemorrhage, severe oligohydramnios requiring immediate delivery**,** known hypersensitivity to prostaglandins or mifepristone were excluded.

Samples were taken based on prevalence reviewed from literature; α-error of 0.05 and β of 0.8 was taken. Depending upon this the sample size should be at least 41 cases per study group. Simple random sampling was used by lottery method.

In Mifepristone arm (Mife plus Miso) tab 200mg of mifepristone to swallow after normal CTG and USG. She was reassessed at 24 hours or earlier if labour pain started. If Bishop Score was ≥ 6 she was shifted to labour room and augmentation started with oxytocin. ARM was done in next 4-hour P/V examination. If Bishop's score was<6 then she was reassessed at 24 hours. If cervix still remained unfavourable she was induced with tab misoprostol 25 mcg 2 doses 6 hours apart. Within 12 hours if the cervix became favourable she was shifted to labour room, augmented if required and ARM was done in next 4-hour P/V examination. At 12 hours whatever the Bishops score this time she was induced with injection oxytocin 5 IU in 1 pint of Ringer lactate in titrating dose maximum up to 3 pints; 4 hourly P/V examinations, 2 hourly maternal vitals and half hourly contraction and FHS were monitored.

Likewise in misoprostol (Miso) arm two doses 25 mcg misoprostol 6 hours apart per vaginally after normal CTG and USG. Within 6 hours of induction with misoprostol if the cervix became favourable she was shifted to labour room, augmented if required and ARM was done in next 4-hour P/V examination. At 12 hours whatever the Bishops score this time she was shifted to labour room and induced with injection oxytocin. 5U in 1 pint of Ringer lactate in titrating dose maximum 3 pints. 4 hourly P/V examination, 2 hourly maternal vitals & half hourly contraction and FHS were monitored**.** If vaginal delivery did not occur, then it was considered as failed induction leading to emergency LSCS.

Computer software SPSS 20 was used for processing and analysis of the data. Chi-square (x2) test and paired sample t test was used. A 'p' value of <0.05 was regarded as statistically significant.

RESULTS

During study period, a total of 4817 women delivered in TUTH. Out of these 696 were postdated pregnancies and among them 100 cases of uncomplicated postdated primigravidae pregnancies were included in the study with 50 in each group. Some cases required Mifepristone only and some required one or two dosage of misoprostole.[Table-1]

Table-1: Distribution by number of dosage of labor inducing drugs

Mife plus Miso arm (N=50)			Miso arm (N=50)	
Mifepristone alone	With 1 dose misoprostol	With 2 dose misoprsotol	1 dose	2 doses
27 (54%)	12 (24%)	11 (22%)	29 (58%)	21 (42%)

Both groups were comparable in terms of Bishops score as there was no statistical significant difference change in it (p=0.84).[Table-2]

Table-2: Comparison of change in mean Bishops score in two groups

Bishops score	Mife plus Miso arm (N=50)	Miso arm (N=50)	p-value
Pre-induction mean Bishops score	2.9200	3.2400	0.84
Post-induction mean Bishops score	5.1800	4.7000	

Induction to delivery interval in patient who had vaginal deliveries was more in Mifepristone group (p <0.001). [Table-3]

Table-3: Induction to Delivery Interval in Vaginal Deliveries in two groups

Group	Mean Duration (minutes)	Std. Deviation	p-value
Mife plus Miso arm (N=33)	1909.5152	621.9282	<0.001
Miso arm (N=21)	835.7619	416.5807	

Vaginal delivery was seen more in Mifepristone group and was found to be statistically significant (p=0.01). [Table-4]

Table-4: Mode of Delivery in Mife plus Miso arm (N=50) and Miso arm (n=50)

Mode of delivery	Mife plus Miso arm	Miso arm	p-value
Vaginal	30 (60%)	18 (36%)	0.01
Instrumental	3 (6%)	3 (6%)	
Caeserean section	17 (34%)	29 (58%)	

Fetal complications were seen more in misoprostol group with statistically significant difference (p=0.01). [Table-5]

Table-5: Neonatal outcome in Mife plus Miso arm (N=50) and Miso arm (n=50)

Fetal Complications	Mife plus Miso arm	Miso arm	p-value
FHR irregularity	1 (2%)	5 (10%)	0.01
MSL	9 (18%)	12 (24%)	
FHR irregularity with MSL	3 (6%)	8 (16%)	
Low APGAR score	0 (0%)	1 (2%)	
Admission to neonate ward	1 (2%)	2 (4%)	
Duration of stay in neonate ward	10 hours	48 hours	
Still Birth/NND	0/0 (0%)	1/1 (4%)	
Total	**13 (26%)**	**25 (50%)**	

DISCUSSION

The complications of post-dated pregnancy have influenced the thinking in obstetrics. Induction of labour in such cases should be clearly indicated and justified to benefit the mother or fetus or both. No consensus has yet been reached in the literature regarding the most appropriate drugs used for IOL. There are ongoing researches in search for best drug for it. Till date misoprostol and mifepristone seem to be the widely used drug in IOL. With ongoing trials, mifepristone has proved to be a new advancement in this field. The aim of present study was to assess the efficacy and safety of mifepristone and misoprostol in IOL in uncomplicated postdated primigravidae. In present study, we enrolled only those women whose indication of induction was uncomplicated postdated pregnancy.

Comparison of change in Bishops score at 24 hours of mifepristone induction and at 6 hours after misoprostol induction was done. Though there was significant change in Bishops score in both groups after use of each drug but the difference in change in mean Bishop's score in two groups was not statistically significant (p=0.84). This demonstrates that both drugs were equally efficient in bringing

change in the Bishops score which is comparable to findings shown by Archana A et al.[8]

Induction to delivery interval in patient who had vaginal deliveries (n=30) was seen more in mifepristone group as compared to misoprostol group with statistically significant findings (Table 3, p<0.001). This could be because of mechanism of action of mifepristone which takes at least 24 hours to act. So this automatically increased the induction to delivery interval in mifepristone group. Wing D et al[9] in their study demonstrated the mean induction to delivery interval of 2209±698 minutes for mifepristone group which was similar to present study. Unlike present study, Yelikar et al[10] demonstrated mean induction to delivery interval less in mifepristone group (1,907 ± 368.4 minutes) in comparison to misoprostol group (2,079 ± 231.6 minutes). This could be because they had excluded the first 24 hours of mifepristone induction interval.

When the mode of deliveries among two groups were compared in present study, more number of vaginal deliveries occurred in mifepristone group (66%) as compared to misoprostol group (42%). The caesarean section rate was high in misoprostol group (58%) in comparison to mifepristone group (34%) showing statistically significant results (p=0.01). Similar to present study, in a study done by Athawale R et al, 76% had vaginal delivery and 24% had caesarean delivery in mifepristone group. This demonstrates that mifepristone is effacious in achieving vaginal delivery.

In the present study, significant difference in the success rate of mifepristone group in comparison to misoprostol group was seen showing mifepristone to be effacious in achieving vaginal delivery (p=0.01). This could be because of favourable cervix after use of mifepristone which after augmentation led to vaginal delivery. Whereas in misoprostol group even though there were favourable changes in the cervix more number of meconium stained liquor (MSL) were seen for which caeserean delivery had to be done leading to more failure rate as compared to mifepristone group. This phenomenon could be explained by the propensity of misoprostol which can enter the fetal circulation which lead to increased fetal bowel motility resulting in MSL.[11] Mifepristone is successful in achieving vaginal delivery than misoprostol similar to study done by Gaikwad V et al.[12]

Contrary to present study, Archana A et al[8] showed more number of vaginal delivery in misoprostol group (90%) than mifepristone group (60%). In mifepristone group more number of caesarean section was done mainly for fetal distress and MSL and it was seen after the use of misoprostol. So this could be because of additive effect of mifepristone and misoprostol both rather than mifepristone alone.

Better neonatal outcome was seen in mifepristone group as compared to misoprostol group similar to study done by Raksha M et al.[13]

CONCLUSIONS

Mifepristone plus misoprostol and Misoprostol only groups both bring a favourable change in the Bishops score in postdated primigravidae. However in terms of vaginal delivery and neonatal outcome mifepristone proves to be effacious and safer. Maternal side effects and complications were low in both groups. Induction to delivery interval was seen longer in the mifepristone group without significant maternal side effects and complications.

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