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Original Research Article

A randomised controlled trial to compare the efficacy of preinduction with mifepristone 12 hours versus 24 hours prior for second trimister pregnancy termination

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ABSTRACT

Background: Since the second trimester termination of pregnancy is on rise due to the detection of anomalies, this study aims to provide a safe regimen with respect to efficacy, side effects and acceptability for second trimester pregnancy termination.
Methods: It is a randomized controlled trial, conducted on 48 cases at BLDE Medical college, Vijayapur, Karnataka. They were divided into two groups; all patients were given mifepristone 200mg orally followed by misoprostol 400mcg vaginally after 12 hours in group I and 24 hours in group II respectively. Subsequent doses were decided depending on the Bishops score. Results were analyzed in terms of induction-abortion interval and dosage of misoprostol.
Results: The mean induction abortion interval was 563.9 minutes (9.3hrs) in group I and 714.6 minutes (11.9hrs) in group II; but was statistically not significant (p value 0.611) The total dose of misoprostol used was 783.3mcg in group I compared to 550mcg in group II, but was statistically not significant. The success rate was 100% in both the groups as none of them had incomplete abortion. There were no cases of uterine rupture, infection, need for check curettage and laparotomy.
Conclusions: Our study proves that the interval between mifepristone and misoprostol can be safely reduced to 12 hours without affecting the efficacy. But in gestational age <16 weeks and primigravida 24 hours interval may be of benefit. Both the regimens were 100% successful.

Keywords: Mifepristone, Misoprostol, Second trimester, Termination of pregnancy

INTRODUCTION

In spite of abortion being legal in India, 8-18% maternal deaths are due to abortion.[1] Second trimester termination rate is increased now because of increased detection of structural, genetic and metabolic disorders.[2] It is responsible for 2/3rd of major abortion related complications. Various surgical and medical methods have been tried for the second trimester MTP with varying success and induction abortion interval. Among them combination of mifepristone and misoprostol has been most widely used.

Prostaglandins have the property of dual action of cervical ripening and induction of uterine contractions. Because of this they are the popular agents for induction

of labour. Mifepristone [RU486] an antiprogesterone, through competitive inhibition increases the sensitivity of uterine musculature to both endogenous and exogenous prostaglandins which have a uterotonic action. Both prostaglandins and mifepristone also have cervical ripening effect. Thus, this forms the basis for combination of these two drugs.[2] Mifepristone was approved for first trimester termination (49 days) in 2002 by drug controller of India and combipack of mifepristone and misoprostol was approved in 2008 for MTP up to 63 days.[1]

Most accepted medical abortion regimen was mifepristone 200mg by oral route followed 36-48 hour later by prostaglandins.[3] But pharmacokinetics studies have shown that after ingestion of mifepristone in dosage of 50,200,500 mg, peak plasma levels had reached within 1-2 hours, indicating that mifepristone doesn't require 48 hours to increase the sensitivity of uterus to prostaglandins.[4] Recently American college of obstetricians and gynaecologists recommended mifepristone 24-48 hours prior to misoprostol but RCOG recommends 12-48 hours interval between mifepristone and misoprostol, so we wanted to study whether this interval can be reduced to 12 hours without affecting the efficacy.[5] If it proves to be successful it can be convenient to both the patient and the doctor.

METHODS

This study was carried out in the department of obstetrics and Gynecology, at BLDE University's Shri B. M. Patil Medical College Hospital and Research Center, Vijayapur, India. The inclusion criteria were all pregnant women between 13-20 weeks, willing for termination and consenting to participate in the study. The exclusion criteria were previous caesarean section, undiagnosed adnexal masses, hypertension, jaundice, diabetes, severe anemia (<7 gm%) heavy smoking, known case of adrenal insufficiency, patients on corticosteroid therapy, known case of coagulopathy, known case of hematological disorders, multiple pregnancy, nursing mothers and pregnancy with IUCD (Intrauterine contraceptive device) in utero. Institutional ethical committee clearance was obtained in the study.

Statistical calculation showed that a total of 48 cases will be required with power of 80% and α error of 95%. Considering the dropout rate of 20% we decided to study 56 cases. But when 48 cases were done we did not have any drop outs, all randomized patients had completed the study protocol. Since we had done block randomization we could stop the randomization at 48 without affecting the sample size in each group.

The patients were randomized into two groups depending on computer generated randomized table. In group I mifepristone 200mg was given orally followed by intravaginal insertion of misoprostol 400µgm after 12 hours and in group II, misoprostol 400 µgm intravaginal was inserted after 24 hours of mifepristone. Subsequent doses of misoprostol were decided depending on the Bishop's score. Usually 200-400µgm misoprostol was used every 6-8thhourly. The primary outcome was to see the induction to abortion interval (IA), total dose of misoprostol required and success rate. The secondary outcome was to see side effects of drugs, such as pyrexia, nausea, vomiting, diarrhea, and complications such as uterine rupture, infection, excessive postabortal bleeding, need for check curettage for retained placenta, need for laparotomy and maternal mortality if any.

RESULTS

A total of 48 pregnant women between 13-20 weeks, willing for termination were studied. The age groups included were between 20-35 years of age, the mean being 23.65% in group I and 25.17% in group II (Table I).

Table 1: Baseline characteristics of patients in both the groups.

Variables	Group 1	Group 2	P value
Age	23.65±3.24	25.17±4.41	P=0.182 NS
Gestational age	19.7±4.7	17.63±2.93	P=0.O76 NS
<16 weeks	9(37)	7(29)	P=0.5403 NS
>16 weeks	15(63)	17(71)	
Gravida			
primigravida	6	4	P=0.5923 NS
nullipara	3	1	
primipara	6	7	
multipara	9	12	
Prev 1st TRI abortion			
spontaneous	3	2	
medical	0	0	
surgical	2	0	
Prev 2nd TRI abortion			
spontaneous	0	0	
medical	1	0	
surgical	0	0	

NS: No significant difference

There were about 9 cases in group who were less than 16 weeks with 7 of them in the other group. Those cases above 16 weeks were 15 in the first group and 17 in another group. The results were also again subdivided in terms of obstetric score as primigravida, nullipara, primipara and multipara. Results were also studied with relation to history of previous first and second trimester abortions with 4 such cases in group I and 2 in group II. The mean induction abortion interval was 563.9 minutes (9.3hrs) in group I and 714.6 minutes(11.9hrs) in group II (Table 2).

Group I had lesser induction abortion interval than group II but it was not statistically significant (p value 0.611).

Table 2: Comparison of primary outcomes in both the groups.

Variable	Group I Mean (SE)	Group II Mean (SE)	P value
IA Interval (hrs)	9.3hrs (0.9)	11.9hrs (4.82)	0.611 NS
Total dosage used (mcg)	783.3 (70.1)	550 (71.5)	0.024*
Success rate	24 (100%)	24 (100%)	

SE: Standard Error, *Significant difference

The amount of total dose of misoprostol used was 783.3mcg in group I as compared to 550 in group II amounting to lesser amount of misoprostol requirement in group II. But this also was not statistically significant.

The success rate was 100%in both the groups as none of them had incomplete abortion.

Subgroup analysis was done among the variables used (Table 3). There was not much a difference with IA interval and misoprostol dosage used in cases with gestational age less than 16 weeks in group I and II with p value of 0.16 and 0.126 respectively. Infect group I took longer duration (9.96 hrs. vs 6.32 hrs.) and more dosage of the drug (889.9 µg vs 571.43µg). Those with gestational age more than 16 weeks, there was a difference of 5hours in IA interval between group I and II, with less time taken by group I (9.06 hrs vs 14.21 hrs.) but with not a significant p value. There was not much difference in the results with the amount of drug used in group I and II.

Table 3: Subgroup analysis for the primary outcome in both the groups.

Variables	Group 1	Group 2	P value
Gestational age			
<16 weeks			
IA intervals (hrs)	9.96±3.73	6.32±3.43	P=0.163 NS
Misoprostol dose (mcg)	888.9±480.7	571.43±292.8	P=0.126 NS
>16 weeks			
IA Interval (hrs)	9.06±3.06	14.21±27.9	P=0.460 NS
Misoprostol dose (mcg)	720.0±224.2	841±379.24	P=0.112 NS
Gravida			
Primigravida			
IA interval (hrs)	10.1±2.87	6.68±5.62	P=0.285 NS
Misoprostol dose (mcg)	866.67±206.56	750±251.66	P=0.568 NS
Nullipara			
IA interval (hrs)	7.2±4.93	14	Test can't be performed
Misoprostol dose (mcg)	550±500	0	
Primipara			
IA interval (hrs)	8.62±3	22.8±43	P=0.774 NS
Misoprostol dose (mcg)	600±219	457±151.18	P=0.181 NS
Multipara			
IA interval (hrs)	10.5±6.10	12.11±6.18	P=0.087 NS
Misoprostol dose (mcg)	822.2±473.8	583.3±421.8	P=0.05 S#
Abortion			
Prev 1st Tri abortion			
Spontaneous			
IA interval (hrs)	8.5±2.78	11.75±3.18	P=0.248 NS
Misoprostol dose (mcg)	600±200	400±565.6	P=0.767 NS
Medical	0	0	
Surgical			
IA interval (hrs)	7.33	-	Test can't be applied
Misoprostol dose	900±424.3		
Prev 2nd Tri abortion			
Medical	0	0	Test can't be applied
Surgical			
IA interval (hrs)	18	-	Test can't be applied
Misoprostol dose (mcg)	2000	-	

For Primigravidas in group I, the IA interval was more compared to group II, with requirement of more doses of misoprostol than that in group II but with no significant statistical difference, p value being 0.285 and 0.568 respectively. The test was not conclusive in case of nullipara as there was only one case in the second group and analysis could not be made. In case of primipara, they took less time interval to expel in group I compared to group II but with a non-significant p value of 0.774, and the amount of misoprostol used was nearly same. In cases of multipara, the second group had apparently shorter IA interval, (p value of 0.087), but the amount of drug requirement was less for the second group with a statistically significant p value of 0.05. Two patients in group II aborted only with mifepristone, one of which was multigravida and took 7.3 hours and other nullipara took 12.3 hours.

There was one case of excessive post abortal bleeding in group I, with no other complications in either group like uterine rupture, infection, need for check curettage for retained placenta, need for laparotomy and maternal mortality. Side effects of medication were apparently more in group I when compared to group II like more cases of nausea, vomiting, diarrhea, pyrexia, and shivering (Figure 1). But the p value was not significant (0.126).

DISCUSSION

Eber papyrus from Egypt performed the first induced abortion in 1550 BC.[6] Successful termination of pregnancy with medical methods in both first and second trimester has drastically reduced the need for surgical intervention. Many studies have been done to know the best possible combination of mifepristone and misoprostol to reduce induction abortion interval. In our study induction abortion interval was 9.3 hours in 12 hours group and 11.91 hours in 24 hours group which was not statistically significant stating that interval between mifepristone and misoprostol can be reduced without affecting the efficacy. Though the misoprostol dose used was more in group I but it was not statistically significant. In both the groups success rate was 100% and none of them had any complications.

Maarit et al conducted a randomized trial on 227 women on one day and two-day dosing interval between mifepristone and misoprostol for second trimester termination of pregnancy and concluded that both regimens are suitable for clinical use.[7] Induction abortion interval was 8.5 hours in one-day group but in our study, it was 11.9 hours. But they did not calculate the misoprostol dose used. In >16 weeks IA interval was longer in one-day group (10.8 hours vs 7.2 hours), but in our study, it was 9.06 hours in 12 hours group and 14.2 hours in 24 hours group. In patients without previous vaginal delivery also the induction abortion interval was 3 hours longer in one-day group compared to two-day group (10.1 vs 7.6 hours). But in our study of 12 hours it was 7.2 hours and there was only one case in 24 hours group and that took 14 hours to expel. In their study, the rate of surgical evacuation was more in two-day group. But we did not have any case of surgical evacuation.

In the year 2011, Tripti and Namrata in their study on use of misoprostol and mifepristone and misoprostol alone in second trimester termination of pregnancy on 200 people concluded that pretreatment with mifepristone 12 hours prior to intravaginal misoprostol improves the induction abortion interval (6.72±2.26 hours).[2] In our study, it was 9.3 hours. But the misoprostol dose used was 1186+/-291µgm where as in present study it was only 783.3µgm. Elami et al carried out a randomized trial in 2013 to compare mifepristone followed by 36 hours later misoprostol or oxytocin for second trimester abortion between 14-24 weeks of gestation and it was seen that misoprostol group had significantly shorter induction abortion interval (7±4.9 vs 11.3±7.4 hours with P value <0.001), but had higher adverse effects.[8] The induction abortion interval is comparable to our study with only 12 hours between mifepristone and misoprostol.

In a study done by Kulkarni et al concluded that pre-induction with mifepristone for second trimester termination of pregnancy that it's a reliable, safe and cost effective option to decrease induction abortion interval.[9] There are many case reports of serious complications with misoprostol when preinduction with mifepristone is not used. Sajjan et al reported a case of complete cervical avulsion with only misoprostol for second trimester termination.[10]

Constant et al in their study of clinical outcome before and after introduction of mifepristone in second trimester abortion services in South Africa concluded that this regimen has been successful in reducing the induction abortion interval, decreasepain, and had greater acceptability by women, but there were higher rates of placental retention and need for surgical evacuation for the same in their study.[11] But we did not have any case of placental retention.

RCOG Best practice in comprehensive abortion care 2015 recommends that 14 weeks and more period of gestation should undergo medical termination in a medical facility.[5] A combination of mifepristone and misoprostol should be used as it shortens the induction abortion interval. Mifepristone 200 mg orally followed 12-48 hours later by misoprostol 800µgm vaginal then 400 µgm every 3 hours till she aborts. ACOG recommends[5] a regimen where in mifepristone 200 mg orally followed in 24-48 hours by misoprostol 800µgm vaginally followed by 400µgm every 3 hours maximum of 5 doses. If abortion is not complete after 5 doses, the women may rest before starting next cycle.

The recommended method for medical abortion by WHO is 200 mg mifepristone administered orally followed 36 to 48 hours later by repeated doses of misoprostol.[3] The

initial misoprostol dose following oral mifepristone administration may be either 800 µgm administered vaginally or 400 µgm administered orally. Subsequent misoprostol doses should be 400 µgm, administered either vaginally or sublingually, every 3 hours up to four further doses. The suggested protocol by FOGSI is also mifepristone 200 mg followed by misoprostol 400µgm after 36-48 hours either oral, sublingual or vaginal every 4-6 hours for maximum of 5 doses.[12]

But present study proved that the duration between mifepristone and misoprostol can be reduced to 12 hours without affecting the efficacy and with no serious complications either because of the termination or side effects of the drug.

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