Original Research Paper

Volume - 10 | Issue - 9 | September - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

A PROSPECTIVE STUDY COMPARING ONE DAY VERSES TWO DAYS MIFEPRISTONE-MISOPROSTOL DOSING INTERVAL FOR SECOND TRIMESTER MEDICAL TERMINATION OF PREGNANCY

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ABSTRACT

Objective: The aim of this prospective study is to compare effectiveness, success rate and induction to abortion time and rate of surgical evacuation outcomes in one(24hrs) and two(48hrs) day mifepristone-misoprostol dosing interval in cases of second trimester medical termination of pregnancy(13-24weeks).

Material and method: A prospective case study done for a period of 2years involving 100 eligible women with gestation age between 13-24 weeks seeking induced abortion in department of obstetrics and gynecology between march 2018 to February 2020.The study was conducted in a tertiary center after taking consent from ethics committee. 70 eligible patients were divided into 2 groups, Group A and Group B with 35 patients in each group. Group A included (one day dosing interval group) 35 eligible patients who were given oral mifepristone (200mg) followed 24hours later by 600 µgm vaginal misoprostol (inserted in posterior fornix of vagina) first dose followed by 400 µgm every 4hours for a total of maximum 5 doses. In Group B (two-days dosing interval) 35 patients were given 200mg mifepristone orally followed by 48hours later 600 µgm misoprostol vaginally first dose followed by 400 µgm misoprostol every 4hours for a total of five doses. If abortion did not take place within 24hours of first dose of misoprostol insertion in any of the two regimens and there was no symptoms suggestive of imminent abortion a second course of vaginal misoprostol was given for a maximum of 5 doses that is 400 µgm every 4hours.In cases of incomplete abortion surgical evacuation of uterus was performed under regional anaesthesia. Women were discharged after 24 hours of abortion if there were no complications.

Result: The induction to abortion time (time to fetal expulsion) was longer (10hours verses 5.5hours) in 24hour interval than in the 48hours interval($p<0.01$). Abortion occurred in91.5% and 100% within 24hours of misoprostol insertion in group A and group B respectively. Mean number of misoprostol application were identical in both the groups. Time to abortion was longer in nullipara than in multiparous women (11hours verses 7.5 hours $p<0.001$). Also, time to abortion was longer in women with gestation 16-22 compared to women with lower gestational age 13-15 weeks.

Conclusion: Women with gestational age exceeding 16 weeks and nulliparous women may benefit from longer interval however both one- and two-day intervals seems to be suitable for second trimester medical termination of pregnancy.

KEYWORDS : second trimester abortion, mifepristone, misoprostol, termination of pregnancy.

INTRODUCTION

Second trimester is a period ranging from 13-26 weeks of gestation. Second trimester abortion (termination of pregnancy) extends from 13-24weeks. Termination of pregnancy (TOP) between 13-24weeks [1] of gestation during second trimester constitute approximately 6-12% of all induced abortion [2]. Most common causes of these late abortions are mainly fetal malformations or chromosomal anomalies.

The method used for second trimester TOP is controversial, but in India second trimester TOP is largely performed by medical method. One of the commonly used regimens for medical termination of pregnancy in the second trimester is misoprostol with or without mifepristone. Pre-treatment with mifepristone enhances the stimulatory effect of misoprostol on uterine muscle resulting in increased amplitude and frequency of uterine contraction. Mifepristone is an antiprogesterone and it binds specifically to the progesterone receptors. Mifepristone stimulates the endogenous prostaglandins synthesis. It also acts by mainly increasing uterine contractility and also increases the sensitivity to prostaglandins. Prostaglandin analogues are used for induction of labour, cervical priming before dilatation and curettage, and as abortifacients in both the first and second trimester. Acting through prostaglandin receptors in the uterus and the cervix, treatment with prostaglandin analogues increases uterine tone, induce uterine contractions and softens the cervix [3]. Most common prostaglandin E1 analogues are used for obstetric purposes which is less expensive and easier to handle. Repeated doses of prostaglandins lead to fetal expulsion in 50-92% of cases within 24hours with a median interval of 10-30hours depending on dose and route in cases of second trimester TOP by medical method [4,5,6]. Pre-treatment with mifepristone facilitates abortion as it reduces the need for prostaglandins and reduces side effects as well. Mifepristone can shorten the induction to abortion interval.

The traditional regimen with an interval of 36-48hours between mifepristone and prostaglandin is based on a half-life of mifepristone of approximately 24hours [7].

In our study for TOP in second trimester by medical method we have given oral 200mg mifepristone pre-treatment followed by repeated doses of vaginal misoprostol and the primary aim of the study was to evaluate the impact of mifepristone misoprostol interval on the efficacy of the regime.

The most efficacious regimen for medical second trimester TOP appears to be the use of a combination of antiprogestrone mifepristone followed by the prostaglandin E1(PGE1) analogue, misoprostol. The recommended time interval between mifepristone and the first dose of misoprostol has been 36-48hours as the maximal effect of mifepristone is reached at that point [8].

MATERIAL AND METHODS

This is a prospective case study done in department of obstetrics and gynaecology in Patna Medical College and hospital between march 2018 and February 2020. A total of 70 women with a viable pregnancy and a gestational age between 13-24 weeks confirmed by ultrasonography underwent medical TOP. Written informed consent was taken from all patients. Patients were divided into 2 groups. Group A included 35 patients who were given oral mifepristone200mg which was followed by vaginal misoprostol 600 µgm insertion in posterior vaginal fornix after 24hours of mifepristone. Thereafter 400 µgm misoprostol was given every 4hours till a maximum of 5 doses. Group B also included 35 patients who were given oral mifepristone 200mg followed by vaginal misoprostol 600 µgm insertion in posterior vaginal fornix after 48hours of mifepristone. Thereafter 400 µgm misoprostol was given every 4hours till a maximum of 5 doses. Ethic committee approval was taken. All patients who entered the study fulfilled the eligibility criteria. If abortion did not take place 24hours of first misoprostol insertion or initiation the misoprostol doses were repeated. As analgesic women were offered diclofenac(100mg), paracetamol when contractions began. Non opioid or opioid analgesics were supplemented as necessary.

Inclusion criteria was i) age >18 years and a viable singleton pregnancy between 13-24 weeks of gestation (85-169 days of amenorrhea), a legal indication for TOP. Exclusion criteria was i)any contraindications to mifepristone ii)any contraindication to misoprostol including mitral stenosis, glaucoma, sickle cell anaemia, severe asthma, allergy to prostaglandins, diastolic pressure over

100mmHg iii)history or evidence of thromboembolism, severe or recurrent liver disease or pruritus of pregnancy iv)a known history of or active medical diseases v)an intrauterine contraceptive device in utero vi)haemoglobin <10g/dl or abnormal liver function test(LFT) or renal function test(RFT) vii)suspected ectopic pregnancy.

All cases were stratified according to parity, gestational age, mifepristone misoprostol interval. Indications for the abortion were registered as either fetal (structural or chromosomal defects) or maternal (patients request) values are reported as the median and range or mean ±SD. Student's t-test. Following recruitment at outpatient clinic. Blood was taken for blood grouping and haemoglobin % and LFT/RFT. An Ultrasonography was done to verify the duration of pregnancy. The side effects, uterine contractions, blood pressure, pulse rate and temperature were recorded every 4hours after misoprostol insertion. Pelvic examination was performed every 3hours before the next dose of misoprostol. If abortion did not occur after 24 hours of first dose of misoprostol insertion and there were no signs and symptoms suggestive of imminent abortion a second course of vaginal misoprostol was given for a maximum of 5 doses(600 µgm for first dose followed by 400 µgm every 4hours for maximum of 4 doses.)If abortion still did not occur, hysterotomy was done. Product of conception were examined for completeness of abortion after expulsion of the fetus. If abortion was incomplete, evacuation of uterus was performed under general anaesthesia. In our centre check curettage was done to ensure that abortion was complete

The patients were discharged 24hours after the abortion if there were no complications. The primary outcome measure was the success rate at 24hours.Success was defined as the expulsion of fetus, irrespective of whether evacuation was necessary because of incomplete abortion. Secondary outcomes measures included the difference in induction to abortion interval and the frequency of side effects between two groups.

Regarding prophylactic management of pain, oral ibuprofen(600-800mg), paracetamol(500mg) plus dihydrocodeine(10mg) were administered at time of first misoprostol dose and thereafter as required oral or parenteral opioid analgesic administered as and when required. Antiemetics oral metoclopramide hydrochloride and oral ondansetron were used for nausea and vomiting.

Potential side effects that is bleeding >500ml, axial temp rise to over 38.0 C and clinical signs of infection defined as temp>38 C with lower abdomen pain and foul-smelling vaginal discharge. If fetus and placenta were expelled complete check curettage done. Women who did not pass the placenta it was removed in OT under general anaesthesia. In cases of having bleeding surgical evacuation was performed. Contraception was advised when necessary.

Follow up assessment was done at 4-6 weeks after abortion. At follow up they were asked about developing any complication that may require any treatment. Clinical examination and ultrasonography performed and contraception advise was given. Routine histological analysis of the residual tissue was not performed but done ion cases of suspicious residual tissue.

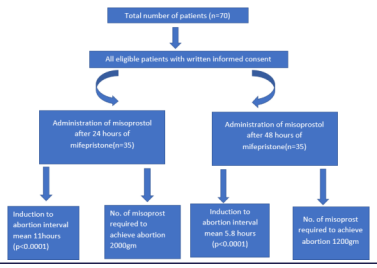
STATISTICALANALYSIS

Difference in continuous variables were analysed with students t -test. Statistical significance was defined as P<0.05. Chi-square test for trend (with one degree of freedom) was used for analysis of misoprostol doses needed.95% CI for difference of proportions were calculated using New comb method (New combe,1998).

RESULT

Induction to abortion interval is defined as the interval between the administration of the first dose of prostaglandin and abortion.

Figure 1 outlines the result of the study group.



In table 1 is shown the demographic pattern of the study population.

Table 1: Baseline demographics of the study population

Sl. no.	Parameters	Total	Group A(24hrs)	Group B(48hrs)
1.	No. of cases	70	35	35
2.	Age(years)		22-35	18-32
3.	Gestational age by USG (weeks)		13-24	16-24
4.	Parity(number)		1-7	0-5
5.	Gravidity(number)		2-8	1-6
6.	Mifepristone/misoprostol interval		24hours	48hours
7.	Misoprostol application(no.)		4-6	2-4
8.	Time to abortion(hours)		7.5-11	5.5-7

Table2: Abortion outcomes after misoprostol given 24hours of mifepristone (Group A) and 48hours of mifepristone (Group B)

I.	Median induction to abortion interval in hours(range)	Group A	Group B	P value
a.	Success rate in6hours (%)	4%	72%	<0.0001
b.	Success rate in 12hours	70.3%	98.6%	<0.0001
c.	Success rate in 24hours (%)	91.5%	100%	0.028
d.	Success rate in 48hours (%)	98.6%	100%	1.000
II.	Median amount of misoprostol used in gm (range)	2000 (1200-5400)	1200 (800-2000)	<0.0001

The difference in abortion rate between group A and Group B remained statistically significant for up to 24hours after first dose of misoprostol administration (91.5% versus 100%respectively p=0.028). All women in both groups aborted within 48 hours as shown in table 2.

Of the 35 women in 48 hour dosing group that is group B, 34 women(98.6%) abortion took place within 12hours of misoprostol administration whereas only 70.3% of women in group A aborted within first 12hours(p<0.0001) and abortion rate within 24hour in both group were 91.5% in group A and in 100% in group B. In next 48hours abortion rate was 98.6% in group A and 100% in group B as shown in table 2.

Table3: Incidence of side effects after prostaglandin administration

Sl. No.		Group A (24h)	Group B(48h)
1.	Nausea, dizziness and fatigue	52%	53%
2.	Headache	10%	9.6%
3.	Diarrhoea(>3episodes)	25%	14.3%
4.	Fever>38	73%	34.3%
5.	Vomiting	22%	12.3%
6.	need for analgesia	14.1%	8.6%

The most common complaints after prostaglandin administration were nausea, dizziness, fatigue, headache, vomiting, breast tenderness, diarrhoea and need for analgesia was not significantly different between the two groups. However, fever and febrile episodes were more in group A as compared to group B. The incidence of complaints after prostaglandins administration is shown in table3.

4 patients from group A required suction evacuation of uterus for retained placenta and none from group B required suction evacuation. All patients had check curettage before discharge as it was a routine practise and according to hospital protocol. Two in group A required blood transfusion. Follow up was done at 6weeks and 8 women from Group A required antibiotic for pelvic infection. However follow up rate in both groups were 58% and 61%.The median time to abortion was larger for nullipara compared to parous women(9.8 verses 6.4hours;p<0.001)Women with fetal malformations, the median time to abortion was approximately 3hours longer(11.2 verses 8hours; p>0.05) than those with social indications, but the difference was not significant. The median induction to abortion time was shorter in women with previous vaginal deliveries and in gestational age between 13-16 weeks. With gestational age between 16-24 weeks the median induction to abortion rate was higher.

DISCUSSION:

In our centre all the 2nd trimester TOP is done by medical method. Amongst the various drugs and regimens for TOP in 2nd trimester most commonly used is prostaglandins. However, there is no clear consensus for the optimal prostaglandin regimen in the second

trimester. Misoprostol is the preferred prostaglandin analogues however the doses vary and also route of administration vaginally, orally or in combination also vary. The bioavailability of misoprostol is more when given vaginally than oral route however rate of absorption is slower vaginally. The peak plasma concentration is after 80minutes[9].When compared between misoprostol doses given vaginally and by oral route, studies have shown that vaginal administration is more effective and is also associated with lesser gastrointestinal side effects and less of febrile morbidity [5,10,11]. Also vaginal application has advantage of allowing surveillance of the progressions of the abortion. Both the efficacy and the side effects of prostaglandins are related to dose and the doseinterval [4,5,6]. Comparative studies have shown that misoprostol in doses of 600 µgm or more are generally associated with a disproportionate number of maternal side effects and therefore the use of 400 µgm doses are recommended[4,5].

Pre-treatment with mifepristone shorten the time to abortion. In a randomised study comparing 200mg and 600mg mifepristone, the median time to fetal expulsion was identically 6.9hours in both groups when followed 36-48hours later by a vaginally administered loading doses of 800 µgm misoprostol, followed by repeated 400 µgm doses[12].In our study the efficacy of our combined mife-miso regimen in termination of 2nd trimester pregnancy depended upon number of earlier vaginal deliveries with a median time to expulsion of 5.8 hours in parous women compared to 11 hours in nulliparous women. This result was comparable to other studies as well using prostaglandin only[13,14] or combined regimen[15,16].The efficacy was however reduced in more advanced pregnancies compared to earlier gestation as supported by other studies as well[15,16].

Patients who were very anxious for abortion as in case of fetal malformations were generally treated with misoprostol 1day following mifepristone while women with other social indications for abortion were generally offered traditional regimen of 48hours interval between the 2 drugs. The median time to abortion was hours longer if the median interval between 2drugs was reduced from 48hours to 24hours.However the number of misoprostol application was almost equal.

The use of one day interval between mifepristone and prostaglandin was first described in a French study of second and third trimester abortions that included case with fetal deaths [17]. Heikinheimo et al[15] published online data on the low dose mifepristone regimen and found a slightly longer time to abortion(7.25 verses 6.20hours) when mife-miso interval was reduced from 46 to 21hours.In the above study only the women requesting termination of pregnancy on basis of fetal indication were offered the one day interval as in our study.

Mifepristone alone can induce abortion but this rarely occurs in the second trimester [16] and none of the women in our study aborted after mifepristone only.

We concluded from our study that medically induced second trimester abortion using pre-treatment with low dose mifepristone and repeated doses of vaginal misoprostol 400 µgm is highly successful. The mife-miso interval can be reduced to one day with only a small increase in the time to abortion after the first misoprostol application. We can therefore individualise patients and offer a short interval between the 2drugs if women have a wish to proceed rapidly with the termination. In our study we have compared the two intervals of administration of misoprostol after pre-treatment with mifepristone for second trimester abortion. Our study result showed that the success rate of medical termination of pregnancy at 24hours with 200mg oral mifepristone followed by vaginal misoprostol was significantly lower with the 24-hours regimen compared with that of 48-hours regimen. The induction to abortion interval and number of misoprostol application was longer in 24hour regimen as compared to 48hour regimen. Also, more side effects in terms of febrile episodes and chills and rigor were also more. The increase in side effects was probably due to increase in total amount of misoprostol required to induce abortion in 24hour group.

Ashoke et al. (2004) reviewed 1002 women undergoing medical abortion using oral mifepristone 200mg followed by 800 µgm vaginal misoprostol at 36-48hour later and then 400µgm oral misoprostol at 3hour interval to a maximum of 4 doses. The result showed that 91.5 and 98.3% aborted within 12 and 24hour of prostaglandin administration respectively. In our study 98.6% aborted within 12hour and 100% within 24hour.

A shorter interval of 24hour between mifepristone and misoprostol administration for 2nd trimester termination of pregnancy has potential to minimize hospital visits, shortens duration of procedure and reduces women anxiety. However, our study showed the shorter interval regimen success rate (induction to abortion time within 24hour of misoprostol initiation as)91.5% within 24 hours interval compared to 100% within 48hour interval. A delay of 48hours before misoprostol is given may be clinically inconvenient for women but it pays off well by reducing the induction to abortion interval and the dosage of misoprostol required significantly. Side effects like abdominal cramps, fever and chills usually develop after the administration of misoprostol. By requiring less misoprostol and shortening the induction to abortion interval women will experience less adverse effects.

The actions of mifepristone on the pregnant uterus were believed to take effects over 24hours ingestions of the medications (Mahajan and London,1997) and the effects was pronounced after 36-48hours (Swahn and Bygdeman,1988) whether gestational age has an impact on the actions of mifepristone remains uncertain.

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