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Original Research Article

A prospective randomized comparison of mifepristone with misoprostol and prostaglandin E₂ gel with misoprostol for medical termination of pregnancy between 13-20 week of gestation

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ABSTRACT

Background: Worldwide mid-trimester abortion constitutes 10-15% of all induced abortions. Similar trend is seen in India where mid-trimester abortion accounts for 12.9% of all abortions. Prostaglandins have been used for therapeutic termination of pregnancy from 9-22 weeks of gestation since 1970s. The ideal method for mid-trimester abortion with best efficacy and acceptability and least side effects are still to be found. Objective of this study was to compare two drug regimens for mid trimester abortion using mifepristone with intra-vaginal misoprostol and prostaglandin E₂ (PGE₂) gel with intra-vaginal misoprostol for efficacy and side effects.

Methods: This prospective randomized comparative clinical study was conducted on 50 women seeking mid trimester abortion, in two groups. One group received PGE₂ gel and misoprostol, second group received mifepristone and misoprostol. Induction abortion interval, side effects were compared between two groups.

Results: The mean induction-abortion interval in Group 1 was 6.50±3.54 hours and in Group 2 was 7.33±2.5 hours. In Group 1, success rate at 15 hours was 88%. In Group 2, success rate was 92% both at 15 and 24 hours. Surgical evacuation was required in 8% women in both groups.

Conclusions: Both regimens are safe and has a few minor side effects. There was no major side effect and blood loss was within acceptable limits in both groups. The cost of abortifacients and hospital stay was lessor in group1 (prostaglandin gel and misoprostol) making it more economical.

Keywords: Mid trimester abortion, Mifepristone, Misoprostol, Prostaglandin E₂ gel

INTRODUCTION

Abortion is defined as termination of pregnancy, spontaneous or induced before period of viability.¹ Termination of pregnancy by induced abortion, either elective or therapeutic, is practiced worldwide and can be done in the first as well as second trimester of pregnancy. Of the 205 million pregnancies that occur each year, >42 million (20%) end in induced abortions.² Most women present in the first trimester, but a significant number also seek termination in the early second trimester. The

medical termination of pregnancy (MTP) Act of India (1971) provides for the termination of certain pregnancies up to 20 weeks of gestation, by a registered medical practitioner, provided all the prerequisites are fulfilled.³ After legalization of abortion facilities, in 1971 by Government of India, a large number of women are seeking termination of pregnancy. Worldwide mid-trimester abortion constitutes 10-15% of all induced abortions.⁴ Similar trend is seen in India where mid-trimester abortion accounts for 12.9% of all induced abortions.⁵

Reasons for second trimester termination

Many women do not keep an accurate record of their menstrual cycles or are not aware that they should seek early termination. Some women conceive in lactational amenorrhea, which leads to late diagnosis of pregnancy. A few women decide late to terminate due to various social and financial reasons. The gradual increase in second trimester abortion is also attributed to the wide scale introduction of prenatal screening programs detecting serious congenital anomalies in the foetus.

The methods used for second trimester abortion includes medical and surgical methods.

Medical methods

This include intra-amniotic instillation of hyperosmolar urea (40%) or hypertonic saline (20%), extra-amniotic instillation of ethacridine lactate, prostaglandin analogues and high dose oxytocin.⁴

Surgical methods

Method are dilatation and evacuation or hysterotomy. These methods require the expertise of an experienced gynaecologist. The immediate risks are cervical tear, uterine perforation, intestinal perforation, haemorrhage, and infection.⁶ The late complications include endometritis, pelvic inflammatory disease, salpingitis and infertility.

Intra-amniotic hypertonic saline was the first effective labour induction method for second trimester abortion⁶. The use of intra-amniotic hypertonic saline can result in intravascular absorption which can cause hypernatremia and necrosis of the affected tissue.⁴ Extra amniotic instillation of ethacridine lactate followed by oxytocin infusion has been commonly used for second trimester MTP in India. However, the induction abortion interval is long and ranges from 25-40 hours which could be reduced to 15-20 hour with concomitant use of oxytocin.^{4,7}

Prostaglandins have been used for therapeutic termination of pregnancy from 9-22 weeks of gestation since 1970s.⁸ Various prostaglandins like misoprostol (PGE1), gemeprost (PGE1), dinoprostone (PGE2), sulprostone (PG E2) and carboprost (PGF2 α) have been used alone or in combination with each other or with other agents like ethacridine lactate and oxytocin. Prostaglandin E1 and E2 alone can be used but the induction abortion interval may range from 10-16 hours.⁹ Pre-treatment with the anti-progesterone mifepristone prior to prostaglandin administration reduces this interval.¹⁰ Misoprostol has been used by various routes, including vaginal, oral and sublingual. Vaginal route has better systemic bioavailability, is more sustained and has lower side effects than oral route.¹¹

The combination of mifepristone followed by misoprostol has been approved by FDA for first trimester abortion up to 7-week gestation. This combination has been studied for 2nd trimester abortion (tablet mifepristone 200 mg is taken orally and after 48 hours misoprostol per vaginally is given to induce abortion). This 48-hour dosing interval poses problem in clinical setting. It is associated with increased duration of hospital stay. There is also a possibility that women may change her mind during time interval between administrations of two drugs.

Combination of intracervical PGE2 followed by serial arborist injections has been studied and was found successful in 100% cases with mean induction abortion interval of 8.4 \pm 0.8 hours.¹² Endocervical PGE2 gel followed by extra-amniotic prostasin (PGF2 α) for second trimester abortion has being studied with no failure and mean induction-abortion interval was found to be 17.32 hours.¹³

Comparison of intra-vaginal misoprostol and intra-vaginal dinoprostone gel followed by oxytocin for termination of second trimester of pregnancy has been done with success rate of 100%. The induction-abortion interval was 13.2 hour for vaginal misoprostol and 15.1 hour for inopportune gel group.¹⁴ The ideal method for mid-trimester abortion with best efficacy and acceptability and least side effects are still to be found.

Aim and objectives

This was a prospective, randomised comparative study of second trimester termination of pregnancy at 13-20-week gestation using mifepristone with intra-vaginal misoprostol and prostaglandin E2 gel with intra-vaginal misoprostol. The objectives of the study were to compare induction-abortion interval, to compare side effects.

METHODS

This prospective, randomised comparative clinical study was conducted in department of obstetrics and gynecology, VMMC and Safdarjung hospital, New Delhi from June 2013 to June 2014.

Fifty women attending Family Planning Outpatient department for legal second trimester abortion i.e., 13-20 week of pregnancy were taken up for the study.

Inclusion criteria

Women between 14-45 year seeking legal MTP between 13-20 week of gestation and fulfilling the prerequisites specified in MTP act 1971.

Exclusion criteria

Women with anaemia, multiple pregnancy, previous caesarean section, women with history of coagulation

disorder, thromboembolism, cardiac disease were excluded from the study

All women fulfilling the inclusion criteria were counselled about the procedure. A written informed consent was taken from women included in the study.

Form-C and Form-I was signed by 2 registered medical practitioner and women, then MTP number was given.

A detailed history was taken, including age and parity, last menstrual period (LMP) previous menstrual history, obstetrics history (including history of previous caesarean section or previous uterine surgery, previous abortions), history of any medical or surgical disorder, including history of coagulopathy or thromboembolism, history of any drug intake, history of allergy to any drug was inquired.

A complete general physical and systemic examination was performed. Per abdomen examination was done to assess period of gestation, external allotment and any other organomegaly.

Per speculum examination was done to rule out any sign of infection or any other abnormality.

Bimanual examination was done to assess the uterine size, status of cervix and to exclude any other pelvic pathology.

After complete evaluation following baseline investigations were done: complete blood counts, blood grouping and rhesus typing, bleeding, clotting and clot retraction time, urine routine and microscopy.

Ultrasonography was done on all subjects using transabdominal probe to Confirm intrauterine pregnancy, Assess the period of gestation, confirm viability of the fetus, to localize placenta. And to rule out any other pelvic pathology.

Randomization was done with lottery method with 50 slips (25 slips for each Group 1 and 2). Two groups of 25 women each were selected to receive two different drug regimens for MTP.

Group 1: received prostaglandin E2 gel (0.5 mg) intracervical. After 6 hours, tab misoprostol 800 µg per-vaginal was given. It was followed by tab misoprostol 400 µg per vaginally 3 hourly to maximum of 4 doses, if required.

Group 2: received tab mifepristone 200 mg orally. After 48 hours, tablet misoprostol 800 µg per-vaginal was given. It was followed by tablet misoprostol 400 µg per-vaginally 3 hourly to maximum of 4 doses, if required

If patient did not abort in either group, then tab mifepristone 200 mg 24 hour after last dose of

misoprostol was given. After 48 hours, tab misoprostol 800µg per-vaginal was given. It was followed by tab misoprostol 400 µg per vaginally 3 hourly to maximum of 4 doses, if required.

All women were given sterile vulval pads weighed previously and were told to save all pads and any expelled products. Women's vital signs were monitored throughout the process of abortion, a note was made of the time of onset of uterine contractions, time of expulsion of the foetus and placenta, amount of blood loss pain, and any side effects like nausea, vomiting, fever or diarrhea. After abortion, the placenta was checked for its completeness and a per-vaginal examination was done to rule out any retained placenta. Blood loss was estimated by weighing the pads soaked and subtracting the original weight of the pads used, plus estimating the additional blood loss during abortion. Rh negative women were given Anti-D 100 µg intramuscularly.

Outcome measures

Primary outcomes were success rate, which was defined as complete abortion occurring within a maximum of total 5 doses of misoprostol, that is within 15 hours of first dose of misoprostol (i.e., within 3 hours of the last dose of misoprostol); induction-abortion interval-was calculated from time of administration of first dose of misoprostol to the expulsion of foetus.

Secondary outcomes were amount of blood loss and duration of bleeding, fall in haemoglobin, any side effects and acceptability of both regimes were noted

Statistical analysis

The data was analysed by SPSS 17.0 statistical software. The difference in the means of continuous variables was analysed with student's t test for the quantitative data (age, gestational age) and with Mann Whitney u-test for the non-normal data (skewed data). Differences in proportions was analysed by χ^2 (chi-square test) or Fischer's exact test as appropriate. Statistical significance was taken at $p \leq 0.05$.

RESULTS

A total 50 women were enrolled in this prospective study were in the age groups ranging from 18 years to 35 years divided in two groups. In Group 1 (prostaglandin E2 gel group), minimum age was 18-year, maximum age was 35 years and mean age was 26.84 ± 4.6 years. In Group 1, 12 (48.0%) women were from age 20-30yrs, 9 women (36.0%) from age >30 years and 4 women (16%) were from age <20 years. In Group 2 (mifepristone group), minimum age was 16 years, maximum age was 38 years and mean age was 26.88 ± 5.53 years. In Group 2, 16 (64.0%) women were from age 20-30 years, 8 (32%) were from age >30 years and one-woman (4%) women

from age <20 years. The difference was statistically not significant (p value 0.978). Parity of the women ranged from 0-6 with a mean parity of 2 in Group 1 and 1.9 in Group 2 as shown in Figure 1.

The reason for second trimester MTP in 40.0% women was late decision, 32% women terminated pregnancy due to gross congenital anomaly and 28% had conceived in lactational amenorrhoea in Group 1. In Group 2, 56% women opt for second trimester abortion due to late decision, 24% terminated for gross congenital abnormally and 20% conceived in lactational amenorrhea as shown in Figure 2.

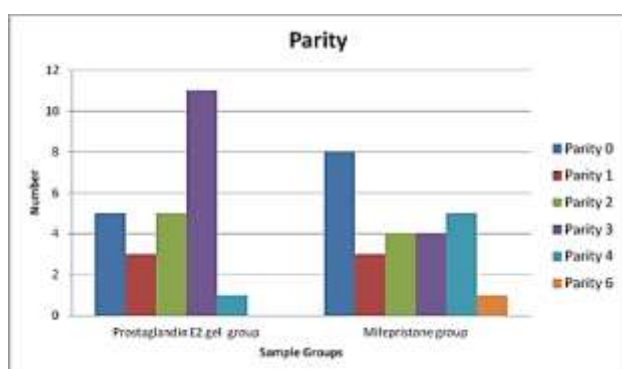


Figure 1: Distribution of parity among the study group.

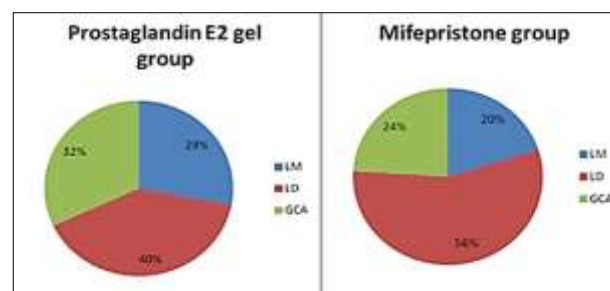


Figure 2: Reasons for seeking abortion Lm: lactational amenorrhea, LD: late decision, GCA: gross congenital anomaly.

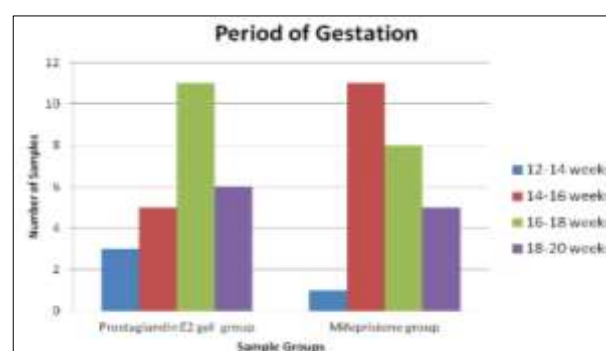


Figure 3: Distribution of women according to period of gestation.

Table 1: Induction-abortion interval.

Induction-abortion interval (hours)	Group 1		Group 2	
	No. of women (n=25)	Percentage	No. of women (n=25)	Percentage
1-7 hours	16	64	12	48
7-13 hours	6	24	12	48
13-19 hours	3	12	1	4
Mean±SD	6.50±3.54 hours		7.33±2.5 hours	
P value	0.344			

The period of gestation at MTP ranged from 13.2 weeks to 20 weeks with mean gestation of 16.42±1.864 weeks in group 1 and 16.10±1.855 weeks in Group 2 (Figure 3). The association between period of gestation in the 2 groups were statistically not significant (p value 0.546).

Table 1 shows induction-abortion interval. In Group 1 (prostaglandin E2 gel group), 16 women (64%) aborted in 1-7 hours, 6 women (24%) aborted in 7-13 hours and 3 women aborted in 13-19 hours. In Group 1, the minimum induction abortion interval was 1.30 hours, maximum induction abortion interval was 15 hours.

The mean induction abortion interval in Group 1 was 6.5±3.45 hours. Group 2, 12 women (48%) aborted in 1-7 and 7-13 hours, each. One woman (4%) aborted in 13-19 hours. In Group 2 (mifepristone group), the minimum

induction abortion interval was 2 hours, maximum induction abortion interval was 13.30 hours. The mean induction abortion interval in Group 2 was 7.33±2.5 hours. The mean induction abortion interval in Group 1 was less than Group 2, although it was not statistically significant (p value 0.344).

Success rate: success was defined as complete abortion (foetus with complete placenta) occurring with a maximum of 5 doses of misoprostol (that is, within 3 hr of last dose of misoprostol). In Group 1 (prostaglandin E2 gel group), 22 out of 25 women had complete abortion within 15 hours, with success rate of 88%. 2 women required surgical evacuation and one woman aborted at 17 hours, so failure rate was 12%.

Mean blood loss in Group 1 was 195±60.8 ml. In Group 2 (mifepristone group), minimum blood loss was 100 ml,

maximum blood loss was 350 ml. Mean blood loss was 194.2 ± 66.98 ml. The association between blood loss in the 2 groups was statistically not significant (p -value=0.965). In Group 1, mean fall in Hb was 0.68 ± 0.42 gm/dl. In Group 2 (mifepristone group), minimum fall in Hb was 0.4 gm/dl, maximum fall in Hb was 2.0 gm/dl. In Group 2, mean fall in Hb was 0.91 ± 0.47 gm/dl. Most women had a fall in haemoglobin ≤ 1 gm/dl (88% in Group 1 and 72% in Group 2). The association between fall in Hb in the 2 groups were statistically not significant (p value 0.071).

Incidence of side effects including fever, chills/shivering, vomiting and headache. Fever occurred in 30% of women in each group. Most women developed fever after 3rd and 4th dose of misoprostol. Schedule was not discontinued. Injectable paracetamol was given for $T > 100^\circ\text{F}$. Chills/shivering occurred in 3 women (12%) in Group 1 and 2 women (8%) in Group 2. Vomiting occurred in 2 women (8%) in Group 1 and 3 women (12%) in Group 2. None of the subjects had diarrhoea.

DISCUSSION

In the present study, 50 women were selected seeking MTP between 13 to 20 weeks of gestation. They were randomised in two groups of 25 women in each group, to receive two regimens for MTP, One with PGE2 gel with misoprostol and second with mifepristone and Misoprostol. Efficacy and side effects of both groups were compared.

The mean induction-abortion interval in Group 1 was 6.50 ± 3.54 hours and in Group 2 was 7.33 ± 2.5 hours. In Group 1, success rate at 15 hours was 88%. Success rate increases if more time is given after 5 doses of misoprostol. Success rate increases from 88% at 15 hours to 92% at 24 hours in Group 1. In Group 2, success rate was 92% both at 15 and 24 hours. Surgical evacuation was required in 8% women in both groups 1 and 2 due to incomplete abortion.

Ashok et al gave 200 mg oral mifepristone, followed after 36-48 hours by 800 µg vaginal misoprostol.¹⁵ After 3 hours, oral misoprostol 400 µg was given 3 hourly for 4 doses (total 5 doses) in 999 women at 13-21 week of gestation. Success rate was 97.1% taking expulsion of foetus with or without placenta within 15 hours. With the same criteria, success rate in present study would be 96% in Group 1 and 100% in Group 2.

Gupta et al gave 200 mg mifepristone orally, followed by 800 µg vaginal misoprostol after 36-48 hours.¹⁶ After another 4-6 hours, 400 mcg misoprostol either orally or sublingually was given 3 hourly in 70 women at 13-20 weeks. of gestation. Success was taken as expulsion of foetus with placenta within 15 hours of first dose of misoprostol, success rate was 91.42 % at 15 hours. With the same criteria, success rate in this study is 88% in Group 1 and 92 % in Group 2.

Surgical intervention was required in case of incomplete expulsion of placenta. In the present study, surgical intervention was required in 8% women (2 out of 25 women) in both Group 1 and Group 2. This result is comparable to 8.1% surgical intervention rate in the study by Ashok et al (81 women out of 999 women) for retained placenta and heavy bleeding.¹⁵

One woman (2.5%) out of 40 women required surgical evacuation in study by Hammada et al.¹⁷ The rate of surgical evacuation was 10% (5 out of 50) in study by Bartley et al.¹⁸

Gupta et al needed surgical evacuation in 7.14% (5 out of 70) women.¹⁶

Success rate at 24 hours: success rate increases if more time is given after 5 doses of misoprostol. In present study, success rate increased from 88% at 15 hours to 92% at 24 hours in Group 1. In Group 2, success rate was 92% both at 15 and 24 hours. surgical evacuation was required in 8% women in both groups 1 and 2 due to incomplete abortion. All women aborted foetus (100%) at 24 hours without placenta in both groups 1 and 2.

Ashok et al found success rate at 15 and 24 hours was same (97.1 %) in 999 women. If abortion does not take place in 24 hours, repeat mifepristone followed by vaginal misoprostol (800 µg followed by 400 µg 3 hourly for 5 doses) was given.¹⁵ If women do not abort on second regimen, a third dose of mifepristone 200 mg and gemeprost 1 mg vaginal pessary 3 hourly for maximum of 5 doses was given. 19 women (1.9%) aborted on second regimen. 9 women (0.9%) aborted on third regimen with gemeprost and one (0.1%) aborted on fourth regimen with repeat dose of gemeprost.

Gupta et al found complete abortion at 15 and 24 hours was similar (91.42%) in 70 women. One woman failed to abort within 24 hours was given ethacridine lactate and aborted.¹⁶

Bartley et al found that at 24 hours, 94 % women (47 out of 50) aborted foetus with or without placenta.¹⁸ In present study expulsion of foetus with or without placenta at 24 hours is higher (100% in both groups) as all doses of misoprostol are given vaginally compared to oral doses (last 4 doses) in Bartley study.

CONCLUSION

It is concluded that both the drug regimen for second trimester abortion are effective and had 92% complete abortion (foetus with placenta) rate at 24 hours. 100% women aborted foetus (with or without placenta) at 24 hours. Both regimens are safe and have a few minor side effects. There was no major side effect and blood loss was within acceptable limits in both groups. The cost of abortifacient in Group 1 was significantly less than Group 2. The duration of hospital stay was significantly less in

Group 1 than Group 2. These two factors make Group 1 regimen more economic and socially acceptable, which is cheaper and allows early discharge from hospital.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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