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Randomised controlled trial of misoprostol alone and mifepristone followed by misoprostol in second trimester medical termination of pregnancy

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Abstract

Introduction: Although the majority of abortions are performed in first trimester, there is still a need for second trimester MTP due to delayed diagnosis of fetal anomalies, financial difficulties in obtaining abortion services and failure to recognize undesired pregnancy in first trimester. Research suggests that with mifepristone pretreatment lower doses of misoprostol may be sufficient to achieve comparable efficacy. However there is little information on optimal medical regimen using mifepristone and misoprostol for second trimester MTP.

Objectives: To compare Induction Abortion Interval (IAI), to evaluate completeness of abortion and to assess the safety of drugs.

Methodology: This study was prospective comparative Randomized Controlled Trial without blinding where 56 eligible women were randomly divided in to two groups. In study group tablet Mifepristone 200 mg was given orally to the selected women. After 24 hrs, tablet Misoprosotol 400mcg was kept pervaginally every 3 hourly to a maximum of 5 doses. In control group, only tablet Misoprostol 400mcg was kept pervaginally every 3 hourly to a maximum of 5 doses.

Results: In Misoprostol alone group mean IAI was 11.18 hrs while in combined group it was 8.51 hrs. In Misoprostol alone group 78.6% cases had complete abortion while in combined group it was 96.4%. Side effects were more common in misoprostol alone group.

Conclusion: Using combination of mifepristone and misoprostol is a safe, non invasive method with a high success rate, short IAI, less side effects

Keywords: mifepristone, misoprostol, pregnancy

Introduction

Abortion is the termination of pregnancy by the removal or expulsion from uterus of a fetus or embryo prior to viability [1]. According to MTP Act, medical termination of pregnancy in India is allowed up to 20 weeks [2]. However, there is no ideal method for MTP between 13 and 20 weeks resulting more unsafe abortion during this period.

Worldwide 42 million legal abortion and 10-12 million clandestine abortion takes place every year of which 10-15% is performed in second trimester [3]. There is gradual increase in second trimester abortion because of the wide scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities such as cardiovascular and skeletal malformation and sex linked genetic and metabolic disorders. Two third of major abortion related complications and half of abortion related mortality occur in pregnancies terminated after 13 weeks of gestation [4].

Previously various methods medical or surgical, either alone or in combination were used to perform MTP in second trimester. Medical method of abortion has the advantage over surgical methods as it is non-invasive. Hence, no complication of anesthesia and administration of drugs are easy in medical methods [5].

Medical abortion in the second trimester with misoprostol alone has been shown to be effective, although in comparison with the combination of mifepristone and misoprostol, misoprostol-only protocols have required higher doses, side effects are more common and the time to complete the abortion is extended [6]. Higher doses (600 and 800 mcg) have shown comparable successful abortion rates but are associated with higher rates of side effects. The 3 hour interval is more effective than 6 hours interval [7].

The induction-to-abortion interval seems to affect acceptability as shorter time intervals often correspond to shorter hospital stays, likely resulting in lower cost for treatment. With this background, the present study was undertaken to analyze the usage of Mifepristone and Misoprostol for a safe and effective medical method of abortion in second trimester of pregnancy.

Aim: To Compare Misoprostol alone with Mifepristone followed by Misoprostol in second trimester medical termination of pregnancy

Objectives: To compare Induction Abortion Interval, to evaluate Completeness of abortion & to assess the Safety of drugs

Methodology

The study was conducted in Obstetrics and Gynaecology Department of Tertiary Health Centre in need of second trimester termination i.e. 13-20 weeks of pregnancy. The study was conducted from 1st July 2015 to 30th June 2017. The calculated sample size was 56. This study was prospective comparative Randomized Controlled Trial without blinding where study population (eligible women) were randomly divided in to two groups and underwent intervention.

Pregnant women having 13 to 20 weeks of pregnancies that fulfilled indications of MTP, as per guidelines of MTP Act of 1971 [8]. Were included in the study. The indications for MTP are pregnancy involve a risk to the life of the pregnant woman or of the grave injury to her physical or mental health**;** substantial risk that if child were born, it would suffer physical or mental abnormalities as to be seriously handicapped**;** pregnancy caused by rape**;** pregnancy resulting from contraceptive failure. Women selected were assessed for following conditions and any women with previous allergic reaction to one of the drugs involved; inherited porphyria; chronic adrenal failure; pregnancy with placenta previa; scarred uterus; acute renal failure; woman on long-term corticosteroid therapy (including those with severe, uncontrolled asthma); women with hemorrhagic disorder; severe anaemia; women with pre-existing heart disease were excluded from the study.

Once the informed consent was taken and intervention group was assigned, all cases under went detailed clinical evaluation. A detailed social, medical and surgical, menstrual and obstetric history was taken. Detailed physical examination including general examination, systemic examination, per vaginal examination, blood pressure measurement, cardiovascular system, respiratory system and bimanual examination was done. Investigation like Hb, BT, CT, Urine analysis, Blood grouping and typing, BSL, HIV, HbsAg, HCV and Ultrasonography were carried out for each case.

Intervention

Study group: Tablet Mifepristone 200 mg was given orally with water to the selected women. After 24 hrs patient, 400mcg Misoprosotol tablet was kept pervaginally every 3 hourly to a maximum of 5 doses.

Control Group: In control group, the selected women were admitted in the hospital and only 400mcg Misoprostol tablet was kept pervaginally every 3 hourly to a maximum of 5 doses.

Operational definitions used in the study

Success: It defined as complete expulsion of products of conception within 24hrs of first dose of Misoprosotol.

Failure: It was defined as no expulsion of products of conception within 24hrs of first dose of Misoprosotol or the occurrence of systemic adverse effects, signs and symptoms severe enough to preclude further use of the drug

Incomplete: in cases where whole or part of placenta was retained. If placenta was retained patient was posted for surgical evacuation of uterus under anaesthesia.

Induction abortion interval: Time period between the first dose of Misoprosotol to complete abortion.

At the end of the procedure we looked for following outcomes:

Primary outcome: Induction abortion interval; completeness of abortion.

Secondary outcome: side effects –nausea, vomiting, bleeding, diarrhoea, fever, shivering, headache; incomplete abortion requiring surgical intervention.

Results

Table 1: Comparison of age of the cases in Mifepristone plus misoprostol group and Misoprostol alone group

Age	Mifepristone & misoprostol (n=28)		Misoprostol (n=28)	
	Cases	Percentage	Cases	Percentage
<20 yrs	2	7.1%	4	14.3%
20-25 yrs	10	35.7%	7	25.0%
25-30 yrs	12	42.9%	7	25.0%
>30 yrs	4	14.3%	10	35.7%
Total	28	100.0%	28	100.0%
Mean in years*	25 ± 4.07 years		26.61 ± 5.81 years	

*t test p value - 0.236 non significant

Table 2: Comparison of Gravidity of the cases in Mifepristone plus misoprostol group and Misoprostol alone group

Gravidity	Mifepristone & misoprostol (n=28)		Misoprostol (n=28)	
	Cases	Percentage	Cases	Percentage
1 (primi)	13	46.4%	9	32.1%
>1 (multi)	15	53.6%	17	67.9%
Total	28	100.00%	28	100.00%
Mean*	2.36 ± 1.54		2.36 ± 1.28	

*t test p value 1.000

Table 3: Comparison of Parity of the cases in Mifepristone plus misoprostol group and Misoprostol alone group

Parity	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
0 (nulli)	15	53.6%	10	35.7%
1 or more (parous)	13	46.4%	18	64.3%
Total	50	28%	28	100.0%
Mean	1.00 ± 1.33		1.07 ± 0.940	

P value 0.818

Table 4: Comparison of Gestational age of the cases in Mifepristone plus misoprostol group and Misoprostol alone group

Gestational age (in completed weeks)	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
13-14	4	14.3%	5	17.9%
15-16	7	25.0%	8	28.6%
17-18	8	28.6%	10	35.7%
19-20	9	32.1%	5	17.9%
Total	28	100.0%	28	100.0%
Mean in weeks	17.43 ± 2.974		16.71 ± 2.034	

P value 0.672

There was no stastically significamt difference in both the groups in terms of age, gravidity, parity and gestational age.

Table 5: Comparison of IAI duration in Mifepristone plus misoprostol group and Misoprostol alone group

IAI* duration in hours	Mifepristone & misoprostol (n=28)		Misoprostol (n=28)	
	Cases	Percentage	Cases	Percentage
0-3	0	0.0%	0	0.0%
3-6	10	35.7%	0	0.0%
6-9	7	25.0%	7	25.0%
9-12	6	21.4%	9	32.1%
12-15	5	17.9%	10	35.7%
>15	0	0.0%	2	7.1%
Mean ± SD#	8.51 ± 3.395		11.18 ± 2.639	

* Induction Abortion Interval; # p<0.01 using unpaired t test

In Mifepristone & misoprostol group mean IAI duration was 8.51 hours while in Misoprostol alone group it was 11.18 hours. Mean IAI duration was significantly higher in Misoprostol alone group.

Table 6: Comparison of Outcome of cases in Mifepristone plus misoprostol group and Misoprostol alone group

Outcome	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
Incomplete Abortion	1	3.6%	6	21.4%
Complete Abortion	27	96.4%	22	78.6%

Unpaired t test P value= 0.0433

In Mifepristone & misoprostol group 96.4% cases were completely aborted while in Misoprostol alone group 78.6% cases had complete abortion. Application of statistical indicate significant difference in complete abortion rate in both group (p<0.05).

Table 7: Comparison of Surgical Intervention of cases in Mifepristone plus misoprostol group and Misoprostol alone group

Surgical Intervention	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
Not required	27	96.4%	22	78.6%
Required	1	3.6%	6	21.4%

P value= 0.0433

In Mifepristone & Misoprostol group 3.6% cases required surgical intervention while in Misoprostol alone group 6 cases (21.4%) required it. This difference is statistically significant in both group (p<0.05).

Table 8: Comparison of Side effects in Mifepristone plus misoprostol group and Misoprostol alone group

Side Effects	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
Nausea	1	3.6%	0	0.0%
Vomiting	0	0.0%	1	3.6%
Diarrhoea	1	3.6%	2	7.1%
Fever	13	46.4%	15	53.6%
Headache	4	14.3%	6	21.4%
Rigor	10	35.7%	10	35.7%
Bleeding	1	3.6%	0	0.0%

Fever is the commonest side effect found in around half of the cases in both group. Rigor was found in 35.7% in both group while headache was other common side effect found in both the group i.e in 14.3% in Mifepristone & misoprostol and in 21.4% in Misoprostol group. Severe bleeding was found in one cases in Mifepristone plus misoprostol group.

Table 9: Comparison of Total Dose of Misoprostol in Mifepristone plus Misoprostol group and Misoprostol alone group

Total Dose of Misoprostol (in mcg)	Mifepristone & misoprostol (n=28)		Misoprostol(n=28)	
	Cases	Percentage	Cases	Percentage
400	2	7.1%	0	0.0%
800	11	39.3%	1	3.6%
1200	8	28.6%	9	32.1%
1600	5	17.9%	14	50.0%
2000	2	7.1%	4	14.3%
Total	28	100.0%	28	100.0%
Dose (Mean ± SD)*	1114.29±426.63		1500± 300.61	

*P value <0.001

In Mifepristone & Misoprostol group average 1114.29 microgram of Misoprostol was used while in Misoprostol alone group 1500 microgram was required. This difference is statistically significant in both group (p<0.05).

Discussion

Second trimester pregnancy termination is still a complicated procedure in developing countries especially in rural areas. This interventional study was conducted among 56 women in need of second trimester termination

Induction Abortion Interval (IAI)

In present study in Mifepristone & Misoprostol group mean IAI duration was 8.36 hrs while in Misoprostol alone group it was 11.18 hrs. Similar results was also observed in a study by Tripti N *et al.* 2011 [9]. where the induction abortion interval was significantly shorter 6.72 ± 2.26 hrs in the study group while it was 12.29 ± 3.41 hrs in the Misoprostol alone group. (P<0.001). Patel U *et al.* in 2013 [10]. Enrolled total 50 eligible women for the study and were divided in two groups of 25 cases each in study group and control group. Women in the case group were given Tablet Mifepristone (200 mg) orally followed by Tablet Misoprostol (200 mcg) vaginally after 24

hrs which may be repeated every 6 hrs till 5 doses. Women in control group were given Tablet Misoprostol (200 mcg) vaginally which may be repeated every 6 hrs till 5 doses. This study found that there was significant difference in the IAI in both the groups, the mean IAI of 18.94 hrs for Group A, whereas in Group B it was 24.29 hrs. Rodger *et al.* [11]. In a double blind study using 600 mg mifepristone 36 hrs prior to gemeprost found that the IAI was significantly reduced to 6.8 hrs as compared to 15.8 hrs in the placebo group. Similar results had been observed by other authors as well using mifepristone followed by prostaglandins [12, 13, 14, 15].

Outcome of abortion: Complete abortion rate

In present study in Mifepristone & Misoprostol group 96.4% cases had complete abortion while in Misoprostol alone group 78.6% cases had complete abortion. In a study by Tripti N *et al.* 2011 [9]. the complete abortion rate was 95% in conbined group while it was 90% in Misoprostol only group. Patel U *et al.* 2013 [10]. In their study found that in combined group the success rate was 84%, while in Misoprostol alone group, the success rate was 60%. All unsuccessful cases required oxytocin augmentation. This difference was found to be statistically significant (P<0.05). In the present study in Mifepristone & Misoprostol one required surgical intervention while in Misoprostol alone group 6 cases (21.4%) required it. This difference is statistically significant in both group (p<0.05). So, requirement of surgical intervention was significantly more in Misoprostol group as compared to two drug group. A 2011 Cochrane review [16]. To compare different methods of second trimester medical termination of pregnancy for their efficacy and side-effects (Wildschut) found: "A range of doses of vaginally administered misoprostol has been used. However low doses of misoprostol appear to be associated with fewer side-effects while moderate doses appear to be more efficient in completing abortion. Four RCTs showed that the induction to abortion interval with 3-hourly vaginal administration of prostaglandins is shorter than 6-hourly. Koh *et al.* [17]. Compared women who received misoprostol 400 mcg (n = 40), misoprostol 200 mcg (n = 37) or gemeprost 1 mg (n = 39) which was administered vaginally at 4 hour intervals up to five doses or until termination of pregnancy (TOP) occurred. The misoprostol 400 mcg group had the highest incidence of successful TOPs (92.5%) as compared to the misoprosto1 200 mcg (70.3%; P = 0.017). The misoprostol 400 mcg group had the highest incidence of fever (70.0%) as compared to misoprostol 200 mcg (24.3%; P < 0.001). Pongsatha *et al.* [18]. Compared a vaginal misoprostol loading dose regimen (600 mcg, then 400 mcg every 6 hourly) with a non-loading dose regimen (400 mcg every 6 hourly) in 157 women. They found that vaginal misoprostol in the loading dose regimen had a similar efficacy to the non-loading dose regimen but was associated with more adverse maternal effects. Brouns *et al.* [19]. Studied 167 women who ingested mifepristone 200 mg, followed by either 200 or 400 mcg misoprostol given vaginally beginning 36-48 hrs later at 4-hr intervals (with a maximum of 10 administrations in 48 hrs) until the fetus was delivered. Both regimens used in this trial proved to be equally effective for termination of both viable and non-viable pregnancies during the second trimester. The time between the first administration of misoprostol and delivery of the fetus was significantly longer in the 200-mcg group than in the 400-mcg group. Chaudhuri *et al.* [20]. Compared 185 women who were given 400 mcg vaginal misoprostol either every 6 hourly (group 1) or every 12 hourly (group 2) for a maximum of four doses. The mean induction abortion interval in group 1 (12.59 hrs) was significantly shorter (P < 0.001) than that in the group 2 (16.41 hrs). The percentage of women who achieved successful abortion within 12 hrs in group 1 (56.52%) was also significantly higher (P = 0.00005) than that in group 2 (25.80%). The incidence of side-effects was comparable and not clinically serious.

Dose of mifepristone and misoprostol

In Mifepristone & Misoprostol group average 1114.29 microgram Misoprostol was used while in Misoprostol alone group 1500 microgram was required. In a study by Tripti N *et al.* 2011 [9]. the mean dose of Misoprostol required was 1,186 ± 291.64 in study group whereas it was 1,736 ± 320.20 in control group. In a study by Patel U *et al.* [10]. In the Mifepristone & Misoprostol group the average dosage of Misoprostol required for abortion was 122 mcg. The dosage of Misoprostol required for abortion in Misoprostol only group was 696 mcg.

Side effect of drugs

In the present study fever, headache and rigor were the most common side effects found in both the groups. Bleeding was found in one case in Mifepristone plus Misoprostol group. In a study by Tripti N *et al.* 2011 [9]. the commonly observed side effects were nausea, vomiting, fever, abdominal cramp and diarrhea. Patel U *et al.* 2013 [10]. In their study found that side effects were more in Misoprostol alone group as compared to Mifepristone & Misoprostol combined group.

Conclusion

From the present study we can conclude that in Second trimester termination of the pregnancy, using combination of mifepristone and misoprostol is a safe, non invasive method with a high success rate and a short IAI. Pre-treatment with mifepristone adds to the effectiveness of the misoprostol as an abortifacient and also significantly reduces its dose. Side effect and blood loss during the procedure was almost similar for misoprostol alone as well as for combination of mifepristone and misoprostol.

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