A Comparative Study of Misoprostol Only and Mifepristone Plus Misoprostol in Second Trimester Termination of Pregnancy

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Abstract

Objective To compare the effectiveness, success rate and induction to abortion interval between administration of misoprostol only and mifepristone with misoprostol in second trimester abortions (14–20 weeks).

Materials and methods The study was conducted by dividing women approaching for second trimester termination, into two groups each consisting of 100 women.

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Group-I received only misoprostol; 600 mcg initial vaginal insertion followed by 400 mcg sublingually every 3 h until termination. Women in Group-II received mifepristone 200 mg and after 24 h started with 600 mcg misoprostol, per vaginal followed by 400 mcg sublingually till abortion was completed, up to a maximum of five doses in both groups.

Results The success rate in Group-I was 89 %, whereas in Group-II it was 96 %. The mean induction abortion interval in Group-I was 10.67 ± 3.96 h compared to Group-II which was significantly less 6.19 ± 2.70 h (p value < 0.01). The mean dose of misoprostol in Group-I was 1610 ± 511.18 mcg and in Group-II, it was lesser 1046 ± 392.71 mcg (p value < 0.01). There was significant difference in the mean blood loss also, 97.20 ± 36.35 ml in Group-I and 52.55 ± 27.96 ml in Group-II. Also among the individual groups multigravidae and lower gestational age (< 17 weeks), women had lesser IAI as well as lesser misoprostol dose was required.

Conclusion Pretreatment with mifepristone significantly reduces the induction abortion interval and the misoprostol dose along with minimal blood loss.

Keywords Misoprostol · Mifepristone · Second trimester · Termination

Introduction

Over the past two decades, the health evidence technologies and human rights rationale for providing safe, comprehensive abortion care have evolved greatly. Despite these advances, an estimated 22 million abortions continue to be performed unsafely each year resulting in the death of an estimated 47,000 women and disabilities for an additional 5 million women [1].

MTP Act was passed by the Indian Parliament in 1971 and came into force from April 1, 1972, and revised again in 1975. Under this Act, termination of pregnancy can be performed up to 20 weeks of gestation where the pregnancy exceeds 12 weeks and not more than 20 weeks (second trimester abortion), the opinion of two registered medical practitioners is required to terminate the pregnancy.

Medical methods of abortion have been proved to be safe and effective [2]. The most effective regimens rely on the antiprogesterin, mifepristone, which binds to progesterone receptors resulting in necrosis and detachment of placenta. It also softens the cervix and causes mild uterine contractions. It sensitizes the uterus to the action of prostaglandin which is given 1–2 days later, like synthetic prostaglandin E1 analogue, misoprostol, which binds to myometrial cells causing strong myometrial contractions and causes cervical softening and dilatation. This leads to expulsion of fetus from the uterus [3].

The effects of medical methods of abortion are similar to those associated with spontaneous abortion and include uterine cramping and prolonged menstrual-like bleeding. Bleeding occurs 9 days on an average but can last up to 45 days in rare cases [4].

Materials and Methods

A prospective randomized control study was conducted by selecting at random 200 cases, attending family planning out-patient at Jyothi Maternity Center from April 2013 to May 2014.

Healthy women requesting for termination of pregnancy between 14 and 20 weeks were selected. A detailed history was taken, clinical examination including gynecological examination and ultrasonography was performed. The

inclusion criteria were: (1) women aged more than 18 Years, (2) singleton pregnancy, (3) closed cervical os, (4) no vaginal bleeding, (5) a legal indication for termination of pregnancy and official approval, (6) willing to follow the study protocol and provide informed consent and (7) willing to undergo required follow-up and surgical management when indicated.

The exclusion criteria were women with (1) missed abortion (dead fetus), (2) multiple pregnancy, (3) nursing mothers, (4) contraindications to mifepristone and misoprostol like chronic or acute adrenal, hepatic or renal failure, (5) cardiovascular disease, (6) inherited porphyria, (7) sickle cell anemia, (8) poorly controlled seizure disorder, (9) on anticoagulant therapy, known clotting defect, (9) hemoglobin less than 10 g/dl and (10) known or suspected pelvic infection.

Women who fulfilled the criteria for the trial were interviewed and given an explanation of the trial. An informed written consent was obtained. A pelvic ultrasound examination was performed to confirm the gestation and to exclude multiple pregnancy and missed abortion.

Women assigned to Group-I were given misoprostol 600 mcg inserted in the posterior fornix, followed by 400 mcg sublingually every 3 h until the abortion occurred or up to a maximum of five doses in 24 h. Women in Group-II were given mifepristone 200 mg stat dose and then after 24 h admitted and started on misoprostol 600 mcg in the posterior vaginal fornix, followed by 400 mcg sublingually until abortion or a maximum of five doses.

The side effects including nausea, vomiting, diarrhea and fever were recorded. The blood pressure, pulse, temperature and frequency of uterine contractions are monitored every 3rd hourly. After abortion, the products of gestation (fetus and placenta) were examined to see whether the abortion was complete. After fetal expulsion if placenta is not expelled within 15–20 min, 20 units of oxytocin in 500 ml of lactated Ringer solution at 125 ml/hr is started until delivery of whole placenta or pieces if any. If placenta partial or complete is retained for more, then 2-h surgical evacuation under general anesthesia was performed. Rh antibody was given to Rh negative mothers.

The induction abortion interval was defined as the interval between the time of administration of the first dose of misoprostol to the time when fetus aborted. Complete abortion was defined as the expulsion of both the fetus and the placenta without operative intervention. The amount of blood loss during abortion was assessed clinically and recorded. The number of doses of misoprostol required are calculated and recorded.

The differences in the means of continuous variables were analyzed with Student's *t* test for normally distributed data and with Levene's test for Equality of variances.

Table 1 Characteristics of abortion process

	Group-I		Group-II		
Successful abortion (%)	89		96		
<i>Induction abortion interval (IAI)</i>					
(1) Primi	12 h 20 min (740 min)		7 h 20 min (440 min)		
(2) Multi	8 h and 10 min (490 min)		4 h 40 min (280)		
(3) 14–17 weeks	8 h (480 min)		4 h 15 min (255 min)		
(4) 17–20 weeks	13 h 28 min (808 min)		7 h 40 min (460 min)		
<i>Misoprostol dose required</i>					
(1) Primi	1806 mcg		1196 mcg		
(2) Multi	1290 mcg		829 mcg		
(3) 14–17 weeks	1286 mcg		786 mcg		
(4) 17–20 weeks	1946 mcg		1242 mcg		
<i>Blood loss (ml)</i>					
(1) Primi	110 ml		53 ml		
(2) Multi	81 ml		48 ml		
(3) 14–17 weeks	81 ml		35 ml		
(4) 17–20 weeks	113 ml		62 ml		
Total					
	<i>N</i>	Minimum	Maximum	Mean	SD
Group-I: descriptive statistics ^a					
Age	100	18	40	24.33	4.708
Induction abortion interval	100	300	1160	640.40	237.435
Misoprostol	100	1000	2600	1610.00	511.188
Blood	100	40	200	97.20	36.351
Valid <i>N</i> (listwise)	100				
	<i>N</i>	Minimum	Maximum	Mean	SD
Group-II: descriptive statistics ^b					
Age	100	18	42	24.84	4.819
Induction abortion interval	100	120	760	371.90	162.049
Misoprostol	100	600	1800	1046.00	392.717
Blood	100	20	100	52.55	27.956
Valid <i>N</i> (listwise)	100				

Group-I: {^a VAR00001 = 1.00}Group-II: {^b VAR00001 = 2.00}

Results

As far as the demographic characteristics were concerned the difference was insignificant. In Group-I the women were aged between 18 and 40 years, where as in Group-II the women were 18–42 years. In Group-I there were 62 primigravida and 38 multigravida where as in Group-II, 59 and 41, respectively. Gestational age less than 17 weeks, 51 women in Group-I and 42 in Group-II; women with gestational age more than 17 weeks, 49 in Group-I and 58 in Group-II. The incidence of side effects was similar in both Groups, nausea (7 %), vomiting (8 %), diarrhea (4 %), headache (2 %), fever (7 %) and shivering (5 %).

The outcome as shown in Table 1, the successful abortion rate in Group-I was 89 %, 89 women had complete abortion, while out of the rest 11 women, 5 women had retained placenta, of which 2 were expelled with 20U oxytocin drip, 3 needed surgical evacuation under general anesthesia, while the rest 6 women needed oxytocin infusion for expulsion of placental bits. In Group-I, the mean induction abortion interval (Fig. 1) was 10.67 h (640.40 min), primigravidae had an IAI of 12.20 h (740 min) and multigravidae 8.10 h (490 min), gestational age between 14 and 17 weeks had an IAI of 8 h (480 min) and 17–20 weeks 13.28 h (808 min). The mean dose of misoprostol (Fig. 2) required was 1610 mcg; primigravidae

Fig. 1 Difference of IAI between Group-I and Group-II

Fig. 2 Comparison of mean misoprostol dose required for completion of abortion

Fig. 3 Comparison of total amount of blood loss between two groups

Table 2 Overall analysis result

Group	N	Mean	SD	SEM
<i>Group statistics</i>				
Induction abortion interval				
I	100	640.40	237.435	23.744
II	100	371.90	162.049	16.205
Misoprostol				
I	100	1610.00	511.188	51.119
II	100	1046.00	392.717	39.272
Blood				
I	100	97.20	36.351	3.635
II	100	52.55	27.956	2.796
Age				
I	100	24.33	4.708	.471
II	100	24.84	4.819	.482

Table 3 Independent sample t test

	Levene's test for equality of variances		t test for equality of means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95 % confidence interval of the difference	
								Lower	Upper
Induction Abortion Interval	13.752	.000	9.340	198	.000	268.500	28.746	211.812	325.188
			9.340	174.786	.000	268.500	28.746	211.765	325.235
Misoprostol	9.882	.002	8.749	198	.000	564.000	64.462	436.879	691.121
			8.749	185.669	.000	564.000	64.462	436.827	691.173
Blood	.035	.852	9.737	198	.000	44.650	4.586	35.607	53.693
			9.737	185.760	.000	44.650	4.586	35.603	53.697
Age	.082	.775	-.757	198	.450	-.510	.674	-1.839	.819
			-.757	197.891	.450	-.510	.674	-1.839	.819

Bold numbers are the *p* values to find the difference in mean values of different parameters between two groups the above table shows that induction abortion interval, misoprostol dosage required and the blood loss are lesser in Group-II (mifepristone + misoprostol group) when compared to Group-I (misoprostol only) and this difference is statistically significant ($p < 0.01$). There was no significant difference in the mean age of both the groups ($p > 0.05$)

required 1806 mcg and multigravidae required 1290 mcg; gestational age between 14 and 17 weeks required 1286 mcg and 17 to 20 weeks required 1946 mcg. The mean blood loss (Fig. 3) was 97.20 ml; in primigravidae it was 110 ml and in multigravidae it was 74 ml; in gestational age 14–17 weeks it was 81 ml and 17–20 weeks it was 113 ml.

In Group-II out of 100 women, 96 women aborted completely, one woman had retained placenta which needed surgical evacuation under general anesthesia, and three women had placental bits which were expelled after oxytocin infusion. The mean IAI (Fig. 1) was 6.19 h (371.90 min); primigravidae aborted in 7.20 h (440 min) and multigravidae in 4.40 h (280 min); gestational age 14–17 weeks aborted in 4.15 h (255 min) and

17–20 weeks aborted in 7.40 h (460 min). The mean dose of misoprostol required (Fig. 2) was 1046 mcg; primigravidae required 1196 mcg and multigravidae required 829 mcg; gestational age between 14 and 17 weeks required 786 mcg and 17 to 20 weeks required 1242 mcg. The mean blood loss (Fig. 3) was 52.55 ml; primigravidae had a blood loss of 53 ml and multigravidae had 48 ml; gestational age between 14 and 17 weeks had 35 ml and 17–20 weeks had 62 ml blood loss.

From Table 2, it is clear that there is significant difference in the IAI, mean dose of misoprostol required and blood loss (p value < 0.01) in both the groups. Also in the individual groups, there was significant difference between primigravidae and multigravidae as well as gestational age 14–17 weeks and 17–20 weeks.

Discussion

This trial compared the difference in IAI, dose of misoprostol required and amount of blood loss in second trimester abortions with misoprostol only and mifepristone plus misoprostol. There was no difference in the prevalence of gastrointestinal side effects between the two groups. Nearly all the women in our study aborted before 24 h like in other similar studies conducted by Elami et al. [5], Dickinson et al. [6], Borgatta and Kapp [7] reported a success rate of 95 % within 24 h. In our study, the success rate was 89 % in Group-I and 96 % in Group-II (Table 1).

In our study the mean IAI in Group-I was 10.67 ± 3.96 h, where as in group-II it was 6.19 ± 2.70 h which was significantly lower with a p value <0.01 (Table 3). Modak et al. [8] in a comparative study of sublingual and vaginal misoprostol in second trimester abortions reported a complete abortion at 24 h of 79.41 % (in sublingual group) and mean IAI of 12.28 h. Ngoc et al. [9] in their double blind study reported the mean IAI was statistically shorter for mifepristone plus misoprostol group compared to misoprostol only group (8.1 h and 10.6 h, respectively, with a p value of <0.01). Rasha et al. [10] in their study reported mean IAI of 10.4 ± 6.8 h in mifepristone group and 20.6 ± 9.7 h in misoprostol only group. Reduction in induction to abortion interval is likely to improve the acceptability of women [9]. Wildschut et al. [11] in their review article on medical methods for mid-trimester termination of pregnancy suggested that mifepristone plus misoprostol is the most efficient regimen and 3-hourly intervals of misoprostol administration are more effective than 6-hourly intervals. Mifepristone enhances the action of misoprostol there by reducing the induction to abortion interval and dose of misoprostol [3]. The mean dose of misoprostol required in Group-II (1046 ± 392.71 mcg) was significantly lower (p value <0.01 , Table 3) compared to Group-I (1610 ± 511.18 mcg) like in other similar studies [9].

Multigravidae and women with gestational age <17 weeks aborted faster and required lesser misoprostol dose than primigravidae and women with <17 weeks gestation in our study. Heini et al. [12] in their study of clinical efficacy of mifepristone and misoprostol in second trimester termination showed majority 94 % of women (<8 h), also multiparous and women with early gestation completed medical termination faster. Mentula et al. [13] in their study reported the median number of misoprostol doses required was 3, and the median IAI was 8.5 h (in 1 day group). The median IAI was 3 h longer in primigravidae and gestational age >16 weeks. We thus speculate that optimizing myometrial contractility is important when treating women whose gestation exceeds 16 weeks as they

seem to be in a risk for longer IAI. Elami et al. [5] in their study showed in women with gestation <19 weeks; the mean expulsion time was 7.7 ± 6 h where as in women with >19 weeks gestation, it was 11.2 ± 6.9 h, also the time of expulsion was shorter in multigravidae (7.9 ± 7 h) compared to nulligravidae (12.4 ± 10.3 h.).

We also observed that in Group-II the mean blood loss (52.55 ml) was less, probably due to shorter IAI. Hou et al. [14] in their study reported a total abortion rate of 95–100 % within 24 h, mean IAI was shorter in parous women (6.3 ± 3.7 h) and the mean blood loss 2 h after expulsion of products of conception was 98.3 ± 76.2 ml. Nagaria et al. [15] reported a success rate of 100 %, and the mean IAI interval was significantly shorter and the mean dose of misoprostol required was less in the mifepristone pretreated group. Also the mean blood loss was slightly higher in the misoprostol only group. Garg et al. [16] reported a success rate of 96 % in the buccal group in the second trimester abortion.

Conclusion

Outcome of the study is pretreatment with mifepristone significantly reduces the induction abortion interval, dose of misoprostol required and blood loss compared to using only misoprostol, thus increasing the patient compliance and thereby reducing the chances of septic abortions, morbidity and mortality. Multigravidae and women with early gestation completed the medical termination faster, this aspect needs further studies so that proper regimens can be developed for second trimester terminations and the hospital stay can be reduced.

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Compliance with Ethical Standards

Conflict of interest Dr Akkenapally Prasanna Latha declares that she has no conflict of interest.

Ethical Standards The study was conducted among the patients requesting for second trimester termination of pregnancy at Jyothi Maternity Center, a project of population health services of India (PHSI) Gaddianaram, Hyderabad, Telangana, India. A written and informed consent was taken from all the patients. The intervention involved in the study is routinely practiced at our center and is safe. The patients were given the right to opt out the study at any time they want. The defined guidelines of central ethics committee for biomedical research on human subjects by ICMR and guidelines as per Helsinki Declaration were strictly adherent in the present project.

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