The Journal of Obstetrics and Gynecology of India (September–October 2023) 73(5):428–433
https://doi.org/10.1007/s13224-023-01800-9

ORIGINAL ARTICLE

Randomised Control Study of Misoprostol and Mifepristone versus Misoprostol Alone in Second Trimester Termination of Pregnancy

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Received: 31 January 2023 / Accepted: 16 June 2023 / Published online: 18 July 2023

Abstract

Introduction This study was done to assess and compare the efficacy and safety of mifepristone and misoprostol combination versus misoprostol alone for second trimester termination of pregnancy in relation to induction abortion interval, average amount of misoprostol required in each group, success rate and side effects.

Materials and Methods This randomised control study was conducted on 100 women admitted in the Department of Obstetrics & Gynaecology, S.C.B. Medical College & Hospital, Cuttack, for second trimester termination of pregnancy, divided into two groups, Group A and Group B of 50 patients each. Group A patients received 200 mg of oral mifepristone followed by 400 mcg of vaginal misoprostol after 48 h, and then 400 mcg of vaginal misoprostol every 3 hourly until complete expulsion or up to a maximum of 6 doses. Group B patients received 400 mcg of vaginal misoprostol every 3 hourly until complete expulsion or up to maximum 6 doses.

Results Complete abortion was seen in 92% and 72% cases in Group A and Group B, respectively. Mean induction abortion interval was 11.59 ± 2.71 h in Group A and 15.57 ± 2.27 h in Group B (p value < 0.001). The average dose of misoprostol required was less in combination regimen, i.e. 1128 ± 384 mcg compared to 1680 ± 302 mcg in misoprostol alone group (p value < 0.001). Side effects like nausea, vomiting and diarrhoea were less in combination regimen than misoprostol alone group.

Conclusion Mifepristone and misoprostol combination is more effective and safer alternative than misoprostol alone in second trimester termination of pregnancy.

Keywords Second trimester termination of pregnancy · Mifepristone · Misoprostol · Induction–abortion interval

Introduction

Induced abortion is defined as purposeful termination of pregnancy before the period of viability. The number of induced abortions done in India each year is 67.27 per 1000 women [1]. Although abortion was legalised in India in 1972, illegal abortion is still five times more common than legal abortion. Around 5% of all abortions are unsafe [2]. The need for developing a safe and effective method for terminating pregnancy in the second trimester is increasing due to the increase in the use of antenatal diagnostic procedures like ultrasound, amniocentesis and cordocentesis. Despite the enactment of the MTP Act, a number of hurdles like insufficient infrastructural facilities, lack of awareness, social stigma and failure to ensure confidential care continue to prevent full access to safe and legal abortions, pushing women to avail of clandestine, unsafe abortions. Various methods of mid-trimester abortion include prostaglandins like PG E1 analogue (misoprostol), PG F 2α analogue (carboprost), dilatation and evacuation till 15 weeks, intrauterine instillation of hyperosmotic solution like—hypertonic urea (40%), saline (20%), extra amniotic-ethacridine lactate,

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oxytocin infusion and rarely hysterotomy. The wonder drug RU486 (mifepristone) functions as an anti-progesterone and prevents implantation and pregnancy development and sensitises the uterus to prostaglandins [3]. Misoprostol, a synthetic PGE1 analogue, is a potent abortifacient which stimulates the myometrium by binding to the E2 and E3 prostaglandin receptors, resulting in calcium influx and cAMP regulation, can be given via oral, vaginal, intracervical, intrauterine, sublingual and buccal routes in various regimens with induction abortion intervals ranging from 12 to 33 h [4]. Thus, a combination of both can significantly shorten the duration and improve the outcome of second trimester termination of pregnancy.

Materials and Methods

After obtaining approval from Institutional Ethics committee, this single blinded randomised controlled study was conducted on 100 selected cases who were admitted to S.C.B. Medical College & Hospital, Cuttack, Odisha, for second trimester termination of pregnancy from April 2021 to October 2022, over a period of 19 months. Patients were randomised into two groups of 50 each using envelopes labelled as Group A and Group B. The patients were blinded about the type of drugs received.

Inclusion Criteria

1. Women who gave consent to participate in the study.
2. Singleton pregnancy.
3. Gestational age 13–24 weeks as determined by last menstrual period and/or 1st trimester (early) ultrasound scan.
4. Women with one previous LSCS.

Exclusion criteria

1. Gestational age less than 12 weeks and more than 24 weeks.
2. Twin or multifetal pregnancy, molar pregnancy.
3. Women who had either taken MTP pill from outside or who came with inevitable or incomplete abortion.
4. Pre-existing bronchial asthma.
5. Confirmed or suspected extrauterine pregnancy.
6. Women on anticoagulant or with hypersensitivity to mifepristone or misoprostol.
7. Women with more than one previous LSCS.
8. Women with active pelvic gynaecological infection like salpingitis, cervicitis.

After taking written informed consent, a detailed history including menstrual and obstetrics history was taken, patients were examined, and ultrasound for gestational age estimation was done following which patients were randomly divided into two groups of 50 each using envelopes labelled as Group A and Group B. Group A patients received 200 mg of oral mifepristone. After 48 h, 400 mcg of vaginal misoprostol was administered in posterior fornix, followed by 400 mcg of vaginal misoprostol every 3 hourly until complete expulsion or up to a maximum of 6 doses. Group B patients were administered 400 mcg of vaginal misoprostol every 3 hourly until complete expulsion or up to a maximum of 6 doses. The cases were monitored closely for onset of contractions, bleeding, expulsion of foetus and placenta and side effects. The aim of this study was to asses and comparatively evaluate mifepristone and misoprostol combination versus misoprostol alone for second trimester termination of pregnancy for outcomes like: induction abortion interval, i.e. time interval between starting of misoprostol and expulsion of product of conception, average amount of misoprostol required in each group, success rate, i.e. rate of complete abortion and side effects. Complete abortion was defined as the expulsion of the foetus and placenta without the need of any other alternative procedures. Study failure was defined as failure to abort despite maximum dose of misoprostol, i.e. 2400 mcg. In case of incomplete abortion or study failure, alternative methods were used, like check curettage, oxytocin augmentation and surgical evacuation. Post-procedure antibiotics were given to all patients and anti-Rh D antibody was given to Rh-negative patients. Sample size was calculated using open Epi software version 2.31 at 95% confidence interval and 80% power of the study. Statistical analysis was done using SPSS 28.0. Continuous variables were presented as mean ± SD, and categorical variables are presented as absolute number and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. p value < 0.05 was considered statistically significant.

Results

In our study, the mean age of patients opting for mid-trimester termination of pregnancy was 25.62 years in Group A and 24.2 years in Group B. Most patient belonged to 21–25 year age group in Group A (46%) and Group B (50%), followed by 26–30 year age group in Group A (30%) and Group B (26%), 76% (38 cases) cases in Group A and 48% (24 cases) cases in Group B belonged to rural habitat, while 24% cases in Group A and 52% cases in Group B belonged to urban habitat. Most patients in our study belonged to low socioeconomic status, i.e. 60% cases in Group A and 44% cases in Group B. Forty-two percent (21 cases out of 50) cases in Group A and 40% (20 cases out of 50) cases in Group B were educated up to class 10th. Most patients were Hindu

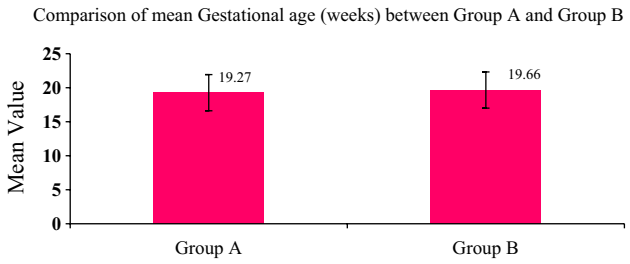

Fig. 1 Comparison of mean gestational age (in weeks)

in both groups, 84% (42 cases out of 50) cases in Group A and 86% (43 cases out of 50) cases in Group B.

Majority women terminated between 13 and 20 weeks in both groups, 60% (30 cases out 50) in Group A and 52% (26 cases out of 50) in Group B. Mean gestational age for mid-trimester termination of pregnancy was 19.27 ± 1.67 weeks in Group A and 19.66 ± 2.66 weeks in Group B (Fig. 1).

Most common cause of termination of pregnancy was congenital anomaly of foetus (62% and 58% in Group A and Group B, respectively) followed by intra-uterine foetal death (24% and 26% cases in Group A and Group B, respectively) and therapeutic indications (14% and 16% in Group A and Group B, respectively). Out of 100 patients, 48 were nulliparous, 15 had previous caesarean section of which 7 (14% cases) belonged to Group A and 8 (16% cases) belonged to Group B. Thirty-seven patients had previous vaginal delivery out of which 23 cases (46%) belonged to Group A and 14 cases (28%) belonged to Group B.

The mean induction abortion interval was 11.59 ± 2.71 h in Group A, and 15.57 ± 2.27 h in Group B which was statistically significant (p value < 0.001). There was no statistically significant relationship between parity of patients and induction abortion interval (Table 1).

The average amount of misoprostol used was 1128 ± 384 mcg in Group A and 1680 ± 302 mcg in Group B which was statistically significant (p value < 0.001) (Table 2).

Ninety-two percentage cases in Group A and 72% cases in Group B had complete placental expulsion, 8% cases in Group A and 26% cases in Group B had incomplete expulsion of placenta, and no case in Group A and 2% case in Group B had study failure which was statistically significant (p value = 0.030) (Table 3).

Group B cases had more side effects than Group A although it was not statistically significant. The most common side effect in both the groups was nausea followed by vomiting and diarrhoea which were more common in misoprostol only regimen (Table 4).

Table 1 Comparison of mean induction abortion interval

Parameter	Group A		Group B		p value
	Mean ± SD	Min–Max	Mean ± SD	Min–Max	
Induction abortion interval (hours)	11.59 ± 2.71	6.17–16.67	15.57 ± 2.27	11.17–20.66	**< 0.001**

Obstetric score	Induction abortion interval			
	Group	Min	Max	Mean induction abortion interval
Primigravida	A	6 h 10 min	15 h 30 min	09 h 04 min
	B	11 h 10 min	20 h 40 min	15 h 56 min
G2	A	7 h 20 min	15 h	11 h 30 min
	B	11 h 20 min	18 h 30 min	15 h 07 min
G3	A	7 h 40 min	15 h 10 min	12 h 35 min
	B	14 h 20 min	17 h	15 h 17 min
G4	A	7 h 30 min	16 h 40 min	11 h 12 min
	B	12 h 30 min	17 h 30 min	15 h 46 min
G5	A	8 h 20 min	13 h 40 min	10 h 25 min
	B	11 h 40 min	11 h 40 min	11 h 40 min

Table 2 Dose of misoprostol used in different groups

Parameter	Group A		Group B		p value
	Mean ± SD	Min–Max	Mean ± SD	Min–Max	
Dose of misoprostol used (mcg)	1128.00 ± 384.94	400–2000	1680.00 ± 302.37	1200–2400	**< 0.001**

Table 3 Distribution of cases according to outcome of termination of pregnancy

Type of abortion	Group A		Group B		*p* value
	Frequency	%	Frequency	%	
Complete	46	92.0	36	72.0	**=0.030**
Failure	0	0.0	1	2.0	
Incomplete	4	8.0	13	26.0	
Total	50	100	50	100	
Chi-square value = 6.984					

Table 4 Comparison of side effects in different groups

Side effect	Group A		Group B		*p* value
	Frequency	%	Frequency	%	
None	34	68.0	22	44.0	**0.016**
Nausea	15	30.0	28	56.0	**0.009**
Vomiting	10	20.0	20	40.0	**0.029**
Diarrhoea	2	4.0	7	14.0	0.081
Fever	0	0.0	5	10.0	**0.022**
Headache	2	4.0	2	4.0	1.000
Pain abdomen	2	4.0	5	10.0	0.240
Shivering	2	4.0	6	12.0	0.140

Discussion

In our study, most patient opting for mid-trimester abortion belonged to 21–25 year constituting 46% in Group A and 50% in Group B. The mean age was 25.62 years in Group A and 24.2 years in Group B. Siraneh Yand Workneh A in their study found that most patients opting for mid-trimester abortion were in between the age group of 15–19 years [5].

We observed 76% cases (38) in Group A and 48% cases (24) in Group B belonged to rural habitat, while 24% cases in Group A and 52% cases in Group B belonged to urban habitat. There was no significant difference in women seeking mid-trimester termination of pregnancy according to habitat. However, study by Siraneh Y and Workneh A showed that more than two-thirds (69.2%) of participants were urban residents [5].

In our study, in Group A 48% were primigravida and 52% were multigravida, whereas Siraneh Y and Workneh A in their study observed that 84% were nulliparous, 9% were primiparous, and 7% were multiparous [5].

In our study, 98% cases were married and only 2 cases were unmarried, indicating such cases mostly resort to private facilities for maintaining confidentiality. According to Ramkrishna S et al., 91.2% were married, 8.3% were unmarried, and 0.5% were either divorced or widowed [6].

We found that 42% (21 cases out of 50) cases in Group A and 40% (20 cases out of 50) cases in Group B were educated up to class 10th. In study done by Ramkrishna S et al. in Mumbai, stratification in terms of the educational backgrounds showed that 45.7% had received only secondary education while 12.7% had no schooling. Educated women are more likely to adopt contraceptives and take advantage of the MTP facilities in early gestational age [6].

The mean gestational age for mid-trimester termination of pregnancy in our study was 19.27 ± 1.66 weeks in Group A and 19.66 ± 2.66 weeks in Group B. Majority women terminated between 13 and 20 weeks in both groups, 60% in Group A and 52% in Group B while 40% cases in Group A and 48% cases in Group B terminated beyond 20 weeks of gestational age. In a similar study by Tripti Nagaria et al. on 200 selected cases, the mean gestational age was 16.04 ± 2.57 and 19.03 ± 3.92 weeks in the combination group and the misoprostol only group, respectively [7].

We observed that the most common indication for mid-trimester MTP was congenital anomaly of foetus, i.e. 60% followed by intra-uterine foetal death (25%) and therapeutic indications (15%). According to Michelle N. Fonseca et al., the most common indication was foetal congenital anomaly (47.22%) followed by contraception failure in 38.88%, missed abortions (8.3%) and intrauterine foetal demise in 5.5% [8]. In a study by Heini Joensuu-Manninen et al. at Oulu University Hospital out of 90 women who had undergone mid-trimester MTP, 34 (37.8%) cases underwent MTP for foetal anomaly and 56 for social causes [9].

The mean induction abortion interval in our study was 11.57 ± 2.71 h in Group A and 15.57 ± 2.27 h in Group B which was statistically significant (p value < 0.001). The minimum induction abortion interval was 6.17 h in Group A and 11.17 h in Group B. The longest induction abortion interval was 16.67 h in Group A and 20.66 h in Group B. In a study by Mukhopadhyay P et al. at Kolkata, induction abortion interval was shorter, i.e. 6.61 ± 2.34 h in mifepristone and misoprostol combination group in comparison to 12.19 ± 3.96 h in misoprostol alone group [10].

In our study, the mean amount of misoprostol used was 1128 ± 384 mcg in Group A and 1680 ± 302 mcg in Group B which was statistically significant (p value < 0.001). Mukhopadhyay P et al. found that mean amount of misoprostol required was significantly less in mifepristone and misoprostol combination group (613.33 ± 156.98 µg) compared to misoprostol alone group (870.96 ± 250.59 µg) [10]. In a similar study by Soren S and Dash P, average misoprostol dose requirement in combination group was 1081.48 mcg and 1675.67 mcg in misoprostol only group [11].

We observed that 68% cases in Group A and 44% cases in Group B had no adverse effects. The most common side effect in both the groups was nausea (30% in Group A and 56% in Group B) followed by vomiting (20% in Group A and

40% in Group B) and diarrhoea (4% in Group A and 14% in Group B). In Group A 10% cases had ≥ 3 side effects, while in Group B 30% cases had ≥ 3 side effects which was statistically significant. (p value 0.047). In a similar study by Deepa Shah et al., 33.3% patients in mifepristone and misoprostol combination group and 66.7% in misoprostol alone group had side effects [12].

In our study, 92% cases in Group A and 72% cases in Group B had complete abortion, 8% in Group A and 26% in Group B had incomplete abortion, and no case in Group A and 2% cases in Group B had study failure. Most cases of incomplete abortion were treated by suction and evacuation or oxytocin augmentation. Wai-Yan Yeung et al. found the complete abortion rate to be slightly higher in the combination group than the misoprostol alone group (13.0% vs 8.3%, $p = 0.459$) [13].

Conclusion

Compared to first trimester termination of pregnancy, mid-trimester termination is more challenging. Medical method is preferred because of its safety, efficacy and non-invasiveness. Our study has the opinion that combination of mifepristone and misoprostol has higher success rate with fewer side effects, shorter induction abortion interval and lesser amount of dose requirement compared to misoprostol alone group. Hence, our study concludes the combination of mifepristone and misoprostol as the preferred method of mid-trimester termination of pregnancy.

Strength and Limitations

This randomised control study compares the groups on the basis of socio-economic status, literacy and marital status. Information regarding most common indication for termination of second trimester pregnancy is obtained, which can be further evaluated and solution can be planned accordingly. This study was a single-centre study limited to only 100 patients. Multicentric study and more sample size are required for better analysis of outcome.

Acknowledgements We would like to thank all the faculties, staffs, junior and senior residents of Department of Obstetrics and Gynaecology, S.C.B. Medical college and Hospital, Cuttack for their active involvement while conducting this study. Our sincere gratitude to the study participants with their family members for their cooperation and support. We would like to thank the IEC committee for allowing us to conduct the study.

Authors Contribution AKN, SM, SM, RP and IM are involved in all process of this study. All authors read and approved the final manuscript. AKN, SM and IM conceived, designed the research work and analysed the data.

Funding None.

Declarations

Conflicts of Interest The authors declare that they have no conflict of interest.

Ethical Approval This study was conducted after obtaining approval from institutional ethics committee.

Human or Animal Rights All parts of declaration of Helsinki have been applied.

Informed Consent Informed and written consent was obtained from all participant of this study.

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