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Original Research Article

Randomized control trial to compare the effectiveness of mifepristone followed by misoprostol at 12 hours interval versus misoprostol alone in second trimester medical termination of pregnancy

Preet Kamal Bedi, Arunima Saini*

Department of Obstetrics and Gynecology, Government Medical College, Amritsar, Punjab, India

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***Correspondence:**

Dr. Arunima Saini,

E-mail: arunima0123@gmail.com

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ABSTRACT

Background: Mifepristone priming in second trimester abortions not only decreases the induction-abortion interval (IAI) but also lessens the total misoprostol dose required and hence reduces adverse effects. The present study aims to compare the role of mifepristone priming 12 hours before misoprostol administration so as to increase patient compliance and shorten the duration of hospital stay.

Methods: This prospective study was conducted over a period of one year, on 50 patients requiring second trimester abortion, at Department of Obstetrics and Gynaecology, Government Medical College, Amritsar. The patients were divided into two groups with 1:1 randomization. In Group A, 25 women were given tablet mifepristone 200 mg orally followed 12 hours later by tablet misoprostol 400 µg per vaginum followed by the same dose 3 hourly for a maximum of five doses per 24 hours. In group B, 25 women received only tablet misoprostol 400 µg vaginally in the posterior fornix followed by the same dose 3 hourly for a maximum of five doses per 24 hours. Primary outcome was to compare the completeness of expulsion of products of conception by pelvic ultrasound after 48 hours of the last dose administered. Secondary outcome was to compare the Induction abortion interval (IAI), mean dose of misoprostol required, side effects, effect of parity, gestational age and cervical dilatation on IAI with both the regimens used.

Results: The success rate was 76% in group A and 64% in group B. The mean induction abortion interval in group A was 8.9±4.70 hours whereas in group B, it was 13.14±6.03 hours and this difference was statistically significant (p = 0.008). A statistically significant difference was also observed in mean dose of misoprostol required in group A and B being 1232.00±398.60 µg and 1584.00±423.94 µg respectively (p=0.004). The side effects were less in group A. Parity and cervical dilatation hold an inverse relation with the mean IAI whereas it has a direct relation with the gestational age.

Conclusions: Regimen involving mifepristone priming 12 hours before misoprostol is better than misoprostol alone regimen with significant reduction in IAI, mean dose of misoprostol and less side effects.

Keywords: Mifepristone, Misoprostol, Second trimester abortions

INTRODUCTION

Second trimester abortions constitute 10-15% of all induced abortions worldwide.¹ A variety of methods were used in the past for second trimester medical termination

of pregnancy which included extraovular (extraamniotic) normal saline instillation, extraamniotic injection of ethacridine lactate, laminaria tent, intraamniotic instillation of 40% formalin (3cc), intraamniotic injection of 20% hypertonic saline and the use of bougies.

These methods had life threatening complications like disseminated intravascular coagulation, thromboembolism, cerebral infarction, acute renal failure making them unsuitable for use.^{2,3}

The ideal second trimester abortion method aims at a procedure that is both simple and safe with minimum incidence of side effects and has a high success rate within a minimum span of use. For abortion at 13-24 weeks of gestation, medical abortion with mifepristone followed by a prostaglandin (PG) analogue is an appropriate method and has shown to be effective.^{4,5} Prostaglandins act on the myometrium and initiate a wave of violent contraction. Pike and Corey were the first to publish about the chemical synthesis of prostaglandins.⁶

Misoprostol, a synthetic prostaglandin E1 (PGE1) analogue, was developed for the prevention and treatment of peptic ulcer caused by prostaglandin synthase inhibitors (Lewis, 1985). When misoprostol is given orally, the levels of misoprostic acid peak between 12.5 to 60 minutes of administration and fall steeply by 120 minutes. But those receiving vaginal dose, the levels rise gradually and reach maximum levels between 60 to 120 minutes and decline slowly. This difference is because of presystemic gastrointestinal and hepatic metabolism that occurs only with oral administration of drug (Tang et al).⁷

Mifepristone, a steroidal antiprogestogen, blocks the progesterone receptors resulting in vascular damage, decidual necrosis and bleeding which leads to cervical softening, increased uterine sensitivity to prostaglandins and conversion of the quiet pregnant uterus into an organ of spontaneous activity with maximal effect at 36-48 hours. The peak plasma concentrations of 1.9 ± 0.8 , 3.8 ± 0.9 and 5.3 ± 1.3 $\mu\text{mol/l}$ are reached within 1-2 hours after oral administration of 50, 200 and 600 mg mifepristone respectively, in women and are maintained at relatively high levels upto 48 or 72 hours depending on the ingested dose.⁸

Norman et al reported that mifepristone given 48 hours prior to misoprostol enhances the stimulatory effect of misoprostol on uterine muscles resulting in increased frequency of contractions.^{9,10} This 36-48 hours interval is too long and it increases the duration of treatment, repeated visits to the hospital and a possibility that a woman may change her mind in the time interval between the administration of two drugs and thereby discontinue midway. The present study aims to compare the role of mifepristone priming 12-hours before misoprostol administration so as to increase patient compliance and shorten the duration of hospital stay.

METHODS

This prospective, single center, randomized control trial was conducted over a period of one year (June 2016 to June 2017), on 50 patients coming in need of Second trimester abortion, at Department of Obstetrics and

Gynaecology, Bebe Nanki Mother and Child Care Centre, Government Medical College, Amritsar. The patients were divided into two groups with 1:1 randomization. The gestational age was determined by the history, clinical and ultrasonographic report. A written informed consent was taken from all the patients after obtaining approval from the institutional ethical committee. As per the guidelines of MTP Act 1971, the patients between 13-20 weeks of pregnancy fulfilling the following inclusion and exclusion criteria were enrolled in this study.

Inclusion criteria

- 13 to 20 weeks of gestation
- Gross congenital malformations not compatible with life
- Conception as a result of failure of contraception
- Rape victims
- Missed abortions
- Grave medical disorders in mother
- Obstetrical indications

Exclusion criteria

- Grand multipara.
- Ectopic pregnancy
- Scarred uterus
- History of thromboembolism or liver disease
- Heavy smoker of >20 cigarettes/day
- Renal disease
- Severe uncontrolled bronchial asthma
- Incomplete abortions

In group A, 25 women were given tablet mifepristone 200 mg and asked to return to hospital 12 hours later for misoprostol administration, when tablet misoprostol 400 μg was given vaginally followed by 400 μg vaginal misoprostol every 3 hours for a maximum of five doses per 24 hours.

In group B, 25 women received only tablet misoprostol 400 μg vaginally in the posterior fornix followed by 400 μg vaginal misoprostol every 3 hours for a maximum of five doses per 24 hours.

In both the groups, injection tetanus toxoid was given to all the patients and injection anti-D 300 μg intramuscularly if patient was Rh negative. Temperature, pulse rate, blood pressure and respiratory rate charting was maintained four hourly. Patients were observed for any side effects of drugs like fever, vomiting, chest pain, diarrhoea. A follow-up pelvic ultrasound scan after 48 hours of last dose of tablet misoprostol was done for all the patients in both the groups.

Primary outcome was to compare the completeness of expulsion of products of conception by pelvic ultrasound after 48 hours of the last dose administered. Patients with

retained products of conception on ultrasound were taken as a failure case.

Secondary outcome was to compare the Induction abortion interval (IAI), doses of misoprostol required, side effects, effect of parity, cervical dilatation and gestational age on IAI with both the regimens used. Success was defined by complete expulsion of conceptus confirmed by ultrasound report.

Failure was defined by retained products of conception on ultrasound report and clinically demonstrable failed expulsion of conceptus within the stipulated time i.e >15 hours of the first dose of misoprostol in both the regimens.

Statistical analysis

Data thus obtained was analyzed by Statistical Package for Social Sciences (SPSS) version 23. Unpaired t test was used to compare different variables between two groups. P value of <0.05 was taken as statistically significant.

RESULTS

Mean age in group A was 24.30±2.52 years and in group B was 25.92±3.45 years but no statistical significance was observed in the two groups in relation to the mean age of the patients (p = 0.06) (Table 1).

Table 1: Basic parameters studied in the two groups.

Parameters	Mean age	Mean gravidity	Mean parity	Mean gestational age
Group A	24.30±2.52	1.85±1.45	0.74±1.1	17.50±2.50
Group B	25.92±3.45	2.44±1.22	0.96±0.93	16.02±2.96
P value	0.06	0.13	0.44	0.06
Significance	Non-significant			

Table 2: Induction-abortion interval (IAI) in the two study groups.

IAI	Group A		Group B	
	No.	%	No.	%
0-3hrs	00	0	00	0.0
3-6hrs	09	36.0	05	20.0
6-9 hrs	10	40.0	09	36.0
9-12 hrs	04	56.0	02	8.0
12-15 hrs	0	00	04	16.0
>15hrs (failure)	02	8.0	05	20.0
Mean IAI (Hrs)	8.9±4.70		13.14±6.03	
p value	0.008			
Significance	Significant			

In group A, 64% (16 out of 25) patients were primigravida, 16% (4 out of 25) were second gravid, 4% (1 out of 25) were third gravida and 16% (4 out of 25) were above third gravid. The mean gravidity was 1.85±1.45. In group B, 28% (7 out of 25) patients were primigravida, 20% (5 out of 25) were second gravida, 40% (10 out of 25) were third gravida, and 12% (3 out of 25) were above third gravida. The mean gravidity was 2.44±1.22. However, no statistical significance was observed between the groups in relation to gravidity of the patients (p = 0.13) (Table 1).

The mean parity was 0.74±1.1 in group A and 0.96±0.93 in group B. However, no statistical significance was observed in the two groups in relation to parity. In group A, 52% (13 out of 25) patients presented between 18-20 weeks of gestation, 32% (8 out of 25) presented between

13-15.6 weeks and 16% (4 out of 25) between 16-17.6 weeks of gestation. The mean gestational age in this group was 17.50±2.50 weeks. In group B, 36% (9 out of 25) of the patients presented between 13-15.6 weeks of gestation, 24% (6 out of 25) presented between 16-17.6 weeks and 40% (10 out of 25) between 18-20 weeks of gestation. The mean gestational age in this group was 16.02±2.96 weeks. However, no statistical significance was observed between the groups in relation to the gestational age (p=0.06) (Table 1).

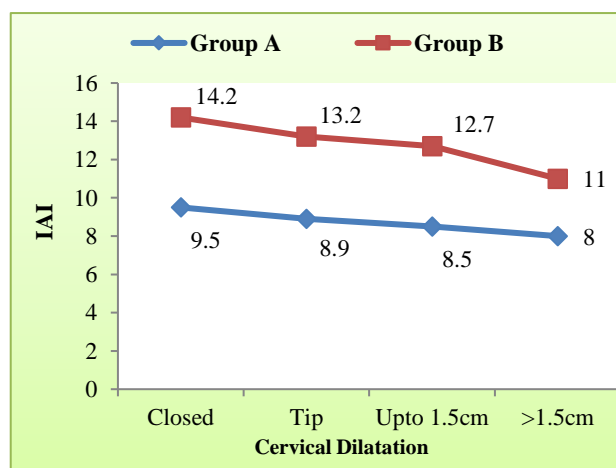


Figure 1: Relation of cervical dilatation with IAI.

The minimum gestation was 13 weeks and maximum was 20 weeks in both the groups. The mean induction-abortion interval was 8.9±4.7 hours in Group A and 13.14±6.03 hours in Group B and this difference was

found to be statistically significant (p=0.008) (Table 2). An inverse relationship is observed in both groups A and B between cervical dilatation and induction-abortion interval (IAI) as depicted in Figure 1.

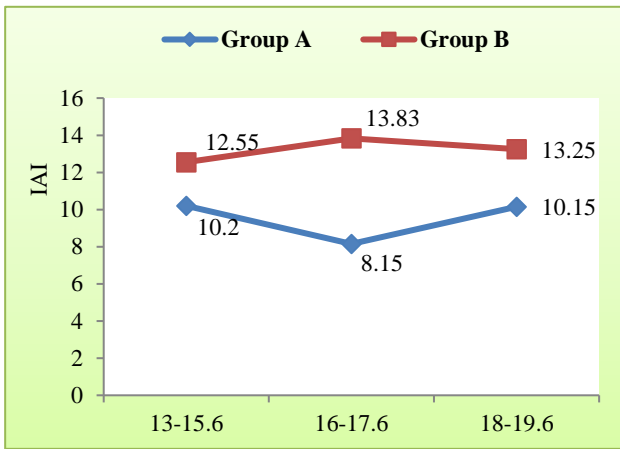


Figure 2: Effect of gestational age on IAI.

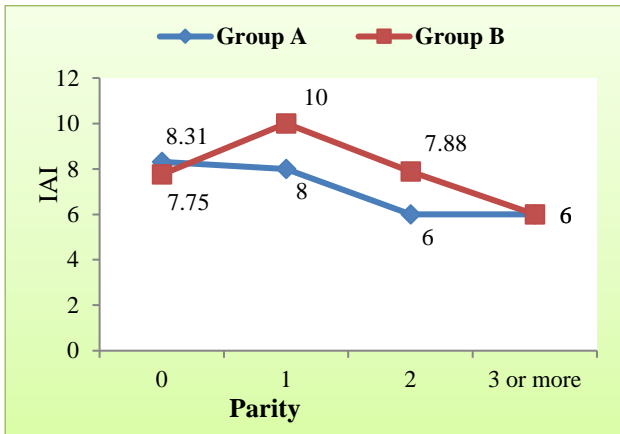


Figure 3: Effect of parity on IAI.

The relationships of gestational age and parity with induction-abortion interval are shown in Figures 2 and 3. The mean dose of misoprostol required was significantly less in group A than in group B in both primigravidas (Table 3) and multigravidas (Table 4).

Table 3: Dose of misoprostol required in primigravida.

Total dose (µg)	Group A (N=16)		Group B (N=07)	
	No.	%	No.	%
400	-	-	-	-
800	5	31.25	-	-
1200	3	18.75	2	28.57
1600	6	37.50	1	14.2
2000	2	12.50	4	57.1
Mean±SD	1325.00±431.28		1885.71±195.18	
p value	0.004			
Significance	Significant			

Table 4: Dose of misoprostol required in multigravida.

Total dose (µg)	Group A (N = 9)		Group B (N = 18)	
	No.	%	No.	%
400	0	0	0	0
800	4	44.4	5	27.7
1200	4	44.4	6	33.3
1600	1	11.2	2	11.1
2000	0	0	5	27.7
Mean±SD	1066.67±282.84		1466.66±433.86	
p value	0.02			
Significance	Significant			

Table 5: Mean dose of misoprostol required in the two study groups.

Mean dose±SD (µg)	Group A (N=25)	Group B (N=25)
Mean	1232.00±398.60	1584.00±423.94
P value	0.004	
Significance	Significant	

Also, the mean dose of misoprostol required to achieve expulsion irrespective of gravidity of the patient was significantly less in group A as compared to group B with a mean dose of 1232.00±398.60 µg and 1584.00±423.94 µg, respectively (p = 0.004) (Table 5).



Figure 4: Side effects in both the groups.

Successful expulsion was achieved in 76% (19 out of 25) patients in group A and 64% (16 out of 25) in group B. Failure of induction was observed in 24% (6 out of 25) patients in group A and 36% (9 out of 25) in group B who were further managed with either evacuation and curettage or intracervical foley’s insertion. Side effects of both regimens were almost similar in both the groups with slightly more incidence in group B (Figure 4).

DISCUSSION

Misoprostol (PGE1) is the most commonly used drug for second trimester medical abortions. Gastrointestinal side effects are more when the drug is used solely for induction. Mifepristone priming helps not only by significantly decreasing the IAI but also lessens the total misoprostol dose required and hence limiting the side

effects. Not only the regimen used determines the IAI, but also the mean gestational age, cervical dilatation and parity change the IAI. Very limited studies have been done on mifepristone priming with 12 hours interval between mifepristone and misoprostol. The reduced interval between the two drugs not only makes it more convenient for the patient but also shortens the duration of hospital stay.

Table 6: Relative comparison of mifepristone priming studies.

Author name and year of study	Mifepristone dose (mg)	Interval (hours)	Misoprostol dose (μ g)	Mean misoprostol dose (μ g)	IAI
Tripti and Namrata ¹¹	200	12	600,400	1186 \pm 291.64	6.72 \pm 2.26
Chai et al ¹²	200	36-38	600,400	1000	5.0
Ngoc et al ¹³	200	24	400	1250	8.1 \pm 2.0
Mukhopadhyay et al ¹⁴	200	48	400,200	613 \pm 156	6.62
Kulkarni et al ¹⁵	200	48	400,200	600	8.15
Patel et al ¹⁶	200	24	200	122	18.94 \pm 9.3
Patil and Biliangady ¹⁷	600	24	600,400	-	8.25
Aayushi et al ¹⁸	200	48	400	769.89	8.12
Present study	200	12	400	1232.00 \pm 398.60	8.9 \pm 4.70

Table 6 shows the relative comparison between various studies with varying doses of mifepristone and misoprostol at different intervals. The mean IAI in the present study is in concordance with the findings reported by Ngoc et al, Kulkarni et al, Patil and Biliangady and

Aayushi et al with minor variations although the mean misoprostol dose in the present study was slightly on a higher side.^{13,15,17,18} When the IAI is almost comparable with no major variations, the 12-hour interval regimen takes the advantage of limiting the hospital stay of patient thereby improving compliance.

Table 7: Relative comparison of misoprostol alone studies.

Author name and year of study	Misoprostol dose (μ g)	Interval	Mean dose required (μ g)	IAI
Tripti and Namrata ¹¹	600,400	3	1736 \pm 320	12.29 \pm 3.14
Ngoc et al ¹³	400	3	1560	10.6 \pm 2.5
Mukhopadhyay et al ¹⁴	400,200	4	870	12.19 \pm 3.9
Kulkarni et al ¹⁵	400,200	6	1600	>24.0
Patel et al ¹⁶	200	6	696	24.29 \pm 11.53
Patil and Biliangady ¹⁷	600,400	4	-	10.99 \pm 3.22
Aayushi et al ¹⁸	400	4	1043.2 \pm 502.36	13.41
Present study	400	3	1584 \pm 423.94	13.14 \pm 6.03

Table 7 shows the comparison of various studies with misoprostol alone regimen. The mean dose of misoprostol in our study is in concordance with the previous studies conducted by Tripti and Namrata, Ngoc et al, Kulkarni et al and Aayushi et al.^{11,13,15,18} Also, the IAI is almost similar with minor variations.

CONCLUSION

Present study concluded that regimen A i. e. mifepristone priming 12 hours before misoprostol administration

improves the success rate (76%) when compared with misoprostol alone (64%) regimen. Also, the mean dose of misoprostol required and hence the side effects were lesser when mifepristone priming was done. We could infer that although no major difference was noted in terms of IAI and mean misoprostol dose when mifepristone priming was done at 12 hours interval or a longer interval (as done in other studies), our regimen with 12 hours interval gives a better compliance to the patient with limited hospital stay and least side effects as compared to 36 or 48 hours interval.

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Conflict of interest: None declared

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

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