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Study of the Efficacy and Success Rate of Single Dose Oral Mifepristone and Vaginal Misoprostol v/s Vaginal Misoprostol alone for Second Trimester Termination of Pregnancy

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Abstract

Background: Second trimester abortions constitute 10-15% of all induced abortions and are considered to be less safe than first trimester abortions. The combination of mifepristone and misoprostol is now an established and highly effective method for second trimester abortion. **Aim:** To compare the efficacy and the success rate of single dose oral mifepristone plus vaginal misoprostol versus vaginal misoprostol alone for second trimester termination of pregnancy. **Materials and Methods:** A comparative study and was conducted in the Department of Obstetrics and Gynecology in a Tertiary Health Care Hospital. The study was carried out by dividing women into two groups (72 each). Group Areceived 200mg of oral Tablet Mifepristone and 400 of vaginal misoprostol (48 hours later) which was repeated every 4 hourly by 200 of vaginal misoprostol up to a maximum of 4 doses. Group B received 400 of vaginal misoprostol directly and the dose was repeated every 4 hourly by 200 of vaginal misoprostol up to a maximum of 4 doses. **Results:** The success rate in Group A was 98.6%, whereas in Group B was 84.7%. The mean induction abortion interval in Group A was lesser (6.2 hours) as compared to Group B (10.8 hours) (*p* value <0.00001). The mean dose of misoprostol in Group A was 613.88mcg compared to the Group B 1591.66mcg (*p* value <0.00001). **Conclusion:** Pretreatment with mifepristone significantly reduces the induction abortion interval (I-A-I) and the misoprostol dose.

Keywords: Induction Abortion Interval I-A-I, Mifepristone, Misoprostol, Second Trimester, Termination

1. Introduction

Abortion is defined as 'Termination of Pregnancy (TOP) by any means before the fetus is viable'. Medical abortion is becoming popular nowadays as a method of termination of pregnancy in the second trimester because it is effective and technically less demanding when compared to surgical methods. Second trimester or mid trimester abortions were done up to 20 weeks.[1]

Abortions in India are legal only up to twenty weeks of pregnancy under specific indications such as:

The continuance of the pregnancy would involve a risk to the life of the pregnant woman or of grave injury of physical or mental health, or there is a substantial risk that if the child were born, it would suffer from such physical or mental abnormalities as to be seriously handicapped.

As a result of rape or failure of contraception in a married couple.

The Indian abortion laws fall under the Medical Termination of Pregnancy (MTP) Act, which was enacted by the Indian Parliament in the year 1971 with the intention of reducing the incidence of illegal abortion and

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consequent maternal mortality and morbidity[2]. The MTP Act came into effect from 1 April 1972 and was amended in the years 1975 and 2002.

Medical methods of abortion are safe and effective. Use of antiprogestins like mifepristone can further reduce risks of abortions. Mifepristoneacts as antagonist to the progesterone receptors causing necrosis and detachment of placenta. It also ripens the cervix and has synergistic effect with misoprostol. Misoprostol (synthetic prostaglandin E1 analogue) binds to myometrial cells causing strong myometrial contractions leading to expulsion of fetus from the uterus[3].

Mifepristone combined with misoprostol is already an established regime for second trimester termination of pregnancy up to 63 days in India. The use of both these drugs i.e., mifepristone followed by misoprostol is likely to improve the efficacy of misoprostol in the second trimester termination of pregnancy.

2. Materials and Methods

A prospective randomized control study was conducted in the Department of Obstetrics and Gynecology by selecting 144 random cases attending the Obstetrics/ Gynecology OPD at a Medical College and Tertiary Health Care Institute (Hospital) from August 2014 to December 2016 after obtaining approval from the Institutional Ethics Committee (IEC) in accordance with Helsinki guidelines.

Healthy women requesting for termination of pregnancy between 12 to 20 weeks were included in the study after detailed history, clinical examination, ultrasonography and complete blood count.

Documentation as per MTP act (Form 1, Form 2, Form 3, Form c) were completed after opinion for MTP was reached by 2 Registered Medical practitioners.

Exclusion criteria were:

- Women with previously scarred uterus.
- Women presenting with bleeding disorders, inherited porphyrias.
- Women with anemia (Hb < 10g/dl).
- Uterine or vaginal infection.
- Any known allergy to the study medication.
- Women with congenital malformations of the uterus.
- Women with cardiac or bronchial asthma.
- Participants not giving voluntary informed consent to be included in study.

The women were randomized by lottery method and allocated to group A and group B.

Group A: Women in this group (n=72) received 200mg of oral Tablet Mifepristone followed 48 hours later by 400 of vaginal misoprostol which was repeated every 4 hourly by 200 of Vaginal misoprostol up to a maximum of 4 doses and any dose more than this was considered as an additional dose.

Group B: Women in this group (n=72) received 400 of vaginal misoprostol directly and the dose was repeated every 4 hourly by 200 of vaginal misoprostol up to a maximum of 4 doses and any dose more than this was considered as an additional dose.

The side effects such as nausea, vomiting, fever was recorded. The blood pressure, pulse and frequency of uterine contractions were monitored. After abortion, the products of conception (fetus and placenta) were examined to see whether the abortion was complete. Injection Anti D was given to Rh negative mothers.

The induction abortion interval was measured from the time of administration of first dose of misoprostol to the time of completion of abortion. The volume of blood loss during abortion was estimated clinically. The dose of misoprostol required was recorded.

In patients with Incomplete abortion (clinically diagnosed), check curettage was resorted to within 24 hours.

Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Data was tested first for normal distribution by Klomogorov–Smirnov test. Comparison of quantitative variables between the two groups was done using Student t test for independent samples if normally distributed. Mann–Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant.

3. Results

40.3% of study subjects aborted within 1-5 hours of induction with misoprostol while only 1.4% of control subjects aborted within 1-5 hours. The rate of abortion was relatively identical in the 5-10-hour induction abortion interval group. Only 1.4% of study subjects required an induction abortion interval of 10-15 hours while 47.2%

of controls needed more than 10 hours to complete the process of abortion (Table 1).

Table 1. Induction Abortion Interval (I-A-I)

Induction Abortion Interval (In Hours)	Group A N=72	Group B N=72
1-5 HRS	29 (40.3%)	01 (1.4)
5-10 HRS	42 (58.3%)	33 (45.8%)
10-15 HRS	01 (1.4%)	34 (47.2%)
15 & ABOVE	0 (0%)	04 (5.6%)
TOTAL	72 (100%)	72 (100%)

Table 2. Induction Abortion Interval (I-A-I)

Induction Abortion Interval (I-A-I)	Group	N	MEAN	SD	P value
	A	72	6.2	2.1	< 0.01
	B	72	10.8	2.5	

The mean I-A-I in group A was 6.2 ± 2.1 (range 3 to 10 hours) and in Group B was 10.8± 2.5 (range 4 to 15.5 hours). The difference was statistically significant with a P value of less than 0.01 (Table 2).

Table 3. Induction Abortion Interval (I-A-I)

I-A-I (In Hours)	Group A (N=72)		Group B (N=72)	
	PRIMI	MULTI	PRIMI	MULTI
1-5HRS	7	22	NIL	1
5-10HRS	7	35	9	24
10-15HRS	NIL	1	14	20
>15HRS	NIL	NIL	NIL	4
TOTAL	72		72	

Group A had 14 primi gravidae, 14 Gravida 2, 32 Gravida 3, 11 Gravida 4 and 1 Gravida 5 (average parity = 1.44)

Group B had 23 primi gravidae, 21 Gravida 2, 20 Gravida 3, 07 Gravida 4 and 1 Gravida 5 (average parity = 1.19).

In Group B, 7 primigravida aborted in the first 5 hours of induction while not a single primigravida aborted from Group B in the first five hours.

In Group A, 7 out of 72 primigravida aborted in 5-10-hour interval while 9 primigravida in Group B aborted in the 5-10-hour interval. 14 primigravida from Group B aborted in the 10-15-hour interval (Table 3).

In Group A, 22 were multigravida who aborted within first 5 hours while only 1 in Group B aborted within the first 5 hours. 35 subjects from Group A aborted in the 5-10-hour interval as compared to 24 from Group B.

In Group A, the 10-15-hour interval had only one multigravida as compared to 20 multigravidas from Group B.

It took 4 multigravidas from Group B to abort in the 15 hours and above time interval while there were no such cases reported in Group A.

All 72 subjects in Group B required the first dose of misoprostol g) and none of them aborted in this first dose as compared to group A in which 12 out of 72 i.e., 16.60% aborted in this first dose.

In Group B, 9 subjects out of 72 i.e., 12.5% aborted in the second dose (200g) as compared to 48 out of 72 from group A i.e., 66.66%. 42 out of 72 subjects from Group B i.e., 58.33% required the third dose of misoprostol as compared to only 11 out of 72 i.e., 15.27% needing the same dose from the group A.

Only one patient from group A i.e., 1.38% required the fourth dose of misoprostol as compared to 21 subjects out of 72 i.e., 29.16% requiring the fourth dose to complete the process of abortion.

71 out of 72 subjects in group A i.e., 98.6% had complete abortion and only remaining one subject had to undergo check curettage for incomplete abortion. However, 61 out of 72 i.e., 84.7% had complete abortion while 11 out of 72 i.e., 15.3% had to undergo a check curettage. The p value in this group was statistically significant (< 0.01)

None of the study subjects suffered blood losses or who required a blood transfusion. However, one of the control subjects had blood loss more than 500ml who needed a transfusion to compensate the blood loss.

4. Discussion

4.1 Induction-Abortion-Interval

In our study, the mean induction abortion interval (I-A-I) in group A was 6.2±2.1h whereas in Group B it was 10.8±2.5h which was statistically significant with a P value of less than 0.01 (Table 5).

In a study conducted by Prasanna Lekha Akkenapally (2016)[3], the mean I-A-I was found to be 6.192.70 with a range of 8 to 13 hours 28 minutes in group A and 10.673.96 with a range of 4 hours 15 minutes to 7 hours 40 minutes.

In a study conducted by Nagaria Tripti, Sirmor Namrata[4] in 2011, the mean induction abortion interval was found to

Table 4. Distribution of study subjects according to dosages of misoprostol needed for complete abortion

Dose of Misoprostol	Cumulative Dose of Misoprostol	Group A (N=72)	Group B (N=72)	*p* VALUE
First (400g)	g	12 (16.60%)	00 (0%)	<0.00001
Second (200g)	600g	48 (66.66)	09 (12.5%)	
Third (200g)	800g	11 (15.27%)	42 (58.33%)	
Fourth (200g)	1000g	01 (1.38%)	21 (29.16%)	
TOTAL		72 (100%)	72 (100%)	

Table 5. Comparison of I-A-I with other studies

Studies	Group A I-A-I (In Hours)	Group B I-A-I (In Hours)	P Value
Prasanna Lekha Akkenapally (2016)[3]	6.19 range (8-13h 28min)	10.673.96 range (4h 15min-7h 40min)	<0.01
Nagaria Tripti, Sirmor Namrata (2011)[9]	6.722.26 range (2-13)	12.293.14 range (5-21)	< 0.001
Present study	6.22.1 range (3-10)	10.82.5 range (4-15h 30min)	<0.01
Premila W. Ashok (1999)[5]	6.08 range (0.75-67.25)	8.67 range (2.17-28.17)	<0.0001

Table 6. Comparison of dose of Misoprostol requirement

Studies	Study Group (Mean Dose of Miso In)	Group B (Mean Dose of Miso In)	*P* Value
Prasanna Lekha Akkenapally (2016)[3]	1046	1610	<0.001
Nagaria Tripti, Sirmor Namrata (2011)[4]	1186	1736	< 0.001
Kulkarni Kranti K. (2014)[1]	600	1600	<0.001
Ashok Templeton (1999)[10]	1200	-	-
Ngai *et al* (2000)[11]	600	1200	<0.001
Present study	613.88	1591.66	<0.00001

be 6.722.26 with a range of 2 to 13 hours in group A and 12.293.14 with a range of 5 to 21 hours in Group B.

In a study conducted by Premila W. Ashok in 1999[5], the mean induction abortion interval in Group A was 6.08 hours with a range of 0.75 to 67.25 and 8.67 hours with a range of 2.17 to 28.17. Modak et al., found induction abortion interval was shorter in sublingual group (12.28 hours)[6]

As a result, the findings mentioned in the above studies were consistent with our study and hence we can state that pre-induction with Mifepristone significantly reduces the induction abortion interval with the difference

being statistically significant. Ngoc *et al.,* (2011)[7] in their double-blind study reported that mean I-A-I was statistically shorter for mifepristone plus misoprostol group compared to misoprostol group only (8.1 h and 10.6 h, respectively, with a *p* value of <0.01).

In another study by Rasha *et al.,* (2015)[8] the mean induction abortion interval in Group A was reported to be 10.46.8h while in Group B it was 20.6 9.7h. Thus, the reduction in the induction abortion interval also improves acceptability of the procedure in women (Table 5).

4.2 Dose of Misoprostol

In our study, the mean dose of misoprostol required for the subjects to completely abort in group A was 613.88 while that required in Group B was 1591.66. Thus, the amount of misoprostol required in patients pre-induced with mifepristone was significantly lower as compared to patients who aborted with misoprostol alone. There was also a decreased amount of blood loss in group A as compared to Group B because of larger doses of misoprostol as mentioned further in the discussion (Table 4).

In a study conducted by Prasanna Lekha Akkenapally (2016)[3], the mean dose of misoprostol required in group A was 1046mcg while that required in Group B was 1610mcg with a *p* value being less than 0.001 which was statistically significant.

In a study conducted by Nagaria Tripti, Sirmor Namrata (2011)[4], the mean dose of misoprostol required in group A was 1186 while that in Group B was 1736.

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In a study conducted by Kulkarni Kranti K. (2014)[9], the mean dose of misoprostol required in group A was 600 as compared to 1600 in Group B.

In a study conducted by Ashok Templeton (1999)[10], the mean dose of misoprostol required was 1200in group A.

In a study conducted by Ngai *et al.,* (2000)[11], the mean dose of misoprostol required in group A was 600 as compared to 1200 in Group B (Table 6).

4.3 Completeness of Procedure and Requirement of any Additional Procedure

The success rate of the procedure in the present study was 98.6% in group A and 84.7% in Group B. The difference between them was significant statistically with a *p* value being less than 0.01

In a study conducted by Prasanna Lekha Akkenapally[3] in 2016, the success rate in group A was 96% while that in Group B was 89%. The difference here too was statistically significant.

In a study conducted by Nagaria Tripti, Sirmor Namrata[4] in 2011, the success rate in group A was 95% as compared to Group B in which it was 90%.

The success rate of the procedure in the present study was 98.6% in group A and 84.7% in Group B. The difference between them was significant statistically with a *p* value being less than 0.01

In a study conducted by Prasanna Lekha Akkenapally[3] in 2016, the success rate in group A was 96% while that in Group B was 89%. The difference here too was statistically significant.

In a study conducted by Nagaria Tripti, Sirmor Namrata[4] in 2011, the success rate in group A was 95% as compared to Group B in which it was 90%.

4.4 Amount of Blood Loss and Requirement of a Blood Transfusion

In a study by Prasanna Latha Akkenapally[3], the mean blood loss in group A was less (mean blood loss 52.55ml) as compared to Group B (mean blood loss 97.20ml).

In a similar study conducted by Nagaria Tripti, Sirmor Namrata[4], the mean blood loss in group A was 61.25 ml while in Group B was comparatively higher being 67.25 ml.

The amount of blood loss in this study was assessed clinically and recorded. In our study, only one patient from Group B had a significant amount of blood loss which was calculated clinically to be more than 500 cc. The same patient had an incomplete abortion requiring check curettage in spite of larger amounts of misoprostol (1000) and an induction abortion interval of 15 hours. This patient needed a blood transfusion (1 PCV) and a longer duration of stay in the hospital. Hence, we can quote that the success rate of complete abortion was significantly higher in Group A as compared with Group B and hence the amount of blood loss was also higher in the patient requiring higher doses of misoprostol as compared to Group A.

5. Conclusion

Pre-induction with Mifepristone in the second trimester termination of pregnancy is highly successful and has a very good outcome with a lesser I-A-I. This will not only help in reducing the dosage of misoprostol required but

also in better patient compliance, relatively shorter hospital stay and being cost effective too.

- Use of Mifepristone significantly reduces the risk of incomplete abortion thus reducing operative intervention like surgical evacuation of retained products of conception.
- This method should be routinely carried out in all Tertiary Centers as it makes second trimester abortions safer due to considerable risk reductions.

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