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Efficacy and safety of misoprostol after 6 hours of mifepristone in medical abortions up to 7 weeks v/s 24 hours: A comparative study

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Abstract
Background/purpose: The aim of the study was to compare the Efficacy and Safety of Misoprostol after 6 Hours of Mifepristone in Medical Abortions up to 7 weeks v/s 24 Hours.
Material and method: The present randomized clinical trial was undertaken in the department of Obstetrics and Gynaecology at Muzaffarnagar medical college and hospital among 60 women seeking abortion up to 7 weeks (49 days). The subjects were divided into two groups i.e. group A (tablet Mifepristone 200mg orally on empty stomach and after 24hrs, 400 microgram Tablet Misoprostol given orally), group B (tablet Mifepristone 200 microgram followed by misoprostol 400 microgram after 6hours). Success was defined as complete expulsion of products of conception within 24 hours of misoprostol Failure was defined as incomplete expulsion of products of conception within 24 hrs of misoprostol.
Results: Mean age of the study subjects was 24.17±5.11 years and 23.93±4.08 years in group A and group B respectively. In group A and B, mean gestation age (in weeks) was 6.37±0.77 and 6.57±0.57 respectively. Success was reported among 96.67% and 90% of the subjects in group A and B respectively with statistically insignificant difference.
Conclusion: Based on the results of the present study, it can be concluded that women can use regimens with vaginal misoprostol without any time delay between medications with efficacy that is similar to those with a delay.

Keywords: Misoprostol, Mifepristone, Abortion, Success

Introduction
There is a need for evolving a safe and effective method for terminating pregnancy most recently due to the increase in the use of antenatal diagnostic procedures like amniocentesis, USG and cordocentesis [1]. In India, 6.7 million induced abortions are performed a year, with a ratio of 452 abortions per 1000 live births or induced abortions per 1000 women of child bearing age [2]. Although abortion was legalized in India in 1972, illegal abortion is still (urban) five (rural) times more common than legal abortion [3].
The age old surgical evacuation of the uterus for abortions is still commonly used. It carries the risk of injury to the genital tract, infection, increased need for blood transfusion etc. To avoid the surgical complications researchers have tried medications to induce abortions. The most widely researched ones are prostaglandins alone, mifepristone alone, methotrexate alone, mifepristone with prostaglandins, methotrexate with prostaglandins and Misoprostol [4-6]. Multiple investigators have evaluated alternative medical abortion regimens to simplify the treatment process and extend the gestational age range. These regimens have included using lower doses of mifepristone, home administration of the misoprostol, varying the dose of misoprostol, use of vaginal misoprostol, and decreasing the dosing interval between mifepristone and misoprostol.
Regimens with a shorter interval between mifepristone and misoprostol administration, if effective, would shorten the amount of time necessary for a medical abortion to occur and, potentially, increase acceptability. A further reduction in the time interval was evaluated in 2 pilot studies at the University of Pittsburgh. These trials included 40 women in each of the gestational age ranges of less than or equal to 49 days, 50 to 56 days, and 57 to 63 days using 200 mg of mifepristone followed 6 to 8 hours later by 800ug of misoprostol administered vaginally. Abortion rates at 24 hours were 88% to 92% [2]. On the basis of the results of these pilot studies, we performed this trial to compare the efficacy and safety of misoprostol after 6 hours of Mifepristone in Medical abortions upto 7 weeks vs 24 hours.

Material and method

The present randomized clinical trial was undertaken in the department of Obstetrics and Gynaecology at Muzaffarnagar medical college and hospital from July 2018 to June 2019 among 60 women seeking abortion up to 7weeks (49 days) of gestation eligible for MTP were taken up for study. The ethical permission was taken from the institute ethical committee. Written informed consent was taken and confidentiality was maintained.

Inclusion criteria

Upto 7 weeks of pregnancies (as per definition of by MTP Act 1971) which fulfilled indications of MTP, as per guidelines of MTP Act of 1971, Therapeutic ground-If the pregnancy would involve a risk to the life of the pregnant woman or of the grave injury to her physical or mental health, Eugenic ground- If there is substantial risk, that if the child were born, it would suffer physical or mental abnormalities as to be seriously handicapped, Humanitarian ground-Pregnancy caused by rape and Pregnancy resulting from contraceptive failure.

Exclusion Criteria

Scarred uterus, Ectopic pregnancy, Grand multipara and contraindications to misoprostol and mifepristone.

Grouping

The selected cases were divided randomly and equally into two groups i.e. Group A-30 and Group B-30. Dose of mifepristone and misoprostol was according to gestational age of patient (WHO 2014). Detailed history and detailed examination was done in all subjects who were included in the study. Routine haematological and urine investigations were done in all subjects. Gestational age was estimated by LMP, clinical examination and confirmed by USG scan.

Method of Administration of Drugs

GROUP 'A': Thirty randomly selected cases received tablet Mifepristone 200 mg orally on empty stomach. After 24hrs, 400 microgram tablet Misoprostol given orally.

GROUP 'B': Thirty randomly selected cases received tablet Mifepristone 200 mg followed by misoprostol 400 microgram after 6 hours.

Parameters observed

In both the groups patients were kept under observation for 24hours after giving misoprostol orally. Both groups received inj. TT. If patient is Rh negative inj. anti D 300 microgram was given intramuscularly after abortion. Success was defined as complete expulsion of products of conception within 24 hours of misoprostol. Failure was defined as incomplete expulsion of products of conception within 24 hrs of misoprostol. In the event of failure, pre–consent was taken that termination of pregnancy would be done by surgical methods or other medical methods like oxytocin acceleration. Patient was asked to follow after one week and USG was repeated to see any retained products of conception, blood clots.

Statistical analysis

Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p < 0.05$.

Results

Maximum subjects were in the age group of >20-25 years in both group A (40%) and B (36.7%). Mean age of the study subjects was 24.17±5.11 years and 23.93±4.08 years in group A and group B respectively. 5 weeks, 6 weeks and 7 weeks gestation was reported among 16.7%, 30%, 53.3% of the subjects in group A and 3.3%, 36.7%, 60% of group B respectively. In group A and B, mean gestation age (in weeks) was 6.37±0.77 and 6.57±0.57 respectively (table1).

Table 1: Age and gestation (in weeks) comparison among the study groups

Parameters	Group A (Mifepristone followed by Misoprostol after 24hours)		Group B (Mifepristone followed by Misoprostol after 6 hours)	
	N	%	N	%
Age group				
18-20 years	9	30	8	26.7
>20-25 years	12	40	11	36.7
>25-30 years	5	16.7	9	30
>30-35 years	2	6.6	2	6.6
>35-40 years	2	6.6	0	0
Gestation (in weeks)				
5 weeks	5	16.7	1	3.3
6 weeks	9	30	11	36.7
7 weeks	16	53.3	18	60
Chi square	3.47			
p value	0.12			
	Mean	SD	Mean	SD
Age (in years)	24.17	5.11	23.93	4.08
Gestation (in weeks)	6.37	0.77	6.57	0.57

Barrier failure was reported among 56.67% of the subjects in group A and 60% of the subjects in group B. Tubectomy failure and maternal kidney disease was reported only in one subject of group A with statistically insignificant difference as $p>0.05$.Multiparous and primigravida was revealed among 86.7%, 13.3% of the subjects in group A and 76.67%, 23.33% of group B respectively (table 2).

Table 2: Indications of MTP and parity distribution among the study groups

Indications	Group A (Mifepristone followed by Misoprostol after 24hours)		Group B (Mifepristone followed by Misoprostol after 6 hours)		Chi square	p value
	N	%	N	%		
Contraceptive Failure						
Barrier Failure	17	56.67	18	60	0.98	0.27
IUCD Failure	3	10	2	6.7		
OCP Failure	8	26.7	10	33.3		
Tubectomy Failure	1	3.3	0	0		
Humanitarian Ground (Risk to Maternal Health)						
Maternal Kidney Disease	1	3.3	0	0	1.08	0.19
Parity						
Multiparous	26	86.7	23	76.67	1.23	0.71
Primigravida	4	13.3	7	23.33		

IAI <6 hours, 7-12 hours, 13-18 hours and 19-24 hours was found among 36.67%, 43.33%, 16.67%, 0% of the subjects in group A and 33.33%, 43.33%, 10.00%, 3.33% of group B respectively. Failure was little more in group B as compared to group A. Mean IAI (hours) in group A was 8.38±3.29 with minimum and maximum of 4 and 17 hours. In group B, mean IAI (hours) was 8.96±4.09 with minimum and maximum of 4 and 20 hours. When IAI mean was compared statistically among group A and group B using t test, it was found to be statistically insignificant as p>0.05 (table 3).

Table 3: Mean comparison of IAI (hours) between two groups

IAI (hours)	Group A (Mifepristone followed by Misoprostol after 24hours)	Group B (Mifepristone followed by Misoprostol after 6 hours)
Minimum	4	4
Maximum	17	20
Mean	8.38	8.96
SD	3.29	4.09
t test	1.78	
p value	0.09	

Success was reported among 96.67% and 90% of the subjects in group A and B respectively. When outcome was compared statistically among group A and group B using chi square test, it was found to be statistically insignificant as p>0.05 (table 4).

Table 4: Comparison of success/failure between two groups

Outcome	Group A (Mifepristone followed by Misoprostol after 24hours)		Group B (Mifepristone followed by Misoprostol after 6 hours)	
	N	%	N	%
Success	29	96.67	27	90
Failure	1	3.33	3	10
Chi square	1.02			
p value	0.15			

All the mentioned complications were more in group A as compared to group B, but with statistically insignificant difference (table 5).

Table 5: Comparison of complications between two groups

Complications	Group A (Mifepristone followed by Misoprostol after 24hours)		Group B (Mifepristone followed by Misoprostol after 6 hours)		p value
	N	%	N	%	
Nausea	27	90.00	25	83.33	0.77
Vomiting	26	86.67	23	76.67	0.71
Shivering	19	63.33	14	46.67	0.26
Fever	23	76.67	17	56.67	0.19
Cramps	20	66.67	16	53.33	0.32
Pain	17	56.67	12	40.00	0.28
Diarrhoea	7	23.33	4	13.33	0.30
Bleeding	22	73.33	15	50.00	0.09

Discussion

The present study was conducted to compare the efficacy, side effects, and acceptability of the administration of 200 mg of misoprostol after only 6 hours of mifepristone in MTP up-to 49 days.

In the present study maximum subjects were in the age group of >20-25 years in both group A (40%) and B (36.7%). Minimum subjects were in the age group of >35-40 years (6.6%) followed by >30-35 years in group A (6.6%) as well as group B (6.6%). Mean age of the study subjects was 24.17±5.11 years and 23.93±4.08 years in group A and group B respectively. Mitchell D. Creinin *et al* [7] reported approximately similar age group among the study groups. Mean age was 25±6 and 25±5 years in study treatment group (interval 6–8 hours) and standard treatment group (interval 23–25 hours) respectively. Yiu-Tai Li *et al* [8] revealed mean age of 25.2 years in their study subjects.

5 weeks, 6 weeks and 7 weeks gestation was reported among 16.7%, 30%, 53.3% of the subjects in group A and 3.3%, 36.7%, 60% of group B respectively in the present study. Ritu Sharma *et al* [9] in their study showed that gestational age as confirmed by ultrasound was < 5weeks in 22% patients, >5 weeks to 6 weeks in 58% and >6 weeks to 7 weeks in 20% patients.

Multiparous and primigravida was revealed among 86.7%, 13.3% of the subjects in group A and 76.67%, 23.33% of group B respectively. Mitchell D. Creinin *et al* [7] reported approximately similar results. Yiu-Tai Li *et al* [8] in their study found that 140 (57.9%) women were nulliparous, 38 (15.7%) were primiparous, and 64 (26.4%) were multiparous.

Success was reported among 96.67% and 90% of the subjects in group A and B respectively in the present study. Mitchell D. Creinin *et al* [7] too reported similar results. They revealed that the complete abortion rate did not vary significantly by treatment group i.e. using mifepristone and vaginal misoprostol as early as 6 hours apart is as effective as waiting 24 hours

between administrations of the 2 medications. In 2005, Murthy and associates [10] concluded that the combined administration of mifepristone and misoprostol to pregnant women less than 7 gestational weeks is an efficacious way of achieving medical abortion.

Mean induction to abortion interval was 6.8 hours as reported by Ritu Sharma *et al* [9] in their study which is little lower than the present study. All the mentioned complications were more in group A as compared to group B in our study. Nausea was the most common complication followed by vomiting, fever and bleeding in both the groups. Diarrhoea was the least common complication followed by pain. Mitchell D. Creinin *et al* [7] revealed similar findings in their study. Women do experience side effects that are attributable solely to the mifepristone, and the longer the interval between the mifepristone and misoprostol is, the more side effects that women experience from the mifepristone. They also find that women in the 6- to 8-hour group experienced less severe side effects (nausea, vomiting, and heavy bleeding) after misoprostol administration as compared with women in the 24-hour interval group.

Mifepristone's known actions on a pregnant uterus include decidual necrosis, cervical softening, and increasing both uterine contractility and prostaglandin sensitivity [11, 12]. Human studies [11] have suggested that uterine contractility does not increase until 24 to 36 hours after mifepristone administration. At this point, the myometrium is 5 times more sensitive to the stimulatory effects of exogenous prostaglandins. Our study suggests that a longer interval between mifepristone and prostaglandin analog administration is not necessary for the medical abortion to be successful, tolerable and acceptable to the patient. Further investigations are needed to better understand which of mifepristone's actions are important and necessary for its abortifacient activity.

Conclusion

Based on the results of the current study, the authors concluded that women can use regimens with vaginal misoprostol without any time delay between medications with efficacy that is similar to those with a delay. Because misoprostol can be used as soon as 6 hours after mifepristone administration, women can now have a medical abortion in a single day with a high level of efficacy, safety, and acceptability.

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