Indian Journal of Obstetrics and Gynecology
Volume 3 Number 1, January - June 2
DOI:https://dx.doi.org/10.21088/ijog.2321.1636.3115.2

Comparative Evaluation of Simultaneous Administration of Mifepristone and Misoprostol; and Misoprostol Alone for Induction of Second Trimester Abortion

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Abstract

The present study was conducted with the aim to assess the safety and efficacy of misoprostol alone and misoprostol with simultaneous mifepristone for second trimester termination of pregnancy. Material & Methods: The study was conducted on 160 cases, divided in two groups of 80 cases each. In the study group 200 mg mifepristone and 200 mg misoprostol given together on admission followed by misoprostol every 3 hrs upto a maximum of 8 doses or until the abortion occurs, whichever occurs early. In the control group only misoprostol was given in the same dose regime. If abortion did not occur within this duration it was considered failure of method. The results were analysed. Results: The success rate in first regimen was 98%. Mean induction abortion interval was significantly shorter in the study group, 8.62 ± 1.96 h as compared to 14.5 ± 3.01 h in the control group. The mean dose of the misoprostol required was significantly less in study group. The side effects like nausea,vomiting,fever,abdominal cramps,diarrhoea were observed more in control group (30%) in comparison to study group (12.1%). Conclusion: Mifepristone with simultaneous misoprostol is better than misoprostol alone and there is no need to wait for 24 hr after mifepristone for administration of misoprostol.

Keywords: *Second Trimester Termination of Pregnancy; Mifepristone; Misoprostol.*

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Introduction

Induced abortions are major cause of maternal mortality. Large population who cannot afford, succumb to cheaper methods of abortion practices that eventually risk their lives. Today mortality rate due to abortions has reached upto 12% of maternal mortality rate.

In an effort to curb criminal abortions and maternal mortality government of India legalized abortion upto 20 weeks of pregnancy in year 1971. Second trimester abortion carries 20 times higher maternal mortality rate as compared to 1st trimester. Mid trimester abortion usually carried out by induction rather than by D & E, though in western world; D & E ~dilatation & evacuation is still being prefered. But in India; nonsurgical methods like i.v oxytocin infusion, dinoprostone gel, intra amniotic infusion by hyperosmolar urea or hypertonic saline, extra amniotic infusion by ethacridine lactate etc singly or in combination are being used, accepting potential complications associated with each method.

But with the introduction of prostaglandin & analogues efficacy improved & complications reduced. Initially Misoprostol alone was used for medical abortion upto 49 days. It was first approved in France in 1988 followed by approval in UK in 1991. Either vaginally or orally it reaches peak level in 20-30 min and level remain in blood upto 3-4 hrs. But many side effects being reported like nausea, vomiting, diarrhea, fever with chills, headache, delirium, hyperpyrexia >40°C. A case has been reported where woman died of multiorgan failure due to overdose of misoprostol. Misoprostol is used in different regimen with induction abortion interval varying from 12 hrs to as high as 33 hrs [1-8].

Later on antiprogesterone drug mifepristone was tried with misoprostol. It typically acts on uterine wall; increases contraction, does cervical priming. Subsequently it was successfully used for later gestation abortions also (>49 days till 20 weeks) associated with lesser side effects than misoprostol and less time consuming.

In our hospital many a times women come for IInd trimester MTP with sterilization. They generally undergo MTP with sequential misoprostol and have to stay in hospital for 24 – 48 hrs with occasional failures. They are parous women with small children at home, staying in the hospital is very inconvenient to them. The addition of mifepristone seems to be a logical option to decrease the induction abortion interval.

Aim & Objectives

To compare the efficacy of Mifepristone with sequential misoprostol vs sequential misoprostol only for second trimester MTP .

Objectives

- To find out primary outcome.
  - Induction abortion interval
- To compare secondary outcome
  - Total dose of miso required
  - No. of incomplete abortions warranting surgical evacuation.
  - Side effects of the drugs in 2 regimens.

Material & Methods

This prospective observational study was conducted on selected 160 cases coming in gyne opd of SVBP hospital,LLRM Medical College Meerut for MTP with tubal ligation from August 2012 to September 2013. A detailed history of the case was obtained. Inclusion criteria were age > 18 yr, singleton pregnancy, gestational week:12-20 weeks ,legal indication for termination of pregnancy General and systemic examination of the cases was done.Criteria like gestation age < 12 weeks and > 20 weeks , ectopic pregnancy, anemia <8gm, bleeding disorder, patients on long term steroids, patients on anticoagulants, chronic renal / adrenal / liver / respiratory / heart disease, any cerebrovascular disorder or any known allergy were excluded from the study. Cases were randomly divided in two groups of 80 each.

- Study group (group A): received 200 mg of mifepristone with misoprostol on admission followed by 200 mg of misoprostol vaginally every 3 hrs until the abortion occurred or up to a maximum of 8 doses.
- Control group (group B): received misoprostol only in the same dose schedule.

The cases were closely monitored for side effects, total dose of misoprostol required, no. of incomplete abortions warranting surgical evacuation. Induction abortion interval was noted . The process was considered failed if abortion did not occur even after 8 doses of misoprostol. If placenta was retained for more than 2 h surgical evacuation was done. In case of failure another method medical or surgical was tried. The data were analyzed by using appropriate statistical methods.

Observations & Results

Majority of the cases in both the groups were between 21 and 30 years of age. The mean gravidity of the cases was 4.59 ± 1.34 years in the study group and 3.98 ± 1.50 in the control group. The mean gestational age was 16.04 ± 2.57 and 14.03 ± 3.92 weeks in the study and the control groups respectively (Table 1).

Table 1

Factors	Mifepristone+misoprostol (group a)	Misoprostol only (group b)
AGE		
Mean in years	26.3±3.08	26.02±4.7
Minimum	22	23
Maximum	35	36
GRAVIDITY		
Mean	4.59±1.34	3.98±1.5
Minimum	3	3
Maximum	8	8
GESTATIONAL AGE		
Mean in weeks	16.04±2.5	14±3.9
Minimum	12	12
Maximum	20	20

Table 2

Title	ABORTION INDUCTION INTERVAL (IN HRS)	
	Group A	Group B
Col. title		
Mean	8.6153846154	14.5540540541
Standard deviation (SD)	1.942	3.097
Sample size (N)	78	74
Std. error of mean(SEM)	0.2199	0.3600
Lower 95% conf. limit	8.177	13.836
Upper 95% conf. limit	9.054	15.273
Minimum	6.000	8.000
Median (50th percentile)	9.000	14.000
Maximum	15.000	22.000

P value The two-tailed P value is < 0.0001, considered extremely significant.

Table 3

Title	COMPARISION OF DOSES OF MISOPROSTOL	
	Group A	Group B
Col. title		
Mean	3.7283950617	6.55
Standard deviation (SD)	0.7248	1.282
Sample size (N)	81	80
Std. error of mean(SEM)	0.08053	0.1433
Lower 95% conf. limit	3.568	6.264
Upper 95% conf. limit	3.889	6.836
Minimum	3.000	4.000
Median (50th percentile)	4.000	7.000
Maximum	6.000	10.000

P value:The two-tailed P value is < 0.0001, considered extremely significant.

Table 4: Showing comparison of abortion induction interval (in hrs) in relation to gravida- parity and gestational age in weeks.

Parity	Mifepristone+ misoprostol	Misoprostol
3-5	9±1.84	14.6±3.01
6-8	7±1.94	11±2.2
Weeks		
12-16	8.4±1.8	15±1.4
18-20	7.2±1.8	10±2.1

Table 5: Comparison of side effects among the two groups

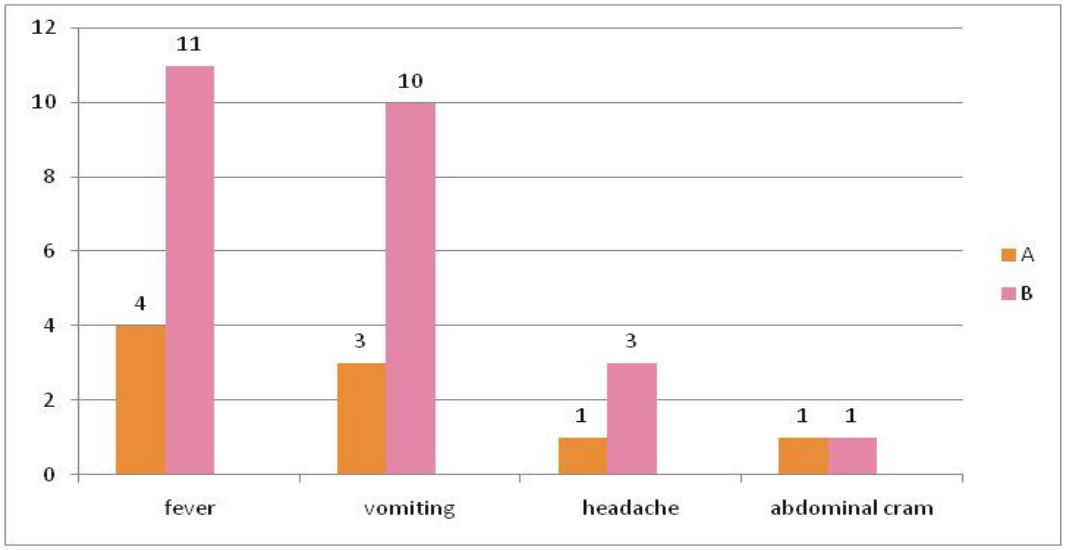

Table 6:

Study	Dosage	Abortion induction interval	Frequency of s/e	Efficacy Rate %
Rodger et al	Mifepristone 600 mg 36 hrs prior to gemeprost	6.8hours	Similar to placebo group	
Netherland study	Mifepristone 200mg 36 hrs prior to misoprostol	9.3hours	Similar to placebo group	
Ashok et al 2004 Gemzell Danielson 2008(10,11)	Mifepristone 48 hrs prior to misoprostol	9.4hours		97%
F.Gary Cunningum et al 2005(12,13)	Mifepristone 200mg 48 hrs prior to vaginal misoprostol	8.4hours		
RCT (2011)Ngoc NT et al(14)	*Mifepristone 36 hrs prior to misoprostol*	*10hours*		*80%*
Present study	Mifepristone with misoprostol without any gap	8.6hours	Fewer side effects (12%)	98%

90% of the cases aborted within 9 hours in the study group after the insertion of the first misoprostol tablet as against only 43% in the misoprostol alone group. All cases except two in the study group aborted within 15 hours as against only 79% in the control group. The mean induction abortion interval was 8.62 ± 1.96 hours as compared to 14.50 ± 3.01 h in the control group ($P < 0.001$). Table 2

The mean dose of the misoprostol required was significantly less in the study group 3.76 ± 291.64 mg as compared to 6.75 ± 320.20 mg in the control group, respectively ($P < 0.001$).Table 3

Success rate varied in both the groups. 2.5% (2 out of 80) cases of study group did not abort even after 8 doses of misoprostol. 7% (6 out of 80) failure cases were reported in control group. The abortion was complete in 80% of the study group while 70% in the control group. Just 18 out of 80 cases in study group require further curettage where as in control group 34 out of 80 cases required curettage. ($P < 0.001$).

The commonly observed side effects were nausea, vomiting, fever, abdominal cramps, diarrhea and were observed more in control group(approx 30%) in comparison to study group(approx 12%).

Discussion

Second trimester abortions constitute 10–15% of all induced abortions worldwide but are responsible for two-thirds of major abortion-related complications. During the last decade, medical methods for second trimester induced abortion have been considerably improved and become safe and more accessible. Today, in most cases, safe and efficient medical abortion services can be offered or improved by minor changes in existing health care facilities. The combination of mifepristone and misoprostol is now an established and highly effective method for second trimester abortion. Where mifepristone is not available or affordable, misoprostol alone has also been shown to be effective, although a higher total dose is needed and efficacy is lower than for the combined regimen. Therefore, whenever possible, the combined regimen should be used. Efforts should be made to reduce unnecessary surgical evacuation of the uterus after expulsion of the fetus.

Combination of mifepristone with misoprostol is now widely used method for second trimester pregnancy termination. Priming of the uterus with mifepristone makes it more sensitive to prostaglandins. It binds with the progesterone receptors and antagonizes the actions of progesterone on prostaglandin synthesis and metabolism resulting in increase in production and decreased deactivation of prostaglandins. It also induces cervical softening thus, enhancing the efficacy of the prostaglandins as an abortifacient.

The time interval between the insertion of the first tablet of misoprostol and start of contraction was found to be significantly shorter in our study group as against the misoprostol alone group ($P < 0.001$). The time interval between the insertion of the first tablet and the start of the bleeding was also significantly shorter in the study group as compared to control group. ($P < 0.001$). The induction abortion interval was significantly shorter 8.62 ± 1.96 h in the study group while it was 14.5 ± 3.01 h in the misoprostol alone group. ($P < 0.001$).

Rodger et al. [9] in a double blind study using 600 mg mifepristone 36 h prior to gemeprost found that the induction abortion interval was significantly reduced to 6.8 h as compared to 15.8 h in the placebo group but in that study patient has to stay or wait for more than one day for sequential misoprostol.In our study our aim was to reduce patient stay in hospital, so mifepristone was given simultaneously with misoprostol and it was found that abortion induction interval was very much reduced (8 hrs) and patient don't have to stay for long in hospital.

Netherland study it was found that time between first administration of misoprostol and abortion induction is significantly longer (time 11.3hr) in comparison to combination of mifepristone and miso (mean time 9.3hr) but no significant difference were found in frequency of side effects like nausea,vomitingetc.In Ashok et al 2004 and Gemzell Danielson 2008 study (10,11) mifepristone was given 48 hours prior to misoprostol and abortion induction interval came out to be 9.4 hours.In F.Gary Cunningum 2005 study (12,13) mifepristone was given 48 hrs prior to vaginal misoprostol.In RCT 2011 ngoc NT et al study (14) mifepristone was given 36 hrs prior to misoprostol and abortion induction interval was 10 hours In this present study we found that abortion interval was reduced very much (8.6 hrs) in comparison to misoprostol only group (15 hrs).Also there was very much reduction in no of side effects in comparison to misoprostol only group (12% vs 30%).

The success rate was 98% in the present study. The mean dose of misoprostol required was significantly less when used in combination with mifepristone. The commonly observed side effects were nausea, vomiting, fever, abdominal cramp and diarrhea and were significantly less in study group as compared to control group.

Conclusion

Though conventionally in medical abortion misoprostol is given after mifepristone after a gap of 24-48hrs, coadministration of mifepristone with misoprostol without any gap is highly cost effective method with a high success rate and shorter abortion induction interval. The availability of second trimester medical abortion as a day care procedure can minimize disruption to the lives of women and their families .

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