Original article:

Comparative study of two different regimes of misoprostol by two different routes for mid trimester pregnancy termination

[1]NARAYAN SUCHITRA* , [2]PRITI KUMARI , [3]SHARMA MANJU , [4]JAIN VIMLA , [5]MEHTA SEEMA ,[6] NARAYAN JAIPRAKASH

[1]Assistant Professor Department of obstetrics and Gynecology Lady Hardinge Medical College Dehli

[2]Assistant Professor Department of obstetrics and Gynecology SP Medical College Bikaner Rajasthan

[3]Professor Department of obstetrics and Gynecology Mahila Chikitsalaya , SMS Medical College Jaipur - 302012 (Rajasthan) Phone: 0141-2378721SMS Medical College Jaipur Rajasthan

[4]Retd Senior Professor Department of obstetrics and Gynecology Mahila Chikitsalaya SMS Medical College Jaipur 302012 Rajasthan Phone: 0141-2378721SMS Medical College Jaipur Rajasthan

[5]Professor Department of obstetrics and Gynecology Mahila Chikitsalaya SMS Medical College Jaipur 302012 Rajasthan Phone: 0141-2378721SMS Medical College Jaipur Rajasthan

[6]Assistant Professor Department of Pediatrics JLN Medical College Ajmer Rajasthan

Corresponding author *

ABSTRACT

Aims: Comparative study of two regimes of Misoprostol by two different routes for midtrimester termination of pregnancy.

Methods: Hundred women who came for midtrimester termination of pregnancy from Aug 2008 to Oct. 2009 were allotted in two different groups. In group A Misoprostol (n=50) 800ug intravaginal followed by 300ug sublingually for maximum 3 doses were given and in group B (n=50) 400ug intravaginally for maximum 5 doses 3hrly were given. They were observed for 24 hours. Main outcome measured were induction abortion interval (IAI), success rate (complete abortion rate), mean dose required, duration of hospital stay, complication, side effects and need of other methods when these methods failed.

Result: In group A out of 50 patients 49 aborted within 24 hrs. of administration of 1st dose of misoprostol without requirement of assisted procedure, giving success rate 98%.Mean IAI was 11.09±7.86hrs, mean dose of misoprostol required was 1454±237.66µg, while in group B out of 50 pts 42 were aborted with in 24 hrs so success rate was 84%.Mean IAI and mean dose of misoprostol 20.56±10.56hrs and 1824.00±255.00µg respectively. The side effects were more in group B.

Conclusions: High intravaginal (800ug) f/b small and repeated sublingual (300ug) dose of misoprostol is a better, safe, more effective and acceptable method than repeated intravaginal dose [400µg×3hrly total 5doses] for second trimester pregnancy termination.

Key words: Induction abortion interval (IAI); Misoprostol; Second/Midtrimester pregnancy termination

INTRODUCTION

Abortion is defined as "termination of pregnancy (TOP) by any means before the fetus is viable". Viability is now considered to be reached at 23-24 weeks of gestation. Second trimester, is ranging from 13 to 28 weeks of gestation, which is subdivided into an early period (13-20 weeks) and late period (20-28)

weeks. In this study, we have limited abortions up to 24 weeks gestation and indications are[1]

1. MTP act 1971 (up to 20 weeks)
2. Obstetrical causes: severe PIH, Separated and ruptured membranes, IUFD, Missed abortion
3. Fetal congenital malformations not compatible with life diagnosed before period of viability till 20 weeks.

For second trimester termination surgical methods are not preferred. All medical methods having variable success rate of 70-90%.PGE1 analogue misoprostol have good uterotonic and cervical ripening effect and is used for the termination of pregnancy with great success.

We compared and assessed the efficacy and safety of high dose vaginal followed by repeated low dose sublingual (subjects) and vaginal only (control) misoprostol for midtrimester pregnancy termination.

METHODS

This prospective study analyzed 100 women admitted for midtrimester pregnancy termination from Aug 2008 to OCT 2009. All the women came for midtrimester termination of pregnancy in Department of Obstetric and Gynecology were screened for inclusion in the study.

A detailed history regarding duration of amenorrhea, gravidity, parity, previous spontaneous or induced abortion and medical diseases were recorded. General physical examination and systemic examination was done. In obstetric examination per abdominal as well as per vaginal examination was done to assess the duration of pregnancy and rule out any pelvic pathology.

The gestational age was determined by patient's menstrual history, pelvic examination and confirmed by ultrasound. All routine investigations like hematogram, blood grouping, blood sugar, platelet counts, bleeding profile, serum VDRL, HBsAg, renal profile with electrolyte, urine routine examination and ultrasonography were done.

An informed and written consent was obtained after counseling regarding the procedure, its advantage disadvantage, side effects as well as need of augmentation process if this method failed and need for follow up was explained.

Women with gestational age 13-24 weeks with IUFD, congenital malformed fetus (confirmed by two different USG up to 20 weeks), severe PIH, and PPROM were included in this study.

Women with adrenal insufficiency, coagulopathy, contraceptive device in situ, on steroid therapy, ectopic pregnancy, hemorrhagic disorder , thrombotic thrombocytopenic purpura, porphyria, adrenal mass, diabetes, jaundice, twin pregnancy, organic heart disease, respiratory disorder, uterine scar, large myoma, pelvic tumor, diagnosed uterine anomalies, severe anemia and allergic to prostaglandins were excluded from study.

A dose of IV antibiotic and inj tetanus toxoid was given (if not given earlier) before starting any regimen.

Hundred women those who were fulfilling inclusion criteria, randomly allocated into two groups (subjects and control) by lottery method of simple randomization.

Subjects: Tablets of misoprostol 800ug per vaginal followed by 300ug sublingual misoprostol at 3 hourly interval for maximum 3 doses were given to these women.

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Control: Tablets of misoprostol 400 ug per vaginal every 3 hourly for maximum 5 doses were given in these women.

Procedure: All inductions were carried out on inpatient basis. Intravaginal misoprostol was kept into posterior fornix and patients were strictly kept into bed in supine position for 30 min and sublingual misoprostol was kept beneath tongue and patients were strictly advice not to chew or spit the tablet and not to take anything per oral for 30 minutes.

All vital parameters were recorded before and after giving doses and 2 hrly up to 24 hours in predetermined proforma, and side effects were monitored and if any occur were treated accordingly. Time of onset of contraction, time of starting of bleeding and expulsion of product of conception were recorded. If abortion did not occur within 24 hours or found to be incomplete and if active bleeding was present after 24 hour then acceleration process with oxytocin drip and surgical evacuation done. All patients were kept under observation for 2 hour after abortion and discharged on next day with the advice to come for follow up after 14 days or earlier if necessary.

Success was defined as complete abortion within 24 hours of instillation of first dose of misoprostol without any acceleration process. Complete abortion was considered if fetus, placenta and membranes were expelled spontaneously and completely. All parameters were recorded in predetermined performa and data were analyzed by z-test by statician and results were compared with previous studies done by other scientists on misoprostol.

RESULTS

Table No- 1 Patients profile:

Parameters	subjects	Control
Age in years (mean± SD)	26.51±4.47	24.34±3.17
Minimum and maximum age	20&40 year	20&35 year
Primigravida	20%	12%
Mean gravidity	2.68±1.49	2.64±1.13
Mean gestational age	20.22±2.71	18.86±2.74

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Table No-2 Induction abortion interval in subjects and control:

IAI in hours	% in subjects(n=50)	% in control(n=50)	Cumulative abortion rate in subjects	Cumulative abortion rate in control
3-7	34	0	34	0
8-12	42	28	76	28
13-17	14	12	90	40
18-22	6	36	96	76
23-27	2	8	98	84
>27	2	16	100	100
total	100	100	100	100

Mean±SD induction abortion interval was 11.09±7.86 hours in subjects and 20.56±10.56 hours in control so IAI was significantly less in subjects than control group (p-value <0.001)

Table No-3 Mean ± SD Induction abortion interval and Mean ±SD dose of misoprostol required according to GA in subjects and control

GA	**Mean ± SD Induction abortion interval**		**Mean ±SD dose of misoprostol**	
	Control	**Subjects**	**Control**	**Subjects**
14-17	18.11 ± 11.31 (n=15)	10.05 ± 3.46 (n=8)	1680.00±299.33 (n=15)	1512.50±297.65 (n=8)
18-21	20.88 ± 10.28 (n=22)	12.12 ± 10.54 (n=22)	1854.54±227.09 (n=22)	1440.91±226.95 (n=22)
22 +	21.24 ± 4.90 (n=13)	10.22 ± 5.05 (n=20)	1938.46±144.32 (n=13)	1445.00±217.89 (n=20)

Mean±SD induction abortion interval and mean±SD of dose of misoprostol required was not statically different in different gestational age in both subjects and control but statically less in subjects in comparison to control in different gestational age groups (p<0.001).

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Table No-4 Mean ± SD Induction abortion interval and Mean ± SD dose of misoprostol required according to gravida in subjects & control

Gravida	Mean ± SD Induction abortion interval		Mean ± SD dose of misoprostol	
	control	subjects	control	Subjects
1	15.95 ± 3.84 (n=6)	11.90 ± 5.09 (n=10)	1800.00±200.00 (n=6)	1580.00±146.97 (n=10)
2	21.17 ± 12.56 (n=19)	12.11 ± 11.64 (n=17)	1789.47±300.69 (n=19)	1452.94±256.94 (n=17)
3	20.51 ± 7.44 (n=16)	10.02 ± 4.91 (n=12)	1875.00±185.40 (n=16)	1425.00±227.76 (n=12)
4+	20.04 ± 7.98 (n=9)	9.43 ± 3.95 (n=11)	1822.22±273.97 (n=9)	1340.00±224.50 (n=11)

The mean ±SD IAI and mean±SD dose of misoprostol requirement both were decrease with increasing gravidity so inversely proportional to gravidity in both subjects and control.

Table No-5 Mean± SD of various parameters

Parameters	Subjects	Control
Total dose of misoprostol required	1454±237.66	1824.00±255.00
Time of starting pain after insertion of 1st dose of misoprostol	2.49±2.41 (82% within 5 hour)	8.35±3.31 (14% within 5 hour)
Time of starting bleeding after insertion of 1st dose of misoprostol	4.70±3.62 (70% within 5 hour)	11.04±3.43 (6% within 5 hour)
IAI	11.09±7.86	20.56±10.56
Duration of hospital stay	33.18±24.29 hour	49.09±21.75

Most common side effects were nausea, vomiting, fever and diarrhea. All of these side effects were more in control than subjects and managed symptomatically. None of the women required prolonged IV antibiotics or blood transfusion. Hospital stay duration after giving first dose of misoprostol till discharge from hospital was statically less in subjects (33.18±24.29 hrs) than control (49.09±21.75 hrs) $p<0.001$.

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DISCUSSION

Table No-6 Comparison with different studies:

Author	Year	Schedule of regimen	Success rate	IAI (hours)	Total dose required (ug)	Side effects
Wong et al[2]	2000	400ug vaginal 3 hrly ×5 400ug vaginal 6 hrly ×3	90.5% 75.7%	15.2 19.0	-	Pyrexia 7%
Tang et al[3]	2004	400ug 3hrly×5 times sublingual v/s vaginal	64 %in sublingual , 85% in vaginal at 24 hr	13.6 hrs in S/L, and 12.0 in vaginal group	-	
Langer et al[4]	2004	800ug vaginal f/b 400ug 3 hrly×3 times	98%	12.7±8	1800	12.2% vomiting 20%pyrexia
Herabutya et al[5]	2005	600ug vaginal 6 hrly v/s 12 hrlya		16 hrs in both regimen	1800 in 6 hrly and 1200 in 12 hrly schedule	
Nagaria Tripti and Somawar Swati[6]	2007	800ug vaginal f/b 300ug 3 times 3 hrly sublingual	98%	9.36±3.50	1485.63±219.25	Vomiting, diarrhea and fever each 12%
Nagaria Tripti, Sirmor Namrata[7]	2007	600ug loading vaginal f/b 400 ug every 4 hrly till abortion or maximum 2600ug	99.26%	12.27±5.71	1638.57±322.67	Fever 14.28%, vomiting 12.85%, diarrhea 1.42%
Present study	2009	800ug loading vaginal f/b 300ug sublingual every 3 hourly×3 doses 400ug vaginal every 3 hourly×5 doses	98% 84%	11.09±7.86 20.56±10.56	1454.54±237.66ug 1824.00±255.00ug	Nausea and vomiting 24%,Fever 8%,diarrhoea8% Nausea and vomiting 52%,diarrhea 12%,fever10%

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Mid trimester pregnancy termination is 12 times more risky, carries more maternal morbidity and mortality as compare to first trimester so this deserve special attention and need for a method which is cost effective, safe, convenient, has shorter IAI, less side effect and least complication[7]. Misoprostol has both uterotonic and cervical ripening properties[7]. Vaginal misoprostol reaches a high peak concentration in blood between 70 to 80 minutes and declines slowly with detectable levels presents up to 6 hour after administration. The greater bioavailability of vaginal misoprostol helps to explain why this route is more effective in medical abortion. Vaginal misoprostol has long duration of action and late peak of concentration. After sublingual administration of misoprostol it resulted in highest peak concentration within shortest time 7.8 to 11.5 minutes with a greatest bioavailability. Its plasma level declines within two and half hours[8]. In our study the mean IAI in subjects was 11.09±7.86 hours and in control was 20.56±10.56. The more successful outcome with loading vaginal dose followed by sublingual dose 3 hourly is due to the high level of circulating misoprostol once attained by loading vaginal dose is subsequently maintained by frequent sublingual dose. The high levels of misoprostol attained by this regimen leads to good cervical ripening and sustained uterine contraction resulting in reduced IAI hence more successful outcome. Various studies have been conducted using misoprostol in different doses and by different routes for midtrimester termination of pregnancy with variable results.

Nagaria Tripti and Somawar Swati[7] in2007 also used similar regimen and found high success rate and shorter IAI and less side effects similar to our study. Wong et al[2], Tang et al[3], Herabutya et al[5] used different regimen of misoprostol intravaginally without loading dose and mean IAI and mean dose of misoprostol was high. Wong reported that 3 hourly dose schedule is more effective than 6 hourly schedules.

CONCLUSIONS

A high loading dose of vaginal misoprostol followed by frequent small sublingual doses is a highly effective, safer, cheaper and acceptable method for midtrimester termination of pregnancy. However larger studies are required before recommending it as major drug for midtrimester termination of pregnancy because in our study sample was small.

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