A STUDY OF DIFFERENT DOSES OF SUBLINGUAL MISOPROSTOL AFTER ORAL MIFEPRISTONE IN MEDICAL TERMINATION OF PREGNANCY

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ABSTRACT: BACKGROUND: Though Mifepristone- Misoprostol combination is well established for early pregnancy termination, the optimal Misoprostol dose is still under much debate.
AIMS: To compare the efficacy of sublingual 400µg Misoprostol and 800µg Misoprostol after oral 200mg Mifepristone in achieving complete abortion, to study the induction abortion interval, complications and adverse effects seen with both groups. Setting 100 antenatal women requesting for medical termination of pregnancy of upto 63 days of gestation in ESI Medical College and Postgraduate Institute of Medical Sciences and Research, Karnataka in India. Design A Prospective Observational study.
METHODS AND MATERIAL: Study population was randomized into 2 groups of 50 patients each. Both groups received 200 mg Mifepristone. Twenty four hours later, Group A received 400µg sublingual Misoprostol and Group B received 800 µg sublingual Misoprostol.
OUTCOME MEASURES: The primary outcome analyzed in this study is the efficacy of the two regimens in achieving complete abortion. Secondary outcome measures are Induction to Abortion interval and adverse effects like pain abdomen, nausea, vomiting, diarrhoea, fever and chills.
STATISTICAL ANALYSIS USED: Averages and proportions were calculated for the study and appropriate statistical tests like Chi Square Test, Fischer Exact Test and Student T Test were done using MiniTab version 16.
RESULTS: Administration of 400µg sublingual Misoprostol 24 hours after 200 mg of Mifepristone has complete medical abortion rates comparable with 800µg sublingual Misoprostol with significantly lesser side effects.
CONCLUSIONS: In the present study, administration of 400µg sublingual Misoprostol after 200 mg of Mifepristone has complete medical abortion rates comparable with 800µg sublingual Misoprostol with significantly lesser side effects. However further research with different doses and routes of administration of Misoprostol in required in a larger study population.

KEYWORDS: Two Different Doses of Sublingual Misoprostol in Early MTP. MeSH Terms Medical Abortion; Mifepristone; Misoprostol.

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INTRODUCTION: Worldwide, 46 million pregnancies end in induced abortions annually, of which 20 million are illegal/unsafe abortions.[1] 13% of maternal mortality is due to unsafe abortions. 20-30% of unsafe ab nortions cause reproductive tract infections and 2% causes infertility.[2] In India, around 10-12 million abortions take place annually, of which 15-20 thousand deaths are due to illegal/unsafe abortions.[3] 90% of induced abortions are in the first trimester alone. To reduce maternal mortality and morbidity, the provision of safe legal abortion to women in a variety of health care settings is the most important component of reproductive health services. Medical abortion offers greater potential for improving abortion access and safety, as it does not require an intensive infrastructure as in the case of surgical abortion and can offer privacy to the woman.

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For first trimester abortions, an alternative safe and effective approach to surgical abortion is the combined use of Mifepristone and Misoprostol regimen as recommended by W.H.O.[4] This is likely to make a positive impact on the reproductive health of women in India by providing support in addition to conventional family planning contraceptive. Mifepristone (RU-486), an antiprogestin, causes abortion by increasing uterine contractility by reversing the Progesterone- induced inhibition of contractions.

In addition, Mifepristone causes cervical collagen degradation, possibly because of increased expression of matrix metalloproteinase-2.[5] Mifepristone also softens and dilates the cervix, causes decidual necrosis (Which leads to placental detachment), increases uterine lining prostaglandin release, increases uterine contractions, and enhances uterine sensitivity to administered prostaglandin.[6]

Misoprostol, a prostaglandin, binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. This agent also causes cervical ripening with softening and dilation of the cervix.[6] Different combinations of Mifepristone and Misoprostol have been used in medical termination of pregnancy which traditionally varies with Mifepristone 100- 600 mg orally followed by Misoprostol 200- 600 µg orally or 800µg vaginally in multiple doses over 6- 72 hours.[5]

The efficacy of Mifepristone- Prostaglandin regimen was not reduced by decreasing the dose of Mifepristone from 600mg to 200mg.[7] A pharmacokinetic study has shown that sublingual Misoprostol has the shortest onset of action, highest peak of concentration and greatest bioavailability among the three routes of administration.[4] A previous study showed complete abortion occurred in 98.2% of women in the sublingual group and 93.8% in the vaginal group.[8]

Rates of serious infection dropped significantly after the joint change to buccal Misoprostol from vaginal Misoprostol and with routine administration of antibiotics.[9] We therefore conducted a prospective observational study to find the optimal dose of sublingual Misoprostol either 400µg or 800µg that can be administered 24 hours after oral Mifepristone 200 mg, to achieve complete abortion with minimal side effects.

METHODS: We conducted a Prospective Comparative Hospital based study of 100 antenatal women attending the Obstetrics and Gynaecology outpatient department at ESIC MC Model Hospital, Rajajinagar, Bengaluru, Karnataka, India requesting for medical termination of pregnancy of upto 63 days of gestation, from October 2011 to October 2013. We obtained permission from the Hospital and Departmental Clinical Research Committee before starting this study.

CLINICAL MANAGEMENT AND DATA COLLECTION: Participants were randomly assigned in a 1:1 ratio by lottery method at the time of qualifying to enrol in the study. Hospital staff and participants were all aware of the study being conducted and an informed consent was taken from the patient.

ETHICAL APPROVAL: We obtained approval from the Hospital and Departmental Clinical Research Committee on 16th September 2011 before starting this study.

STUDY POPULATION AND SETTING: 100 antenatal women with a single live intrauterine foetus of gestational age ≤9 weeks, requesting for termination of pregnancy, eligible as per terms of the MTP Act, 1971, were randomized into 2 groups of 50 patients each. Both groups received 200mg Mifepristone orally. Twenty four hours later, Group A received 400µg sublingual Misoprostol and Group B received 800µg sublingual Misoprostol.

The exclusion criteria were-threatened and missed abortion: molar pregnancy: pregnancy with a coexisting Uterine fibroid or ovarian cyst: lactating women: medical disorders like Anaemia, Renal disease, Asthma: women on Corticosteroids or on Anticoagulant therapy and women allergic to Mifepristone or Misoprostol.

Informed consent was obtained for the procedure, the need for surgical procedure (Suction evacuation or dilatation and curettage) that may arise and for the necessary follow up in the present study. Gestational age was assessed by her L.M.P and pelvic examination, which was confirmed by ultrasonography. This also provided information regarding viability and site of implantation of pregnancy.

On day 1 of the admission, any complaints like pain abdomen, nausea, vomiting, diarrhoea, chills and fever were assessed. Oral Mifepristone 200mg was given under supervision. 24 hours later, the patient was administered with either 400µg or 800µg sublingual Misoprostol according to the group she was allotted to. Prior to administration of Misoprostol, if any complaints like pain abdomen- mild, moderate or severe, nausea, vomiting, bleeding per vagina, diarrhoea, chills and fever were again noted. She was advised to place two tablets of 200µg Misoprostol beneath the tongue and to allow them to dissolve spontaneously. In the 800µg dosage group, the patient was advised to place four tablets sublingually.

All patients received Inj. Tetanus Toxoid and prophylactic antibiotics. Rh negative women were administered with 50µg of Inj. Anti D.

The patient was observed for a period of 4-8 hours. They were monitored hourly for the possible expulsion of products of conception, vaginal bleed and adverse effects such as nausea, vomiting, diarrhoea, abdominal cramps, chills and fever and treated accordingly. Once the patient reported passage of products of conception as assessed by history of expulsion of mass, clots or heavy bleed followed by decrease in pain abdomen and flow of vaginal bleed, this time was noted as the time of complete abortion and pelvic ultrasonography was repeated to confirm completion of abortion.

Patient was then discharged and during the follow up period of 1- 14 days, they were requested to observe the days of vaginal bleeding and to fill the questionnaire administered to them to evaluate their side effects. They were provided with an emergency contact number to contact in case of excessive bleeding- soaking of two pads every hour for two consecutive hours, severe pain abdomen not relieved with medication, easy fatigability or a sustained fever of more than 100.4º F. A follow up date was also provided to them on the 7th and 14th day post abortion.

They were also requested to record any of the above adverse effects and asked to return for follow up evaluation on Day 14. The patient was asked to review earlier if no bleeding occurs, if soaking of two pads occurred for two consecutive hours, had severe pain abdomen or if patient has a sustained fever of more than 100.4º F.

In case patient had an ongoing pregnancy, missed abortion or an incomplete abortion even on the 14th day after Misoprostol intake or requested for surgical termination of the pregnancy at any point in the study, she was classified as a failure of this study and surgical termination (Either vacuum aspiration or instrumental evacuation) was performed. Patient was counselled for a suitable contraceptive method after termination of pregnancy.

STATISTICAL ANALYSIS: The data obtained was analyzed using Chi Square Test, Fischer Exact Test and Student T Test were done using Minitab version 16.

STUDY OUTCOMES: The primary outcome was the efficacy of the two regimens in achieving complete abortion, defined as passage of products of conception with the assigned regimen without surgical intervention in the follow up period and confirmed by empty uterine cavity and ultrasonography. Secondary outcome measures were induction to abortion interval, number of days of bleeding and adverse effects which were nausea, vomiting, diarrhoea, abdominal cramps, chills and fever. This was evaluated with the help of a questionnaire on which pain abdomen was recorded as mild (Felt but easily tolerated), moderate (Uncomfortable enough to interfere with normal activity) or severe (Incapacitating normal activity). The presence or absence of diarrhoea defined as passage of three or more stools per day was recorded along with the presence or absence of nausea,

vomiting, chills and fever of more than 100.4º F for 14 days post abortion.

The above terminologies in our study were defined as Ongoing Pregnancy- No products of conception expelled and cardiac activity present on ultrasound: Missed miscarriage- No products of conception expelled and ultrasound showing evidence of a gestational sac without cardiac activity: Incomplete miscarriage- Endometrial Thickness of ≥20mm on ultrasound even after 14 days of Misoprostol administration: Induction to Abortion Interval- The time interval between administration of Misoprostol and the clinically estimated- ultrasonologically confirmed time of abortion which was noted, as explained above.

RESULTS:

Study Group: Demographic characteristics between both the groups (Table 1) were analyzed with respect to age, weight, haemoglobin status, parity and gestational age.

Successful Medical Abortion: 92% of patients in Group A had a complete abortion with 400µg Misoprostol and 95% of patients in Group B had a complete abortion with 800 µg Misoprostol (Table 2). The p value was 1 between both the groups and hence there was no statistical significance between the complete medical abortion rates of both groups. There were 7 failures in the study. 1 patient in Group A and 1 patient in Group B requested for a surgical abortion after intake of Misoprostol citing pain abdomen following intake of Misoprostol as reason to elect surgical abortion. The other 5 failures of this study- 3 in Group A and 2 in Group B had an incomplete abortion at the end of 14 days and needed a surgical evacuation to complete the abortion.

Abortion Interval: The mean abortion interval after intake of Misoprostol was 3.52 hours in Group A and 3.09 hours in Group B (Table 3). There was no difference between the mean Induction to Abortion Interval between Group A and Group B (p value 0.097).

No. of Days of Bleeding in Both Groups: In Group A, the mean duration of bleeding was 7.85 days and was 7.38 days in Group B (Table 4). The difference between the mean average duration of bleeding between both the groups was not significant.

ADVERSE EFFECTS (Table 5)Demographic Characteristics	Group A (n= 50)	Range	Group B (n= 50)	Range	P- value
Age (Years)	25.66	18- 35	25.18	18- 33	0.574
Weight (kg)	55.36	38- 82	56.04	39- 89	0.761
Hemoglobin (gm/dl)	10.5	9- 14.2	10.4	9- 13.6	0.88
Parity					
Primigravida	5	9	0.12		
Parous	45	41	0.24		
Prev. abortion	4	5	>0.05		
Gestational Age (Days)					
≤49	12	13	0.81		
50- 56	23	17	0.22		
57- 63	15	20	0.29		
Table 1: Demographics of the study population					

P value between groups- 1	Duration of Gestation	No. of Patients	Successful complete medical abortion	Percent of Number Aborted	Requiring instrumental evacuation
Group A	≤49	12	11	91.60%	1
	50- 56	23	21	91.30%	2
	57- 63	15	14	93.30%	1
	Total	50	46	92%	4
Group B	≤49	13	13	100%	0
	50-56	17	17	100%	0
	57-63	20	17	85%	3
	Total	**50**	**47**	**95%**	**3**
Table 2: Successful Medical Abortion in the two groups.					

Group	N	Mean (hours)	Range (hours)	Std. Deviation	t value	p value
A	46	3.52	1- 6	1.243	1.670	0.097
B	47	3.09	1- 5	1.265		
Table 3: Mean Abortion Interval						

Group	N	Mean (days)	Range (days)	Std. Deviation	t value	Degree of freedom	Pvalue
A	46	7.85	4- 17	3.169	0.792	92	0.43
B	47	7.38	4- 14	2.524			

Table 4: Number of Days of bleeding

	Group A(n= 50)		Group B (n= 50)			
	Number	Percentage	Number	Percentage	Chi square	P value
Lower Abdominal Pain						
At Admission	0		1	2		
Mifepristone to Misoprostol	0		1	2		
After Misoprostol	50	100	50	100		
Mild	25	50	3	6		<0.001
Moderate	24	48	23	46	0.04	0.84
Severe	1	2	24	48		<0.001
Nausea						
At Admission	10	20	16	32	1.87	0.17
Mifepristone to Misoprostol	10	20	17	34	2.48	0.11
After Misoprostol	10	20	29	58	15.17	<0.001
Vomiting						
At Admission	2	4	8	16		0.09
Mifepristone to Misoprostol	3	6	8	16		0.11
After Misoprostol	7	14	20	40	8.57	0.003
Diarrhoea						
At Admission	0	0	0	0		
Mifepristone to Misoprostol	2	4	3	6		>0.99
After Misoprostol	15	30	27	54	5.9	0.01
Chills						
At Admission	0	0	0	0		
Mifepristone to Misoprostol	0	0	3	6		
After Misoprostol	12	24	46	92		<0.001
Fever						
At Admission	0	0	0	0		
Mifepristone to Misoprostol	0	0	1	2		
After Misoprostol	18	36	29	58	4.85	0.02

Table 5: Adverse Effects

	Complete Abortion		Induction to Abortion Interval	Pain Abdomen		Nausea		Vomiting		Diarrhoea		Fever		Chills	
	n	%	mean	n	%	n	%	n	%	N	%	n	%	n	%
Group A (n= 50)	46	92	3.52	mild-25	50	10	20	7	14	15	30	18	36	12	24
Group B (n= 50)	47	95	3.08	moderate-24	48	29	58	20	40	27	54	29	58	46	92

Table 6: Comparison of results obtained in thestudy between Group A and Group B

ABDOMINAL PAIN: All patients in the study had pain abdomen of some degree. No patients in Group A had pain abdomen at admission or between Mifepristone to Misoprostol and 1 patient in Group B had pain abdomen at admission and between Mifepristone to Misoprostol. In Group A, 50% had mild pain abdomen, 48% had moderate pain and 2% had severe pain abdomen after Misoprostol. In Group B, 6% had mild pain abdomen, 46% had moderate pain and 48% had severe pain abdomen after Misoprostol administration.

Incidence of mild pain abdomen was significantly more in Group A than in Group B (p value- <0.001). Incidence of moderate pain abdomen was not significantly different between the groups A and B (p value-0.84). Incidence of severe pain abdomen was significantly more in Group B than in Group A (p value-<0.001)

NAUSEA: In Group A, 20% had nausea at admission, 20% between Mifepristone to Misoprostol and 20% had new onset nausea after Misoprostol intake. 5 patients in Group A continued to have nausea from admission up to after intake of Misoprostol, and have not been included as an adverse effect of either of the two drugs.

In Group B, 32% had nausea at admission, 34% between Mifepristone to Misoprostol and 58% had new onset nausea after Misoprostol intake. 10 patients in Group A continued to have nausea from admission up to after intake of Misoprostol, and have not been included as an adverse effect of either of the two drugs. There were significantly more number of patients with nausea after administration of 800 µg sublingual Misoprostol in Group B (p value <0.001).

VOMITING: In Group A, 4% had vomiting at admission, 6% between Mifepristone to Misoprostol and 14% had new onset vomiting after Misoprostol intake. 1 patient in Group A continued to have vomiting from admission up to after intake of Misoprostol, and who have not been included as an adverse effect of either of the two drugs.

In Group B, 16% had vomiting at admission, 16% between Mifepristone to Misoprostol and 40% had new onset vomiting after Misoprostol intake. 10 patients in Group A continued to have vomiting from admission up to after intake of Misoprostol, and who have not been included as an adverse effect of either of the two drugs. There were significantly more number of patients with vomiting after administration of 800µg sublingual Misoprostol in Group B (p value-<0.05).

DIARRHOEA: In Group A, 4% had diarrhoea between Mifepristone to Misoprostol and 30% had diarrhoea after Misoprostol. In Group B, 6% had diarrhoea between Mifepristone to Misoprostol and 54% had diarrhoea after Misoprostol. No patients had diarrhoea at admission. There were significantly more number of patients with diarrhoea after administration of 800 µg sublingual Misoprostol in Group B (p value 0.01).

CHILLS: In Group A, no patients had chills at admission and between Mifepristone to Misoprostol and 24% had chills after Misoprostol. In Group B, no patients had chills at admission, 6% had chills between Mifepristone to Misoprostol and 92% had chills after Misoprostol. There were significantly more number of patients with chills after administration of 800µg sublingual Misoprostol (p value-<0.001).

FEVER: Group A, no patients had fever at admission and between Mifepristone to Misoprostol and 36% had fever after Misoprostol. In Group B, no patients had fever at admission, 2% had fever between Mifepristone to Misoprostol and 58% had fever after Misoprostol. There were more number of patients with fever after administration of 800µg sublingual Misoprostol, and this was statistically significant (p value-0.02)

DISCUSSION:

Main Findings: In the combined Mifepristone-Misoprostol regime for termination of pregnancy with gestation <63 day, administration of low dose sublingual Misoprostol (400µg) after 24 hours of 200 mg Mifepristone is effective in achieving successful complete medical abortion with lower incidence of adverse effects when compared with 800 µg sublingual Misoprostol.

Strengths and weaknesses of the study: The major strength of this trial was compared with previous studies was a pregnancy gestation and live pregnancy validated by ultrasound in all of the participants and the use of ultrasound immediately after the reported expulsion to look for complete abortion. Additionally, the study compared the efficacy of two varied strengths of Misoprostol administered by the same route, i.e., sublingual. The trial population was homogeneous with a 100% short-term follow-up rate at 7 and 14 days.

Some limitations to this study may apply as this was a small study conducted in a unit of a teaching hospital. Large multi-centric studies with a mixed ethnic population would be of value in this field. Another limitation to the current study may be that the outcomes evaluated were all short-term.

Interpretation: Before applying the results to other populations and settings, several factors have to be considered. Overall, the study population had a low body mass index and was very homogeneous, and the study aimed to only include healthy women with no a priori risks.

CONCLUSIONS: In the present study, Group A had 92% complete abortion rate and Group B had 95% complete abortion rate (p value-1). Both regimens were equally successful in achieving a complete medical abortion. There was no significant difference in mean Induction to Abortion Interval between both the groups with it being 3.52hrs in Group A and 3.08hrs in Group B (p value-0.097).

Adverse effects of Misoprostol are reduced in Group A compared to Group B. There is higher incidence of severe pain abdomen in Group B (48%) and mild pain abdomen in Group A (50%) though it was observed that all patients had some degree of pain abdomen in the study.

There was lower incidence of nausea, vomiting, diarrhoea, fever and chills observed in Group A.

The statistical results conclude that 400µg sublingual Misoprostol is as effective as 800µg sublingual Misoprostol in achieving complete abortion with lesser incidence of side effects (Table 6).

Contribution to Authorship: All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version of the paper.

Details of Ethics Approval: The study was approved by ESI Hospital Ethical Committee.

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