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RESEARCH ARTICLE

Comparative study of sublingual versus vaginal misoprostol following mifepristone in early first trimester medical termination of pregnancy - a prospective study

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ABSTRACT

Aim: To compare the efficacy and side effects of sublingual versus vaginal administration of misoprostol after a single oral dose of 200 mg of mifepristone in termination of early first trimester pregnancy. **Methods**: This is a randomised prospective study comparing the use of sublingual misoprostol with vaginal misoprostol in combination with mifepristone for termination of pregnancy up to 63 days. A total of 100 women who requested legal termination of pregnancy were randomised into two groups and given 200mg of oral mifepristone followed 48 hours later by either 800 microgram of sublingual (n=50) or vaginal (n=50) misoprostol. **Results**: Complete abortion occurred in 96% of women in the sublingual group and 94% in the vaginal group. There was no case of ongoing pregnancy or missed abortion. The median duration of bleeding was 14.65 days in sublingual group and 14.96 days in vaginal group. There were no serious complications reported. Fever, chills and gastrointestinal side effects (nausea and diarrhoea) were significantly more common in the sublingual group. **Conclusion**: The combination of mifepristone and misoprostol is effective for medical abortion up to 63 days of gestation. Both the sublingual and vaginal are effective routes of administration. Further randomised trials are required to find out the optimal dose of sublingual misoprostol that can give the highest complete abortion rate and lower incidence of side effects.

Keywords: Mifepristone, misoprostol, medical abortion.

The history of induced abortions is as old as the history of mankind. Aristotole in Greece (384-322 BC) accepted abortion as a permissible act and advocated that parents with sufficient number of children should be allowed to procure abortion before the mother gets the sensation of a living baby inside the uterus[1]. Contraception may be used incorrectly, yet even when used properly, no method is 100% effective. Induced abortion is the third commonest means of fertility control next to sterilisation and oral contraceptives [2]. Medical Termination of Pregnancy (MTP) Act has legalized termination of such an unwanted pregnancy in India in 1971. The statistics of abortions are grossly inadequate, as only legal abortions are reported and the ratio of legal to illegal abortions vary from 2:1 (ICMR) to 10:1 . The maternal mortality attributed to abortions in India is

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12-18% in different states [3]. The majority of induced abortions are performed in the first trimester by Vacuum aspiration with a complete abortion rates of 95–98% [4]. Immediate abortion related complications, are heavy bleeding (0.01-0.25%), uterine perforation (0.01-0.4%), cervical laceration(0.01-0.35%) and anaesthesia related complications [5]. Medical abortion offers an alternative to surgical methods, and some of the complications related to surgery, such as uterine ruptures and cervical tears, as well as anaesthesia related complications can be avoided. Medical abortion induced with a combination of mifepristone and a prostaglandin analogue was licensed and taken into routine use between 1982 and 1992 in France, UK and Sweden, and in 2006 in several European countries [6]. In India, Medical method of termination was approved only in 2002 up to 49days of gestation after the last menstrual period [7]. The MTP act allows the use of medical abortion only up to 49 days of gestation. But after the approval of combipack (1 tab of mifepristone and 4 tab of misoprostol 200mg) by the Central Drugs Standard Control Organization, Director General of Health services approve medical termination of pregnancy for up to 63 days of gestation in December 2008, and the Ministry of Health and Family Welfare, Government of India is taking action on modifying the MTP rules in accordance with this approval [8].

Mifepristone, a synthetic antiprogestin compound, was found to possess high affinity not only for the glucocorticoid receptor but also for the progesterone receptor as well as a weak affinity for the androgen receptor [9]. Mifepristone acts by binding to the progesterone receptor, thus inhibiting the effect of progesterone. The affinity of mifepristone for the human uterine progesterone receptor is twice that of progesterone [10]. The blockade of the progesterone receptor with mifepristone leads to necrosis in capillary endothelial cells in the post–ovulatory endometrium [11] and in early pregnancy decidua, to increase prostaglandin synthesis [12,13] and to decrease in the concentration of prostaglandin dehydrogenase[14]. The endogenous prostaglandins produced in the decidua diffuse to the myometrium, where they induce uterine contractions. The sensitivity of the myometrium to exogenous prostaglandins is also increased by administration of mifepristone[15,16].

Misoprostol is a synthetic prostaglandin E_1 analogue administered orally for the treatment of peptic ulcers. Misoprostol is stable at room temperature and is inexpensive. Because of its uterotonic and cervical–ripening actions, misoprostol is also widely used for various gynaecological and obstetrical purposes, such as for cervical ripening and induction of labour, for pretreatment of the cervix prior to surgical termination of pregnancy and, in combination with mifepristone, for medical abortion [17]. This drug is now widely used for inducing pregnancy terminations and its complete abortion rate has been reported between 61% and 93%. The effectiveness of this drug is dependent on the dose of usage, following its repeated dose as well as using it in combination with other drugs that led to a complete abortion rate of 98%. After oral administration, misoprostol rapidly de–esterifies to its biologically active form, misoprostol acid. Misoprostol acid is 85% albumin–bound and has a half–life of approximately 30 minutes[18]. The peak serum concentrations of misoprostol acid are reached in 30 minutes after oral and sublingual administration and in 72 minutes after vaginal administration [19]. This is due to rapid absorption through the sublingual mucosa as well as the avoidance of the first pass metabolism. Despite Misoprostol can be used with different routes including oral, sublingual and vaginal, however a few evidences are available in drug effectiveness as well as its related side effects when used in different routes. Hence, the present study aimed to compare the efficacy of misoprostol in combination with mifepristone in first trimester abortion through sublingual and vaginal routes of administration.

Materials and Methods

After the approval of Institutional Ethical Committee and proper counseling and consent of the patients, this randomized prospective study was conducted at Department of Obstetrics and Gynaecology, Assam Medical College & Hospital, Dibrugarh, Assam from January 2011 to January 2012. A total of 100 women who fulfilled the inclusion criteria and requested legal termination of pregnancy were randomised into two groups [Group A: Sublingual Misoprostol Group (50 cases), Group B: Vaginal Misoprostol Group (50 cases)].

Inclusion criterias**:** Gestational age up to < 9 weeks or

63 days; single intrauterine pregnancy; patient having immediate access to emergency health services, if required; patient willing to undergo surgical abortion in case of failure or excessive bleeding.

Exclusion criterias: Patient not giving written informed consent; Hb < 8 gm%; suspected/confirmed ectopic pregnancy; presence of intrauterine device; pregnancy with adnexal mass, coagulopathy, anticoagulant therapy; cardiovascular, renal, liver, respiratory disease and any other known medical disorders.

Drug regime:

Table 1: Drug regime

Day	Group–A (Sublingual Misoprostol)	Group–B (Vaginal Misoprostol)
Day 1	Oral mifepristone 200 mg	Oral mifepristone 200 mg
Day 3	Sublingual Misoprostol 800 µgm	Vaginal Misoprostol 800 µgm
Day 15	Women were called for follow-up for history, clinical and ultrasound evaluation	

Anti-D was given to Rh negative women. Data obtained were collected and analyzed statistically by proportions and tests of significance. Statistical significance was set at $p< 0.05$.

Results and Observations

In Group-A, 64% were in the gestational age between 50 -56 days, 22% in ≤ 49 days and 14% in 57-63 days when they came seeking termination of pregnancy. In Group-B, 60% were in the gestational age between 50-56

Table 2: Period of gestation in weeks at the time of request for MTP

Period of gestation (in days)	Group–A (Sublingual Misoprostol group)		Group–B (Vaginal Misoprostol Group)	
	No.	%	No.	%
≤49	11	22	12	24
50-56	32	64	30	60
57-63	07	14	08	16
Total	50	100	50	100
Mean	52.58		52.04	

days, 24% belonged to ≤ 49 days of gestation, and 16% were between the gestational age of 57-63 days. Mean gestational age in Group A is 52.58 days (7.5 weeks) and in Group-B is 52.04 days (7.4 weeks) (Table 2).

In Group-A, 66.7% and in Group-B, 77% expelled the product within 4-6 hrs. The mean induction to abortion interval in Group A is 4.14 hours and in Group-B is 4.34 hours. Induction abortion time minimum is 3.2 hours and maximum is 7 hours in group-A and in Group-B minimum is 3.3 hours and maximum is 6.15 hours (Table 3).

In Group-A, 96% and in Group-B, 94% had complete abortion. There was no case with continuing of pregnancy or missed abortion. The findings in the above table are not statistically significant in both the groups (Table 4). One woman in Group-A had a history of previous lower segment caesarean section and she had complete abortion without any complication.

In Group-A (54.2%) and in group-B (61.7%) had bleeding up to 15 days. Bleeding was heavy for the first two days. Then it was moderate or just spotting thereafter. Median duration of bleeding was similar in both the groups (Table 5). There were 2 incomplete abortion in Group-A and 3 in Group-B and so duration of bleeding was not counted for those cases. All the cases of incomplete abortion in both groups subsequently had undergone dilatation and evacuation to complete the abortion process. Women in Group-A (64%) had nausea compared to Group-B, (32%). 'P' value is <0.001 which

Table 3: Induction abortion interval

Induction abortion interval in hours	Group–A (Sublingual Misoprostol)		Group–B (Vaginal MisoprostolGroup)	
	No.	%	No.	%
After mifepristone	0	0	0	0
After misoprostol				
2-4	14	29.1	10	21
4-6	32	66.7	36	77
6-8	02	4.2	01	2
TOTAL	48	100	47	100
Mean±SD	4.14±1.03		4.34±0.66	
Median	4.07		4.2	

Table 4: Outcome

Outcome	Group–A (Sublingual Misoprostol) No (%)	Group–B (Vaginal Misoprostol) No (%)	P value
Complete Abortion	48(96%)	47(94%)	0.65
Incomplete Abortion	02(4%)	03(6%)	> 0.05
Total	50(100%)	50(100%)	

shows that the result is highly significant. In Group-A (26%) women and in Group-B (18%) had vomiting. The above data shows no significant difference in vomiting in both the groups when compared. Diarrhoea was seen in Group-A in 52% and no case of diarrhoea was noted in Group-B. Data showed very highly significant 'p' value of <0.0001. Maximum patient passed loose stool for five to six episodes in Group - A but none required active intervention. The table above shows 38% of women in Group-A and 2% in Group-B had fever with 'P' value of <0.0001 which is very highly significant. Thirty two percent of women in Group-A had chill while only 8% in Group-B complained of chill. Statistical analysis of the data shows highly significant difference between the two with' p' value of <0.003. Lower abdominal pain in both the groups were similar and there was no statistical difference found between the two (Table 6).

Table 5: Showing duration of bleeding

Duration of bleeding in days	Group–A (Sublingual Misoprostol) No (%)	Group–B (Vaginal Misoprostol Group) No (%)
<11	05(10.4%)	01(2.1%)
11-15	26(54.2%)	29(61.7%)
>15	17(35.4%)	17(36.2%)
Total	48(100%)	47(100%)
Median	14.65	14.96

Table 6: Showing side effects

Side effects	Group–A (Sublingual Misoprostol) No (%)	Group–B (Vaginal Misoprostol Group) No (%)	'P' Value
Nausea	32(64%)	16(32%)	0.001
Vomiting	13(26%)	9(18%)	0.33
Diarrhoea	26(52%)	0	<0.0001
Fever	19(38%)	1(2%)	<0.0001
Chill	16(32%)	4(8%)	<0.003
Lower abdominal pain	48(96%)	50(100%)	<0.153

Discussion

The study compared the efficacy and side effects of sublingual and vaginal administration of misoprostol in combination with mifepristone in medical abortion up to 63 days of gestation. The findings suggest mean gestational age in weeks is similar in sublingual (7.4wk) and vaginal (7.5wk) route when compared with the study done by Tang (7.7wk) [20]. Median induction to abortion interval shows no significance in induction to abortion interval in both the groups [20]. Also there was no significant difference in the efficacy of the two routes with other studies as done by Tang et al[20] and Hamoda et al[21].

It has also been reported that induction to abortion interval significantly increases with advanced gestation [22].The median duration of bleeding in days in our study was 14.65 in sublingual and 14.69 in vaginal group which was slightly lesser when compared with a study done by Tang [20]. Outcome seen with other authors Tang et al.[20] and Hertzen et al.[23] are almost similar with the present study. Regarding the route of administration, sublingual is an effective alternative to vaginal administration, although the prevalence of side effects was higher in the sublingual group[23,24]. The majority of the women were managed as day care cases. Hertzen et al [23] found that median time from misoprostol administration to abortion was 1 hour shorter in sublingual group compared to vaginal. Vaginal administration of 800 microgram of misoprostol remains an important option for medical abortion, as fewer women reported adverse effects in the vaginal group in the present as well as in the previous study.

Conclusion

Sublingual and vaginal misoprostol after pre-treatment with mifepristone are both effective methods of medical abortion up to 63 days of gestation. In order to reduce the incidence of side-effects, a lower dose of misoprostol can be considered when given sublingually. However, further randomized trials are required to find the optimal dose of sublingual misoprostol that can give highest complete

abortion rate with minimal side effects. The success of the method lies in the eligibility of the patient to undergo medical abortion with proper dose schedule. So, awareness and knowledge among people regarding medical abortion is important as misuse of drugs leading to failure of abortion not only increases the morbidity and mortality but also the doubt about the efficacy of the method among common people.

Conflict of interest: None. **Disclaimer:** Nil.

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