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ORIGINAL ARTICLE

Comparative Study of Misoprostol in First and Second Trimester Abortions by Oral, Sublingual, and Vaginal Routes

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Abstract

Objective To identify an effective misoprostol-only regimen for termination of pregnancy between 12 and 20 weeks of gestation, a prospective randomized study comparing sublingual, vaginal, and oral routes of administration of misoprostol was done.

Methods One hundred and fifty women (12–20 weeks gestation) were randomly divided into three groups and given 400 mcg misoprostol sublingually, vaginally, and orally every 4 h up to a maximum of four doses. Primary outcome was the success rate at 24 h. Secondary outcomes were failure rate, induction–abortion interval, and need for surgical intervention. Various side effects and patients' subjective assessment of comfort with the route of administration were also studied.

Results Success rate at 24 h of sublingual (86 %) group was higher compared to oral (64 %) group ($P = 0.011$). Complete abortion rate of sublingual (76 %) group was higher than that of oral (48 %) group ($P = 0.004$). There was no significant difference in the failure rate and need for surgical intervention in the three groups. Induction–abortion interval in sublingual (9.8 ± 3.6 h) and vaginal (10.6 ± 2.9 h) groups was shorter than that in oral group (14.3 ± 3.3). Diarrhea occurred significantly more in the oral group (28 %) and sublingual (22 %) compared to vaginal group (6 %). Fever was significantly higher in vaginal (36 %) than that in the oral group (12 %). Oral route of administration was most comfortable.

Conclusion Sublingual route results in significantly higher abortion rate compared to oral route. Vaginal route has efficacy similar to sublingual route.

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Keywords Misoprostol · Abortion · Sublingual · Vaginal · Oral

Introduction

Mid-trimester abortion constitutes 10–15 % of all induced abortions but is responsible for two-thirds of all major complications. There is a gradual increase in second trimester abortions because of the wide-scale introduction of prenatal screening programs detecting women whose pregnancies are complicated by serious fetal abnormalities. During the last decade, medical methods for mid-trimester-induced abortions have shown a considerable development and have become safe and more accessible.

Misoprostol has emerged as a critical component of these regimens both as a stand-alone method and in combination with other medications like mifepristone. The combination of mifepristone and misoprostol is the most effective and fastest regimen [1]. However, mifepristone is not widely available and is expensive. Misoprostol is being more widely used because it is inexpensive and stable at room temperature. It can be absorbed via oral, vaginal, sublingual, buccal, and rectal routes.

Initially, misoprostol was used orally for medical abortion. Many clinical trials have found vaginal administration to be more effective than oral administration [2]. There has been suggestive evidence showing that absorption through vaginal route is inconsistent [3]. Recently, the use of sublingual misoprostol has been explored for medical abortion.

A pharmacokinetic study has demonstrated that sublingual administration could achieve the peak concentration in the shortest time and has the highest bioavailability [4]. Previous studies have shown that sublingual misoprostol is effective in first trimester medical abortion [5, 6]. A pilot study has demonstrated that it was feasible for second trimester medical abortion [7].

A study showed that doses higher than 400 mcg did not significantly improve the efficacy but caused more side effects and lower doses such as 200 mcg were clearly less effective [8].

The aim of this randomized study was to compare the effectiveness, side effects, and outcome of sublingual, oral, and vaginal routes of administration of misoprostol in the late first and early second trimester abortions.

Materials and Methods

The study was conducted at Kamala Nehru Memorial Hospital, Allahabad, over a period of 1 year (May 2012 to May 2013). It was a prospective randomized study. One hundred and fifty women with a period of gestation between 12 and 20 weeks scheduled to have pregnancy termination as per MTP Act were included in the study. Inclusion criteria were healthy women with 12–20 weeks of gestation and single live intrauterine pregnancy as determined by last normal menstrual period, clinical examination and confirmed by ultrasound if required. Exclusion criteria were pregnancy less than 12 weeks and more than 20 weeks, any indication of serious past or present illnesses, severe anemia, any contraindications to use of misoprostol like uncontrolled bronchial asthma, irritable bowel syndrome, scar in uterus/cervix (including previous cesarean and myomectomy), allergy to misoprostol, and cardiovascular disease.

All participants were provided with written informed consent before enrolment. All women were admitted, and detailed history and physical examination were done. Routine baseline investigations were also performed.

Women were divided into three groups of 50 each by block permuted randomization:

Group A = sublingual route ($n = 50$)
Group B = vaginal route ($n = 50$)
Group C = oral route ($n = 50$).

All three groups received misoprostol 400 mcg at 4-hourly interval up to a maximum of four doses each.

After misoprostol administration, pulse, blood pressure, and temperature were recorded every 4 h. Women were observed for pain in abdomen, uterine contractions, bleeding per vaginum, and expulsion of fetus. Side effects like nausea, vomiting, diarrhea, chills, fever, and significant vaginal bleeding were also recorded, and they were given symptomatic treatment.

Fever was defined as temperature >100.4 °C. Diarrhea and vomiting were recorded as side effects if more than two episodes occurred. Estimated blood loss of more than 250 ml or the need for blood transfusion was considered for significant vaginal bleeding. After abortion, products of conception were examined and if incomplete, evacuation of the uterus was performed. Women who achieved dilatation without expulsion of abortus also underwent surgical intervention.

Subjective assessment of the women's comfort with the different routes of administration in the three groups was also made. The women were discharged 24 h after the abortion if there were no complications and called for a follow-up visit after 1–3 weeks. Post-abortion contraception counseling was also given. Women who did not abort within 24 h of starting the induction were labeled as failure and given alternative methods. The methods used were repeat schedule of misoprostol by the same or different route or high dose of oxytocin. These cases were considered as a failure.

Primary outcome measure was the success rate at 24 h. Success rate was defined as abortion (complete/partial) occurring without the need for further prostaglandin analogs or syntocinon. Complete abortion was defined as the expulsion of both fetus and placenta without operative intervention. Secondary outcome measures were failure rate, incidence of cases where surgical evacuation was required, and induction to abortion interval. Failure was defined as cases with incomplete dilatation or no dilatation. Women with incomplete dilatation and partial abortion underwent surgical intervention. Surgical intervention in women who achieved only dilatation of cervix was done if they did not expel within 12 h of administration of last dose of misoprostol. Induction–abortion interval was defined as the time interval from the administration of first dose of misoprostol up to the time when the fetus aborted.

Statistical Methods

Tests of normality (Kolmogorov–Smirnov test) were done to check if data were skewed or normal. Differences in means of continuous variables were analyzed with ANOVA for normally distributed data followed by Tukey's HSD post hoc tests. Mann–Whitney *U* test for pair-wise comparisons was applied wherever applicable. Differences in proportions were analyzed with Chi-square or Fisher's exact test as appropriate. *P* value of less than 0.05 was considered significant. SPSS software 16.0 was used for analyzing the data.

Results

One hundred and fifty women were divided into three groups—A, B, and C—and given misoprostol by sublingual, vaginal and oral routes, respectively.

Women in three groups were comparable in terms of age, number of previous abortions, number of previous deliveries, BMI, socioeconomic status, and gestational age (Table 1).

Success rate was 86 % in the sublingual group, which was significantly higher than that in the oral group, 64 % ($P = 0.011$). Complete abortion rate of sublingual misoprostol (76 %) was significantly higher compared to the oral group (48 %, $P = 0.004$). Total dose (in mcg) requirement in the oral group was 1413 ± 269 which was significantly higher than that in both the sublingual (1,172 ± 331, $P = 0.002$) and vaginal (1,172 ± 259, $P = 0.007$) groups. There was no significant difference in the failure rate and need for surgical intervention in the three groups. Induction–abortion interval in the sublingual (9.8 ± 3.6 h) and vaginal (10.6 ± 2.9 h) groups was significantly shorter that in than the oral group (14.3 ± 3.3, $P < 0.001$) (Table 2)

The incidences of side effects were similar in all the groups except diarrhea and fever. Diarrhea was significantly more in the oral and sublingual groups compared to the vaginal group. Fever was significantly higher in the vaginal group (Table 3).

Preference for the routes of administration was also assessed. 92% women in the sublingual group and 100% women in the oral group were comfortable with the route of administration which was significantly higher as compared to women in the vaginal group 40% (Table 4).

Table 1 Demographic characteristics

Parameters	Group A ($n = 50$)	Group B ($n = 50$)	Group C ($n = 50$)	Result
Age (years)	28.2 ± 4.3	27.8 ± 4.5	27.6 ± 4.3	ANOVA $F_{(2,147)} = 0.314$ $P = 0.731$(NS)
No. of women with previous delivery	42 (84 %)	42 (84 %)	44 (88 %)	Chi-square test $\chi^2 = 0.426$ $P = 0.808$ (NS)
No. of women with previous abortions	20 (40 %)	16 (32 %)	21 (42 %)	Chi-square test $\chi^2 = 1.188$ $P = 0.552$ (NS)
BMI	22.4 ± 2.2	22.3 ± 1.9	22.9 ± 2.0	ANOVA $F_{(2,147)} = 1.348$ $P = 0.263$(NS)
Gestational age(weeks)	15.6 ± 2.2	16.1 ± 2.5	15.7 ± 2.2	ANOVA $F_{(2,147)} = 0.647$ $P = 0.525$(NS)

S significant; *NS* not significant

Table 2 Treatment outcomes

	Group A ($n = 50$)	Group B ($n = 50$)	Group C ($n = 50$)	P value
Abortion/success rate (%)*	43 (86)	40 (80)	32 (64)	0.027(S)
Complete abortion (%)**	38 (76)	33 (66)	24 (48)	0.013(S)
Failure rate (%)	3 (6)	5 (10)	10 (20)	0.085(NS)
Mean induction–abortion interval in hours(range)[§]	9.8 (4.5–17.9)	10.6 (6–19)	14.3 (7.5–19.4)	ANOVA $F_{(2,129)} = 22.891$(S)
Patients requiring surgical intervention (%)	9 (18)	12 (24)	16 (32)	0.265(NS)

S significant, *NS* not significant

* A versus B: $P = 0.424$ (NS), A versus C: $P = 0.011$ (S), B versus C: $P = 0.075$ (NS)

** A versus B: $P = 0.270$ (NS), A versus C: $P = 0.004$ (S), B versus C: $P = 0.069$ (NS); § $P < 0.001$ for A versus C and B versus C(S)

Table 3 Side effects

Side effects	Group A ($n = 50$)	Group B ($n = 50$)	Group C ($n = 50$)	Result
Nausea	7 (14)	5 (10)	10 (20)	$P = 0.363$ (NS)
Vomiting	6 (12)	3 (6)	8 (16)	$P = 0.284$ (NS)
Diarrhea*	11 (22)	3 (6)	14 (28)	$P = 0.014$ (S)
Chills	15 (30)	16 (32)	14 (28)	$P = 0.909$ (NS)
Fever**	12 (24)	18 (36)	6 (12)	$P = 0.019$ (S)
Significant vaginal bleeding	3 (6)	5 (10)	2 (4)	$P = 0.472$ (NS)

Values are expressed in *n* (%)

S significant; *NS* not significant

* A versus B: $P = 0.021$, A versus C: $P = 0.488$, B versus C: $P = 0.003$

** A versus B: $P = 0.190$, A versus C: $P = 0.118$, B versus C: $P = 0.005$

Table 4 Subjective assessment of comfort

Groups	A (sublingual) ($n = 50$)	B (vaginal) ($n = 50$)	C (oral) ($n = 50$)	Result
Comfortable*	46 (92)	20 (40)	50 (100)	$P < 0.001$
Not comfortable	04 (8)	30 (60)	0	Highly significant

Values are expressed in *n* (%)

* A versus B: $P < 0.001$, A versus C: $P = 0.117$, B versus C: $P < 0.001$

Discussion

Misoprostol has been extensively studied for mid-trimester abortion. It can be given alone or in combination with mifepristone. Pretreatment with mifepristone results in a shorter induction–abortion interval compared to regimen without mifepristone [9]. However, it is not freely available and is expensive. Therefore, there is a need to explore the use of misoprostol alone in termination of mid-trimester pregnancy. Various people have used different doses, time interval between doses and route of administration of misoprostol but consensus is yet to be reached.

In some studies, vaginal route has been found to be more promising than oral route [10] probably due to accumulating plasma levels with fewer gastrointestinal side effects. It has been shown that absorption through vaginal route is inconsistent and undissolved misoprostol tablets are found several hours after vaginal administration [3]. Sublingual mucosa being very vascular serves the purpose of absorption better. Misoprostol tablets, when put under the tongue, dissolve within 10 to 15 min [4]. Few pilot studies [5, 7] have been performed on the use of sublingual misoprostol for medical termination of pregnancy and has been found to be very effective and convenient.

The present study showed that sublingual and vaginal misoprostol have similar abortion rate at 24 h. Abortion rate in the oral group was significantly lower than that in the sublingual, although similar to the vaginal group. This result is similar to studies by Karsidaq et al. [11] and Tanha et al. [12]. Tang et al. [13] and Hertzen et al. [14] showed different results that vaginal misoprostol is more effective than sublingual. They also made comparisons by parity which showed that vaginal misoprostol is more effective in nulliparous women, while in multiparous women both vaginal and sublingual misoprostol were found to be equally effective. Due to less number of nulliparous women (6–8) in each group in the present study, comparison in the success rate on the basis of parity could not be made.

The complete abortion rate of sublingual misoprostol was also similar to vaginal and higher than that of oral route.

The induction–abortion interval in both the sublingual and vaginal groups was similar and less than 12 h, implying that both sublingual and vaginal misoprostol are

effective for medical abortion in mid-trimester. Oral group had the longest induction–abortion interval of 14.3 h. The difference in efficacy and induction–abortion interval by different routes of misoprostol may be explained by variable pharmacokinetics by sublingual, vaginal, and oral routes. The failure rate and need for surgical intervention were similar in all the three groups.

In general, the frequency and severity of side effects depend on the route of administration of misoprostol, its dosage, and interval between the doses. Previous pilot studies [7] suggested that sublingual misoprostol was associated with higher incidence of side effects especially diarrhea and fever, while in the present study, diarrhea occurred equally in the sublingual and oral groups and least in the vaginal group. Fever occurred equally in the sublingual and vaginal groups and least in the oral group. The incidences of other side effects like nausea, vomiting, chills, and significant vaginal bleeding were similar.

Oral and sublingual routes of administration have shown to be more acceptable compared to vaginal route of administration. But the efficacy of oral administration is less. Therefore, sublingual misoprostol has the advantage that it can avoid the uncomfortable vaginal administration. Also absorption of the drug may be affected when the patient starts bleeding.

The study demonstrates that both vaginal and sublingual misoprostol have similar and higher success rates in inducing abortion compared to oral route.

Compliance with ethical requirements and Conflict of interest The study was approved by research committee of Kamala Nehru Memorial Hospital, Allahabad, and by the Ethics Committee of Population Resource & Research Centre, Allahabad. The authors of the article declare that they have no conflict of interest.

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