Comparison of Effectiveness of Sublingual and Vaginal Misoprostol for Second-Trimester Abortion

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Abstract

Objective The aim of this study was to compare the efficacy and safety of sublingual and vaginal misoprostol in second-trimester termination of pregnancy in 24 and 48 h. **Study Design** This is a retrospective study of 240 pregnant women seeking termination in second trimester (13–18.5 weeks), in which the patients are subdivided into two groups—first group received 400 mcg of misoprostol sublingually ($n = 120$), and second group received 400 mcg of misoprostol vaginally ($n = 120$) every 4 h for a

maximum of five doses. The course of misoprostol was repeated if the patient did not abort within 24 h.

Results The mean induction-to-abortion interval was shorter in sublingual group (10.28 ± 3.1 h) versus 14.68 ± 4.2 h in vaginal group in 24 h ($p = 0.0001$), and 36.9 ± 4.4 h in sublingual versus 29.7 ± 14 in vaginal group in 48 h ($p = 0.0933$). Mean dose requirement for misoprostol by sublingual route was low as compared to vaginal misoprostol (1048 ± 301 mg versus 1250 ± 375 mg; $p = 0.0001$ in 24 h and 1110 ± 833 mg versus 1325 ± 536 mg; $p = 0.0231$ in 48 h). No significant difference was found in the success rate (both at 24 and 48 h) and in side effects among the two comparison groups. **Conclusion** Misoprostol as such by any route has been proven as an effective abortifacient in second trimester. Both sublingual and vaginal routes are effective for medical abortion. But shorter induction-to-abortion interval in sublingual route, less dose requirement and higher acceptability makes sublingual route as a better choice.

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Introduction

One of the direct causes of maternal mortality all over world is unsafe abortion. Incidence for unsafe abortion is 8%, which is a preventable factor. Second-trimester abortion is an important component of women's health care, and women seek termination later in pregnancy for a variety of medical and social reasons. Circumstances that can lead to second-trimester abortion include delays in suspecting and testing for pregnancy, poverty, difficulties in locating and traveling to a provider, lower education level, having multiple disruptive life events and major anatomic or genetic anomalies which have been associated with higher rates of seeking second-trimester abortion. Some obstetric and medical indications for second-trimester termination include preeclampsia and preterm premature rupture of membranes or pregnancy failure before 20 weeks of gestation [1]. The development of safe and effective technique for second-trimester abortion has become a major challenge. With the introduction of prostaglandins, medical methods for mid-trimester abortion have improved considerably during last decades in terms of efficacy and safety [1]. A synthetic prostaglandin E1 analog initially approved by US FDA for treatment and prevention of intestinal ulcer disease resulting from nonsteroidal anti-inflammatory drugs use was found to have good uterotonic and cervical ripening properties. After serial trials in recent two decades, misoprostol became one of the most useful drugs in termination of pregnancy. Till date, it is not approved by FDA for pregnancy termination in second trimester though it is being (off label) used for termination of pregnancy in different doses and different routes, in between 13 and 20 weeks with satisfactory results [1–4]. The advantages of misoprostol are as follows: it is inexpensive, stable at room temperature, easily available and can be used by any route.

Two common routes of misoprostol administration are sublingual and vaginal, but they have different pharmacokinetics and effectiveness [5]. Sublingual misoprostol reaches its peak concentration in a shortest time due to rapid absorption and has highest bioavailability [6]. The previous studies have shown that sublingual misoprostol is effective in first-trimester abortion. A pilot study [7] has demonstrated that it is feasible for second-trimester termination of pregnancy. The vaginal route causes more prolonged regular uterine contractions. The vaginal route has less adverse effects such as nausea, vomiting and diarrhea after administration. Absorption through vaginal route is inconsistent [8].

Materials and Methods

This retrospective observational study of 240 cases of second-trimester medical termination of pregnancy was carried out at Mukherjee Multispecialty Hospital Private Center at Nagpur, Maharashtra, India, for 5 years, from January 2012 till December 2017. This hospital has a Government-approved center for MTP since last 23 years. Pregnant women seeking MTP in second trimester of pregnancy were counseled regarding various options and their safety and informed consent for MTP as per MTP Act with second opinion of second obstetrician taken. Indications for second-trimester termination (fetal) were intra-uterine fetal death, chromosomal anomalies, fetal anomaly and legal abortion which were based on maternal reasons.

Exclusion criteria were contraindications to prostaglandins use (cough, bronchial asthma, glaucoma), previous scar on uterus, cardiovascular disorders, parity > 3, multiple pregnancy, vaginal bleeding. All cases were admitted in the ward. A detailed information regarding age, marital status, education, socioeconomic conditions, duration of amenorrhea, gravidity, parity, previous spontaneous or induced abortions and medical diseases was recorded. General, systemic and bimanual examination was performed to assess the duration of pregnancy and to rule out cervico-vaginal infections. Ultrasonography was performed, when there was discrepancy in the assessment of gestational age. Blood investigations like Hb, blood grouping and Rh typing, BT, CT, VDRL, HIV, HbSAg were done.

All 240 study subjects, having live pregnancies, were admitted to ward. They were divided into two groups equally: group A ($n = 120$) was given a starting dose of 400 mcg of misoprostol sublingual, and group B ($n = 120$) was given 400 mcg of misoprostol vaginally and a dose of 400 mcg repeated at 4-h interval (maximum of five doses) in 24 h. The case was declared as failure if patient did not abort in 24 h in any group. Such cases were then reassessed, and if there were no signs and symptoms of eminent abortion, a second course with the same regimen was repeated 24 h after the start of the first dose of misoprostol (maximum ten tablets of misoprostol 200 mg). If abortion still failed to occur, the pregnancy was terminated by suction evacuation and IV oxytocin drip of 20 units. Abortion process was taken as complete, when fetus and placenta with membranes were expelled completely without any surgical intervention in this study.

Out of 240 cases, 13 have failed—two patients of 13 weeks, two patients of 15 weeks, and had retained placenta and uncooperative, and for placental removal, we require suction evacuation. Means overall out of 13 patients, four have retained placenta which were managed

Fig. 1 Flowchart indicating the selection and exclusion criteria of total 270 subjects depending on various parameters as mentioned

by manual removal of placenta under short G.A. Remaining nine patients, out of them, we had six patients: at 14 weeks—four patients, and 15 weeks—two patients. In these patients, doing suction evacuation was possible with injection carboprost and pitocin drip (chances of uterine perforation (0.25–0.4%) only as per US data by Dr. Perry—reference given below 10). Two patients of 16 weeks and one patient of 18 weeks, in them the internal os of the uterus was open partially or fully so products can be separated with finger and sucked out by suction under pitocin drip. In our study, we did not have any uterine perforation.

Cases were monitored for progress of abortion by observing pain, uterine contractions, bleeding per vagina, assessing cervical dilatation and expulsion of products of conception. In case any side effects of misoprostol were observed, they were managed by symptomatic treatment. If needed, patients were put on 10 units of oxytocin drip. A pre-designed proforma was used for gathering information on maternal and clinical characteristics like age, parity, past obstetrics history, the time interval between misoprostol first dose and complete abortion, the dose required, the side effects and complications of misoprostol and patients preference for route of misoprostol. Patients were discharged after 12–24 h post-complete abortion if there were no complications. Post-abortion contraceptive counseling was also given. At the time of discharge, qualitative assessment about comfort levels of patients was also noted. Follow-up visit was advised to monitor events after 1–2 weeks.

Main outcomes were as follows: induction abortion interval assessment, calculation of dose required, the

success rate and side effects and comfort to the route of administration (Fig. 1).

Statistical Analysis

Data were coded and analyzed in a statistical software, STATA, version 10.1, 2011. Two independent samples *t* tests were used to compare difference in means of quantitative parameters, while Chi-square test was used to compare difference in proportions of categorical parameters in two comparison groups.

Results

Totally, 240 patients with pregnancy duration between 13 and 20 weeks were included for this retrospective study. One hundred and twenty patients were given sublingual misoprostol, and 120 patients were given vaginal misoprostol. Both the groups were matching similar with respect to demographic profile, obstetrical parameters, clinical symptoms, laboratory findings. There was no statistically significant difference between these two groups (Table 1). The mean maternal age was 24.05 ± 3.8 years in the sublingual group and 24.4 ± 4.0 years in the vaginal group ($p = 0.8686$), and the mean gestational age was 16.7 ± 1.8 weeks in the sublingual group and 16.6 ± 1.8 weeks in the vaginal group ($p = 0.9148$). The success rate, determined as no need for surgical evacuation, was found to be 84.16% in the sublingual group and 75.83% in the vaginal group ($p = 0.3169$) at 24 h, and at

Table 1 Demographic characteristics

	Sublingual	Vaginal	<i>p</i> value
<i>Heading</i>			
Gestational age (weeks)	16.7 ± 1.8	16.6 ± 1.8	0.9148
Maternal age (years)	24.5 ± 3.8	24.4 ± 4.0	0.8686
BMI (kg/msq), mean ± SD	24.0 ± 3.3	24.0 ± 3.3	0.9689
Hb%	10.8 ± 1.3	10.8 ± 1.3	0.9596
	Sublingual (<i>n</i> %)	Vaginal (<i>n</i> %)	<i>p</i> value
<i>Parity</i>			
0	47 (39.17%)	47 (39.17%)	
1	40 (33.33%)	40 (33.33%)	
2	31 (25.83%)	31 (25.83%)	
> 2	2 (1.67%)	2 (1.67%)	
<i>Pregnancy loss (number of previous abortions)</i>			
0 (no abortion)	56 (46.71%)	56 (46.71%)	1.000
1 (one abortion)	44 (36.7%)	45 (%)	1.000
2 (two abortion)	17 (14.2%)	17 (%)	1.000
> 2 (more than 2 abortions)	3 (2.5%)	3 (%)	1.000

the end of 48 h, it was 95% for sublingual and 94.16 for vaginal route ($p = 0.7755$) (Table 2). Six (5%) out of 120 patients in sublingual route and 7 (5.8%) out of 120 patients in vaginal route underwent surgical evacuation. That means the failure rate is almost same in both the groups (Table 2). The frequency and the type of side effects in both the groups are almost same (Table 2; Fig. 2). Satisfaction rate in sublingual route (95%—114/120) was found significantly ($p = 0.001$) higher as compared to vaginal route (67.5%—81/120 patients) (Table 3; Fig. 3).

The mean induction-to-abortion interval was significantly shorter in the sublingual group 10.28 ± 3.1 h in sublingual as compared to 14.68 ± 4.2 h in vaginal group ($p = 0.0001$) [$n = 103$] in 24 h. But in 48 h, the induction

abortion interval in both the groups was almost same [$n = 31$] ($p = 0.0933$). The drug requirement is 1048 ± 833 mg in sublingual group which is significantly low as compared to vaginal group 1250 ± 375 mg ($p = 0.0001$) (Table 2).

Discussion

Misoprostol has proven its efficacy as an effective abortifacient for second-trimester termination of pregnancy by both routes with different regimens [4]. In general, the frequency and severity of side effects depend on the route of administration, dose and the interval between the doses.

Table 2 Effectiveness and side effects of sublingual versus vaginal misoprostol for complete abortion

Success rate in hours		Sublingual	Vaginal	<i>p</i> value
Success rate in 24 h		101 (84.16%)	95 (79.15%)	0.3169
In 48 h		114 (95%)	113 (94.16)	0.7755
Pt. Requiring surgical intervention (suction evacuation)		6 (5%)	7 (5.8%)	0.7755
Induction-abortion interval 24 h (<i>n</i> = 103)		10.28 ± 3.1	14.68 ± 4.2	0.0001
48 h (<i>n</i> = 23)		36.9 ± 4.4	29.7 ± 14.0	0.0933
Drug requirement		1048 ±	1250 ± 37.5	0.0001
S. no.	Side effects and complications	Sublingual	Vaginal	<i>p</i> value
1	Fever with chills	62 (51.7%)	58 (48.3%)	0.11
2	Nausea/vomiting	60 (50%)	55 (45.8%)	0.451/0.761
3	Diarrhea	25 (20.8%)	25 (20.8%)	0.499
4	Pain in abdomen	72 (60%)	74 (61.99%)	0.483
5	Excessive vaginal bleeding	6 (5%)	6 (5%)	0.581

Fig. 2 Frequency (%) and type of side effects in two groups **Table 3** Qualitative assessment about route of administration

Qualitative assessment	Sublingual (<i>n</i> = 120)	Vaginal (<i>n</i> = 120)	<i>p</i>
Comfortable	114 (95%)	81 (67.5%)	0.001
Not comfortable	6 (5%)	39 (32.5%)	0.001

Fig. 3 Qualitative assessment of comfort level of route of administration

The previous pilot studies have suggested that sublingual misoprostol is associated with the increase in the incidence of side effects, but in our study the side effects were almost same and comparable (Table 2). The low dose of misoprostol appears to be associated with fewer side effects, while moderate doses appear to be more effective in completing abortion. A dose of misoprostol more than 400 mcg did not improve efficacy but causes more side effects, and lower dose of 200 mcg is clearly less effective. Four RCTs showed that the induction-to-abortion interval, with three-hourly administration of misoprostol, is shorter than six-hourly administration without any increase in side effects. In our study, we used a dose of 400 mcg at the

interval of 4 h for a maximum of five doses successfully [2, 3, 9, 10]. Complete abortion rate as observed at the end of 24 h was significantly higher in sublingual group as compared to vaginal route. In our study, only 10.8% (13/240) of the patients required surgical evacuation, which shows that misoprostol is a powerful abortifacient by both the routes.

There were many studies published about comparison between the routes of administration of misoprostol with different results about the success rate of termination of second-trimester pregnancy in 24 h, in 48 h, the induction-to-abortion interval and the side effects.

In Fateme Davari Tanha's study [11], they reported similar effects of both the routes of misoprostol

administration, after giving misoprostol 400 mcg every 6 h. The median induction-to-abortion interval was 16 h which is longer than our study (12.72 h in sublingual and 14.67 in vaginal routes) which may be due to longer interval between drugs application.

In a study by Bhattacharjee et al. [12], they used 400 mcg every 3 hourly by both sublingual and vaginal routes and achieved similar success rate in both groups in 48 h, (> 90%), but the success rate in 24 h was higher in the vaginal group. In our study, more success in the form of complete abortion is seen with sublingual route which is same in line with Milani et al. [6].

The induction-to-abortion interval is shorter in sublingual group and needed lower dose of drug in our study. These facts of our study are similar to Milani's study [5]. It can be due to different pharmacokinetics of both routes. Sublingual misoprostol can achieve the higher peak concentration and bioavailability very quickly as per the study done by Nautiyal et al. [8].

The drug activity and bioavailability are higher in vaginal route as there is no intestinal–hepatic bypass of drug; also, sustained and long-lasting effect is seen with vaginal absorption. But it has been shown that absorption through vaginal route is inconsistent, and again this factor is further disturbed by local factors like infection (disturbed pH of vagina), vaginal bleeding, tablet not dissolving for several hours [8], practical problems like tablet not inserted properly as noncooperation from patients (most of the times). At times while passing stools, patient strain and tablets are not retained. Thus due to these few but practical problems the success rate of the procedure is affected. These drawbacks can be overcome by sublingual route as sublingual mucosa is very vascular so tablet get dissolved within 10–15 min [8] and we can confirm it too but not so with vaginal route, as for confirmation, one has to do repeated per vaginal examinations which is not acceptable in terms of infection and comfort level of patient.

Our study was in the same opinion with Milani et al. [5] that sublingual administration is more convenient and preferable and less uncomfortable route.

A study by Nautiyal et al. suggested that the side effects such as fever, chills, diarrhea and vomiting are more common with sublingual route, but our study found side effects are almost equal in both the routes, which is similar to Von Hertzen H's study [6, 8].

Conclusion

Our study concludes even though both sublingual and vaginal routes have effective in mid-trimester abortions, still sublingual route is a better option in terms of shorter

induction abortion interval, lower dose requirement and patients acceptability.

Compliance with Ethical Standards

Disclosure of potential conflict of interest There are no conflicts of interests for any author (financial or otherwise).

Ethical Statement Ethical committee approval has been obtained before the study.

Informed Consent Informed consent has been taken.

Human and Animal Rights This article does not contain any studies with animal subjects.

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