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Research Article

Comparative study of sublingual and vaginal misoprostol in second trimester induced abortion

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ABSTRACT

Background: To recognize an effective Misoprostol only regime and to compare the efficacy, safety and acceptability of sublingual and vaginal Misoprostol for the termination of second trimester of pregnancy.
Methods: The study was a prospective randomized trial. Women attending OPD from January2012 to December 2013, for medical abortion between gestational ages 13-20 weeks were screened, selected and divided in to two groups. Group-A received misoprostol 400 µg then 200 µg sublingually 3 hourly, Group-B received misoprostol 400 µg then 200 µg vaginally 3 hourly. They were observed for 24 hours. Main outcomes were induction-abortion interval, dose required, success rate and side effects and comfort to the route of administration.
Results: Mean induction-abortion interval was 9.28 ± 5.824 hours, 95% CI: 7.62-10.94in sublingual misoprostol group and 13.68 ± 6.179 hours, 95% CI: 11.92-15.44 in vaginal group. Mean dose required for abortion was 948 ± 389.264 µg, 95% CI: 837.37-1058.63 in sublingual and 1248 ± 415.142 µg, 95% CI: 1,130.02-1,365.98in vaginal group. Success rate was 98% and 94%, respectively in two groups. The differences were statistically significant. Comfort to the route of administration was 90% in sublingual and 60% in vaginal group.
Conclusions: Both sublingual and vaginal routes of Misoprostol are equally effective, safe, inexpensive and acceptable method. Sublingual route is better and preferred by women.

Keywords: Misoprostol, Second trimester pregnancy termination, Sublingual route, Vaginal route, Abortion, Midtrimester Abortion

INTRODUCTION

Abortion is defined as termination of pregnancy before the period of viability, which occurs at 20 weeks of gestation and the foetus weighing 500 g. About 40-60 million abortions occur per year globally. Medical abortion is a safe alternative to surgical methods. MTP was legalized in India in 1971.[1] Estimate indicate that 46 million pregnancies are voluntarily terminated each year, 26 million legally and 20 million outside the legal system.[2] Various management protocols have been used for second trimester pregnancy termination. These includes surgical techniques (D&E) and medical approaches such as intra-amniotic prostaglandin (PG) F_2-α instillation, PGE_2 vaginal suppositories, PGE_2 and high-dose oxytocin.[3]

All these methods require hospitalization and have disadvantage of surgical trauma and anaesthetic complication. PGE_1 analogue, misoprostol, originally used for the treatment of peptic ulcer, has been found to have uterotonic effect as well and is used for termination of pregnancy for great success. Chemical formula of misoprostol is $C_{22}H_{38}O_5$ or (±) -methyl (13E)-11, 16-dihydroxy-16 methyl-9-oxo-prost-13-eonate. Misoprostol is available as 100 and 200 µg tablets and can be used orally, vaginally and rectally. It is cheap, stable at room temperature, does not need refrigeration and is associated with few side effects.[4-5]

The present study had been undertaken to assess the efficacy and safety of Misoprostol by sublingual route as compared to vaginal route for induction of second trimester termination of pregnancy.

METHODS

It was a prospective randomized trial carried out in Dept. of Obstetrics and Gynecology, Chhattisgarh Institute of Medical Sciences from January 2012 to December 2013. All the cases coming to the Dept. Of Obstetrics and Gynecology for second trimester termination of pregnancy (13-20 weeks) were screened for inclusion in the study. A detailed history regarding duration of amenorrhea, gravidity, parity, previous spontaneous or induced abortions and medical diseases was recorded. General and systemic examination was done. Vaginal examination was done to assess the duration of pregnancy and to rule out any pelvic pathology. The gestational age was determined by menstrual history and vaginal examination. Sonography was done if required. Then routine investigations like hemogram, BT, CT, blood sugar, urine examination, VDRL, sickling test, serum creatinine and HIV were done. Cases with respiratory tract disease, organic heart disease, diabetes mellitus, renal disease, uterine scar, pelvic pathology, uterine anomalies, hemorrhagic disorder, jaundice, severe anemia and allergy to prostaglandins were excluded from the study.

After taking an informed consent, cases were divided into two groups.

• Group A (n = 50): 400 µg then 200 µg misoprostol sublingually 3 hourly.
• Group B (n = 50): 400 µg then 200 µg misoprostol vaginally 3 hourly.

In Group A, induction was carried out on inpatient basis by giving 400 µg sublingually, there after 200 µg sublingually 3 hourly till abortion. In Group B, induction was carried out on inpatient basis by inserting 400 µg misoprostol tablets into posterior fornix, keeping the patient strictly in bed for half an hour. There after 200 µg tablets were inserted intravaginally every 3 hourly until abortion. Time of onset of contraction, bleeding, pain, cervical dilatation, expulsion of fetes including placenta and membrane were looked for. All vital parameters were closely monitored and side effects if any were symptomatically managed. They were kept under observations for two hours after abortion. Patients were discharged with the advice to come for follow-up after two weeks or earlier if necessary. The data was entered and analyzed through software program SPSS (Statistical Package for the Social Sciences) for statistical analysis. The results were represented as mean and standard deviation. The mean induction abortion interval and mean dose required were analyzed by standard error of difference between two means. Success rate and side effects due to different routes of administration were analyzed by their percentage and compared by chi-square test.

RESULTS

Majority of our patients were married, of 20-30 years of age (Table 1). Forty-nine (98%) women aborted within 24 hours in sublingual misoprostol group as compared to 47 (94%) in vaginal group. In majority of women pain started within two hours (mean 3.5 ± 2.33) in sublingual misoprostol group as compared to (mean3.9 ± 2.46) the vaginal group. Vaginal bleeding started within 4-6 hours (mean 5.26 ± 2.9) in the sublingual misoprostol group as compared to (mean 6.29 ± 2.33) the vaginal group.

Table 1: Patients' characteristics.

Variables	Sublingual group	Vaginal group
Married	46	45
Unmarried	04	05
Mean age in years	22.16 ±3.228	22.50 ± 3.541
Mean weight in kg	45.18 ±7.558	45.88 ± 7.644
Mean height in cm	148.68 ± 8.558	150.80 ±10.690
Mean gravidity	3.28 ±1.443	3.66 ±1.560
Mean GA in weeks	16.72 ±2.356	16.78 ±2.332

GA: Gestational age

The mean induction interval was 9.28 ± 5.824hours, 95% CI: 7.62-10.94 in sublingual misoprostol group as compared to 13.68 ± 6.179 hours 95% CI:11.92-15.44 in vaginal group. It was decreased with increase in gravidity. It was inversely proportionate to the gravidity (Table 2).

The mean dose of misoprostol 948.00 ± 389.264 µg(95% CI 837.37-1058.63) in sublingual misoprostol group was much less as compared to 1,248.00 ±415.142 µg (95% CI 1,130.02-1,365.98) in vaginal group. Misoprostol requirement and induction abortion interval were decreased with increasing gestational age (Table 3).

Table 2: Gravidity, induction-abortion interval and mean dose of misoprostol.

Gravidity	Mean induction-abortion interval (hours)		Mean dose of misoprostol (µg)	
	Sublingual	Vaginal	Sublingual	Vaginal
1	20 ±1.414	23.83 ±1.472	1,666.67 ± 103.280	1,900 ± 109.545
2	4.89 ±1.764	19.89 ±1.453	1,311.11 ±105	1,688.89 ± 105.409
3	8.80 ±1.740	13.80 ±1.935	920 ±126.491	1,266.67 ±97.590
4	5 ± 0.707	10.11 ±0.928	44.44 ±88.192	1,000 ±00
5	3.43 ± 0.535	6.71 ±1.113	4,250 ±100.0	600 ± 00
6	2.25 ± 0.500	4.25 ± 0.500	4,250 ±100.0	1,248 ±415.142
Total	**9.28 ± 5.824**	**13.68 ±6.179***	**948 ± 389.264**	**1,248 ±415.142**

*Difference between the two mean is 3.9. I.e. more than three times the SE which is highly significant?

Table 3: Gestational age, induction-abortion interval and mean dose of misoprostol.

Gravidity	Induction Abortion Interval (Hours)		Mean Dose of Misoprostol (µg)	
	Sublingual	Vaginal	Sublingual	Vaginal
13	20.40 ± 1.140	24.1581	1,680 ±109.545	1920 ± 109.545
14	16.50 ±1.049	21.33 ±1.033	1,433.33 ±81.650	1,766.67 ±81.650
15	12.43 ±1.272	17.71 ±1.113	1,142.86 ±97.590	1,514.29 ±106.904
16	9.17 ±0.753	14.17 ±1.169	966.67 ±81.650	1,266.67 ±103.280
17	7.17 ±0.753	12 ±0.00	800 ± 000	1,200 ±000
18	5.50 ± 0.577	11 ±00	700 ±115.470	1,000 ±000
19	4.38 ±0.518	8.75 ±1.035	600 ± 00	825 ±103.510
20	2.63 ±0.518	5.13 ± 1.126	525 ±103.510	675 ±103.510
Total	**9.28 ± 5.824**	**13.68 ±6.179**	**948 ±389.264**	**1,248 ±415.142***

*Difference between the two mean is 4.8 i.e. more than 3 times of SE and is highly significant

Abortion was considered to be successful, if there was expulsion of fetus with or without expulsion of placenta occurring within 24 hours of insertion of first dose. Success rate was 98% for sublingual group and 94%for vaginal group. A significant observation was that all women in the sublingual group aborted within 24 hours while only 89% in the vaginal group aborted in 24 hours.

There was no difference in success rate with reference to parity and gestational age in both the groups.

Abortion was said to be incomplete, if either whole of placenta or part of it was retained for more than three hours after expulsion of fetus or if excessive bleeding started and required evacuation. Abortion was complete in 87.8% and 81% of case in sublingual and vaginal group, respectively. This difference was not statistically significant indicating that misoprostol administered through any route is equally effective but there was a definite reduction in induction-abortion interval on sublingual administration. The various side effects observed were nausea, vomiting, pyrexia ($p < 0.05$), abdominal cramps and fatigue (Table 4).

Table 4: Side effects.

	Sublingual (n = 50)	Vaginal (n = 50)	p value
Nausea	5 (10%)	4 (8%)	NS
Vomiting	3 (6%)	2 (4%)	NS
Fatigue	1 (2%)	2 (4%)	NS
Diarrhea	1 (2%)	3 (6%)	NS
Fever	1 (02%)	6 (12%)	$p < 0.05$
Abdominal cramps	1 (2%)	1 (2%)	NS
Total	**12 (24%)**	**18 (36%)**	-

Table 5: Subjective assessments of patients comfort to the route of administration.

Characteristic	Sublingual	Vaginal
Comfortable during administration	45 (90%)	30 (60%)
Shows discomfort during administration	05 (10%)	20 (40%)

Sublingual route was the most acceptable, subjective assessment of patient comfort to the route of administration was high in sublingual group (90%) and 60% in Vaginal group. Sublingual route was convenient to administer, had less side effects, required short hospital stay.

DISCUSSION

Medical abortion is becoming more popular now days as a method of termination of pregnancy in second trimester because it is effective and technically less demanding when compared to surgical methods.[1]

Prostaglandin analogs are the mainstay of drugs used for this purpose. Among them, misoprostol is the most commonly used one, as it is cheap and stable at room temperature. It has been shown to be effective for second trimester termination of pregnancy.[2]

Misoprostol has been used to induce medical abortion by various routes of administration. Vaginal misoprostol has been shown to be more effective than oral misoprostol. However, evidence that absorption through the vaginal route is inconsistent and that the patients find vaginal administration uncomfortable has led to the sublingual route as an alternative. Oral misoprostol reaches a high peak concentration in blood very quickly before a rapid fall in plasma level. After vaginal administration there is gradual rise up to peak level and then a slow fall of level.[3-7]

Earlier studies by various authors[2-7] comparing oral with vaginal administration with the dose regimes varying from 400-800 µg at 3-hourly to 8-hourly interval have reported the success rate on vaginal administration to be in range of 56.8-99.26%.The induction-abortion interval observed was shorter than that observed in the other studies using misoprostol by various routes or by combination of routes for second trimester termination of pregnancy (Table VI).

Recently, it has been shown that misoprostol can be administered sublingually. A pharmacokinetic study has shown that after a single dose of sublingual misoprostol, the peak concentration is achieved in a shorter time than with vaginal misoprostol. The peak concentration and bioavailability were also higher with sublingual administration. Therefore, it was postulated that sublingual route of administration might be the most effective route for administration of misoprostol by Tang et al.[5]

A study by Tang et al[8] of 18 cases administered misoprostol 200 ug. administered 3-hourly sublingually demonstrated 100% success rate with a mean induction abortion interval (12 ± 3.6 hours). In the same author study, sublingual misoprostol in gestational age <12 weeks reported success rate of about 86%.[9]

Helena et al[11] demonstrated that repeated administration of 400 µg Misoprostol either vaginally or sublingually is an effective and acceptable option. However vaginal administration appears to produce better results among multiparous women, but more women had fever >38C in Vaginal route. Shah et al[12] studied role of vaginal Misoprostol for second trimester termination. They found it is effective and time saving drug for second trimester abortion. 96.6% women aborted within 20 hours. Mean Induction abortion interval was 9.43 hours with very low drug related side effects. Milani et al[13] reported similar results as in our study. Dickson et al[14] studied Oral, Vaginal and sublingual Misoprostol for second trimester abortion. They found that Vaginal or sublingual Misoprostol administrated after vaginal loading dose in second trimester abortion with Mifepristone is associated with a shorter time to pregnancy termination compared with an oral regime.

Table 6: Comparative study of different studies.

Author	Year	Dose schedule	Observation time (hours)	IAI (hours)	Success rate (%)	Dose required (µg)	Side effects
Tang OS et al[6]	2004	400 µg s/l 3 hourly 400 µg oral 3 hourly	24	13.8 12	64		
Guix et al[2]	2005	400 µg oral + 400 µg vg 8 hourly 400µg vg 3 hourly	24	25.5 ±24.45 15 ±7.14	56.8 85.7		
Tripti et al[3]	2007	600 µg vg + 400 µg 4 hourly	24	12.27 ±5.71	99.26	1,638.7±322.67	N.V.D.F
Bhattacharjee et al[7]	2008	400 µg s/l 3 hourly 400 µg vg 3 hourly	24	14.1 14.5	64.03 61.59		
Caliskan et al[4]	2009	100 µg s/l 2 hourly 200 µg s/l 2 hourly	24	14.75 15.2	92.6 91.4	1,274 612	
Helena et al[12]	2009	400µg Sublingual 3hourly 400µg intra vaginally 3 hourly	24	12 Hours .N-14.4 hrs. .P-11 hrs. .N-11hrs .P-11.8hrs	79.8% 85.9%		F.>38C 29.9% F.>38C 39.7%
Shah et al[13]	2010	400µg intra vaginally followed by 200µg intra vaginally every 4 hours	24	9.43 hrs.	96.6%	666±315	High grade Fever
Milani et al[14]	2014	400µg sublingually 4 hrly maximum 5 doses 400µg Vaginally 4 holy maximum 5 doses	24	Sublingual 12.42 Vaginally 14.67	72% 76%		
Dickson et al[15]	2014	800µg Vaginal loading dose followed by 400µg .Oral 3hrly .Sublingual 3 hrly .Vaginal 4 hrly	24 hours	Oral 9.5 Sublingual 7.4 Vaginal 7.8	Rate same in sublingual and vaginal		
Modak et al[16]	2014	400µg Sublingual 3hourly 400µg intra vaginally 3 hourly	24	Sublingual 12.28 Vaginally 13.11	79.41% 88.24%		Fever >38C 26.47% 51.51%
Garg et al[17]	2015	Buccal 400µg loading 200µg 6 hrly Vaginal 400µg 6 hrly	24	Buccal 14.64 Vaginal 11.85	Buccal 80% Vaginal 76%		
Present Study	2013	400 µg followed by 200 µg s/l 3 hourly 400 µg followed by 200 µg intravaginally 3 hourly	24	9.28 + 5.824 13.60 + 6.17	98 94	9.48 + 389.264 1248 +415.192	N.V.D.F N.V.D.F

Modak et al[15] found induction abortion interval was shorter in sublingual group (12.28 hours), we found the similar results. Subjective assessment of comfort to the route was 88.24% in sublingual group and 54.55% in vaginal group. We also found the patients who took sublingual drug are more comfortable (90%) while the vaginal rout the level of comfort was 60%.High grade fever (>38C) was more in Vaginal group (51.51%) as compared to sublingual group (26.47%).

Garg et al[16] found buccal route may serve an alternative to vaginal route with similar efficacy.

In the present study, induction-abortion interval was 9.28 ± 5.824 hours in sublingual and 13.68 ± 6.179 hours in intravaginal route. Shortest being only3.18 hours in 3rd gravida with 20 weeks pregnancy in sublingual and 4.28 hours in vaginal in 4th gravida of 20 weeks in vaginal route; largest being 22 hours in sublingual and 26 hours in vaginal route.

Using a high loading dose initially followed by low-dose at proper intervals to maintain sustained effect brings about effective uterine contraction and shorter induction-abortion interval. In our study, we used an initial high dose of 400 µg sublingually followed by 200 µg 3 hourly in Group A and 400 µg intravaginally followed by 200 µg 3 hourly in Group B. In our study, we compared sublingual land vaginal route of administration of misoprostol and sublingual route of administration have a short induction abortion interval, better success rate and less side effects which were statistically significant as compared to vaginal route of administration. Side effects observed were minor in nature and required symptomatic management only.

Sublingual misoprostol has the advantage that it can avoid the uncomfortable and inconvenient vaginal administration. This is especially true if women start to bleed, when the absorption of the drug may be affected.

Although other studies[1,7,14] have advised against carrying out caesarean myomectomy in patients with multiple fibroids, fundal intramural fibroids in the vicinity of the tubes, and patients with dense pelvic adhesions; we would clarify that the danger in multiple fibroid is significant if there are >10 fibroids. We also avoided caesarean myomectomy in patients with big broad ligament fibroids. The impact of this study however, maybe limited by our small sample size (n=64). Further research with larger sample size could help explore our findings.

CONCLUSIONS

Misoprostol administered alone either sublingually or vaginally is an efficient drug for second trimester medical termination of pregnancy. Sublingual route is better because of its high acceptability, short induction abortion interval, more efficacies with more comfort on route of administration and lesser side effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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