

Comparison of Efficacy and Safety of Two Different Doses of Sublingual Misoprostol 400µg AND 200µg with Vaginal Misoprostol 400µg in Cervical Ripening in First Trimester Abortion

Running Head: Sublingual Misoprostol in First Trimester Abortion

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Abstract: *Despite wider availability of contraception methods, the incidence of induced abortion is increasing. Cervical priming prior to first trimester abortion facilitates the procedure and reduces the risk of cervical injury and uterine perforation that are often associated with mechanical cervical dilatation. The main objective of the study is to compare the efficacy of two different doses of sublingual misoprostol 200 µg and 400 µg with vaginal misoprostol 400 µg in cervical ripening in women undergoing first trimester abortion. An open label, randomized, prospective study was done in family planning inpatient department in MGMH, Hyderabad. 120 pregnant women with < 12 wks of gestation requiring suction evacuation for first trimester abortion were enrolled and divided into three groups of 40 each. Groups 1,2,3 received misoprostol 400µg vaginally, 400µg sublingually, 200µg sublingually respectively. After 5 hrs of administration the cervical dilatation was measured and suction evacuation was done. Misoprostol 400 µg showed no difference in efficacy when administered by vaginal and sublingual routes. Cervical dilatation was more with sublingual misoprostol 400 µg compared to sublingual misoprostol 200 µg, though there was no significant difference in initiating the process of abortion. Sublingual route is preferred because of easy availability and patient's acceptability. Sublingual misoprostol 200 µg can be preferred to 400 µg as it is associated with less side effects.*

Keywords: misoprostol, abortion, cervical dilatation, sublingual route, vaginal route

1. Introduction

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability¹. Abortion can be spontaneous or induced. Despite wider availability of contraception methods, the incidence of induced abortion is increasing. Although surgical abortion has been found to be safe and effective method with a success rate of > 95%, associated with major morbidity in upto 1% of women and minor morbidity in 10%. Many of the complications of surgical abortion can be avoided by medical abortion and this is especially important in developing countries where surgical evacuation is in usage.

Cervical priming prior to first trimester abortion facilitates the procedure and reduces the risk of cervical injury and uterine perforation,² that are often associated with mechanical cervical dilatation.

Cervical priming can be achieved with the use of prostaglandins or hygroscopic dilators.¹ Among the various prostaglandins, misoprostol is commonly used as it has short half life, few side effects, stable at room temperature, inexpensive and easy accessibility.³

Misoprostol has been administered orally, buccally, sublingually, rectally and vaginally.⁴ Several comparative studies of sublingual, oral, and vaginal misoprostol has been carried out in different parts of the world, however the data is scanty in Indian patients⁵. Previous studies shown that sublingual misoprostol is effective than vaginal or oral misoprostol in cervical ripening before first trimester

abortion and was associated with side effects include abdominal pain, shivering, nausea, vomitings and preoperative vaginal bleeding⁶. Hence the present study is to investigate the sublingual route further and compare two dose regimens 200 micrograms and 400 micrograms with vaginal misoprostol 400 micrograms in an effort to minimise the side effects by maintaining the efficacy.

2. Aims and Objectives

To compare the efficacy and safety of two different doses of sublingual misoprostol 200 microgram and 400microgram with vaginal misoprostol 400 microgram in cervical ripening in women undergoing first trimester abortion, upto 12 wks of gestation. To investigate

- Efficacy of the dose
- Acceptability and compliance
- Side effects and complications

3. Abortion

Definition: Abortion is the expulsion or extraction from its mother of an embryo or fetus weighing 500 g or less when it is not capable of independent survival (WHO). This 500 g of fetal development is attained approximately at 22 weeks (154 days) of gestation. The expelled embryo or fetus is called abortus. The term miscarriage is the recommended terminology for spontaneous abortion⁷.

Abortion can be

- 1) **Spontaneous abortion** — this category includes threatened, inevitable, incomplete, complete, and missed abortion
- 2) **Recurrent abortion** — this term is variably defined, but it is meant to identify women with repetitive spontaneous abortions so that an underlying factor(s) can be treated to achieve a viable newborn.
- 3) **Induced abortion** — this term is used to describe surgical or medical termination of a live fetus that has not reached viability¹.

Incidence: The incidence of abortion is difficult to work out but probably 10–20% of all clinical pregnancies end in miscarriage and another optimistic figure of 10% are induced illegally. 75% abortions occur before the 16th week and of these, about 75% occur before the 8th week of pregnancy⁷.

First-Trimester Spontaneous Abortion

More than 80 percent of spontaneous abortions occur within the first 12 weeks of gestation. With first-trimester losses, death of the embryo or fetus nearly always precedes spontaneous expulsion¹.

Etiology⁷

The etiology of miscarriage is often complex and obscure. The following factors (embryonic or parental) are important:

- Genetic
- Endocrine and metabolic
- Anatomic
- Infection
- Immunological
- Antifetal antibodies
- Thrombophilias
- Others

Techniques Used for First-Trimester Abortion¹

Surgical:

- Dilatation and curettage
- Vacuum aspiration
- Menstrual aspiration

Medical:

- Prostaglandins E2, F2 α , E1, and analogues
 - a) Vaginal insertion
 - b) Parenteral injection
 - c) Oral ingestion
 - d) Sublingual
- Antiprogestones—RU-486 (mifepristone) and epostane
- Methotrexate—intramuscular and oral
- Various combinations of the above

All procedures are aided by pretreatment using hygroscopic cervical dilators.

Surgical abortion is currently the standard management for the termination of pregnancies occurring in the first 12 weeks gestation in many countries. The success rate of this method is more than 95%. However, the procedure is associated with major morbidity in up to 1% and minor

morbidity in 10% such as pelvic infection, uterine perforation, cervical trauma and Asherman's syndrome⁸.

Cervical Preparation

Cervical dilatation becomes increasingly necessary as gestation progresses and has been recommended for all pregnancies of more than 10 weeks, for pregnancies over 9 weeks in nulliparous women and for all women younger than 18 years of age⁹. There are several methods that will soften and slowly dilate the cervix to minimize trauma from mechanical dilatation. It may be achieved by using mechanical dilators, laminaria or synthetic hygroscopic dilators, mifepristone or a prostaglandin such as gemeprost or misoprostol¹⁰.

A Cochrane review confirmed that hygroscopic dilators and cervical ripening medication had similar efficacy in decreasing the length of first-trimester procedures¹¹. Of these, hygroscopic dilators are devices that draw water from cervical tissues and expand to gradually dilate the cervix. One type is derived from various species of *Laminaria* algae that are harvested from the ocean floor. Another is *Dilapan-S*, which is composed of an acrylic-based gel¹.

Prostaglandins ripen the cervix and stimulate uterine contractility. They can bring about successful termination when used alone, but the high doses required can cause significant adverse effects. The most commonly used prostaglandins are gemeprost and misoprostol; others that have been used include carboprost and sulprostone, but these have been associated with more severe adverse effects¹⁰.

The antiprogestogen mifepristone also ripens the cervix and stimulates uterine contractility; in addition, it increases the sensitivity of the myometrium to prostaglandins with a maximum effect about 24 to 48 hours after dosing. Mifepristone is not sufficiently effective to be used as an abortifacient on its own, but is used synergistically with a prostaglandin, usually gemeprost or misoprostol, to achieve expulsion of the uterine contents.

Other options include formulations of *prostaglandins E2* and *F2a*, which have unpleasant side effects and are usually reserved as second-line drugs (Kapp, 2010)

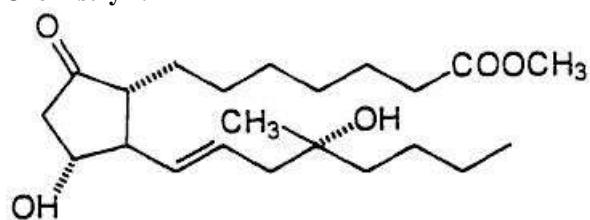
4. Misoprostol

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is a stable, synthetic form of prostaglandin E1 analogue¹². It has anti-secretory and mucosal protective properties and was originally developed in the 1970s for the prevention of nonsteroidal anti-inflammatory drugs (NSAIDs)-induced peptic ulcers⁹. Apart from its gastro cytoprotective effects, it is also used as an abortifacient. It is used off label in other regimens for abortion, labour induction, treatment of early pregnancy loss, prevention and treatment of postpartum haemorrhage, and cervical priming before uterine procedures like hysteroscopy¹².

The tablets are thermo-stable and have a long shelf life at room temperature whilst in aluminium blister packets. Misoprostol tablets could also be easily administered by unskilled attendants or the women themselves thus making

them available for women giving birth at home or in isolated areas⁹.

Chemistry¹⁰:



Misoprostol is a synthetic prostaglandin analogue structurally related to natural PGE₁. It is chemically (±)-Methyl 7-[(1*R*,2*R*,3*R*)-3-hydroxy-2-[(*E*)-(4*R**S*)-4-hydroxy-4-methyloct-1-enyl]-5-oxocyclopentyl]heptanoate; (±)-Methyl (13*E*)-11,16-dihydroxy-16-methyl-9-oxoprost-13-enoate. Misoprostol has a structural formula of C₂₂H₃₈O₅, with molecular weight of 382.5.

Pharmacokinetics¹³:

Misoprostol is rapidly absorbed after oral administration and then is rapidly and extensively de-esterified to form misoprostol acid, the principal and active metabolite of the drug. Some of this conversion may occur in the parietal cells. Peak plasma concentrations of misoprostol acid occur after about 15 to 30 minutes. Food and antacids decrease the rate of misoprostol absorption, resulting in delayed and decreased peak plasma concentrations of the active metabolite. The free acid is excreted mainly in the urine, with an elimination t_{1/2} of 20-40 minutes. Misoprostol acid is distributed into breast milk.

Mechanism of Action

Prostaglandins exert their actions by interacting with specific G protein linked receptors that are localized in the plasma membrane of cells. After binding to the specific receptors prostaglandins activate chemical messengers like cyclic AMP and calcium. PGE activates adenyl cyclase where as PGF is weak or inert in this regard.

Misoprostol bind to β adrenergic receptors in uterine muscle and inhibit the action of adenyl cyclase and decrease cyclic AMP. This increases the concentration of intracellular calcium, which triggers myometrial contraction. In adipose and renal tissues, PGE decrease cyclic AMP and oppose the action of several hormones.

Uses and Administration¹⁰:

- Misoprostol is used in the treatment of benign gastric and duodenal ulceration including that associated with NSAIDs. The usual oral dose is 800 µg daily in two to four divided doses with food. Treatment is initially given for at least 4 weeks, even if symptoms are relieved sooner, and may continue for up to 8 weeks if necessary. Further courses may be used to treat relapse.
- Misoprostol is also used prophylactically with NSAIDs to prevent NSAID-induced ulcers. The usual oral dose is 200 µg two to four times daily. A dose of 100 µg four times daily may be used in patients not tolerating the higher dose.
- Misoprostol may be used to ripen the cervix before surgical termination of pregnancy in the first trimester. A

single oral dose of misoprostol 400 µg is given 3 to 4 hours before surgery. It may also be used for medical termination of pregnancy at up to 49 days of amenorrhoea, in a single oral dose of 400 µg given 36 to 48 hours after mifepristone. Misoprostol has also been used for induction of labour and in the management of postpartum haemorrhage.

- Misoprostol is also used for labour induction. When misoprostol given vaginally it increased cervical ripening and induced labour. It was more effective than vaginal or intracervical dinoprostone, reducing the need for oxytocin augmentation and improving the rate of vaginal cervical ripening and induced labour. Most studies used misoprostol tablets in a dose of 50 µg vaginally every 4 hours, but reported doses have varied from 25 µg every 2 to 3 hours, to 100 µg every 6 to 12 hours.
- Misoprostol can also use for control of postpartum haemorrhage, using single doses of 800 or 1000 µg when administered rectally.
- Misoprostol can be used for termination of pregnancy. In the first trimester, misoprostol is used for cervical ripening before the surgical termination; it has been reported to be effective when given orally, sublingually, or vaginally usually in a dose of 400 µg. Oral misoprostol (400 µg) given after mifepristone is effective in medical termination of early pregnancy of up to 63 days, and especially so at up to 49 days. Misoprostol 800 µg has also been given vaginally after mifepristone, and a regimen of 2 or 3 doses of sublingual misoprostol after oral mifepristone has been reported to be effective. In countries where mifepristone is unavailable, a dose of 800 µg vaginally, repeated after 24 hours, has been suggested for pregnancy of up to 63 days.
- Misoprostol has also been studied for termination of pregnancy during the second trimester. It can be given either alone or after oral mifepristone and reported to be effective when given vaginally, sublingually or orally.
- In management of first trimester pregnancy failure, intravaginal misoprostol in doses 400 µg - 800 µg can be used.
- Misoprostol has also been used with mifepristone for uterine evacuation after pregnancy failure, and to induce labour where late intra-uterine fetal death has occurred.

Adverse Effects¹⁴:

- The most commonly reported adverse effect of taking a misoprostol orally for the prevention of stomach ulcers is diarrhoea.
- -The next most commonly reported adverse effects of taking misoprostol orally for the prevention of gastric ulcers are abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting, and constipation.
- Misoprostol can cause uterine hyperstimulation, which can negatively affect the blood supply to the fetus and increases the risk of complications such as uterine rupture.

Precautions¹⁰:

- Misoprostol should not be used to treat peptic ulcer disease in patients who are pregnant or who may become pregnant because it can cause uterine contractions.

- Patients with conditions such as inflammatory bowel disease, for whom profound diarrhoea could be dangerous, should be monitored carefully if misoprostol is given.
- Misoprostol should not be used in women at increased risk of uterine rupture, such as those with multiple pregnancy or a uterus scarred by previous caesarean section.
- Misoprostol should not be given to breast-feeding women because misoprostol acid could potentially cause diarrhoea in the infant.

Drug Interactions:¹⁰

It has been suggested that aspirin and NSAIDs, which are prostaglandin synthetase inhibitors, might alter the efficacy of misoprostol used for termination of pregnancy by inhibiting uterine cramping.

5. Patients and Methods

An open label, randomized, prospective study was carried out in family planning inpatient department in Govt. Maternity Hospital, Petlaburz, Hyderabad for the duration of 6 months. The present study included 120 pregnant women with < 12 wks of gestation required suction evacuation for first trimester abortion.

Inclusion criteria

- 1) Patients who has given informed consent.
- 2) Age group: 18-35 yrs.
- 3) Single intrauterine pregnancy < 12 wks as per USG for elective MTP.

Exclusion criteria

- 1) Patients with cardiac, pulmonary diseases, epilepsy, asthma, renal failure.
- 2) Coagulation abnormalities.
- 3) Known hypersensitivity to prostaglandin administration.
- 4) Patients with active infections.
- 5) Patients with any organ diseases.
- 6) Patients having any type of uterine anomaly.
- 7) Patients with confirmed or suspected ectopic pregnancy.
- 8) Patients with bleeding PV.

120 women who fulfilled the inclusion criteria required medical termination of pregnancy were taken up for the study.

A complete case record was prepared and detailed history of all the patient was taken. A thorough clinical examination including general, per abdominal and per vaginal examination was done. All the patients were subjected to investigations like complete urine examination, haemoglobin estimation, blood grouping and Rh typing prior to the administration of the regimen. Ultrasonogram was done to confirm the gestational age.

All the patients were informed about the medication and surgical procedure. A written consent was taken. The 120 women were randomized and divided into three groups.

- Group 1 receive 400µg misoprostol vaginally
- Group 2 receive 400µg misoprostol sublingually
- Group 3 receive 200µg misoprostol sublingually

The doctor was responsible for the administration of vaginal misoprostol in group 1 by placing the two misoprostol tablets into the posterior fornix of vagina. The patients in group 2 & 3 are instructed to keep misoprostol under the tongue themselves and are not allowed to have food or drink for 20 mins and not to swallow tablet. The blood pressure, pulse rate were recorded.

After 5 hrs.of administration the cervical dilatation is measured and suction evacuation was done.

The degree of cervical dilatation is measured by noting the largest Hegar's dilator that could pass through internal os without any resistance at the time of procedure. Other parameters like onset of bleeding after drug administration, amount of blood loss, amount of further dilatation required to permit passage of suction canula are noted.

After the intake of misoprostol the patients are observed for the side effects like abdominal pain, diarrhoea, fever, nausea, vomiting and vaginal bleeding and any other effects. They are managed appropriately.

Data analysis was done by using Graph pad Prism version 6.05. To compare the efficacy of three regimens in terms of onset of bleeding and size of the Hegar's dilator ANOVA test was done. For other parameters and to compare vaginal and sublingual misoprostol 400µg unpaired student's t test was done. Similarly to compare vaginal and sublingual misoprostol 200µg unpaired student's t test was done. The level of significance in present study was p value < 0.05.

6. Results

In the present study total 120 women posted for first trimester abortion were enrolled. They are randomly divided into 3 groups of 40 in each group. In group 1 the women were given vaginal misoprotol 400 µg 5 hrs before the suction evacuation. In group 2, 400 µg of misoprostol was given sublingually and in group 3, 200 µg of misoprostol was given sublingually.

The demographic details are as follows.

Table 1: Distribution of Women According to Age

Age	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
< 20 yrs	6	4	9
20 - 25 yrs	17	14	15
26 - 30 yrs	14	16	11
> 30 yrs	13	6	5
Mean ± SD	25.475 ± 4.20	26.37 ± 4.72	25.65 ± 4.95

As shown in above table The mean age in vaginal group is 25.47 ± 4.2 yrs, The mean age in sublingual 400 µg of misoprostol is 26.37 ± 4.72 yrs and the mean age in sublingual 200 µg is 25.65 ± 4.95 yrs. p value is > 0.05 as calculated by ANOVA shows that it is statistically not significant.

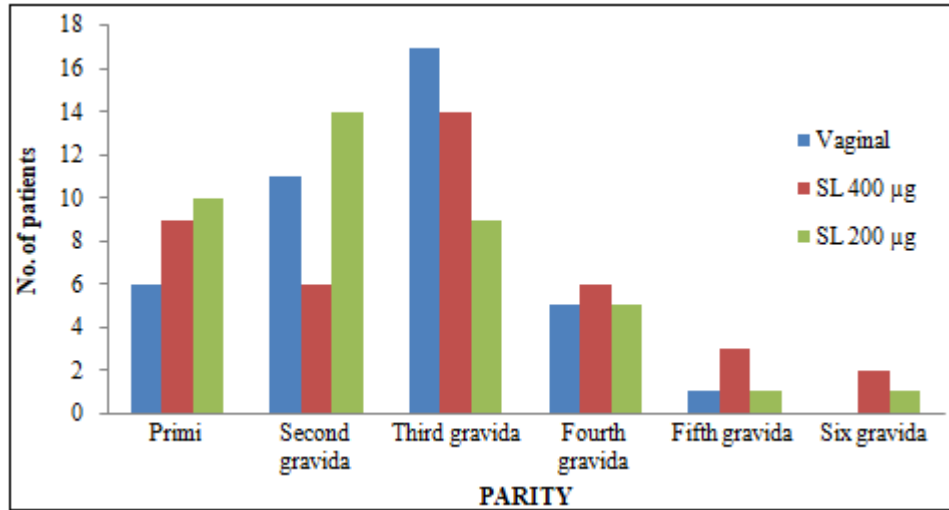


Figure 2: Distribution of Women According to Parity

Table 2: Distribution of Women According to Parity

Parity	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
Primi	6 (15%)	9 (22.5%)	10 (25%)
G2	11 (27.5%)	6 (15%)	14 (35%)
G3	17 (42.5%)	14 (35%)	9 (22.5%)
G4	5 (12.5%)	6 (15%)	5 (12.5%)
G5	1 (2.5%)	3 (7.5%)	1 (2.5%)
G6	-	2 (5%)	1 (2.5%)

This is the table showing distribution of patients according to their parity. In vaginal group patients with third gravida are more than others. In sublingual 400 µg group patients with third gravida are more than others. In sublingual 200 µg group patients with second gravida are more than others.

Table 3: Distribution of Women According to GA

Gestational Age	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
< 6 Wks	11	14	6
6 - 9 Wks	20	19	18
9 - 12 Wks	9	7	16
Mean ± SD	7.9 ± 1.80	7.7 ± 2.04	8.82 ± 2.06

This is the table showing number of patients distributed according to their gestational age among three groups. The mean gestational age in vaginal group is 7.9 ± 1.80 wks,

mean gestational age in sublingual 400 µg group is 7.7 ± 2.04 wks and mean gestational age in sublingual 200 µg is 8.82 ± 2.06 wks.

Table 4: Distribution of Women According to Onset of Bleeding

Duration in hrs	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
1 hr	1	13	1
2 hrs	16	7	4
3 hrs	16	11	18
>3 hrs	4	5	10
No bleeding	3	4	7
Mean ± SD	2.62 ± 0.72	2.18 ± 1.15*	3.11 ± 0.73*

* p value > 0.05, not significant, ANOVA * p value > 0.05, not significant, ANOVA test

In present study, the mean time for onset of bleeding is 2.62 ± 0.72 hrs in vaginal misoprostol group. In patients with sublingual misoprostol 400µg the mean time for onset of bleeding is 2.18 ± 1.15 hrs. In patients with sublingual misoprostol 200µg the mean time for onset of bleeding is 3.11 ± 0.73 hrs. p value is > 0.05, calculated by ANOVA test which is not significant. That is there is no significant difference in three regimens in initiating the process of abortion.

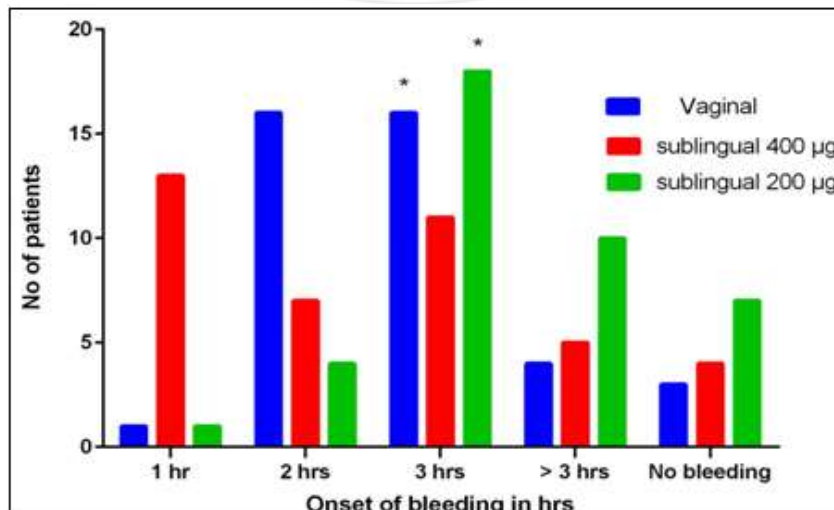


Figure 3: Distribution of Women According to Onset of Bleeding

* P value > 0.05, not significant, ANOVA test

In present study, the onset of bleeding was earlier in patients received sublingual misoprostol 400 µg and late in patients received sublingual 200 µg. P value is > 0.05, calculated by ANOVA test which is not significant. There is no difference in efficacy of all three regimens in initiating the onset of bleeding.

Table 5: Size of Hegar's Dilator Easily Passes Through The Cervical OS in Women

Size of dilator	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
8	5	5	9
10	1	4	-
12	16	11	26
14	17	9	4
16	1	11	-
Mean ± SD	12.4 ± 2.03	12.85 ± 2.61**	11.25 ± 1.90

** p value < 0.05, significant, ANOVA test

In vaginal group the mean size of Hegar's dilator that passes easily through the cervical os is 12.4 ± 2.03. In sublingual misoprostol 400 µg the mean size of dilator is 12.85 ± 2.61. In sublingual misoprostol 200 µg the mean size of the dilator is 11.25 ± 1.90. p value is < 0.05, as calculated by ANOVA test is significant, that indicates sublingual misoprostol 400 µg is more efficient in causing cervical dilatation than others.

Table 6: Side Effects among Women Received Misoprostol

Side effect	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
Pain	21	28	24
Nausea	6	10	10
Vomiting	2	8	-
Diarrhoea	3	2	-
Fever	2	1	1
Bleeding	2	4	-
Chills and rigor	-	2	-
No side effects	12	12	14

As shown in above table, most of the women experienced pain as a side effects and it was more in sublingual misoprostol 400 µg. In sublingual misoprostol 200 µg the side effects were less than others. Pain was experienced more in sublingual 400 µg group. Bleeding, nausea and vomiting also more in sublingual 400 µg group

Table 7: Acceptability of the Route of Administration by Women

Acceptability	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
YES	24 (60%)	26 (65%)	28 (70%)
NO	16 (40%)	14 (35%)	12 (30%)

In present study, in vaginal group 60% of the patients accepted the vaginal route and 40% of the patients not accepted the vaginal route of administration. In sublingual misoprostol 400 µg group, 65% of the patients accepted the sublingual route and in sublingual misoprostol 200 µg group, 70% of the patients accepted the sublingual route.

Table 8: Convenience of the Route of Administration

Convenience	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
Yes	9 (22.5%)	27 (67.5%)	29 (72.5%)
No	31 (77.5%)	13 (32.5%)	11 (27.5%)

In present study 77.5% of patients felt that vaginal route is not convenient. In patients who received sublingual misoprostol 400 µg group 67.5% of the patients felt that sublingual route is convenient. In sublingual misoprostol 200 µg group 72.5% of the patients felt that sublingual route is convenient.

Table 9: Willing of the Women to Administer the Drug In Future:

Willing to administer in future	Vaginal (400µg)	Sublingual (400µg)	Sublingual (200µg)
Yes	8 (20%)	21 (52.5%)	28 (70%)
No	32 (80%)	19 (47.5%)	12 (30%)

In present study 80% of the patients were not ready to administer the drug in future by vaginal route. In sublingual 400 µg route 52.5% of the patients were ready to administer misoprostol in future by sublingual route. In sublingual misoprostol 200 µg, 70% of the patients were ready to administer the drug in future.

Table 10: Comparison of Various Parameters in Women

parameters	vaginal	Sublingual 400µg	Sublingual 200µg
No. of patients	6	9	10
Age in yrs Mean ± SD	21 ± 2.36	21.8 ± 2.66	21.7 ± 4.47
GA Mean ± SD in wks	8.66 ± 1.03	8.11 ± 2.36	9.4 ± 1.17
Onset of bleeding time Mean ± SD hrs	3.2 ± 0.83	2.12 ± 0.99**	3.4 ± 0.54*
Hegar's dilator No	11.23 ± 2.73	10.66 ± 2.44**	9.8 ± 1.98*
Pain	4 (66.6%)	8 (88.8%)	7(70%)
Nausea	1	1	1
vomiting	1	-	1
Bleeding	-	2	-
Fever	-	-	1
Diarrhoea	1	-	-
No side effects	2	1	4
Acceptability	1 (16.6%)	5 (55.5%)	7(70%)

* p value >0.05, not significant, **p value <0.05, significant; unpaired student's t test done between vaginal and sublingual misoprostol 400 µg; unpaired student's t test done between vaginal and sublingual misoprostol 200 µg.

As shown in above tables, in primi, the onset of bleeding was earlier in sublingual 400 µg group than in others. There is no significant difference between the vaginal and sublingual 200 µg groups in onset of the bleeding. Sublingual misoprostol 400 µg causing more cervical dilatation than others. Side effects were more in sublingual 400 µg group than others. 70% of the women in sublingual misoprostol 200 µg group accepted the sublingual route.

Table 11: Comparison of Various Parameters in Second Gravid Women:

Parameters	Vaginal	Sublingual 400µg	Sublingual 200µg
No. of patients	11	6	14
Age in yrs Mean ± SD	25.18 ± 3.25	26.33 ± 3.14	25.61 ± 4.05
GA Mean ± SD in wks	8.18 ± 1.83	8 ± 2.19	9.5 ± 1.78
Onset of bleeding time Mean ± SD hrs	2.63 ± 0.67	1.8 ± 2.12*	3.30 ± 0.75**
Hegar's dilator No	12.54 ± 2.01	13 ± 3.52*	11.14 ± 1.70**
Pain	6 (54.5%)	5 (83.3%)	9 (64.2%)
Nausea	4	1	5
vomiting	4	-	-
Bleeding	1	-	-
Fever	-	-	1
Diarrhoea	1	-	-
No side effects	2	1	3
Acceptability	6 (54.5%)	4 (66.6%)	9 (64.2%)

*p value > 0.05, not significant, ** p value < 0.05, significant. unpaired student's t test done between vaginal and sublingual misoprostol 400 µg; unpaired student's t test done between vaginal and sublingual misoprostol 200 µg.

As shown in above table in women with second gravida, there is no significance between between vaginal and sublingual 400 µg in onset of bleeding and cervical dilatation (p > 0.05). There is significant difference between vaginal and sublingual 200 µg group in cervical dilatation and onset of bleeding. The side effects were more in women with sublingual misoprostol 400 µg than other groups. 66.6% of the women in sublingual misoprostol 400 µg accepted the sublingual route and willing to administer in future.

Table 12: Comparison of Various Parameters in Third Gravid Women

Parameters	Vaginal	Sublingual 400µg	Sublingual 200µg
No. of patients	17	14	9
Age in yrs Mean ± SD	25.9 ± 4.23	28.07 ± 5.04	26 ± 4.55
GA Mean ± SD in wks	7.94 ± 1.85	7.92 ± 1.89	7.55 ± 1.29
Onset of bleeding time Mean ± SD hrs	2.31 ± 0.60	2.15 ± 0.98*	2.87 ± 0.83*
Hegar's dilator No	12.58 ± 1.69	12.71 ± 2.30*	11.77 ± 1.56*
Pain	8 (47%)	8 (57.1%)	5 (55.5%)
Nausea	2	3	1
vomiting	2	1	-
Bleeding	1	1	-
Fever	-	-	-
Diarrhoea	1	2	-
No side effects	6	5	4
Acceptability	8 (47%)	7 (50%)	8 (88.8%)

*p value > 0.05, not significant, unpaired students t test done in vaginal and sublingual 400 µg group

As shown in above tables, in third gravida, there is no significant difference between the vaginal, sublingual 400 µg group and sublingual 200 µg groups in onset of the bleeding and cervical dilatation. Side effects were more in sublingual 400 µg group than others

7. Discussion

Unsafe abortion is a major cause of mortality among women in India, accounts for approximately 16% of maternal deaths. For first trimester abortion both medical and surgical methods are available. There has been a constant endeavour to make abortion safer and accessible to women. Although the idea of using medication into induce abortion dates back centuries, medically proven regimens are available only in the last 50 yrs.

In 1950 folic acid antagonist, "aminopterin" was used orally to induce medical abortion in women at less than three months of gestation. As it is associated with severe adverse effects it is no more in use.

In 1970s the researchers found that natural prostaglandins PGE2 and PGF2 were effective in inducing abortion when administered intra vaginally or intra cervically.

In 1982, Erienne - Ernili Baulieu discovered and developed an antiprogesterin, mifepristone (RU486). Mifepristone only therapy for termination of early pregnancy was evaluated initially in clinical studies with a success rate of 50 - 86%.

Later several studies have evaluated the efficacy of mifepristone and prostaglandin combination in terminating early pregnancy in women with gestational age of 49 - 63 days.

However mifepristone is expensive and is not available in many developing countries. Therefore an effective misoprostol alone regimen is important for women who want the medical abortion in these countries. A misoprostol alone regimen will be considered effective if the complete abortion rate reaches 90%.

WHO conducted various trials for medical termination of pregnancy by using combination of mifepristone & misoprostol. In all trials misoprostol 800 µg is administered vaginally. But the exact dose required for cervical ripening is not clear. In the trials they compared the efficacy of the mifepristone 200mg and mifepristone 600 mg. In other 2 studies conducted by WHO in 2004, misoprostol vaginal administration was more efficacious than oral administration.¹⁵

Surgical method is the safe and effective method for first trimester abortion. Among the various surgical methods available vacuum aspiration is a commonly used method. Cervical dilatation before the first trimester abortion facilitates the operative procedure ease and decreases the risk of pain and duration of procedure. Cervical priming before the procedure reduces the risk of cervical injury and uterine perforation associated with mechanical dilatation.

For cervical ripening previously laminaria tent, gemeprost and PGE2 gel were used. Nowadays misoprostol, a synthetic PGE1 analogue is used because of short half life, less side effects, less cervical injuries, minimal intraoperative blood loss, stable at room temperature and easy availability in various dosage forms. Misoprostol can be given by oral,

buccal, sublingual, intra vaginal and intra mg et l., done pharmacokinetics of different routes of misoprostol in women came for first trimester abortion. The patients were given 400 µg of misoprostol through sublingual, oral and vaginal routes. The serum peak concentration and time to reach peak concentration was highest in sublingual group. The area under misoprostanoic acid concentration versus time curve is significantly higher in sublingual group.¹⁶

According to Rebecca Allen et al., the effective regimens for cervical ripening in first trimester abortion are 400 µg misoprostol administered vaginally 3 - 4 hrs before the procedure, 400 µg misoprostol orally 8 to 12 hrs before procedure or 400 µg misoprostol given sublingually 2 to 4 hrs prior to suction evacuation. Compared to oral route, vaginal route is more effective and is associated with fewer side effects. The sublingual route is more effective than oral or equally effective with vaginal administration. But sublingual administration is associated with side effects more than oral or vaginal administration.¹⁷

The present study was conducted in 120 patients, admitted for first trimester abortion. The patients were randomized and divided into 3 groups, 40 each. In group 1 the patients were given misoprostol 400 µg vaginally. In group 2 the patients were instructed to keep misoprostol 400 µg sublingually. In group 3 the patients were instructed to keep misoprostol tablet 200 µg sublingually. Suction evacuation was done after 5 hrs of administration. During the procedure cervical dilatation was measured with Hegar's dilator number easily passes through the cervical os. The efficacy of the drug is compared in 3 drugs in terms of cervical dilatation. Onset of bleeding, side effects and acceptability of the dose regimen were assessed.

The following parameters discussed here are:

- 1) Routes of drug administration
- 2) Age distribution
- 3) Distribution according to parity
- 4) Distribution according to gestational age
- 5) Onset of bleeding
- 6) Induction abortion interval
- 7) Cervical dilatation
- 8) Side effects
- 9) Acceptability of the regimen

1) Routes of Drug Administration

The present is supported by studies done by Vimala et al., Parneeth et al., Parveen et al. Vimala et al., done a comparative study of efficacy of sublingual misoprostol 200 µg and sublingual misoprostol 400 µg in first trimester abortion. Both regimens have same efficacy but side effects were less in sublingual 200 µg group.⁴

Parveen et al., compared the efficacy of sublingual, oral and vaginally administered 400 µg of misoprostol. With sublingual misoprostol cervical dilatation was sufficient and duration of operation procedure is less.⁵

Parneet Kaur et al., compared sublingual misoprostol 400 µg with oral misoprostol 400 µg in first trimester abortion. According to their study sublingual is effective for cervical priming before suction evacuation.¹⁸

2) Age Distribution

In the present study among the total 120 patients, the mean age in vaginal group is 25.475 ± 4.20 yrs. The mean age in sublingual 400 µg group is 26.37 ± 4.72 yrs. The mean age in sublingual 200 µg is 25.65 ± 4.95 yrs. p value is 0.66 calculated by ANOVA which is not significant. Similar results were obtained by Shagufta Parveen et al., who compared the efficacy of sublingual, oral, vaginal misoprostol 400 µg in first trimester abortion. (p value 0.71, not significant).⁵

Similar studies done by Sharma Monika et al.,³ (study group mean age 24.77 ± 7.18 yrs, control group 24.69 ± 4.17 yrs, p value 0.91), Parneet Kaur et al (sublingual group 29.78 ± 4.03 yrs, vaginal group 29.84 ± 3.61 yrs, p value 0.93)¹⁸

3) According to Parity

In present study in vaginal group, third gravid patients were more (42.5%), in patients received sublingual misoprostol 400 µg 35% patients were third gravid and 22.5% patients were primi. In patients received sublingual misoprostol 200 µg 35% patients were second gravid, 25% patients were primi and 22.5% were in third gravida.

4) According to Gestational Age

In the present study the mean gestational age in vaginal group is 7.9 ± 1.80 wks, mean gestational age in sublingual 400 µg group is 7.7 ± 2.04 wks and mean gestational age in sublingual 200 µg is 8.82 ± 2.06 wks.

Similar results were obtained by Sharma Monika et al.,³ mean gestational age in study group is 7.06 ± 1.40 wks and in control group is 7 ± 1.7 wks with p value 0.77, which is not significant.

The present study supported by Saxena et al¹⁸, mean gestational age in sublingual group is 7.9 ± 2.1 wks and in vaginal group is 8.0 ± 1.8 wks, with p value 0.41 which is not significant.

Parneet et al., obtained similar results with mean gestational age in sublingual group is 7.76 ± 1.37 wks and in vaginal group is 7.60 ± 1.27 wks, with p value 0.60, which is not significant.¹⁸

5) Onset of Bleeding

In present study, the onset of bleeding was earlier in patients received sublingual misoprostol 400 µg and late in patients received sublingual 200 µg. The mean time for onset of bleeding in vaginal group is 2.62 ± 0.72 hrs. In sublingual 400 µg group is 2.18 ± 1.15 hrs, and in sublingual 200 µg is 3.11 ± 0.73 hrs. p value is 0.20 (p > 0.05) is not significant. When compared to vaginal, sublingual misoprostol 400 µg is more effective with p value is 0.04 (p < 0.05, significant, unpaired student t test). When compared to sublingual 200 µg, vaginal misoprostol is more effective with p value 0.003 (p < 0.05, very significant, unpaired student's t test). When compared to sublingual 200 µg, sublingual 400 µg is extremely effective in onset of bleeding with p value 0.0001 (p < 0.05, very significant, unpaired student's t test).

In primi who received sublingual misoprostol 400 µg is more effective than vaginal and sublingual 200 µg in

causing onset of abortion (p value 0.04). There is no significant difference between vaginal and sublingual 200 µg groups (p value is 0.56, unpaired student's t test).

In patients with second gravida there is no difference between vaginal and sublingual 400 µg groups (p value 0.22, unpaired student's t test). Both vaginal and sublingual 400 µg groups are more effective than sublingual 200 µg in starting the abortion process (p value 0.02, unpaired student's t test).

In patients with third gravida there is no significant difference between vaginal and sublingual 400 µg groups (p value 0.58, unpaired student's t test). Similarly there is no significant difference between sublingual 400 µg and sublingual 200 µg groups (p value 0.08, unpaired student's t test). Similarly there is no significant difference in starting the process of abortion between vaginal and sublingual 200 µg groups (p value 0.06, unpaired student's t test).

6) Induction, Abortion Interval

In present study the patients were instructed to take the tablet sublingually in early morning on the day of procedure. The patients who received vaginal misoprostol, the tablet was inserted in posterior fornix of vagina early morning on the day of suction evacuation. After 5 hrs of drug administration suction evacuation was done in operation theatre.

Several studies like Vimala et al.,⁴ Sharma Monika et al.,³ Shagfta Parveen et al.,⁵ Parneet Kaur et al.,¹⁸ Ritu Agarwal et al.,¹⁹ and Saxena et al.,²⁰ done suction evacuation after 3 - 4 hrs after the drug administration.

Nusrat Shah et al., compared the efficacy of sublingual and vaginal misoprostol in first trimester abortion. The patients received 400 µg misoprostol either sublingually or vaginally every 3 hrs upto maximum of 5 doses.²¹

Similarly Rupali Modak et al., conducted a comparative study of efficacy of sublingual and vaginal misoprostol in second trimester abortion. The patients were administered 400 µg misoprostol were given either sublingual or vaginal and dose repeated for every 3 hrs upto 5 doses.²²

7) Cervical Dilatation

In present study cervical dilatation was measured in terms of size of Hegar's dilator easily passes through the cervical os without any resistance. In patients in vaginal group the mean size of Hegar's dilator passed is 12.4 ± 2.03 . In patients with sublingual 400 µg is 12.85 ± 2.61 . In patients who received sublingual 200 µg of misoprostol, the mean size of Hegar's dilator easily passed is 11.25 ± 1.90 . Among the three dose regimens sublingual misoprostol 400 µg is causes more dilatation than vaginal and sublingual 200 µg misoprostol (p value 0.005, significant, ANOVA). There is no significant difference between effect of vaginal and sublingual misoprostol 400 µg (p value 0.39, unpaired student's t test).

Similar results obtained by Vimala et al.⁴ According to them, preoperative cervical dilatation was achieved better with sublingual 400 µg (70%) than sublingual 200 µg (20%).

The present study is supported by a comparative study done by Parneet Kaur et al.¹⁸ In this study they compared the cervical dilatation in terms of size of the Hegar's dilator. It is more in sublingual group than vaginal group with p value < 0.05.

Other studies done by Sharma Monika et al.,³ showed that sublingual misoprostol causes cervical priming faster.

Similar results were obtained by Shagfta Parveen et al.⁵ They measured cervical dilatation in mm and it is more in sublingual group than oral and vaginal groups (p value < 0.05). 74% cervical ripening occurs with sublingual misoprostol than oral and vaginal groups.

In present study in primi patients there is no significant difference in cervical dilatation with vaginal, sublingual 400 µg and sublingual 200 µg with p value > 0.05 (done by unpaired student's t test). In patients with second gravida there is no significant difference between vaginal and sublingual 400 µg and sublingual 200 µg (p value >0.05). In patients with third gravida there is no significant difference between the three dose regimens.

There is no significant difference in efficacy of vaginal and sublingual 400 µg and sublingual 200 µg in cervical dilatation.

8) Side Effects

A) Pain

In present study most of the patients experienced abdominal pain and lower back pain in patients taking misoprostol. In patients received vaginal misoprostol 21 patients (52.5%), in patients with sublingual misoprostol 400 µg 28 patients (70%) and in patients with sublingual misoprostol 200 µg 24 patients (60%) experienced lower back pain. NSAIDS were given to decrease the pain.

In present study in 88.8% of the patients with primi, pain was experienced more in patients with sublingual misoprostol 400 µg. In patients with vaginal misoprostol 66.6% and in patients with sublingual misoprostol 200 µg it is 70%. In patients with second gravida pain was more in patients taken sublingual misoprostol 400 µg (83.3%) than in sublingual misoprostol 200 µg (74.2%) and in vaginal group (33.3%). In patients with third gravida pain was experienced more in sublingual 400 µg group (57.1%) than in sublingual 200 µg (55.5%) and vaginal group (47%).

Similar results were obtained by Parneet Kaur et al.¹⁸ According to their study pain was experienced more in sublingual group than in vaginal group (p value > 0.05).

The present study is also supported by Saxena et al. In their study pain was more in sublingual than in oral group (p value < 0.05).²⁰ According to Nalini Sharma et al., pain was more in sublingual group than in vaginal group.²³ According to Vimala et al., pain was more in patients received 400 µg than in patients received 200 µg of misoprostol sublingually.⁴

The present study is contradicted by Shagufta Parveen et al.⁵. According to their study pain was less in sublingual group than in vaginal and oral groups. Similarly in a study done by Sharma monika et al., indicates that pain was less in patients received sublingual misoprostol than in control groups (p value < 0.04, significant).³

B) Nausea

In present study nausea was experienced by patients in all groups. 10 patients each in vaginal group and in patients with sublingual misoprostol 200 µg and 6 patients in sublingual misoprostol 400 µg group experienced nausea. In primi more patients experienced nausea in patients received sublingual misoprostol 200 µg. In patients with second gravida nausea was more in patients with sublingual misoprostol 400 µg. In patients with third gravida nausea was more in sublingual 400 µg group than other groups.

According to Saxena et al.,²⁰ nausea was more common in sublingual group than in oral group. According to Nalini Sharma et al.,²³ nausea was more in vaginal group than in sublingual group. Similar results were done by Devendra Singh et al.,²⁴ who done the comparison between oral and sublingual misoprostol. According to their study nausea was more in patients received sublingual misoprostol.

C) Vomiting

In present study vomiting is more in patients with sublingual 400 µg group than other groups. As nausea and vomitings are self limiting they did not required any specific treatment. Misoprostol when administrated by sublingual route directly enters the systemic circulation and is responsible for side effects like nausea and vomiting. The present study is supported by Vimala et al.,⁴, Sharma Monika et al.³, Rupali Modak et al.,²² and Oi Shan Tang et al.¹⁶ In all the studies p value is > 0.05, so it is not significant between the different dose regimens like sublingual and vaginal groups.

D) Fever

Misoprostol is a Prostaglandin E1 analogue. Prostaglandins are naturally released in response to tissue damage and cause fever. Prostaglandin E also acts on the central thermoregulatory centres, which causes nausea and vomiting. As sublingual misoprostol reaches its plasma concentration early, the side effects were more in patients with sublingual misoprostol. In present study fever is present in patients received vaginal misoprostol and in patients received sublingual misoprostol 400 µg.

E) Diarrhoea

Misoprostol is a prostaglandin PGE1 analogue. Prostaglandins inhibits gastric and pancreatic secretions and markedly increases intestinal motility, chloride and water secretion resulting in diarrhoea. Fluid and electrolyte balance was necessary to prevent dehydration.

In present study diarrhoea was present in vaginal group (3 patients), and also in sublingual 400 µg group (2 patients) but statistically there is no significance (p value > 0.05).

Sharma Monika et al.,³ obtained similar results that diarrhoea is more common in sublingual group than vaginal

group. In contrast to present study there were no patients reported diarrhoea in a study by Parneet et al.¹⁸

F) Bleeding

Misoprostol has direct effect on uterus and cervix causing uterine hyperstimulation and bleeding. Prostaglandin PGE1 has vasodilating effects. Sublingual misoprostol does not have any direct effect on uterus as it directly enters the systemic circulation. Therefore uterus hyperstimulation is less with sublingual misoprostol than vaginally administered misoprostol.

In present study heavy bleeding was seen in 2 patients in vaginal misoprostol group and 4 patients in sublingual group who received 400 µg of misoprostol and no one experienced heavy bleeding in sublingual misoprostol 200 µg group (p value is < 0.05, which is not significant). As the parity increases risk of bleeding also increases.

According to Vimala et al.,⁴ bleeding was more common in sublingual misoprostol 400 µg than in sublingual misoprostol 200 µg group. According to Sharma Monika et al.,³ the vaginal bleeding and amount of blood loss is more in patients taken sublingual misoprostol (p value < 0.05, significant).

Parneet Kaur¹⁸ et al., compared sublingual and vaginal misoprostol in first trimester abortion. In their study bleeding was more in sublingual group than in vaginal group.

The present study is also supported by Areerat Sonsanoh et al., who compared sublingual and vaginal misoprostol for cervical priming. The bleeding was more in sublingual group in their study.²⁵

According to Kevin et al.,²⁶ the bleeding was more in multigravida than in primigravida patients. Oral misoprostol 200 µg when compared to 400 µg group results in less preoperative vaginal bleeding and clinically significant change in cervical dilatation.

Abdul Khader et al.,²⁷ compared the sublingual misoprostol to vaginal placebo in first trimester abortion contradicting the present study by their study results. According to them there is no significant difference in the bleeding and mean operation time.

9) Acceptability of the Regimen

In present study sublingual route (70%) is more acceptable than vaginal route (60%). In primi, more patients accepted the sublingual route (70%) than vaginal route. In sublingual group more no. of the patients preferred sublingual misoprostol 200 µg than 400 µg. Similar results were obtained in second gravida and third gravida patients.

Most of the patients accepted sublingual route as it is easily administered and avoid unnecessary vaginal insertion of tablet. The tablet can be taken by patients themselves at home and they can come to hospital on the day of surgery. There is no need for prior hospital administration. Whereas for vaginal insertion the patients were administered day before the procedure and tablet should be inserted by the

doctor in early morning on the day of surgery. Most of the patients felt that sublingual route is easy and convenient. Many of the doctors also felt that sublingual route is easy as there is no need to admit and monitor the patient before the procedure.

Some of the patients felt that sublingual route is not convenient as the tablet is kept under the tongue and it should not be swallowed. The patients rejected the tablet because of its unpleasant taste.

Most of the patients preferred the sublingual 200 µg dose because there is only one tablet to be taken instead of two tablets for 400 µg dose, and there is no significant difference in their efficacy and side effects are lesser for less dose.

Similar results were obtained by Devendra Singh et al.,²⁴ who compared the sublingual and oral route for abortion, sublingual route is more accepted than oral route as there are less side effect (p value is <0.05, significant).

The present study also supported by Nalini Sharma et al.,²³ and Vimala et al.,⁴ who found sublingual route is more acceptable and convenient to take than vaginal tablet. According to Premila et al.,²⁸ there was no significant difference in patient acceptability in relation to primig agent between the oral and sublingual routes. In a study done by Ingrid Saav²⁹ patients preferred the vaginal route because of unpleasant taste of sublingual misoprostol. Vaginal treatment was also perceived as quicker to administer (p value < 0.05, significant).

Strengths and weaknesses of the study:

The present study was conducted in patients who require suction evacuation for first trimester abortion. We used misoprostol as a cervical priming agent in three different regimens, vaginally 400 µg, sublingual 400 µg and sublingual 200 µg regimens. As misoprostol is cheap and easily available in government setup it is widely used for cervical priming. As patients preferred sublingual route it can be widely used. Most of the patients preferred sublingual misoprostol 200 µg than 400 µg as there are less side effects.

In present study patient compliance is not checked. Even though the objective parameters are present patients can be asked to return empty blister packets so that we can know how many tablets they have taken. If the packets are empty, patients should be enquired about by what time they have taken the tablet. Pain, nausea, vomitings and bleeding were the main side effects with misoprostol.

Sample size is also very small. Further studies should be done with respect to dosage, preference according to parity and dosage regimens in patients with previous caesarean section.

8. Summary

In present study 120 women requesting termination of pregnancy in the first trimester (<12 wks) were studied. The patients were divided randomly into 3 groups. 40 women received 400 µg of misoprostol vaginally and 40 women

received 400 µg of misoprostol sublingually and another 40 women received 200 µg of misoprostol sublingually.

Among them 40% of the patients in vaginal group were in 26 - 30 yrs and 35% of the patients in vaginal group were in 20 - 25yrs. In sublingual 400 µg group 37.5% of the patients were in 20 - 25 yrs and 27.5% patients were in 26 - 30 yrs. In sublingual 200 µg group 42.5% of the patients were in 20 - 25 yrs of age and 35% of the patients were in 26 - 30 yrs of age.

Most of the patients in vaginal group were in third gravida in vaginal group and in sublingual 400 µg groups. In sublingual 200 µg the majority of them were in second gravida.

Majority of the patients in vaginal group were in 6 - 9 wks of gestational age with mean GA is 7.9 ± 1.80 wks. In sublingual 400 µg group many of them comes under 6 - 9 wks of gestation with mean age of 7.7 ± 2.04 wks. In sublingual 200 µg group majority of them comes under 6 - 9 wks of gestation with mean 8.82 ± 2.06 wks of gestational age.

Majority of the patients in vaginal group had onset of bleeding in 2 - 3 hrs with mean time 2.62 ± 0.72 hrs. In sublingual 400 µg group, in 50 % of the patients bleeding started within 2 hrs of drug administration with mean time is 2.18 ± 1.15 hrs. In sublingual 200 µg, in majority of the patients bleeding started in 3 hrs with mean 3.11 ± 0.73 hrs after drug administration. p value > 0.05, the study is not significant that means all three regimens have similar efficacy in initiating the process of abortion.

In 85% of the patients in vaginal group cervical dilatation was satisfactory with no need for mechanical dilatation. In sublingual groups the cervical dilatation was satisfactory in 75% of the patients. This difference is statistically not significant (p value >0.05). The efficacy of the drug to cause cervical dilatation was similar whether the drug is given in vaginal or sublingual route.

The mean size of the Hegar's dilator easily passes through the cervical os without any resistant is 12.4 ± 2.03 in vaginal group, in sublingual 400 µg group it is 12.85 ± 2.67 and in sublingual 200 µg group is 11.25 ± 1.90 . Among the three dose regimens sublingual misoprostol 400 µg is causes more dilatation than vaginal and sublingual 200 µg misoprostol (p value > 0.05, calculated by ANOVA and unpaired student's t test was done between the groups).

The side effects were more in patients with vaginal and sublingual 400 µg than in sublingual 200 µg group. Majority of the persons experienced pain in sublingual 400 µg group than in vaginal and sublingual 200 µg. Bleeding also more in sublingual 400 µg group than other groups. Majority of the patients (30%) in sublingual 200 µg does not experienced any side effects.

60% of the patients in vaginal group accepted the vaginal route because of unpleasant taste of misoprostol. 65% in sublingual 400 µg and 70% in sublingual group preferred sublingual route as it is easy to administer at home and effect is satisfactory for suction evacuation. Majority of the

patients in sublingual group found that sublingual route is convenient for them as there is no need for prior hospital administration. Most of the patients willing to take sublingual misoprostol in future.

In primi, there is no significant difference between efficacy of the vaginal and sublingual misoprostol 400 µg in causing cervical dilatation and onset of bleeding. Whereas sublingual misoprostol 200 µg is less efficacious than others in causing cervical ripening. Side effects were more in patients with sublingual misoprostol 400 µg.

In patients with second gravida, there is no significant difference between vaginal and sublingual misoprostol 200 µg in causing cervical dilatation and initiating bleeding. Whereas sublingual misoprostol 400 µg was more efficacious than others in causing cervical dilatation. Side effects were more in sublingual misoprostol 400 µg group.

In patients with third gravida, there is no significant difference between efficacy of the vaginal misoprostol 400 µg, sublingual misoprostol 400 µg and sublingual misoprostol 200 µg. Side effects were less in sublingual misoprostol 200 µg group.

9. Conclusion

As misoprostol use in obstetrics is off label use, its efficacy in cervical priming should be evaluated further. There is no difference in efficacy of vaginal and sublingual misoprostol 400 µg and because of easy availability and patient's acceptability sublingual route is preferred. When sublingual misoprostol 400 µg is compared with sublingual misoprostol 200 µg, there is no significant difference in initiating the process of abortion but cervical dilatation was more with sublingual misoprostol 400 µg. Side effects are also more with sublingual misoprostol 400 µg. As parity increases like in third gravida there is no significant difference in efficacy of sublingual misoprostol 400 µg and sublingual misoprostol 200 µg. So lesser dose can be preferred as it is associated with less side effects. Usage of misoprostol in obstetrics can be evaluated for further studies. Guidelines for usage of misoprostol in abortion should be given in terms of route of administration, dosage, time of administration, induction abortion interval and management of side effects.

References

- [1] Williams Obstetrics 24th edition, abortion 350 - 376.
- [2] Grimes DA, Schulz KF, Cates WJ. Prevention of Uterine perforation during curettage abortion. JAMA 1984; 2108-11.
- [3] Sharma Monika. Sublingual misoprostol for cervical ripening in surgical first trimester pregnancy termination: The Journal of Obstetrics and Gynecology of India (September - October 2011) 61 (5):531-533.
- [4] Vimala N, Mittal S, Kumar S. Sublingual misoprostol before first trimester abortion: A comparative study using two dose regimens. Indian J Med Sci 2004;58:54-6.
- [5] Parveen S, Khateeb ZA, Mufti SM, Shah MA, Tandon VR, Hakak S, Singh Z, Yasmeen S, Mir SA, Tabasum R, Jan N. Comparison of sublingual, vaginal and oral

- misoprostol in cervical ripening for first trimester abortion. Indian J Pharmacol 2011; 43: 172-175.
- [6] Vimala N, Mittal S, Kumar S. Sublingual misoprostol for pre-abortion cervical ripening in first trimester pregnancy termination. Contraception 2002; 76:295-7.
- [7] DC Dutta' s Textbook of Obstetrics, 7th edition, Hemorrhage in Early Pregnancy, 158 - 199.
- [8] Comparison of Sublingual and Vaginal Misoprostol for Termination of Early Pregnancy Failure: A Randomized Controlled Trial, Areerat Sonsanoh MD, Teerapat Chullapram MD. Thai Journal of Obstetrics and Gynaecology, July 2014, Vol. 22, pp. 128-136.
- [9] Elati A, Weeks A. The use of misoprostol in obstetrics and gynaecology. BJOG 2009;116 (Suppl. 1):61-69.
- [10] Matrinale, 36th edition, Obstetric drugs, Misoprostol, 2013- 2015.
- [11] Cervical preparation for first trimester surgical abortion (Review) Kapp N, Lohr PA, Ngo TD, Hayes JL; The Cochrane Collaboration and published in The Cochrane Library 2010, Issue 3.
- [12] Medical management of first trimester abortion, Clinical management guidelines for obstetrician - gynaecologist, practice bulletin, The American College of Obstetricians and Gynaecologists, Number 143, March, 2014.
- [13] Goodman & Gillman The Pharmacological Basis Of Therapeutics, 12th edition, Pharmacotherapy of Gastric Acidity, Peptic Ulcers, and Gastroesophageal Reflux Disease , Page No1315
- [14] Pfizer (September 2006). "Cytotec US Prescribing Information" (PDF). Retrieved 2007-03-15.
- [15] Grossman D. Medical methods for first trimester abortion: RHL commentary (last revised: 3 September 2004). The WHO Reproductive Health Library; Geneva: World Health Organization.
- [16] Oishi Tang, Horst Schweer, H. W. Seyberth, Sharon W.H.Lee, Pak Chung Ho, Pharmacokinetics of different routes of administration of misoprostol; Human reproduction, Volume 17, No. 2, Page no 332 - 336, 2002
- [17] Rebecca Allen, MD, MPH, Barbara M. O'Brien, MD: Uses of Misoprostol in Obstetrics and Gynaecology: Reviews In Obstetrics & Gynaecology Vol. 2 No. 3; 2009; 159-168.
- [18] Parneet Kaur, Manjeet Kaur, Balwinder Kaur, Manjot Kaur Mohi; Khushpreet Kaur, Preeti Jindal, Comparative Study of Sublingual versus Vaginal Misoprostol on Preoperative Cervical Priming in First Trimester Abortion, Indian Journal of Clinical Practice, Vol. 23, No. 9 February 2013, page no 543 - 546.
- [19] Ritu Agarwal, Comparison of 800 Mcg Oral and Vaginal Misoprostol Prior to First Trimester Surgical Abortion: A Hospital Based Clinical Study, International Journal of Scientific Research, Volume 4, Issue 7, page no. 216 - 218.
- [20] Pikee Saxena, Sudha Salhan and Nivedita Sarada; Comparison between the sublingual and oral route of misoprostol for pre-abortion cervical priming in first trimester abortions; Human Reproduction , 2004, Vol.19, No.1 pp. 77 - 80.
- [21] Nusrat Shah, Syed Iqbal Azam, Nusrat Hasan Khan, Sublingual versus vaginal misoprostol in the

- management of missed miscarriage; JPMA Vol. 60, No. 2, February 2010, Page no. 113 - 116.
- [22] Modak, R., Biswas, D.K., Ghosh, A., Pal, A. and Mandal, T.K. (2014) Comparative Study of Sublingual and Vaginal Misoprostol in Second Trimester Induced Abortion. Open Journal of Obstetrics and Gynecology, 4, 751-756.
- [23] Nalini Sharma, JK Goel, Randomized Controlled Study Comparing Sublingual to Vaginal Misoprostol for Cervical Priming Prior to Surgical Termination of Pregnancy in First Trimester; Indian Journal of Clinical Practice, Vol. 25, No. 7, December 2014; Page no. 671 - 674.
- [24] Kushwah DS, Kushwah B, Salman MT, Verma VK. Acceptability and safety profile of oral and sublingual misoprostol for uterine evacuation following early fetal demise. Indian J Pharmacol 2011;43:306-10
- [25] Areerat Sonsanoh MD, Teerapat Chullapram MD; Comparison of Sublingual and Vaginal Misoprostol for Termination of Early Pregnancy Failure: A Randomized Controlled Trial; Thai Journal of Obstetrics and Gynaecology July 2014, Vol. 22, pp. 128-136
- [26] Kevin S Oppegaard, Mikael Abdulnoor, The use of oral misoprostol for pre abortion cervical priming, a randomised controlled trial of 400 versus 200 µg in first trimester pregnancies; BJOG, February 2004, Volume 111, Page no 154 - 159
- [27] Bahaa Abdel Kader Fateen, Noha Homed Rabei and Waleed Mohamed Mostafa, Sublingual versus Vaginal Misoprostol for Preoperative Cervical Priming in First Trimester Missed, Nature and Science 2013;11(8) Page No 72 - 77
- [28] Premila W. Ashoka, Haitham Hamodaa, Fatima Nathanib, Gillian M.M. Flett, Allan Templeton, Randomised controlled study comparing oral and vaginal misoprostol for cervical priming prior to surgical termination of pregnancy, BJOG: an International Journal of Obstetrics and Gynaecology, December 2003, Vol. 110, pp. 1057-1061
- [29] Ingrid Saav, Helena Kopp Kallner, Christian Fiala and Kristina Gemzell-Danielsson; Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 h prior to surgical abortion: a double-blinded RCT; Human Reproduction, 2015, Vol.0, No.0 page no. 1-9.
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