



Comparative study between sublingual misoprostol and vaginal misoprostol for cervical priming prior to surgical termination of pregnancy in first trimester pregnancy.

Shashi Bala Singh

Arshi Perween

ABSTRACT

Introduction: Suction and evacuation had been standard method for surgical termination of first trimester pregnancy. Cervical priming before suction and evacuation is a critical step to reduce risk of cervical injury, uterine perforation, haemorrhage and incomplete evacuation associated with forceful mechanical dilatation. Misoprostol had been used as a cervical priming agent since long time either by oral, vaginal or sublingual route.

Aims and objectives: To compare the effectiveness, tolerability and acceptability of sublingual misoprostol compared to vaginal misoprostol as a cervical priming agent prior to first trimester vacuum aspiration.

Material and methods: In this randomised clinical study, a total of 100 women with the gestational age between 6 and 12 weeks were selected randomly and sequentially allocated into two groups of 50 each. Selected women were administered 400 µg of misoprostol 3 hours before suction and evacuation either by sublingual or vaginal route. The degree of cervical dilatation was the primary outcome to be observed and secondary outcomes being total duration of procedure, intra-operative blood loss and pain. The patient's tolerability was noted on the basis of side effects.

Results: Demographically, both groups were similar. There was no significant difference in mean cervical dilatation (sublingual: 8.40 ± 1.17mm; vaginal: 8.03 ± 1.45mm), mean blood loss (sublingual: 43.36±6.28 ml; vaginal: 41.8 ± 6.43 ml) and duration for the procedure (sublingual: 8.31±2.83 minutes; vaginal: 7.95 ± 2.63 minutes). Pre-operative side effects were also similar.

Conclusion: Both sublingual and vaginal are effective route of misoprostol administration for cervical priming prior. Sublingual misoprostol has advantage of being more convenient to administer with high patient and staff acceptability.

KEYWORDS : Cervical priming, misoprostol, sublingual, vaginal.

Introduction

India is second most populous country. Lack of awareness about contraceptive measures, moreover limited access to effective contraception have made M.T.P. an integral part of natural population control programme. The ideal technique for termination should be painless, safe and accompanied by minimal side effects. For first trimester abortion, surgical dilatation of the cervix followed by suction and evacuation under sedation or anaesthesia is the most popular method. It is an effective method with a success rate of >95%. However it is associated with morbidities - major being in < 1% and minor being in 10% of women²

Cervical priming is a critical step before suction and evacuation. Forceful mechanical dilatation in non primed patient is associated with several complications such as incomplete evacuation of the uterine cavity, excessive bleeding due to retained products, damage to the cervix in the form of cervical laceration or cervical stenosis and incompetence with possible negative impacts on future pregnancies and uterine perforation⁵.

Various method of cervical ripening includes laminaria tent, mifepristone and prostaglandins analogue^{6,7}. In the present scenario suction and evacuation is often performed as day care surgery. Laminaria tent has to be inserted for 12 hours and mifepristone has to be taken 36-48 hours to have adequate cervical priming effect. Therefore they are less convenient for day care patient. Prostaglandins used are Gemeprost and Misoprost (both are prostaglandin E1 (PGE1) analogue). Gemeprost have been found to be more beneficial, because they are easy to administer and very effective but they are expensive and require refrigeration storage and are associated with high gastrointestinal effects like nausea, vomiting and diarrhoea.

Misoprostol is an orally active, synthetic 15-hydroxy 16 hydroxy 16-methyl analogue of naturally occurring prostaglandin E1 (PGE1) principally used for prevention of peptic ulcers⁸. Misoprostol has the advantage of easy availability, ease of administration by various routes, lower cost and stability at room temperature with few systemic side effects.

Previous studies have shown that its oral, vaginal and sublingual routes are effective in cervical priming^{7,9,10}. Ngai et al 1999 found that both oral and vaginal routes of administration were effective for cervical priming¹¹. Oral misoprostol has the advantage that patient can take medication at home prior to hospital admission, although oral misoprostol administered 12 hours prior to surgery for cervical priming has not been recommended because of the unpredictability of action of oral misoprostol¹². Recently it had been shown that oral administration of 400 µg misoprostol 3 hour before the vacuum aspiration is as effective as a similar regimen of vaginal misoprostol^{13,14,15}. However administration of oral drug with water 3 hours before operation may cause problems if the patient undergoes the operation under general anaesthesia.

Most commonly used method for cervical priming is vaginal application of 400 µg misoprostol 3 hour before the vacuum aspiration. But the disadvantage with cervical misoprostol is poor patient acceptability and is not suitable for a busy day care surgery admission clinic.

Misoprostol is absorbed through the vaginal mucosa in vaginal administration. The buccal mucosa, being very vascular should be able to serve the same purpose. The misoprostol tablet is very soluble in water and dissolves within 10-15 minutes when administered under tongue. Sublingual administration of misoprostol avoids the first pass metabolism effect via liver as in oral administration. Tang et al 2002a, in their pharmacokinetic study showed that sublingual misoprostol was more rapidly absorbed than oral or vaginal misoprostol¹⁶. The peak serum concentration after sublingual misoprostol and area under curve was also significantly higher than those after oral or vaginal misoprostol¹⁶. Sublingual misoprostol has the advantage of convenient to use, avoids painful vaginal administration and avoids the ingestion of water before anaesthesia.

It is the aim of this randomised study to assess the efficacy and patient acceptability of sublingual misoprostol and compare it with vaginal misoprostol for pre-operative cervical priming before surgical termination of pregnancy in first trimester.

Material and methods

It is a prospective randomised controlled study. The study comprised of 100 pregnant women with gestational age between 6 and 12 weeks, requesting legal termination of pregnancy from March 2015 to September 2016 in Rajendra Institute of Medical Sciences, Ranchi, and Jharkhand. Approval from the local ethical committee was taken and written informed consent was obtained from patients after explaining the study. Women aged > 16 years with period of gestation between 6 to 12 weeks were included in the study. Women with normal general and gynaecological history and physical examination were included in the study. Gestational age was calculated by last menstrual periods (LMP) and was confirmed by clinical examination or ultrasonographic examination. Exclusions criteria were women suffering from chronic diseases like hypertension, diabetes, asthma, haemoglobin <9 gm/dl, allergic to prostaglandins, with in situ intrauterine contraceptive device (IUCD) and previous lower segment caesarian section (LSCS).

The study comprised of two groups - sublingual misoprostol group and vaginal misoprostol group, containing 50 women in each groups. The patients were randomly allocated to both groups and the record was kept with the sister in-charge.

All the patients were admitted to the hospital in the morning of the operation. They were given 400 µg misoprostol by sublingual route or vaginal route (after wetting the tablet with water in order to increase the absorption through the vaginal route) 3 hours prior to the scheduled operation. The operating surgeon was unknown about the group to which the patient belonged.

The blood pressure, pulse rate and temperature were routinely recorded. Before operation all the patient were enquired about the preoperative side effects like abdominal pain graded from 0 to 3 (0 for no pain, 1 for mild pain, 2 for moderate pain that did not required treatment with analgesics and 3 for severe pain), nausea, vomiting, chills and fever and any vaginal bleeding was noted.

The operation was done under sedation. Intra-operatively we noted cervical dilatation before performing vacuum aspiration using Hegar's dilators. The largest Hegar's dilator passing through the internal os without resistance was the dilatation achieved. Paracervical block was given to the patient who did not achieve the cervical dilatation appropriate for the gestational age to reduce pain perception during the procedure. Suction evacuation was done by Karman's Cannula. At the end of the procedure, uterus was gently curetted by a curette.

The intra-operative blood loss, duration of surgery, intra-operative pain score and any other complications such as cervical laceration, uterine perforation were noted. Duration of surgery was measured from the start of dilatation until the end of procedure. Intra-operative blood loss measured as the volume of the uterine aspirate after sieving away the products of the conception and subtracting the amount of the liquor for the gestational age. The patient was kept under observation for 3 hours postoperatively before discharge from the hospital. Patients were followed on the OPD basis.

The primary study outcome measured was cervical dilatation before suction and evacuation, secondary outcomes being amount of blood loss during surgery and time taken for the procedure. Other factors were pain intensity, complications during the surgery, side effects of the misoprostol and acceptability of route of administration.

The data was recorded in mean ± standard deviation (SD). P< 0.05 was considered statistically significant. The chi square test was applied whenever applicable.

Results

Table No.1: Demographic characteristic of the 100 women who underwent surgical abortion.

Characteristics	Sublingual group	Vaginal group
Age in years(Mean)	27.4	27.18
Gestational age in weeks (Mean)	8.6	8.64
Parity (P ₀ to P ₃₅)	2.32	2.54

Table No.2: Preoperative side effects

Side effects	Sublingual group	Vaginal group
Nausea	14	08
Vomiting	06	02
Vaginal bleeding	Mild -12 16 Moderate -04 Heavy- 00	Mild -07 10 Moderate -03 Heavy- 00
Diarrhoea	05	02
Pain	Mild -12 20 Moderate -07 Severe -01	Mild -10 18 Moderate- 07 Severe -01
Fever	04	02
Passage of products of conception before operation	Nil	Nil

Table No.3: Intra operative Parameters

Parameters Observed	Sublingual group	Vaginal group	P value
Baseline cervical dilatation (mm)	8.40 ± 1.17	8.03 ± 1.45	P = 0.1634 (Not Significant)
Mean blood loss (ml)	43.36 ± 6.28	41.8 ± 6.43	P = 0.2227 (Not Significant)
Mean time taken (minutes)	8.31 ± 2.83	7.95 ± 2.63	P = 0.5115 (Not Significant)
Para-cervical block	3	7	

No significant difference was observed between the two treatment groups with respect to age, parity and gestational age (Table no.1).Table No.2 shows preoperatively 12 (24%) patient of the sublingual group had spotting or mild bleeding as compared to the 07 (14%) of the vaginal group 1-2 hours after ingestion of misoprostol and 4 (8%) patient of the sublingual group and 3(6%) patient of the vaginal group had moderate bleeding. 20 (40%) of sublingual group versus 18 (36%) of vaginal group complained of mild to moderate spasmodic pain. Nausea was complained by 14 (28%) patients of the sublingual group compared to the 8 (16%) patient of the vaginal group and vomiting was seen in 6 (12%) of the sublingual group and 2 (4%) of the vaginal group. In sublingual group 05(10%) patient had incidence of diarrhoea as compared to 02(4%) patient of the vaginal group. 4 (8%) of the patients in the sublingual group compared with the 2 (4%) of the patient in the vaginal group developed fever within 2-3 hours after administration of the misoprostol. None of the patient had heavy bleeding or passage of products of the conception through vagina during the waiting period.

Table No.3 shows the mean cervical diameter in the sublingual group was 8.40 ± 1.17 mm as compared to 8.03 ± 1.45 mm in the vaginal group and p value=0.1634 showing that there was no significant difference between the two group when we look at the mean cervical dilatation. The time taken for the procedure was also almost same in both group, 8.31 ± 2.83 minutes in sublingual group and 7.95 ± 2.63 minutes in vaginal group. The mean blood loss in the sublingual group was 43.36 ± 6.28 ml and 41.8 ± 6.43 ml in the vaginal group, P value=0.2227 showing that there was no significant difference between the two groups with respect to the total amount of the blood loss. 3 (6%) patient of the sublingual group and 7 (14%) patient of the vaginal group were given paracervical block for the mechanical dilatation, as the women had a cervical dilatation less than that required for that particular gestational age. No major complications occurred in either of the two groups. In 6 women out

of 50 in the vaginal group misoprostol tablet was partially absorbed after 3 hours of administration, in sublingual group tablet was absorbed in all women within 10- 15 minutes.

A higher patient acceptability of the sublingual routes as compared to vaginal route was noted. Reasons were that vaginal route requires the patient to report the hospital 3 hours prior to vacuum aspiration, while sublingual route was convenient and time saving.

Discussion

This study suggest the feasibility of the sublingual route of misoprostol administration for cervical priming prior to first trimester surgical abortion using vacuum aspiration as the commonly used method for the first trimester abortion.

Various routes of administration of misoprostol have been used for cervical priming in the first trimester. Both oral and vaginal routes were shown to be equally effective when given 3 hours before the vacuum aspiration. The vaginal route has been found to be more beneficial than oral route probably due to constant absorption leading to an accumulating plasma level with fewer gastrointestinal side effects^{8,12,17}. Vaginal absorption of misoprostol is inconsistent with large individual variation. Sometimes remnants of tablets can be obtained from the vagina hours after its administration. Therefore although used widely, vaginal route may not be the ideal route of administration for clinical practice.

On the other hand, misoprostol is rapidly absorbed through the vascular buccal mucosa completely within 10-15 minutes⁶. Sublingual misoprostol can avoid the uncomfortable vaginal application and oral intake of fluid before operation. Patient can take sublingual tablet at home thus reducing the time of hospital admission. Its clinical effectiveness in cervical priming was proven to be same as vaginal misoprostol for surgical abortion.

The present study observed cervical ripening effect of the misoprostol as the primary outcome. There was no significant difference in the mean cervical dilatation observed in two groups. Our result was consistent with the observation by various studies (Hamoda et al 2004¹⁸, Carbonell et al 2006¹⁹, Caliskan E et al 2007²⁰, Saav I et al 2015²¹). The result of our study is different with that of Vimala N et al 2004²² and Saxena P et al 2006²³, which showed that sublingual misoprostol improved the cervical dilatation significantly as compared to that of cervical misoprostol.

There was no significant difference in the total duration of the procedure and the amount of blood loss in both groups. The result was consistent with the observations of studies by Hamoda et al 2004¹⁸, Vimala N et al 2004²², Tang et al 2004, Carbonell et al 2006¹⁹, Caliskan E et al 2007²⁰ and Saav I et al 2015²¹). Our result of total duration of procedure contradicted the result of study by Saxena P et al 2006²³ which showed sublingual misoprostol reduced the total duration of procedure. With respect to the amount of blood loss. Jayanti et al 2013²⁴ reported application of sublingual misoprostol resulted in increased vaginal bleeding.

Side effects like nausea, vomiting, diarrhoea and fever was more in sublingual group than that in vaginal group which correlate with earlier studies Carbonell et al 2006¹⁹, Jayanti et al 2013²⁴, Hamoda et al 2004¹⁸ and Vimala N et al 2004²². However Tang et al 2004¹⁰ showed in their study that there was no significant difference between two groups.

Conclusion

It can be concluded that sublingual misoprostol is an effective and favourable cervical priming agent for the first trimester abortion as compared to the vaginal route. It can be conveniently self administered at home thereby decreasing hospital stay and cost. It also has a good patient acceptability rate.

References

- Child, Tim J., et al. "Morbidity of first trimester aspiration termination and the seniority of the surgeon." *Human Reproduction* 16.5 (2001): 875-878.
- Frank, P. I., et al. "Outcome of pregnancy following induced abortion Report from the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists." *BJOG: An International Journal of Obstetrics & Gynaecology* 92.4 (1985): 308-316.
- Hakim-Elahi, E., HAROLD MM TOVELL, and MICHAEL S. BURNHILL. "Complications of first-trimester abortion: a report of 170,000 cases." *Obstetrics & Gynecology* 76.1 (1990): 129-135.
- RCOG clinical effectiveness support unit. *The care of women requesting induced abortion*. London; RCOG Press, 2000.
- Schulz, Kenneth F, David A Grimes, and Willard Cates. "Measures to prevent cervical injury during suction curettage abortion." *The Lancet* 321.8335 (1983): 1182-1185.
- El-Refaey, H. A. Z. E. M., et al. "Cervical priming with prostaglandin E1 analogues, misoprostol and gemeprost." *The Lancet* 343.8907 (1994): 1207-1209.
- Ngai, Suk Wai, et al. "Oral misoprostol versus mifepristone for cervical dilatation before vacuum aspiration in first trimester nulliparous pregnancy: a double blind prospective randomised study." *BJOG: An International Journal of Obstetrics & Gynaecology* 103.11 (1996): 1120-1123.
- Ziemann, Miriam, et al. "Absorption kinetics of misoprostol with oral or vaginal administration." *Obstetrics & Gynecology* 90.1 (1997): 98-92.
- Ashok, Premila W., Gillian MM Flett, and Allan Templeton. "Mifepristone versus vaginally administered misoprostol for cervical priming before first-trimester termination of pregnancy: a randomized, controlled study." *American journal of obstetrics and gynecology* 183.4 (2000): 998-1002.
- Tang, Oi Shan, Kam Hung Mok, and Pak Chung Ho. "A randomized study comparing the use of sublingual to vaginal misoprostol for pre-operative cervical priming prior to surgical termination of pregnancy in the first trimester." *Human Reproduction* 19.5 (2004): 1101-1104.
- Ngai SW, Suk Wai, et al. "The use of misoprostol for pre-operative cervical dilatation prior to vacuum aspiration: a randomized trial." *Human reproduction* 14.8 (1999): 2139-2142.
- Lawrie, Alasdair, Gillian Penney, and Nan Templeton. "A randomised comparison of oral and vaginal misoprostol for cervical priming before suction termination of pregnancy." *BJOG: An International Journal of Obstetrics & Gynaecology* 103.11 (1996): 1117-1119.
- Fong, Y. F., Kuldip Singh, and R. N. V. Prasad. "A comparative study using two dose regimens (200 µg or 400 µg) of vaginal misoprostol for pre-operative cervical dilatation in first trimester nulliparae." *BJOG: An International Journal of Obstetrics & Gynaecology* 105.4 (1998): 413-417.
- Singh, Kuldip, et al. "Evacuation interval after vaginal misoprostol for pre-abortion cervical priming: a randomized trial." *Obstetrics & Gynecology* 94.3 (1999): 431-434.
- Singh, Kuldip, et al. "Vaginal misoprostol for pre-abortion cervical priming: is there an optimal evacuation time interval?." *BJOG: An International Journal of Obstetrics & Gynaecology* 106.3 (1999): 266-269.
- Tang, Oi Shan, et al. "Pharmacokinetics of different routes of administration of misoprostol." *Human reproduction* 17.2 (2002): 332-336.
- Danielsson, K. Gemzell, et al. "Comparison between oral and vaginal administration of misoprostol on uterine contractility." *Obstetrics & gynecology* 93.2 (1999): 275-280.
- Hamoda, Haitham, et al. "A randomized controlled comparison of sublingual and vaginal administration of misoprostol for cervical priming before first-trimester surgical abortion." *American journal of obstetrics and gynecology* 190.1 (2004): 55-59.
- Esteve, Josep Lluís Carbonell, et al. "Sublingual versus vaginal misoprostol (400 µg) for cervical priming in first-trimester abortion: a randomized trial." *Contraception* 74.4 (2006): 328-333.
- Caliskan, E., et al. "Sublingual versus vaginal misoprostol for cervical ripening PRIOR TO manual vacuum aspiration under local anaesthesia: A randomized study." *The European Journal of Contraception & Reproductive Health Care* 12.4 (2007): 372-377.
- Säav, Ingrid, et al. "Sublingual versus vaginal misoprostol for cervical dilatation 1 or 3 h prior to surgical abortion: a double-blinded RCT." *Human Reproduction* (2015): dev071.
- Vimala, N., et al. "A randomized comparison of sublingual and vaginal misoprostol for cervical priming before suction termination of first-trimester pregnancy." *Contraception* 70.2 (2004): 117-120.
- Saxena, Pikee, Sudha Salhan, and Nivedita Sarda. "Sublingual versus vaginal route of misoprostol for cervical ripening prior to surgical termination of first trimester abortions." *European Journal of Obstetrics & Gynecology and Reproductive Biology* 125.1 (2006): 109-113.
- Jayanti Nath, Snehal shah, Rina Sharma. "To compare the effectiveness and tolerability of misoprostol as a cervical ripening agent in first trimester abortion through sublingual and vaginal routes of administration." *Journal of Evolution of Medical and Dental sciences/Volume2/ Issue25/ June27,2013: 4563-4567*