Original Research Article

Randomized comparison of vaginal and sublingual misoprostol with mifepristone priming in termination of second trimester pregnancy

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ABSTRACT

Background: Sublingual Misoprostol 200 ug 4 hrly is as effective or less effective than vaginal Misoprostol 200ug 4hrly with 200mg oral Mifepristone in termination of second trimester pregnancy. To compare effectiveness, side-effects, and patient satisfaction of sublingual vs vaginal misoprostol administration.

Methods: It was prospective randomized open label study. 60 women 13-20 weeks of gestation with a valid legal indication for termination of pregnancy as per MTP act in INDIA were enrolled for study, randomly divided into Group A- Sublingual (n=30) group B- Vaginal (n=30). For group A, 200 mg of Mifepristone was given, 48h later Misoprostol 200 µg was given sublingually 4hrly up to a maximum of 5 doses. If abortion does not occur, the pregnancy was terminated with vaginal misoprostol, in group A. Same procedure repeated in group B. If abortion fails to occur after 5 doses, then second course of vaginal misoprostol was given in group B. Failure of procedure was defined as failed expulsion of foetus at 48 hrs.

Results: Mean induction-abortion interval in vaginal group was 12.8±4.38h and 11.47±4.42h in sublingual group was comparable with insignificant p value (p=0.136). All the side effects were comparable in both groups. The overall success rate was 93.3% in the sublingual group while it was 100% in the vaginal group.

Conclusion: Vaginal misoprostol with oral mifepristone priming in second -trimester medical abortion has a shorter time to pregnancy termination compared with a sublingual regimen. However, both the routes are equally effective for induction of abortion.

Keywords: Mifepristone, Misoprostol, Second Trimester, Sublingual, Vaginal

INTRODUCTION

Safe and legal abortion is considered to be a key intervention for improving women’s health and quality of life.1

Worldwide 42 million legal abortion and 10 to 12 million clandestine abortion takes place every year of which 10 to 15% are performed in second trimester.2,3 In India alone, 6.7 million induced abortions occur annually, of which late abortions constitute 10.7 to 15%.5 According to the MTP Act, medical termination of pregnancy (MTP) in India is allowed up to 20 weeks. Two-thirds of major abortion related complications and half of abortion related mortality occur in pregnancies terminated after 13 weeks of gestation.6,7 For second trimester medical termination of pregnancy, the optimal regimen is still under development but is likely to be characterized by a short induction abortion- interval, devoid of any serious side effect, high acceptability, easy to perform and cost effective. Published evidence provides reassurance on the safety and efficacy of medical abortion using
mifepristone in combination with a prostaglandin analogue.\textsuperscript{9-13} Mifepristone, a progesterone receptor antagonist has been shown to be effective in shortening the induction abortion interval.\textsuperscript{14,15}

Misoprostol is used by four routes in India (Oral, Vaginal, Sublingual, and Rectal). Two common routes of administration of misoprostol are sublingual and vaginal; they have different pharmacokinetics and effectiveness.\textsuperscript{16} We used mifepristone 200mg for priming followed by misoprostol every 4h which is according to WHO guidelines (2012).\textsuperscript{17,18} Failure rate of this combination is very low ranging from 0.3% to 3%.\textsuperscript{19}

**METHODS**

It was a Randomised Open Label Study of 60 cases conducted in patients at Obstetrics and Gynaecology department of T. N. Medical college and BYL Nair hospital, Mumbai from June 2016 to October 2017.

All of 60 women 13-20 weeks of gestation with a valid legal indication for termination of pregnancy as per MTP act in INDIA were enrolled for study.

**Inclusion criteria**

Healthy women (aged between 18 and 35 years) requesting legal second trimester (13-20 weeks) termination of pregnancy were recruited in this study.

**Exclusion criteria**

Women with anaemia, suspected ectopic and molar pregnancy, pelvic infection and congenital malformation of uterus, haemorrhagic disorders and treatment with anticoagulants, history of cardiac disease, an intratuterine device in utero, nursing mothers, multiple pregnancies, contraindications to prostaglandins use (bronchial asthma, glaucoma), previous uterine surgery and caesarean section, placenta praevia were excluded.

A structured form was used to record age, previous obstetric history, the time interval between misoprostol application and foetus expulsion, the number of tablets required, side effects and patient’s preferences on the route of administration. In all cases written informed consent was taken and duration of pregnancy was confirmed by history, clinical and sonological examination. Routine blood investigations were done at the initial consultation.

Selected cases were randomly divided into Group A- Sublingual (n=30) group B- Vaginal (n=30). For group A, 200 mg of Mifepristone was given, 48h later Misoprostol 200 μg was given sublingually 4hrly up to a maximum of 5 doses. Following administration of misoprostol, the vitals were monitored hourly. Analgesia was administered as required.

If abortion does not occur after 5 doses, the pregnancy was terminated with vaginal misoprostol, in group A. Same procedure repeated in group B. If abortion fails to occur after 5 doses, then second course of vaginal misoprostol was given in group B. Failure of procedure was defined as failed expulsion of foetus at 48 hrs.

After expulsion of the fetus, 10 units of oxytocin was administered intramuscularly into the upper thigh to facilitate placental delivery. 20 Spontaneous expulsion of the placenta within 60 minutes of abortion was awaited, if not digital exploration of the uterine cavity and blunt curettage done.

**Statistical analysis**

Statistical Analysis was done from the outcome. All variable were calculated by±2SD. Collected data were analysed and statistical test was done with the help of Microsoft excel and Med Calc software. Test for the statistical significance was applied by using Chi square test and Mann-Whitney U test for analyzing the differences between the two groups (p<0.05 was considered significant).

**RESULTS**

The mean age in sublingual group was 27.1±5.59 yrs. and in the vaginal group was 27.9±4.67yrs. (TABLE-1)

The mean gestational age was 16.77±2.03 weeks and 17.49±1.8 weeks respectively in the two groups, the difference was not statistically significant. 26.66% of the patients in sublingual group were nullipara while 73.34% were multiparous. 13.33% of the patients in pervaginal group were nullipara while 86.67% were multiparous. Both groups were comparable with regard to parity.

In the sublingual group the indications for termination were contraceptive failure (60%), fetal anomalies (6%), maternal (10%), social indications (6%). In the pervaginal group the indications were contraceptive failure (60%), fetal anomalies (10%) and maternal (23.3%), social indications (10%).

The mean induction abortion interval was 12.8±4.38 hrs in the sublingual group while it was 11.47±4.42 hrs in the prevaginal group. Although duration of abortion was less in vaginal group, the difference in duration between two groups was not statistically significant.

The overall success rate was 93.3% in the sublingual group while it was 100% in the per vaginal group.

The mean deficit in Hb% between Day 1 post aortal was 0.237±0.09 % in the sublingual and 0.233±0.08% in the prevaginal group. Hb% deficit was same in both groups.
**Table 1: Demographic characteristic. Values are expressed as n (%) or mean (SD).**

| Parameters               | Sublingual group(n=30) | Vaginal group(n=30) | p value | Odds ratio | 95% CI for difference in the mean |
|--------------------------|------------------------|---------------------|---------|------------|----------------------------------|
| Age (year)               | 27.1 (5.59)            | 27.9 (4.67)         | 0.550   |            | -1.8620 to 3.4620                |
| BMI (kg/m²)              | 21.90 (2.38)           | 21.21 (2.45)        | 0.273   |            | -1.9383 to 0.5583                |
| Gestational age (weeks)  | 16.77 (2.03)           | 17.49 (1.8)         | 0.153   |            | -0.2715 to 1.7115                |
| Haemoglobin level (g/dL) | 11.073 (0.51)          | 11.076 (0.46)       | 0.979   |            | -0.2480 to 0.2540                |
| Previous deliveries      | 22 (73%)               | 26 (86.6%)          | 0.6668  | 0.8462     | 0.03955 to 1.8104                |

**Table 2: Induction-abortion interval and success rate according to group.**

| Induction abortion Interval | Sublingual group(n=30) | Vaginal group(n=30) | p value |
|-----------------------------|------------------------|---------------------|---------|
| 12 h                        | 8 (26.66%; 8/30)       | 14/46.66% 14/30     | 0.11    |
| 12-24 h                     | 20 (66.66%; 20/30)     | 16/53.33% 16/30     | 0.29    |
| 24-36 h                     | 2 (6.66%; 2/30)        | 0                   | 0.00    |
| Mean (h)                    | 12.84±3.8h             | 11.47±4.42h         | 0.136   |
| Success rate in 24h         | 28/30 (93.33%)         | 30/30 (100%)        | 0.19    |

**Table 3: Comparison of side effects in two groups.**

| Side effects | Sublingual group(n=30) | Vaginal group(n=30) | p value |
|--------------|------------------------|---------------------|---------|
| Nausea       | 10 (33.33%)            | 14 (46.66%)         | 0.29    |
| Vomiting     | 12 (40%)               | 9 (30%)             | 0.42    |
| Diarrhoea    | 3 (10%)                | 2 (6%)              | 0.57    |
| Fever        | 3 (10%)                | 1 (3.33%)           | 0.30    |
| Shivering    | 1 (3.33%)              | 4 (13.33%)          | 0.16    |

The side effects seen in the sublingual group were nausea (33.33%), vomiting (33.33%), diarrhoea (10%), fever (10%), shivering (3.33%). The side effects in the prevaginal group were Nausea (46.6%), vomiting (30%), nausea (20%), diarrhoea (10%), fever (3.33) and shivering (13.33%). All the side effects were comparable in both groups.

Regarding acceptability, sublingual group was the more preferred route between the two groups, because of less discomfort caused to women by vaginal insertion.

**DISCUSSION**

Nearly all the women in our study aborted within 24 h of receiving misoprostol, and the induction to abortion interval for both study groups was less than half of that noted by Tang et al. (2004).

Milani et al (2014) and Bartusevicus et al (2005) demonstrated that induction to abortion period is significantly shorter in the sublingual group and this group needed lower dose of drug for abortion period.21,22 These results were contrary to our present study as we found less induction-abortion interval in vaginal group.

El-Refaey et al (1995) and Ashok and Templeton (1999) have shown that using a combination of vaginal and oral misoprostol, upto 97% of women aborted within 15 h of administration the induction-abortion interval was also shorter when compared with the regimen from our study.23,24

In Most published regimens there is an increase in abortion duration with an increase in gestation.25,26 Although we found association of gestational age with induction-abortion interval, but the results were not uniform for gestational age groups. Earlier gestation has not been consistently been associated with a shorter abortion interval in the present study.

The vaginal group required less misoprostol to effect abortion compared with the sublingual group (<600 micrograms compared with >600 micrograms, vaginal compared with sublingual, respectively).23

A study on the pharmacokinetics of the sublingual, vaginal and oral route might explain the higher prevalence of side effects reported with the sublingual route of misoprostol administration.27,28 Our study had similar side effects in either group, contrary to study by Tang et. al, 2002b.29

Two patients in the sublingual group had surgical evacuation for incomplete abortion. None of the patients aborted with mifepristone alone. 96.66% (58/60) aborted within 24h, while two in the sublingual group had an induction to abortion interval of 24-36h.

Tang et al, (2004) believed that sublingual administration was acceptable to more women. We found similar results in our study.30,31
Single or double blinded placebo controlled study would have been more robust study but as we could not get placebo or similar vitamin tablet, it was not possible to conduct placebo controlled study.

CONCLUSION

Vaginal misoprostol administered after oral mifepristone priming in second trimester medical abortion is associated with a shorter time to pregnancy termination compared with a sublingual regimen. There is no significant difference in efficacy and complications between the two routes, although a larger cohort is required to get more dependable result. Sublingual regimen should be offered to those women who consider vaginal administration unacceptable. 

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REFERENCES

1. Dhillon BS, Chandhiok N, Kambo I, Saxena NC. Induced abortion and concurrent adoption of contraception in the rural areas of India (an ICMR task force study). Indian J Med Sci. 2004;58:478-84.
2. Sedgh G, Henshaw S, Singh S, Alman E, Shah IH. Induced abortion: Estimated rates and trends worldwide. The Lancet. 2007 Oct 13;370(9595):1338-45.
3. Padubidri VG, Daflary SN. Shaw’s textbook of gynaecology (13th ed), New Delhi. Elsevier. 2004:241.
4. Tejai P, Bakul A. 17-year review of voluntary termination of pregnancy (MTP). J Obstetr Gynecol India. 2006;56(6):522-8.
5. Tejai P, Bakul L. A 17-year review of voluntary termination of pregnancy (MTP). J Obstetr Gynecol India. 2006;56(6):522-8.
6. World Health Organization. Medical methods for termination of pregnancy, World Health Organization, Geneva 1997,871. Available at: extranet.who.int.
7. Cabrera Y, Fernández-Guisasola J, Lobo P, Gamir S, Alvarez J. Comparison of sublingual versus vaginal misoprostol for second trimester pregnancy termination, A meta-analysis. Aust N Z Y Obstet-Gynecol. 2011;51(2),158-65.
8. Darney PD, Sweet RL. Routine intraoperative ultrasonography for second trimester abortion reduces incidence of uterine perforation. J Ultrasound Med. 1989;8(2):71-5.
9. Ngai SW, Tang OS, Chan YM, Ho PC. Vaginal misoprostol alone for medical abortion up to 9 weeks of gestation: efficacy and acceptability. Human Reproduct. 2000 May 1;15(5):1159-62.
10. Tang OS, Ho PC. Pilot study on the use of sublingual misoprostol for medical abortion. Contraception. 2001;64(5):315-7.
11. Autry AM, Hayes EC, Jacobson GF, Kirby RS. A comparison of medical induction and dilation and evacuation for second-trimester abortion. Am J Obstet Gynecol. 2002;187(2):393-7.
12. Bartley J, Baird DT. A randomised study of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy. BJOG 2002;109(11):1290-4.
13. Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. Contracept. 2004;69(1):51-8
14. Urquhart DR, Bahzad C, Templeton AA. Efficacy of the antiprogestin mifepristone (RU 486) prior to prostaglandin termination of pregnancy. Human Reproduct. 1989 Feb 1;4(2):202-3.
15. Urquhart DR, Templeton AA. The use of mifepristone prior to prostaglandin-induced mid-trimester abortion. Human Reproduct. 1990 Oct 1;5(7):883-6.
16. Tanha FD, Golgachi T, Nirooamand N, Ghajarzadeh M, Nasr R. Sublingual versus vaginal misoprostol for second trimester termination: a randomized clinical trial. Archiv Gynecolo Obstetr. 2013 Jan 1;287(1):65-9.
17. Tanha FD, Golgachi T, Nirooamand N, Gajaradeh M, Nasr R. Sublingual versus vaginal misoprostol for second trimester termination; a randomized clinical trial. Arch Gynecol obstet. 2013;287(1),659.
18. Fogsi Icog Good Clinical Practice Recommendation Medical Termination of Pregnancy: J Obstetr Gynecol of India. 2011:91.
19. World Health Organisation; Safe abortion: Technical and Policy guidance for health systems 2nd ed. Geneva; 2012. Available at: apps.who.int.
20. Wildschut H, Both MI, Medema S, Thomee E, Wildhagen MF, Kapp N. Medical methods for Mid-trimester termination of pregnancy. Cochrane Database Syst Rev. 2011;19(1):CD005216.
21. Dickinson JE, Brownell P, McGinnis K, Nathan E. Mifepristone and second trimester pregnancy termination for fetal abnormality in Western Australia: worth the effort. Aust NZ J Obstetr Gynaecol. 2010;50(1):60-4.
22. Milani F, Sharami SH, Arjmandi S. Comparison of sublingual and vaginal misoprostol for second-trimester pregnancy terminations. J Family Reprod Health. 2014 Mar;8(1):41-4.
23. Bartusevicius A, Barcaite E, Nadisauskiene R, Oral, vaginal and sublingual misoprostol for induction of labor. Int J of Gynecol Obstet. 2005; 91:2-9.
24. el-Refaey H, Templeton A. Induction of abortion in the second trimester by a combination of misoprostol and mifepristone: a randomized comparison between two misoprostol regimens. Hum Reprod. 1995;10(2):475-8.
25. Ashok PW, Templeton A. Nonsurgical mid trimester termination of pregnancy: a review of 500 consecutive cases. BJOG: Intern J Obst Gynaecol. 1999 Jul;106(7):706-10.

26. Ashok PW, Templeton A, Wagaarachchi PT, Flett GM. Midtrimester medical termination of pregnancy: a review of 1002 consecutive cases. Contracept. 2004 Jan 1;69(1):51-8.

27. Dickinson JE, Brownell P, McGinnis K, Nathan E. Mifepristone and second trimester pregnancy termination for fetal abnormality in Western Australia: worth the effort. Aust NZ J Obstet Gynaecol. 2010;50(1):60-4.

28. Tang OS, Chan CC, Ng EH, Lee SW, Ho PC. A prospective, randomized, placebo-controlled trial on the use of mifepristone with sublingual or vaginal misoprostol for medical abortions of less than 9 weeks gestation. Human Reprod. 2003 Nov 1;18(11):2315-8.

29. Hamoda H, Ashok PW, Dow J, Flett GM, Templeton A. A pilot study of mifepristone in combination with sublingual or vaginal misoprostol for medical termination of pregnancy up to 63 days gestation. Contracept. 2003;68(5):335-8.

30. Tang OS, Schweer H, Seyberth HW, Lee SW, Ho PC. Pharmacokinetics of different routes of administration of misoprostol. Human Reprod. 2002;17(2):332-6.

31. Tang OS, Lau WN, Chan CC, Ho PC. A prospective randomised comparison of sublingual and vaginal misoprostol in second trimester termination of pregnancy. BJOG. 2004;111(9),1001-05.

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