Sublingual versus vaginal route of misoprostol for cervical ripening prior to surgical termination of first trimester abortions

Pikee Saxena a,*, Sudha Salhan b, Nivedita Sarda b

a Department of Reproductive Biomedicine, National Institute of Health and Family Welfare, New Mehrauli Road, Munirka, New Delhi 110067, India
b Department of Obstetrics and Gynecology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India

Received 22 September 2004; received in revised form 27 April 2005; accepted 28 July 2005

Abstract

Background: Sublingual and vaginal routes of misoprostol have been found to be effective for pharmacological ripening prior to surgical termination of first trimester abortions. We conducted this study to compare the effectiveness and acceptability of sublingual versus vaginal route of misoprostol for cervical priming prior to vacuum aspiration (VA).

Methods: In this prospective clinical trial, a total of 100 women with period of gestation between 6 and 12 weeks scheduled for day surgery abortion were sequentially allocated into two groups of 50 each. All participating women received 400 μg of misoprostol 3 h prior to VA either by sublingual (self-administered at home) or by vaginal route (inserted by the doctor in hospital) after wetting the tablet with water.

Results: Demographic characteristics of both the groups were comparable. For all periods of gestation, sublingual misoprostol significantly improved cervical dilatation (p < 0.001) and reduced the time duration of surgery (p < 0.001) compared to vaginal group without increasing the side effects. Mean pain score of the sublingual group was 2.7 ± 1.1 as compared to 3.2 ± 1.6 of the vaginal group (p = 0.57). Misoprostol tablet was found intact in the vagina of three patients and was only partially absorbed amongst five patients at the time of VA.

Conclusion: Sublingual route is an effective and convenient alternative to vaginal administration of misoprostol for cervical dilatation. It can be conveniently self-administered at home thereby decreasing hospital stay and cost. It also has a good patient acceptability rate.

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Keywords: Sublingual; Vaginal; Misoprostol; Cervical dilatation; First trimester; Abortion

1. Introduction

Cervical injury is one of the most frequent complications that occur during vacuum aspiration for first trimester abortions. Pharmacological cervical ripening is preferable to mechanical cervical dilatation as it reduces cervical trauma and increases operative ease. Although laminaria tents, dilapan, magnesium sulphate have been used for this purpose, prostaglandins are found to be more beneficial because they are easy to administer and are very effective. Most prostaglandin analogues are expensive, unstable and require refrigeration for storage. But misoprostol has the advantages of easy availability, ease of administration, lower cost, stability at room temperature and few systemic side effects. Misoprostol is a synthetic 15 deoxy-16 hydroxy-16-methyl analogue of naturally occurring Pg E1, used for prevention and treatment of peptic ulcers. It is being administered in several treatment regimens with varying degree of success for pre-abortion cervical ripening [1–4]. Consensus has not been reached regarding the ideal route, dose and time interval of misoprostol for cervical ripening before VA [1–5]. Vaginal route has been found to be more effective than oral because of a slower but more constant absorption through the vaginal mucosa, but most women try
to avoid vaginal administration due to inconvenience and lack of privacy. Despite its shortcomings, vaginal route is currently the most widely used route at present. In our previous studies, the authors have shown that 400 μg of sublingual misoprostol was very effective for cervical ripening prior to first trimester abortions [2,6]. Sublingual route has been proven to be more effective than oral [6,7]. To the best of our knowledge, there exist only three studies in literature comparing the effect of sublingual with vaginal misoprostol for cervical ripening prior to first trimester abortions [8–10]. Therefore, the current study was undertaken to assess the efficacy and patient acceptability of 400 μg of sublingual misoprostol, self-administered by the patient at home compared with vaginal misoprostol administered by the doctor, 3 h prior to VA on the day of surgery.

2. Materials and methods

One hundred women scheduled for day case termination of pregnancy were enrolled in this prospective randomized clinical trial carried out at the Family Planning Services of our hospital from January to June 2002. The local ethical committee approved the study protocol. Patients were recruited after signing a written informed consent. All women received detailed oral and written information regarding what to expect after misoprostol administration.

One hundred women seeking first trimester abortion were sequentially allocated alternately into either sublingual or vaginal group of 50 each. A total of 118 patients were recruited after signing a written informed consent. All patients were instructed to keep a record of any side effect related to misoprostol. They were also told to note how much time it took for complete dissolution of the sublingual tablets. Patients of the vaginal group were instructed to report to the Out Patient Department at 7:30 a.m. where the misoprostol was inserted in their posterior fornix after wetting the tablet with a drop of water by the recruiting investigator. All patients were instructed to reach the operation theatre by 10 a.m. The order of surgery was on the basis of their arrival time at the operation theatre. This ensured that the operating surgeon was masked to the route of administration of the drug.

Pre-operatively, no other premedication was given, but the women were informed that analgesics were available in case they experienced severe pain. In addition, their pulse, blood pressure, temperature and other side effects associated with misoprostol including pain, nausea, vomiting, diarrhea, fever, shivering and bleeding per-vaginum were recorded.

Intra-operatively, cervical dilatation before performing VA was measured using Hegar dilators. The dilators were passed through the cervix in descending order starting with size 12. The largest Hegar’s dilator passing through the internal os without resistance was regarded as the dilatation achieved. No further dilatation was performed if the cervix had a gestation appropriate dilatation [1]. In patients with insufficient dilatation, paracervical block was given in order to facilitate dilatation and to reduce pain perception [12]. No other analgesics were given to these patients. Suction evacuation was done by using appropriate size of Karman’s cannula. At the end of this procedure, the uterus was curetted gently by a curette. Duration of surgery was measured from the start of dilatation until the end of curettage. Intra-operative blood loss was measured with a graduated cylinder as the volume of total uterine aspirate, after sieving away the products of conception. The appropriate amount of liquor for that period of gestation was subtracted from this amount to achieve the amount of actual blood loss [1]. The pain scoring using visual analogue score (VAS) was done by the patients themselves on completion of suction evacuation. Recordings were made on a 0–10 numeric scale where severity at the extreme left of the scale was considered as 0, i.e., no pain, and the severity at the extreme right of the scale was considered as maximum, i.e., 10. To simplify our results, scores between 0 and 3 were considered to be mild pain, 4 and 6 as moderate pain, and 7 and 10 was considered as severe pain [13]. All patients who gave a score of 7 or more were given injectable analgesics.
Any cervical or uterine injury was noted. All patients underwent IUCD insertion or sterilization during the same sitting by choice. Pain intensity was measured before these procedures were done to avoid any bias. Following the operation, the women were kept in the hospital for 3–4 h before discharge. The incidence of nausea, vomiting, diarrhea, fever, shivering and bleeding per-vaginum was noted during this period. As a routine, all patients received analgesics for 2 days and antibiotics for 5 days at discharge from the hospital (tablet Ibuprofen 400 mg twice a day for 2 days and capsule Amclox 500 mg four times a day for 5 days).

Follow-up was done twice, first after 7–10 days and subsequently after 1 month or the first menstrual period. Any unscheduled hospital visit was noted.

The main study outcome measures were cervical dilatation prior to suction evacuation, amount of blood loss during surgery and the time duration of surgery. Other factors evaluated were pain intensity, complications during surgery, side effects of misoprostol, operative ease and acceptability of the route of administration.

The difference in pre-operative cervical dilatation was the main outcome indicator for the calculation of sample size. A sample size of 37 patients in each group has 80% power to detect a difference in mean cervical dilatation of 2.0 mm. Taking a mean pre-surgical cervical dilatation in the vaginal group as 7.2 [14], assuming that the common standard deviation is 3.0 using a two group Student’s t-test. A p-value of 0.05 has been considered as significant.

### 3. Results

Table 1 summarizes the demographic characteristics of the women recruited in each group. We were unable to include any primigravida in our study because socio-cultural values in India consider abortion during first pregnancy as inauspicious and most of the unmarried women avoid coming to a government set up in order to avoid embarrassment. Pre-operatively, of the 100 patients who were given sublingual (n = 50) or vaginal (n = 50) misoprostol, 22 (44%) in the sublingual group versus 11 (22%) in the vaginal group had spotting after 1–2 h of ingestion of misoprostol. Mild spasmodic pain was experienced by 12 patients (24%) of the sublingual group versus 7 (14%) of the vaginal group. No patient reported any nausea, vomiting, diarrhea, during the pre-operative period. One patient (2%) developed fever, 2 h after sublingual administration of misoprostol.

A single experienced investigator conducted all the cases of vacuum aspiration. During vacuum aspiration, 2 (4%) patients of the sublingual group as compared to 10 (20%) of the vaginal group were given paracervical block for mechanical cervical dilatation, as these patients had cervical dilatation less than the required amount for that gestational age. Out of a total of 50 patients of the vaginal group, in 5 (10%) patients, the tablet was only partially absorbed while in 3 (6%), it was totally unabsorbed after 3 h of administration. In the sublingual group, tablet was absorbed in all patients within 10–46 min. Operative findings are depicted in Table 2.

For the operating surgeon, operative ease was more in the sublingual group where only 2 patients required mechanical cervical dilatation as compared to 10 in the vaginal group. No complication occurred in any of the two groups.

Post-operative, side effects profile is depicted in Table 3. One (2%) subject of the sublingual group developed hyperthermia and shivering which was managed by cold sponging and injectable acetaminophen.

Fifty patients had a history of previous abortion or miscarriage, of which 8 had a spontaneous miscarriage, while 32 had induced surgical abortion by usual mechanical cervical dilatation. Women were more satisfied with pharmacological cervical dilatation as compared to mechanical dilatation done during previous suction evacuation.

A higher patient acceptability of sublingual misoprostol as compared to the vaginal route was noted in our study (94% versus 36%). When questioned regarding the choice for route of administration, 94% patients stated that they would opt for sublingual route, especially in preference to the vaginal route if the option was available. The reasons given were that the vaginal route of administration requires the patient to report to the hospital 3 h prior to VA (86%),

<table>
<thead>
<tr>
<th>Table 1: Patient characteristics</th>
<th>Sublingual (n = 50)</th>
<th>Vaginal (n = 50)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (±S.D.) (range, years)</td>
<td>27.3 ± 3.5 (18–38)</td>
<td>26.8 ± 3.4 (18–38)</td>
<td>0.24</td>
</tr>
<tr>
<td>Mean parity (range)</td>
<td>3.1 ± 2 (P1–P6)</td>
<td>3.6 ± 2.0 (P1–P6)</td>
<td>0.31</td>
</tr>
<tr>
<td>Mean gestational age (weeks) (range)</td>
<td>8.1 ± 0.9 (6–12)</td>
<td>8.0 ± 1.1 (6–12)</td>
<td>0.26</td>
</tr>
<tr>
<td>Religion (percentage of Hindus)</td>
<td>44 (88%)</td>
<td>43 (86%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Low socio-economic status</td>
<td>48 (96%)</td>
<td>47 (94%)</td>
<td>0.35</td>
</tr>
<tr>
<td>Previous abortion</td>
<td>21 (42%)</td>
<td>19 (38%)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

S.D.: standard deviation.
was embarrassing (92%) or inconvenient (95%), whereas sublingual drug can be conveniently self-administered at home by the patient, thereby saving time.

All patients were followed up at 7–10 days and after 1 month. None of these patients had any major complaints and their pelvic examination revealed no abnormality.

4. Discussion

Vacuum aspiration is a commonly used method for first and early second trimester abortion and is one of the most common surgical procedures performed worldwide [15,16]. Cervical dilatation is the most critical step in VA as most cervical and uterine injuries are due to forceful dilatation of cervix. Adequate dilatation decreases pain and time duration of surgery and increases operative ease. Women with a period of gestation between 6 and 12 weeks were included in this study. Patients undergoing surgical termination at a period of gestation less than 7 weeks have a higher risk of failed abortions. Adequate and easy cervical dilatation reduces this risk by facilitating VA.

The beneficial effects of pharmacological over mechanical cervical priming have already been well established [17,18]. Previously, laminaria tent, gemiprost and cervigel have been used for cervical ripening [19]. Although gemiprost is the only licensed prostaglandin which has been approved for cervical ripening till date, its use in clinical practice is restricted because it is expensive and requires refrigeration for storage. These days misoprostol is being used extensively for this purpose. Due to lack of evidence from large randomized studies, consensus has not been drawn regarding the ideal route of administration of misoprostol for pre-abortion cervical priming. The vaginal route has been claimed to be more beneficial than the oral route [3–5]. According to the study conducted by Zieman et al. [5], systemic bioavailability after vaginal administration is three times higher than that after oral route probably due to prolonged contact with a highly vascular vagina, leading to a long lasting and progressively increasing plasma level. But as compared to oral or sublingual route, absorption through the vaginal mucosa is inconsistent with large individual variations. Sometimes remnants of vaginal tablets may be found in the vagina hours after administration [5]. On the other hand, misoprostol is rapidly absorbed through the vascular buccal mucosa completely within 10–15 min [20]. Therefore, the vaginal route may not be the ideal route of administration for clinical practice.

In our study, although the surgeon was blinded to the route of administration of misoprostol initially, during VA traces of misoprostol were present in a few patients of the vaginal group, which could have caused some bias. We did not have a tonometer to measure the actual force applied for dilatation. This was a shortcoming in our study and we had to measure this subjectively as ease of operation as graded by the surgeon.

Few studies conducted so far have evaluated the response of sublingual misoprostol for cervical ripening before VA [2,6,7–9]. In this study, majority of patients of both the sublingual and vaginal misoprostol groups who already had good cervical dilatation felt mild pain (86% versus 80%) during surgery. Mean pain score (Table 4) of the sublingual group was 2.7 ± 1.1 as compared to 3.2 ± 1.6 of the vaginal group (p = 0.57). The fact that 10 patients of the vaginal group as compared to 2 of the sublingual group were given para-cervical block could have ultimately influenced our final pain score.

Patient acceptability for this route is better than the vaginal route as it can be self-administered and avoids painful and embarrassing vaginal administration. There was a significant difference in acceptability (94% versus 36%) between sublingual versus vaginal route in our study. This marked difference in acceptability is probably because most of the patients found vaginal insertion by the investigators

Table 2
Intra-operative parameters

<table>
<thead>
<tr>
<th>POG 6–12 weeks</th>
<th>Sublingual (n = 50)</th>
<th>Vaginal (n = 50)</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ID mean ± S.D. (mm) 95% CI</td>
<td>9.84 ± 2.2 (9.2–10.4)</td>
<td>7.84 ± 2.9 (7.0–8.6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mean blood loss (ml) 95% CI</td>
<td>17.08 ± 7.1 (15.0–19.1)</td>
<td>17.18 ± 7.3 (15.1–19.2)</td>
<td>0.9447</td>
</tr>
<tr>
<td>Mean time (min) 95% CI</td>
<td>3.51 ± 0.9 (3.22–3.8)</td>
<td>4.68 ± 1.4 (4.3–5.1)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

POG: period of gestation; ID: initial cervical dilatation; S.D.: standard deviation.

Table 3
Incidence of post-operative side effects

<table>
<thead>
<tr>
<th>Post-operative</th>
<th>Sublingual (n = 50)</th>
<th>Vaginal (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>WNL</td>
<td>WNL</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>1 (2%)</td>
<td>Nil</td>
</tr>
</tbody>
</table>

WNL: within normal limits; NS: not significant.

Table 4
Intra-operative pain score

<table>
<thead>
<tr>
<th>During surgery</th>
<th>Sublingual (N = 50)</th>
<th>Vaginal (N = 50)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracervical block</td>
<td>2 (4%)</td>
<td>10 (20%)</td>
<td>p = 0.57</td>
</tr>
<tr>
<td>Pain score (mean)</td>
<td>2.7 ± 1.1</td>
<td>3.2 ± 1.6</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>43 (86%)</td>
<td>40 (80%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (10%)</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2 (4%)</td>
<td>9 (18%)</td>
<td></td>
</tr>
</tbody>
</table>
increased cervical dilatation. It can be conveniently self-administered at home thereby decreasing hospital stay and cost. It also has a good patient acceptability rate.

Numerous methods like the addition of a drop of water, saline or acetic acid to the tablet have been used previously in order to improve absorption by vaginal route [11]. On the other hand, misoprostol was rapidly absorbed through the vascular buccal mucosa completely within 10–15 min in 43 (86%) patients. Range of time absorption of sublingual misoprostol varied from 10 to 46 min after administration.

5. Conclusion

Sublingual route is an effective and convenient alternative to vaginal administration of misoprostol for cervical dilatation. It can be conveniently self-administered at home thereby decreasing hospital stay and cost. It also has a good patient acceptability rate.

References