INTRODUCTION

There is no general agreement about the ideal management of the women with pre-labour rupture of membranes (PROM). Both expectant management and induction of labour are currently practiced in modern obstetrics. However, induction of labour decreases the risk of maternal and neonatal infections and increases maternal satisfaction.1

The usual options for induction of labour in women with PROM are medical methods including oxytocin, prostaglandins and combination of both.2 Oxytocin only affects uterine contractions so is less likely to be effective in presence of unfavourable cervix. Prostaglandins especially PGE2 have been used successfully for cervical ripening and for induction of labour since early 1970's, however, these are expensive and require refrigeration for storage. Misoprostol, which is a methyl ester of prostaglandin E1 is a recent addition to the list of the prostaglandins. It was originally marketed for the treatment of duodenal ulcer but also has uterotonic properties and is useful for cervical ripening.3 It is not licensed at present for the induction of labour, but various groups successfully used the agent by oral or sublingual routes for the induction of labour on the basis of its effect on uterine contractions.4,5

Currently, misoprostol is considered at least as effective as other methods in inducing labour when the cervix is immature.6 Its off label indication for induction of labour has been endorsed by the American College of Obstetricians and Gynaecologists and Royal College of Obstetricians and Gynaecologists.7,8

Misoprostol is easily stored at room temperature and has only a few systemic side effects.9 Furthermore, it is cost-effective as compared to the commercial dinoprostone prostaglandin preparations for the induction of labour in women with an unfavourable cervix. This agent is especially relevant for a country like Pakistan with scarce economic resources and high temperature.10 However, the safest and most effective dosage and route of administration of the drug is generally not yet agreed. As yet, there is no published report about the comparison of oral versus sublingual administration of misoprostol for PROM at term in Pakistani population.

ABSTRACT

Objective: To compare the efficacy of sublingual with oral misoprostol for induction of labour in primigravida with pre-labour rupture of membranes at term.

Study Design: Randomized controlled trial.

Place and Duration of Study: Department of Obstetrics and Gynaecology Unit-II, Sir Ganga Ram Hospital, Lahore, from June 2004 to January 2006.

Methodology: The study included 100 primigravida with singleton pregnancy at term, having pre-labour rupture of membranes and unfavourable Bishop score with no contraindication of induction of labour, vaginal delivery or misoprostol use. The cases were randomized into two equal groups, A and B. Women in the group A were given 100 μg of misoprostol orally at an interval of 4 hours to a maximum of 2 doses while patients in the group B were prescribed the medicine sublingually (50 μg, 4 hourly, maximum of 2 doses). Induction to delivery interval, mode of delivery and fetomaternal complications were main outcome measures of the study.

Results: In the sublingual misoprostol group (B), 92% women delivered within 12 hours of induction while 84% of subjects delivered in this time period in oral group (A, p < 0.05). There was no failed induction in either group. Regarding dosage, 64% of women delivered with single dose in group B while only 32% delivered with single dose in group A (p < 0.05). The frequency of vaginal delivery was 92% in group B versus 80% in group A, while rate of caesarean section was 8% in the group B and 20% in the group A, which is statistically insignificant. No significant fetomaternal complications were seen in both groups.

Conclusion: The efficacy of sublingual misoprostol in the dosage of 50 μg was comparable to 100 μg oral dose for the induction of labour in the primigravida at term with pre-labour rupture of membranes.

Therefore, the aim of the present study was to compare the efficacy and safety of sublingual with oral misoprostol for induction of labour in primigravidae at term with PROM.

**METHODOLOGY**

This randomized controlled trial was conducted in the Department of Obstetrics and Gynaecology, Unit-II at Sir Ganga Ram Hospital/Fatima Jinnah Medical College, Lahore, from June 2004 to January 2006 after obtaining approval by Institutional Ethical Review Board.

A total of 100 live singleton primigravidae at term with cephalic presentation who were diagnosed to have prelabour rupture of membranes, normal fetal heart tracing and unfavourable (< 5) Bishop score were recruited in this study after informed consent. Exclusion criteria were known hypersensitivity to the use of prostaglandins, asthmatic, and subjects having uterine contractions, chorioamnionitis, macrosomia, growth retardation, previous uterine surgery and any contraindication of vaginal delivery.

In each case, detailed evaluation was carried out by complete history, general physical and systemic examination at the time of admission. Ruptured membrane was diagnosed by sterile speculum examination. Vaginal examination was carried out under sterile condition to assess Bishop score. Fetal well-being was assessed by admission cardiotocography (CTG) in each case. Induction of labour with misoprostol was planned 6 hours after rupture of membranes.

The cases were randomized into two equal groups. A sampling frame was drawn of all patients coming with the above-mentioned criteria. Random number table was used to draw the list for both the groups. All women in the group A were induced with oral misoprostol 100 µg, 2 doses with an interval of 4 hours, while the patients in the group B were induced with sublingual misoprostol 50 µg, 2 doses 4 hours apart. However, the second dose was only given in both groups if Bishop score remained unfavourable and the uterine contractions did not start or were mild at that time. Cardiotocography was repeated before administration of second dose and intermittently during labour.

Partogram was maintained in each case. If the progress of labour was slow in active phase according to partogram and the CTG trace was normal, oxytocin infusion in normal saline (1 milli unit/min) was given for augmentation of labour and increased at half hourly interval.

Outcome measures of the study were induction to delivery time, augmentation with oxytocin, tachysystole (at least 6 contractions in 10 minutes during two consecutive 10 minutes), hyperstimulation (presence of tachysystole or prolonged contraction > 2 minutes, accompanied with non-reassuring fetal heart pattern), nausea, vomiting, pyrexia after administration of agent and in first post natal day, mode of delivery and fetal outcome in terms of Apgar score at one and five minutes of birth, admission to neonatal intensive care unit (NICU) and perinatal death. These variables were recorded on a specially-designed proforma.

The data was analyzed with SPSS version 10.0 software. The group A and B were compared for dosage, induction delivery interval 12 hours or more, mode of delivery and fetomaternal complications using chi-square as the test of significance with p < 0.05 as level of significance.

**RESULTS**

During the study period, 100 primigravidae with PROM and unfavourable Bishop score at term were selected for induction of labour. All women were divided randomly into two groups, A and B. There was no significant difference with respect to the mean age and estimated gestational age between the groups. Fifty women (group A) received oral misoprostol while other 50 women (group B) were prescribed the drug sublingually for induction of labour. Oxytocin infusion was given for augmentation of labour, if progress of labour was slow in the active phase.

In the group B, 64% of women were delivered with a single dose of misoprostol as compared to 32% in group A (Table I, \( \chi^2 10.25, df = 1, p < 0.05 \)). Thirty six percent women required augmentation with oxytocin in group B as compared to 70% in group A (Table I, \( \chi^2 2.01, df =1, p < 0.05 \)). About 92% women delivered within 12 hours of induction in the group B and 84% in the group A (Figure 1). The incidence of vaginal delivery was 92% in the group B and 80% in the group A, while the rate of caesarean section was 20% in the group A and 8% in the group B (Table I, \( \chi^2 3.49, df =2, p > 0.05 \)).

No occurrence of prolonged labour, failed induction of labour and hyperstimulation of uterus were noted in either group. However, vomiting was noted in 10% cases in both groups and tachysystole was noted in only 2% cases of both groups. However, vomiting was noted in 10% cases in both groups and tachysystole was noted in only 2% cases of both groups.

**Table I**: Comparison of various parameters in both groups of the study population.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A (oral)</th>
<th>Group B (sublingual)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses of misoprostol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single dose</td>
<td>16 (32.0%)</td>
<td>32 (64.0%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Double dose</td>
<td>34 (68.0%)</td>
<td>18 (36.0%)</td>
<td></td>
</tr>
<tr>
<td>Oxytocin augmentation</td>
<td>35 (70.0%)</td>
<td>18 (36.0%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>38 (76.0%)</td>
<td>45 (90.0%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Instrumental</td>
<td>2 (4.0%)</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Caesarean</td>
<td>10 (20.0%)</td>
<td>4 (8.0%)</td>
<td></td>
</tr>
<tr>
<td>Maternal complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (10.0%)</td>
<td>5 (10.0%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Tachysystole</td>
<td>1 (2.0%)</td>
<td>5 (10.0%)</td>
<td></td>
</tr>
<tr>
<td>Passage of meconium</td>
<td>6 (12.0%)</td>
<td>4 (8.0%)</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Admission of neonate to ICU</td>
<td>6 (12.0%)</td>
<td>4 (8.0%)</td>
<td>&gt; 0.05</td>
</tr>
</tbody>
</table>
cases of group A and in 10% cases of group B (Table I, $\chi^2$ 2.85, df =2, $p > 0.05$).

In 12% of women of group A and 8% of group B, there was a history of passage of meconium (Table I, $\chi^2$ 0.444, df =1, $p > 0.05$). However, the mean Apgar score at 1 and 5 minutes were 7.20 ± 0.45 and 8.95 ± 0.32; and 7.08 ± 0.34 and 9.04 ± 0.28 for group A and B respectively. Six neonates in group A 12% and 4 (8%) in group B were admitted to ICU (Table I, $\chi^2$ 0.444, df =1, $p > 0.05$).

**DISCUSSION**

The present study demonstrated comparable efficacy and safety of 50 $\mu$g of misoprostol sublingually to 100 $\mu$g oral dose for induction of labour in women with PROM at term. Elhassan also concluded the safety and efficacy of 50 $\mu$g misoprostol sublingual while comparing it with oral and vaginal route.\textsuperscript{11} Muzonzini quoted sublingual misoprostol at least as effective as when the same dose was administered orally for labour induction at term.\textsuperscript{12} Shetty using 50 $\mu$g sublingual or orally, suggested that in comparable dose, the sublingual route had better efficacy with no increase in uterine contractility.\textsuperscript{13} In another study, 50 $\mu$g of sublingual misoprostol every 4 hours had the same efficacy and safety profile as compared with 100 $\mu$g orally.\textsuperscript{14} Wolf described that 100 $\mu$g of sublingual misoprostol was more effective than 50 $\mu$g of sublingual misoprostol but the incidence of tachysystole and uterine hyperstimulation syndrome was higher with that dose.\textsuperscript{15} In the present study, 50 $\mu$g of sublingual misoprostol was comparable with a more optimal oral dose of 100 $\mu$g for induction of labour in primigravida at term with PROM. In this study, 92% women delivered vaginally with sublingual misoprostol while 80% were delivered vaginally with oral administration. Shetty reported a vaginal delivery rate of 75.2% with sublingual and 75.1% with oral misoprostol.\textsuperscript{14} In the present study, caesarean section rate (8%) was lower in sublingual group as compared to the rate of 24.8% by Shetty.\textsuperscript{14} The difference was likely to be due to the different selection criteria. In the later study, the indication of induction of labour was variable and mostly the distinction between women with intact and ruptured membranes was not made. In the present study, misoprostol was used for induction of labour only in primigravida at term with PROM. In the present study, no significant maternal side effects were noted in either group, while nausea and vomiting was much higher in another study in addition to headache, fever and chills,\textsuperscript{16} reason for which could be comparatively higher dose. A recent systematic review suggested that low dose misoprostol is more effective than prostaglandin E2 in achieving vaginal delivery within 24 hours without affecting the caesarean section rate.\textsuperscript{17} In the present study, tachysystole was in 10% women with sublingual misoprostol while it was reported to be 9% to 12.5% with 25 microgram sublingual administration at 6 hours interval.\textsuperscript{18,19} There was no case of hyperstimulation in our study while it was 1.6% in both groups as reported by Shetty and 9% by Wolf.\textsuperscript{14,15} Difference could be due to inter observer variations and variable demographic profile of the women in these studies. About 16.8% of the women had vomiting in both groups in Shetty's study while 10% of the presently studied women experienced this side effect.\textsuperscript{14} Bartusevicius reported nausea and vomiting in 5.7 % of women with sublingual route while no vomiting was reported with oral route.\textsuperscript{20,21} None of the presently studied patient had chills and fever in both groups. The trial conducted by Abbasi quoted chills in 12.5% and fever in 2.5% of cases with oral administration.\textsuperscript{22} Regarding neonatal outcome, there was no significant difference in both group in this study which is similar to the study of Shetty.\textsuperscript{14}

**CONCLUSION**

Sublingual misoprostol in dose of 50 mg has the same efficacy and safety profile as compared to 100 mg oral misoprostol for induction of labour in primigravida at term with PROM. Therefore, sublingual misoprostol may be an option for induction of labour in these cases.

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Misoprostol for induction of labour in prelabour rupture of membranes


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