ORIGINAL ARTICLE

Comparison between Sublingual and Vaginal Misoprostol for Labor Induction at Term

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ABSTRACT

Aim: To compare the efficacy and safety of 50 microgram of sub-lingual misoprostol with 25 microgram of vaginal misoprostol administered for labor induction at term.
Design: Randomized control study
Place and duration: Surayya Azeem (waqf) Hospital from May, 2011 to November 2012.
Method: Total of 140 women at term with indication of induction were included in the study. Women were randomized to receive either 50 microgram of sub-lingual misoprostol with vaginal placebo or sub-lingual placebo with 25 microgram of vaginal misoprostol every four hours. The number of women delivering vaginally within 24 hours of labor induction.
Results: 58 women (83%) in the sub-lingual misoprostol and 53 (76%) in the vaginal group delivered vaginally within 24 hours (relative risk RR 1.1). However, the induction to vaginal delivery time was significantly shorter in the sub-lingual group (15 □ 3.7 hrs compared with vaginal group 16.7 □ 4.1 hours. P=0.03). The incidence of tachysystole was more than three fold higher in the sublingual than in vaginal group. 14 versus 4.3%, RR 3.3, 95% (CI) confidential interval 0.9-11.6 but this was not statistically significant. There were no significant differences in the incidence of hypertonus or hyper stimulation syndrome, mode of delivery, intervention for fetal distress or neonatal outcomes between the two groups.
Conclusion: A 50 microgram of sublingual misoprostol four hourly for labor induction at term seems to have similar efficacy as 25 microgram of vaginal misoprostol
Keywords: Labor Induction, Misoprostol, Sublingual & Vaginal

INTRODUCTION

Induction of labor at term in the presence of unfavourable cervix is associated with an increase risk of failed induction and caesarean section. The use of prostaglandin preparation with or without oxytocin infusion is widely recognized and accepted as a standard method of labor induction[1,2].

Misoprostol (Cytotec) is prostaglandin E_1 analogue originally intended for the prevention of gastric ulcers caused by non-steroidal anti-inflammatory drugs.

Although not registered for such use, misoprostol has been widely used for induction of labour[3]. Vaginal misoprostol appears to be more effective than the equivalent dosage administered orally, but is associated with a high risk of uterine hyperstimulation either with or without fetal heart rate (FHR) changes[4,5].

The objective of the study was to compare the efficacy and safety of 50 microgram of sublingual misoprostol with vaginal misoprostol in its currently recommended dose of 25 microgram administered at 4 hours interval for labor induction at term.

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MATERIAL & METHOD

This was double blinded randomized control study performed from May, 2008 to November 2009 at Surraya Azeem Waqf Hospital. Women were eligible for enrolment, if they presented with obstetric or medical indications for labor induction including gestational age more than 41 week (dates confirmed by 2nd trimester ultrasound), prelabor rupture of membranes, chronic, gestational hypertension or mild eclampsia (characterized by blood pressure > 140/90 and <than 160/110mmHg and protein urea > 300mg/l). Gestational diabetes without need for insulin treatment. Additional requirement for enrolment included a singleton live pregnancy at term in the cephalic presentation, absence of active labour, a normal fetal heart rate tracing and unfavourable cervix (Bishop Score ≤ 6). Exclusion criteria were known hypersensitivity to prostaglandin, previous caesarean section or other type of uterine surgery, chorioamnoitis or hyperthermia > 38^0C, the need for immediate birth, ultrasonically estimated oligohydramnios, polyhydramnios, suspicion of fetal malformation, macrosomia or growth restriction and parity >5. Each women was allocated to receive either 50 microgram sublingual misoprostol with vaginal placebo (n=70) or sublingual placebo with 25 microgram of vaginal misoprostol (n=70) every 4 hours (maximum 6 doses). The subsequent dose of

medication was withheld in the presence of any of the following, at least 3 regular uterine contractions in 10 minutes, active phase of labor (defined as regular uterine contractions with cervical dilatation ≥ 3cm), cervix favourable for amniotomy (Bishop score 7,8). If frequency of contractions was < 3 per 10 minutes or contraction pattern was dysfunctional oxytocin infusion was administered not earlier than 4 hours after last misoprostol dose, starting at 1mu / minute until adequate contractions persisted.

Continuous fetal cardiotocography was used throughout the study. To find out whether hypertonus, tachysystole or hyperstimulation syndrome was associated with route of administration of misoprostol, all fetal heart rate graphs were reviewed closely. Tachysystole was defined as at least six contractions per 10 minutes during two consecutive 10 minutes period. Hypertonus was defined as a single uterine contraction lasting for two minutes or more. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with non-reassuring FHR pattern. All the episodes of hyperstimulation syndrome were included in the analysis regardless of the interval from the time of misoprostol administration to the occurrence of the abnormal fetal heart rate pattern. Recognized episodes of hyperstimulation were managed by intra-uterine resuscitation, which included stopping the oxytocin infusion, maternal repositioning, hydration and oxygen administration. Epidural analgesia was used upon patient's request when cervical dilatation ≥ 4cm and regular uterine contractions were maintained. Cord blood samples for arterial acid base analysis were taken after each delivery.

The primary outcome measure was the number of women delivering vaginally within 24 hours of first dose of misoprostol in two groups. Secondary outcome variables included number of women delivering within 12 hours of induction, the interval from the start of induction to vaginal delivery, the number of misporstrol doses given, the need of oxytocin augmentation, the mode of delivery, uterine hyperstimulation rate and maternal adverse effects. A neonatal outcome included birth rate, incidence of meconium stained amniotic fluid, umbilical arterial pH values and neonatal intensive care unit admission.

Statistical analysis was performed using small SPss system. The means between groups were compared using an unpaired two tailed students 't' test. Categorical variables were analyzed using chi square test. $P<0.05$ was considered statistically significant. For discrete data, relative risk (RR) with 95% confidence interval (CI) was used.

RESULTS

A total 350 women were scheduled for labor induction within study period. 140 women consented and were enrolled in the study. 72 sub-lingual groups and 72 vaginal groups. Demographical characteristics and the indications for labor induction were similar in two groups (Table 1).

There were 49(70%) primiparous women in sublingual groups and 43(61%) in the vaginal group and 50 & 51% inductions were post term pregnancies in the two groups respectively.

The number of participants delivering vaginally in less than 24 hours from start of induction was not significantly different between two groups. In sublingual group, 58 women (83%) and in the vaginal group 53 women (76%) delivered vaginally within 24 hours (RR 1.1, 95% CI 0.9–1.3). There were also a similar number of women delivered vaginally within 12 hours of induction in the sublingual (19%) and vaginal (13%) groups (RR 1.4, 95% CI 0.7-3.2). However, the interval from the start of induction to vaginal delivery was significantly shorter in the sublingual misoprostol group (15± 3.7 hours) compared with vaginal misoprostol group (17±4.1 hours P=0.03). The mean number of misoprostol doses used was significantly lower in the sublingual group than in the vaginal group. There were no differences between the two groups in epidural analgesia requirement or oxytocin used. The modes of delivery and indication for caesarean section were not different in two groups. Seven cases (10%) in the sublingual and 8 cases (11%) in the vaginal group required emergency caesarean section for fetal distress (Table 2).

The incidence of tachysystole was more than three fold higher in the sublingual group than in vaginal group. No difference in the incidence of hypertonus was noted. Five women in each group had uterine hyperstimulation syndrome. There were no differences in the neonatal outcomes in the two groups (Table 3). Similar number of neonates in each group had Apgar score < 7 at five minutes and an umbilical artery pH < 7.16. The number of babies requiring NICU admission was similar in both groups. The indications for intensive care unit admission were neonatal respiratory distress syndrome in two cases, in the sublingual group, suspected congenital infection and neonatal respiratory distress syndrome in the vaginal group. The incidence of maternal adverse effect was similar in the sublingual and vaginal group. Nausea and vomiting was observed in four women (5.7%) in sublingual group and 5 (7.1%) in the vaginal group.

Table 1: Main characteristics of women in the trial group

	50 microgram of sublingual misoprostol (n=70)	**25 microgram of vaginal misoprostol (n=70)**
Age (years)	27 ± 4	27 ± 4
Parity	1.5 ± 0.8	1.5 ± 0.7
Gestational age	49 (70)	43 (61)
Bishop Score	41 ± 0.9	40 ± 1.1
Indication for induction post term (>41 weeks)	35 (50)	36 (51)
Hypertension / mild pre-eclampsia	18 (26)	15 (21)
Gestational diabetes	10 (14)	10 (14)
Pre-labor rupture of membranes	7 (10)	9 (13)

Values are given as mean=SD or number (percentages)

Table 2

	50 microgram of sublingual misoprostol (n=70)	**25 microgram of vaginal misoprostol (n=70)**	**RR (95% CI) OR p value**
Mode of delivery			
Spontaneous vaginal delivery	53(76%)	54(77%)	1.0(0.8–1.2)
Instrumental delivery	5(7.1%)	2(2.9%)	2.5(0.5-12.5)
C-section	12(17%)	14(20%)	0.9(0–1.7)0.85
Indication for C-section			
Fetal distress	7(10%)	8(11%)	
Arrest of labor first stage	3(3.4%)	2(2.8%)	
Arrest of labor second stage	2(2.9%)	3(3.4%)	
Prolapse of umbilical cord	0	1(1.4%)	
Epidural anaesthesia	30(43%)	35(50%)	0.9(0.6-1.2)
Oxytocin use	34(49%)	34(49%)	1.0(0.7-1.4)
Tachysystole	10(14%)	3(4.3%)	3.3(0.9-11.6)
Hypertonus	2(2.3%)	3(4.1%)	0.7(0.3-2.9)
Hyperstimulation syndrome	5(7.1%)	5(7.1%)	1.0(0.3-3.3)

Values are given in numbers (percentages)

DISCUSSION

The results show that 50 microgram of sublingual misoprostol resulted in a shorter delivery interval, with a lower number of misoprostol doses required and a higher number of women delivered vaginally after single dose of misoprostol compared with those given 20 microgram of vaginal misoprostol. However, the number of women delivered vaginally within 12 to 24 hours of induction was similar, suggesting that above mentioned statistically significant differences have no major clinical significance. Further more, the incidence of tachysystole was more than 3 fold higher in sublingual than in the vaginal group.

There were no significant differences between the two groups with respect to the number of women experiencing hyperstimulation syndrome, or with regard to the mode of delivery or neonatal outcome, bearing in mind that our sample size was not powered to evaluate the parameters for safety.

Sublingual route has showed to produce significantly higher serum peak concentration of misoprostol than either oral or vaginal administration. In addition, the area under the curve for plasma level over four or six hours was significantly greater following sublingual administration than for either oral or vaginal administration. In the sublingual application misoprostol has effects on the myometrium at least as rapid as effect on uterine contractility as oral administration and is similar to vaginal adminsitration. These findings may explain the more rapid delivery with sublingual misoprostol in our study. It must, however, be emphasized that we compared a higher sublingual dose (50 microgram) with a lower dose of vaginal misoprostol 25 microgram. This approach was adopted because data from two studies comparing 50 microgram of sublingual with 50 or 100 microgram of oral misoprostol for labor induction, suggested that 50 microgram of misoprostol administered sublingually might be the optimal dose that maintains the balance between efficacy and safety , and a dose that might not have been effective was not acceptable. Different routes of misoprostol administration for labor induction necessitate care, balancing the benefits of shorter time delivery against the risk (uterine hyperstimulation, adverse neonatal and maternal outcomes). The considerably higher rate of tachysystole with 50 microgram of misoprostol given sublingually when compared with vaginal administration of 25 microgram 15 versus 4.3% RR 3.4, 95% CI 1.0 – 11.9 . Similar rates of hypertonus and hyperstimulation syndrome was observed. This

suggests that avoidance of the direct effect on the cervix did not reduce the risk of excessive uterine activity. Meanwhile, recent findings regarding the effect of sublingual misoprostol on uterine contractility might explain not only the shorter induction to delivery interval but also the increase in excessive uterine activity compared with vaginal misoprostol. Overall, rates of uterine hyperstimulation syndrome were not higher 7.1% than in other clinical trials of 50 microgram of sublingual misoprostol for labor induction[5]. Despite the higher rate of tachysystole in the sublingual misoprostol group, the neonatal outcomes were similar in both the trial groups. Comparable neonatal outcome were noted in another study after 50 microgram of misoprostol administered sublingually or vaginally. There has been no previous report in the literature of a comparison of 50 microgram of sublingual misoprostol with 25 micorgram of vaginal misoprostol used every four hours for labor induction at term. The serum concentration of sublingual misoprostol is greater than those following vaginal administration so the possibility of rare but serious adverse events (uterine rupture) should not be forgotten. However, sublingual dose for labor induction is attractive because of ease of administration, less frequent need for vaginal examination, greater freedom of position, the possibility of its use and despite vaginal bleeding or ruptured membranes. Even though it was assessed in the present study, we assume higher patience acceptance of sublingual route, which was observed with oral when compared with vaginal administration. On the basis of our results, we find no persuasive benefits to the use of 50 microgram of sublingual misoprostol for labor induction at term compared with 25 microgram of vaginal misoprostol. The use of sublingual misoprostol is associated with more tachysystole but no increase number of women delivering vaginally within 24 hours when compared with vaginal misoprostol.

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