The Professional Medical Journal
www.theprofesional.com

ORIGINAL PROF-2544

# LABOUR INDUCTION;

## USE OF SUBLINGUAL MISOPROSTOL VERSUS OXYTOCIN IN CASE OF RUPTURED MEMBRANES AT TERM.

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**ABSTRACT…Objective:** To compare the efficacy of misoprostol 50ug (sublingual) in comparison with oxytocin infusion than for induction of labour in cases of PROM (premature rupture of membrane at term). **Design:** Prospective randomized study. **Setting:** Mujahid Trust Hospital, Faisalabad. **Duration:** Conducted from Dec 2006 to April 2008. **Methods:** Women were randomized to receive either 50 microgram of sublingual misoprostol every 4 hours with Ringer's lactate solution or oxytocin infusion 10 IU in one litre of Lactated Ringer's solution with a sublingual placebo. **Main outcome measures:** The number of women delivering vaginally within 24 hours of labour induction. **Results:** Fifty two women (83%) in misoprostol group and 48 (77 %>) in oxytocin group delivered vaginally within 24 hours [relative risk (RR)1.1. However, the induction to vaginal delivery was significantly shorter in the misoprostol group 15+3.7 hours compared with the oxytocin group 18+4.1. The incidence of tachysystole was more than three folds higher in misoprostol than in the oxytocin group (14%) versus 4.3%) RR3.3) but this was not statistically significant. There was no significant difference in the incidence of hypertonus or hyperstimulation syndrome, mode of delivery intervention for fetal distress or neonatal outcomes between the two groups. **Conclusions:** The group of women received misoprostol for labour induction were found more successful in achieving vaginal delivery in comparatively shorter time and more acceptable to patients. Further studies on safety with large numbers of women need to be conducted before routine use.

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**Article received on:**
05/06/2014
**Accepted for publication:**
10/10/2014
**Received after proof reading:**
16/10/2014

**Key words:** labour, misoprostol, PROM, oxytocin, vaginal delivery

**Article Citation:** Ameen S. Labour Induction; Use of Sublingual Misoprostol Versus Oxytocin In Case of Ruptured Membranes at Term. Professional Med J 2014;21(5):1070-1074.

## INTRODUCTION

Premature rupture of membranes (PROM) is defined as rupture of fetal membranes occurring prior to the onset of labour. Its management is one of the most controversial topics in obstetrics. The incidence of PROM has remained constant through the years and has been reported to be between 3-18.5%[1]. As in most of PROM we found unfavourable cervix and needs induction of labour. Induction of labour is associated with an increased risk of caesarean section and its comphcations[2].

The use of prostaglandin preparations with or without oxytocin infusion is widely recognized and accepted method of labour induction has been shown to reduce induction time and risk of failed induction[1,2]. However natural prostaglandin are expensive, inconvenient to use and difficult to store as they require refrigeration.

Misoprostol (Cytotec; Pharmacia) is a prostaglandin El analogue originally intended for prevention of gastric ulcers caused by non steroidal anti- inflammatory drugs. Although not registered for such use it has been used widely for induction labour[3]. It had been given by various routes oral, vaginal and submucosal. Vaginal misoprostol appears to be more effective than oral but is associated with higher risk of uterine hyperstimulation[4,6]. That might be due to avoidance of first pass effects of the gastrointestinal and hepatic system and direct effect on cervix and uterus[7,8].

Recently published a pharmokinetics studies shows that sub lingual misoprostol used for first trimester abortions produce earlier higher concentrations of misoprostol than vaginal and rectal routes[9,10]. So sublingual route is expected to be more effective and avoiding a direct effect on the cervix might reduce the risk of uterine hyperstimulation make it more safe.

The objective of this study was to compare efficacy and safety of 50 microgram sublingual misoprostol at 4 hourly interval with oxytocin infusion alone for labour induction in cases of PROM. We decided to use 50$\mu$g misoprostol sublingual because its safety has been shown in many studies when compared to other routes[11].

## MATERIAL AND METHOD

This was a randomized controlled study performed from Dec2006 to April2008 at Mujahid trust hospital Faisalabad. Women enrolled those presented with history of leakage (confirmed by per speculum examination) per vaginum at term >37 weeks and did not have complications as preeclamsia, previous caserean section, multiple gestation IUGR or. sign and symptoms of chorioamnionitis. Cases of mild hypertension and gestational diabetes without insulin were not excluded.

A total of 124 women were involved in study .Two types of induction methods were used alternatively. Those who(62) were given misoprostol every 4 hours, the subsequent dose was withheld in the presence of following ;at least three regular uterine contractions in 10 minutes, active phase of labour (regular uterine contractions with cervical dilatation >3cm).And Ringer's solution was also given in active phase of labour to all patients .And other 62 were induced with oxytocin infusion 10 IU in one litre starting at rate of Imiu/ minute increasing every fifteen minutes until adequate contraction persist. Prophylatic antibiotics were given to all patients. Continuous fetal cardiotocography was used throughout the study. To determine whether hypertonus, tachysystole or hyperstimulation syndrome was associated with the method of induction, all the FHR graphs were reviewed before final analysis. Tachysystole was defined as at least six contractions per 10 minutes during two consecutive 10 minutes periods. Hypertonus was defined as single uterine contraction lasting for 2 minutes or more. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with a non reassuring FHR pattern (fetal tachycardia, late decelerations, severe variable deceleration or loss of FHR variability). Recognised episodes were managed by resuscitation including stoppage of oxytocin, maternal repositioning, hydration and oxygen administration. Analgesia requirement also noted in both groups. Epidural analgesia was used on patient's request when cervical dilatation was >4cm and regular uterine contractions were maintained. The primary outcome measure was the number of women delivering vaginally within 24 hours of the first dose or start of oxytocin. Secondary outcome included number of women delivering within 12 hours of induction. The interval from induction to vaginal delivery. The number of misoprostol doses given, mode of delivery, uterine hyperstimulation and maternal satisfaction. Neonatal outcome included birth weight incidence of meconium stained amniotic fluid, neonatal care unit (NICU) admission.

## RESULTS

A total of 124 women who presented with pre labour rupture of membranes were enrolled in study 62 to misoprostol group and other 62 to oxytocin group. Demographic characteristics of the women were similar in the two groups (Table I) .There were 41(70%) primiparous women in misoprostol group and 34(60%) in oxytocin group.

| | Misoprostol group (n=62) | Oxytocin group (n=62) |
|---|---|---|
| Age | 20+5.2 | 22+5.3 |
| Parity | 1.5+0.8 | 1.5+0.7 |
| Primiparas | 41 | 34 |
| Gestational age (weeks) | 37+2.3 | 37+3.5 |
| Bishop score | 0-3 | 0-3 |

**Table-I. Main characteristics of women in the trial groups**

The number of participants delivering vaginally in less than 24 hours from the start of induction was not significantly difference between the two groups. In the misoprostol group 52 and in oxytocin group 48 women vaginally within 24 hours RR1.2 (95) There was a similar number of women delivered vaginally within!2 hours of induction in 21 misoprostol group and oxytocin 12 group RR1.4(95) However the interval from the start of induction to vaginal delivery was significantly shorter in sublingual misoprostol

Group 14+3.7hours compared with oxytocin group 18+4.2, P=0.04. The mean number of doses misoprostol used was 3-4 on average (table II). There was difference in analgesia requirement in two groups, it was two times more in oxytocin group. The modes of delivery and indications for caesarean section were not different in two groups. Five cases in misoprostol group and seven in oxytocin group required emergency caesarean section for fetal distress (table III).

| | Misoprostol group (n=62) | Oxytocin group (n=62) | RR |
|---|---|---|---|
| Vaginal delivery <24hrs | 52 | 46 | 1.2 |
| Vaginal delivery <12hrs | 13 | 09 | 1.4 |
| Induction delivery interval | 14 | 18+4.2 | 0.04 |

Table-II. Duration of labour in two groups

| | Misoprostol group (n=62) | Oxytocin group (n=62) | RR |
|---|---|---|---|
| **Mode of delivery** | | | |
| Spontaneous vaginal delivery | 48 | 45 | 1.0 |
| Instrumental vaginal delivery | 04 | 03 | 2.5 |
| Caesarean section | 10 | 14 | 0.9 |
| **Indications caesarean delivery** | | | |
| Fetal distress | 06 | 07 | |
| Arrest of labourist stage | 02 | 04 | |
| Arrest of labour,2"''stage | 02 | 02 | |
| Prolapse of umbilical cord | - | 01 | |
| Epidural analgesia | 08 | 15 | 0.5 |
| Tachysystole | 07 | 02 | 3.3 |
| Hyperstimulation syndrome | 05 | 05 | 1.0 |
| Pyrexia | 01 | 03 | 3.0 |

Table-III. Maternal outcomes in labour

The incidence of tachysystole was 3 fold higher in the sublingual misoprostol group than oxytocin group 14 versus 4.3 RR3.3, no difference in hypertonus was noted. Four women in each group had hyperstimulation syndrome (table III), it was observed after first dose of misoprostol in3 cases and one after second dose. In oxytocin group 2 occurred in first five hours and 2 after 8 hours. When fetal condition does not improve after resuscitation emergency caesarean section performed. The infant delivered in misoprostol group required immediate resuscitation but did well thereafter; two delivered in oxytocin group did not need resuscitation. There was no difference in the neonatal outcome in the two groups (table IV).

| | Misoprostol group (n=62) | Oxytocin group (n=62) | RR |
|---|---|---|---|
| Birth weight (Kg) | 3.2+0.4 | 3.2+0.3 | 1.2 |
| Apgar score <7 at 5 minutes | 02 | 02 | 1.0 |
| Meconium passage | 12 | 12 | 1.0 |
| NICU admission | 02 | 02 | 1.0 |

Table-IV. Neonatal outcome

Maternal satisfaction was much higher in misoprostol group than oxytocin as women need not to confine in bed from start of induction. The incidence of side effects was similar in two groups. Nausea and vomiting was observed in four in misoprostol group and two in oxytocin group There was one case of pyrexia in misoprostol group compared with three (3,4) in oxytocin group. The caesarean section rate in sublingual misoprostol group was 10(6.2%) compared with 14 (22.5%) in oxytocin group. However difference in mode of delivery was not statistically significant. p=0.38.

## DISCUSSION

The results show that 50 microgram of misoprostol resulted in a shorter induction to delivery interval time with a fewer number of misoprostol doses as compared to other group. However, the number of women delivered vaginally within 12-24 hours of induction was almost similar suggesting that above mentioned statistically significant difference have no major clinical significance. The results are consistent with other systematic reviews comparing misoprostol with oxytocin for cervical ripening and labour induction, which found lower rates of caesarean delivery among those receiving misoprostol[18]. Among indications of caesarean sections, it was higher due to arrest of labour in oxytocin group that in turn increase the maternal morbidity making patients acceptance more in misoprostol group. Further the incidence of tachysystole was more in misoprostol group. There was no difference in

respect of hyperstimulation syndrome, neonatal outcome that might be due to small sample size. The sublingual route has been shown to produce significantly higher serum peak level than oral or vaginal administration in a recent study evaluating different routes M. This may explain the more rapid delivery with misoprostol in our study We choose 50 microgram misoprostol because it has been shown in another study to be optimal dose that maintains balance between efficacy and safety[11,12] and fewer side effects like nausea and vomiting. Considerably higher rates of tachsystole with 50 microgram misoprostol given sublingual was a cause for concern even though similar rates of hypertonus and hyperstimulation syndrome was observed This suggest that avoidance of direct effect on the cervix did not reduce the excessive uterine activity as noted before 8. In our study there was no difference in hyperstimulation syndrome than in other clinical trial of 50 microgram of sublingual misoprostol for labour induction 5-8[15,16]. In two other though hyperstimulation syndrome rate was low 1.6[11,12] but caesarean section due to it was higher, that may reflect difference ift definition and labour management. Despite the higher rate of tachysystole in the misoprostol group the neonatal outcome was comparable to other studies on misoprostol[11,5]. There are concerns expressed in Cochrane database regarding excessive uterine, particularly uterine rupture associated with vaginal misoprostol[16]. Given that serum concentration of sublingual misoprostol are greater than those following vaginal administration, the possibility of rare but serious adverse events should not be forgotten. However sublingual misoprostol is attractive because of ease of administration, less need for vaginal examination, greater freedom of position and possibility of its use in cases of ruptured membranes, we find patients acceptance was higher, with sublingual route which was also seen when compared oral with vaginal misoprostol[17]. We believe further large studies on safety with large number of women need to be conducted, to advocate its use in cases of PROM for labour induction.



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