

## ORIGINAL ARTICLES

## A COMPARISON OF ORAL MISOPROSTOL AND VAGINAL PROSTAGLANDIN E2 TABLETS FOR INDUCTION OF LABOUR AT TERM

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## ABSTRACT

**Objective:** To compare the efficacy and safety of oral misoprostol with prostaglandin E2 vaginal tablets for ripening of cervix and induction of labour at term.

**Study Design:** A non blinded, randomised, controlled trial.

**Place and Duration of Study:** Department of Obstetrics and Gynaecology, Pakistan Air Force Hospital, Air Headquarters Islamabad from July 2005 to January 2006.

**Patients and Methods:** Hundred pregnant women with a singleton live pregnancy, at term (37-42 weeks) with cephalic presentation were selected for induction of labour for various indications having a Bishop's score of  $<$  or  $=$  5. These women were randomly allocated to receive either 100 $\mu$ gm of misoprostol orally repeated four hourly to a maximum of four doses or a 3mg PGE2 tablet vaginally repeated six hourly to a maximum of two doses.

Main outcomes measured: Cervical score before and after oral misoprostol and prostaglandin E2 vaginal tablets, vaginal birth within 24 hours of first prostaglandin dose, no of patients having failed induction, caesarean sections (all), caesarean section for fetal distress and uterine hyperstimulation with associated changes in fetal heart rate.

**Results:** Over the period of one year 100 women were recruited for the study, 50 to the misoprostol group and 50 to the vaginal prostaglandin E2 group. There was no significant differences between the two treatment groups in the primary outcomes: improvement in bishops score in both the groups, no of patients with failed induction in both the groups misoprostol 2/50 (4%) v PGE2 3/50 (6%) , vaginal birth achieved in 24 hours (misoprostol 27/50 (54%) v PGE2 29/50 (58%), caesarean sections 14/50 (28%) v 12/50(24%) caesarean section for fetal distress 4/50((8%) v 5/50(9%); uterine hyperstimulation with fetal heart rate changes 2/50 ((4%) v none in the PGE2 group.). Neonatal outcomes were not significantly different in the two groups.

**Conclusion:** Oral misoprostol in strength of 100  $\mu$ gm has similar efficacy to vaginal PGE2 tablets for ripening of cervix and induction of labour, although difference in outcomes between the two routes is not significant but data on optimal dosage regimes and safety are still lacking.

**Keywords:** Bishop's score, Labour induction, Oral misoprostol, Prostaglandin E2.

## INTRODUCTION

Labor induction is a common obstetric intervention, generally indicated when the benefits of delivery to the mother or fetus outweigh the potential risks of continuation of pregnancy, and presence of an unfavorable cervix presents the greatest challenge in most of these cases<sup>1</sup>. In 1930 Calkins and colleagues found out that the length, thickness and particularly the consistency of cervix were very important parameters<sup>2</sup>. In 1955 Edward H. Bishops devised a cervical scoring system, he found out that nulliparous women with a score of less than 3 have a 23 fold increased risk and

multiparous women with a score less than 3 have a six fold increased risk of failed induction. These failed inductions result in a higher caesarean delivery rate of more than 20%<sup>3</sup>.

Labour can be induced pharmacologically by prostaglandins and oxytocin and meta analyses have shown that prostaglandins are superior to oxytocin in ripening of cervix<sup>4</sup>. Widespread use of prostaglandins is limited because of their high cost and thermal instability and oxytocin is required in most of the cases following initial cervical ripening with PGE2 tablets<sup>5</sup>.

A synthetic prostaglandin E1 (PGE1) analogue misoprostol has been a subject of numerous articles since the past few years describing its use as a cervical ripening agent, because majority of patients experience regular

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uterine contractions soon after the initial dose, it should be considered primarily as a labour inducing agent<sup>6</sup>. Trials published so far show intravaginal misoprostol to be as effective as PGE<sub>2</sub> for labour induction<sup>7</sup>, moreover here is no evidence that oral misoprostol is inferior to vaginal misoprostol, rather it has lower rates of hyper stimulation because systemic bioavailability of oral misoprostol is three times lesser than the vaginally administered misoprostol<sup>8</sup>.

Misoprostol which can be given by various routes is not yet licensed for induction of labour but its use is becoming increasingly common because it is inexpensive, highly effective and stable at room temperature so ideal for setups where storage facilities are not available. The main concern with its use is excessive uterine contractions which can lead to adverse maternal and perinatal effects especially with a higher dose. Some trials also indicate increased frequency of meconium passage, neonatal acidemia and cesarean delivery for fetal distress in women receiving higher doses of misoprostol<sup>9</sup>. Many studies are being carried out in the past few years to find its optimal dose, route of administration, interval between the doses for induction of labor, and comparison with oxytocin and prostaglandin E<sub>2</sub><sup>10</sup>.

The purpose of this study was to compare prostaglandin E<sub>2</sub> vaginal tablet with oral misoprostol for cervical ripening and induction of labour at term in terms of efficacy safety and cost effectiveness.

## **MATERIAL AND METHODS**

This randomized controlled trial was conducted in Gynaecology and Obstetrics department of Pakistan Airforce Hospital Islamabad from July 2005 and January 2006,

Sampling technique used was convenience sampling by lottery method, inclusion criteria was singleton pregnancy of 37 weeks or more with normal cephalic presentation, reassuring fetal status, an unfavorable cervix (bishop's score < or = 5), and intact membranes.

Women with a bishop's score > 5, multiple pregnancies, parity over 5, previous cesarean

section, breech presentation, placenta praevia, polyhydramnios and congenitally abnormal fetus were excluded from this study.

100 women admitted in obstetric ward having the inclusion criteria were selected for this study. Baseline data included maternal age, parity, gestational age, indication for induction, and cervical score prior to induction. All patients undergoing the trial had a pre induction cardiotocography (CTG) to confirm the fetal status and wellbeing. After a fully informed consent women were randomly assigned to receive oral Misoprostol or vaginal PGE<sub>2</sub> tablet.

Patients assigned to the oral misoprostol received a 100 µgm Misoprostol tablet (Arthotec half tablet) orally with a sip of water, repeated after four hours to a maximum of four doses; the second group received a 3 mg PGE<sub>2</sub> vaginal tablet inserted in the posterior vaginal fornix, repeated after six hours if needed to a maximum of 2 doses. Fetal wellbeing was confirmed by repeating CTG prior to every dose of prostaglandin. Cervical score was reassessed six hours after the first and the second dose to assess any improvement. When regular uterine contractions started or the cervical score improved to 8 or more the patient was shifted to the labour room and an artificial rupture of membranes (ARM) was done. Use of Oxytocin was done according to the ward protocol and was not started less than 6 hours after the last dose of prostaglandin and was used only in patients which did not show a progress of labour. Vaginal examination was repeated at 2 hourly intervals and partogram was maintained as per labour ward routine. Fetal heart rate was recorded half hourly CTG was repeated 4 hourly Patients were closely observed for any hyper stimulation (a uterine contraction lasting for > 2 minutes) or fetal distress (fetal tachycardia, fetal bradycardia, non-reactive CTG, reduced beat to beat variability on CTG), continuous CTG monitoring was done during labour especially in cases of hyper stimulation or meconium staining. If cervix was found to be unfavorable even after four doses of misoprostol or two doses of PGE<sub>2</sub> pessary then induction was

considered to have failed and then patient was advised to undergo a caesarean section. Patients with poor progress during labour and fetal distress were also shifted to the theatre for caesarean section.

Data was collected on a specially designed performa, for quantitative variables as age, gestation, induction to delivery time means and

PGE2 group ( P value 0.3978) , there were 37 (74%) primigravidas and 13 (26%) multigravidas in misoprostol group, and there were 30 (60%) primigravidas and 20 (40%) multigravidas in PGE2 group, post maturity was the most common indication for induction of labour in both groups, 18 (36%) in misoprostol group and 20 (40%) in PGE2 group were induced due to post maturity, 12 (24%)

**Table-1: Mean comparison of cervical score.**

	Misoprostol n=50	PGE2 n=50	p-value
Pre-induction cervical score	2.41 ± 0.97	2.62 ± 1.06	0.29
Post induction Cervical score (12 hours after first dose)	5.96 ± 1.51	6.62 ± 1.24	0.01

**Table-2: Percentage distribution of mode of delivery.**

	Misoprostol n = 50	PG E2 n = 50	p- value
Vaginal delivery	36 (72%)	38 (76%)	0.648
Caesarean section	14 (28%)	12 (24%)	

**Table-3: Complications during delivery in both the groups.**

Indications	Misoprostol n=50	PGE2 n=50	p-value
No given oxytocin	20 (40%)	14(28%)	0.21
Meconium staining	5 (10%)	4 (8%)	0.99
Uterine Hyper stimulation	2 (4%)	0 (0%)	0.495
Failed Induction	2 (4%)	3 (6%)	1.0

standard deviations were calculated using SPSS windows 10 and for quantitative variables like indication of caesarean sections, indications for induction, dose requirement, induction to delivery interval, maternal and neonatal complications percentages were presented. Independent t test was applied on quantitative variables (Table-1) and Fisher's exact and chi square test for qualitative variables (Table-2 and 3).

## RESULTS

A total of hundred women were recruited for this study out of which 50 women were given oral Misoprostol 100 µgm 4 hourly for a maximum of 4 doses and 50 PG E2 3mg vaginally every 6 hours to a maximum of 2 doses.

Age in misoprostol group was 27.50 ± 4.54 years and 28.40 ± 5.90 years in PGE2 group ( P value 0.3947) , gestation was 39.7±1.10 weeks in misoprostol group and 39.9 ± 1.25 weeks in

were induced due to PROM, 10 (20%) due to PIH , 7(14%) due to diabetes, and 3 (6%) due to oligohydramnios in misoprostol group and 10 (20%) were induced due to PROM , 9 (18%) due to PIH, 6 (12%) due to diabetes, and 5(10%) due to oligohydramnios in the PGE2 group. 27 out of misoprostol group i.e. 54% and 29 out of PGE2 group i.e. 58% delivered in 24 hours of start of induction. Out of the 14 patients in misoprostol group 6 (42%) had failed induction, 4 (28.57%) patients had fetal distress, 2 (7.1%) had failed progress of labour and 2 (7.1%) had failed instrumental delivery, out of the 12 patients who had caesarean section in PGE2 group 5 (41.6%) had fetal distress, 5 (41.6%) had failed induction, 19 (4.1%) had failed progress, and 1 (4.1%) had failed instrumental delivery, there was meconium staining in 4 patients with fetal distress ending up in caesarean section in misoprostol group and in 5 patients in PGE2 group otherwise neonatal outcomes were no different in the two groups with an apgar score

at birth of  $6.94 \pm 1.18$  in misoprostol group and  $6.24 \pm 1.23$  in PGE2 group ( $p$  value 0.3190) and a birth weight of  $3.60 \pm 0.43$  kg in misoprostol and  $3.50 \pm 0.56$  kg in PGE2 group.

Two patients in the misoprostol group had hyperstimulation with fetal heart rate irregularities and both ended up in caesarean section. The cost of misoprostol is 23.80 +/- 11.7 rupees as compared to PGE2 which is 910 +/- 324 rupees.

## DISCUSSION

Misoprostol is being used worldwide for termination of first and second trimester pregnancies and since past ten years various trials have been conducted all over the world to find the optimum dose, route of administration and safety of misoprostol in term pregnancies.

It has already been proven that vaginal misoprostol is an effective easy and cheap drug as compared to vaginal PGE2 tablets; intravaginal administration of misoprostol was found to be as effective as intra cervical PGE2 vaginal tablets for cervical ripening and labour induction<sup>11</sup>. This study proves that oral 100 µgm misoprostol is as effective as prostaglandin E2 vaginal tablets for induction of labour

Complications associated with prostaglandin insertion are not statistically different from misoprostol although number of patients having hyper stimulation are more in misoprostol group, depending on the dose of misoprostol the incidence of uterine hyper stimulation varies between 1-10%<sup>9</sup>, a trial showed that oral misoprostol could be an effective agent for labour induction but close monitoring is essential for these patients as there was a higher frequency of hyper stimulation<sup>13</sup>. In this study hyper stimulation was seen in only 2 cases (4.0%) in the misoprostol group.

Pongsatha et al in 2002 showed that 100 µgm Misoprostol orally every 3 hours seemed to be an optimum and new option for labour induction<sup>14</sup>. In this study 100 µgm misoprostol orally every 4 hours resulted in vaginal delivery in 36 (72%) patients and 27 delivered within 24 hours of first dose and the results were comparable to PGE2 vaginal tablets where 38

patients delivered vaginally and 28 delivered in 24 hours after the first dose thus showing that this dose of misoprostol can be the optimum dose but further trials are needed.

Comparison of oral and vaginal misoprostol showed that vaginal misoprostol for induction of labour at term results in a shorter induction delivery time with fewer doses required per patient and vaginal misoprostol but it may be associated with higher rates of caesarean section than oral misoprostol<sup>15</sup>. In this study caesarean section occurred in 28 % of patients in misoprostol group which was almost same as prostaglandin E2 group i.e. 24% and induction to delivery time was also comparable in both the groups.

A systematic review on misoprostol for induction of labour was published in 1999 by Hofmeyr et al he found out that overall misoprostol seems to be more effective than conventional methods of cervical ripening and labour induction, although no differences in perinatal outcome were shown but studies were not large enough to exclude the possibility of uncommon side effects specially hyper stimulation and fetal heart rate changes<sup>16</sup>. In this study meconium staining occurred in 5 patients who were induced with misoprostol and 4 had caesarean section due to fetal distress whereas 4 patients in prostaglandin E2 vaginal tablets had meconium staining and 5 patients had caesarean section due to fetal distress.

Le Roux et al in a trial gave 50 µgm of oral Misoprostol, and 50 µgm of vaginal misoprostol randomly to women and compared them with vaginal dinoprostone, and showed that vaginal misoprostol was as effective as dinoprostone tablet but associated with more tachysystole and caesarean section for fetal distress<sup>17</sup>. Another trial showed that 100 µgm oral misoprostol while slower acting was not associated with any increased uterine activity as compared to vaginal misoprostol<sup>18</sup>. In this study there were 2 cases hyper stimulation in the misoprostol group and none in the prostaglandin E2 group.

In another trial it was proven that oral 50 µgm dose was associated with higher incidence of failed induction than 100 µgm which is the



preferred dose regime<sup>19</sup>. Our study compared the results of oral 100µgm misoprostol with prostaglandin E2 vaginal tablets, 27 (54%) patients delivered vaginally in misoprostol group in 24 hours and 2 (4%) patients had failed induction as compared to 29 (58%) patients in PGE2 group with 3 (6%) patients with failed induction, this shows the efficacy of misoprostol in this dose is same as compared to prostaglandin vaginal tablets.

Feltosa et al in 2006 showed that 25µgm of sublingual Misoprostol given 6 hourly was effective for labour induction in high risk patients resulting in labour in 100% of patients<sup>20</sup>. In 2000 Alfirevic Z showed that clinically effective dose of oral Misoprostol can have an unacceptably high incidence of complications as uterine hyperstimulation and possibly uterine rupture<sup>20</sup>. In 2003 Dallenbach P et al compared low dose oral Misoprostol i. e. 25 µgm 2 hourly with 3 mg Dinoprostone and showed no difference in terms of effectiveness and safety and this regime avoids the excessive uterine contractility noted in previous studies where higher doses of Misoprostol were administered at longer intervals<sup>21</sup>. In BJOG in 2004 it was shown oral 100µgm of dose at four hourly intervals was cheap and effective alternative to vaginal Prostaglandin E2 tablets and not associated with significant hyper stimulation and tachysystole producing similar maternal and neonatal outcomes<sup>22</sup>, these results are confirmed by our study that oral 100 µgm of oral misoprostol is a safe and economical alternative to prostaglandin vaginal tablets and the results in our study show similar outcomes without any significant differences in the two groups regarding the cervical score, the induction to delivery time, the number of patients delivering vaginally, the caesarean rates and the neonatal outcomes. The number of patients requiring Oxytocin was slightly more in the misoprostol group. Misoprostol is stable at room temperature, easy to store and definitely cheaper than prostaglandin E2 vaginal tablet which makes it highly recommendable for patients who cannot afford costly drugs and for hospitals and clinics not having proper storage systems for the PGE2 vaginal tablets, with proper monitoring patients

having hyper stimulation can be easily be detected and dealt with immediately.

In conclusion oral Misoprostol is a much cheaper alternative to prostaglandin E2 pessaries which is very important in a developing country like ours.

### CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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