Original Article

Induction of Labour with Intravaginal Misoprostol Versus Prostaglandin E2

Syeda Batool Mazhar[1], Misbah Jabeen[2], Majida Zafar[3] Hina Emanuel[4]

[1]Professor Obstetrics and Gynecology, [2-3] FCPS Residents, Department of Obstetrics and Gynaecology Unit II, Pakistan Institute of Medical Sciences, Islamabad.[4]Final year MBBS Student.
***Correspondence:** Prof. Syeda Batool Mazhar, Department of Obstetrics and Gynaecology Unit II, Pakistan Institute of Medical Sciences, Islamabad.*
Email: batool@isb.comsats.net.pk

Abstract

Objective: To compare the efficacy and safety of intravaginal misoprostol 50µg and PGE_2 3mg for induction of labor.

Study Design: Birth register based cohort study

Settings: Maternal and Child Health Centre, PIMS, from January 1 to June 30, 2010.

Methodology: A total of 249 women between 36 to 43 weeks gestation, undergoing induction of labour (IOL) with misoprostol or PGE_2 at bishop's score ≤ 6 were included. Primary outcome measures were induction to delivery interval, mode of delivery, and neonatal admission in SCBU. Secondary outcome measures were number of doses required, postpartum haemorrhage and tachysystole. Chi square and t test were used to determine the significance of difference between two groups.

Results: Out of 249 women, 142 (57%) were primigravidae and 107 (43%) multigravidae. There was no significant difference in baseline characteristics between two groups. Misoprostol was used in 162 (65%) while, PGE_2 in 87(35%) women, repeated every 6 hours, for a maximum of three doses. There were no significant differences in the mean induction to delivery interval, doses required (p=0.39), percentage of women achieving vaginal delivery within twelve hours (p= 0.45), frequency of caesarean delivery (p=0.52) or complications as tachysystole, and PPH (p=0.7). PGE_1 group had higher but statistically insignificant caesarean section rate due to failed induction (p=0.06). A higher proportion of babies in the misoprostol group needed admission in SCBU (p=0.03).

Conclusion: Vaginal misoprostol is cheaper than and as effective as PGE_2 for induction of labour at term, but is associated with more SCBU admissions.

Key Words: Misoprostol, Prostaglandin E2, Vaginal pessary, Oxytocics, Induced Labor, Neonatal outcome.

Introduction

Labour is a natural process that usually starts spontaneously. Intentional initiation of labour before its spontaneous onset, labeled as, 'induction of labour' is a relatively common procedure in obstetrics. Induction of labour is not without risks and many women find it uncomfortable. It should be performed only when there is a clear medical indication and expected benefits outweigh the potential risk of harm,[1] thereby discouraging the trend of social inductions on request. Its rate is currently around 20-30 % of hospital deliveries in the developed as well as many developing countries.[2,3] Labour induction by pharmacological means has most commonly been initiated with vaginal prostaglandin E2 (Dinoprostone) as it is registered and recommended for this indication, the world over. Although vaginal PGE2 is currently the gold standard in well resourced settings, it is costly, unstable to heat, requiring maintenance of cold chain and refrigeration.

Misoprostol (prostaglandin E1) has the advantages of being cheap, widely available, stable at room temperature and has fewer adverse effects. Misoprostol has been registered for induction of labour in Pakistan. However, in majority of the countries, misoprostol is being used off label in obstetrical practice. It was added to Complementary List of WHO in 2005 for induction of labor and has also been included in WHO Model list of essential drugs for abortion, where permissible since 2009.[4,5] Misoprostol (PGE1) is approved by FDA for induction of abortion. It was first used for induction of labour in a woman with dead fetus in 1987 in the dose of 200 µg. This dose had a high incidence of hyperstimulation and tachysystole. Over the past two decades much research has been driven by the need to arrive at a safe dose which affects normal vaginal delivery but avoids hyperstimulation. The success of labour induction depends on cervical status at the time of initiation and this is determined by universally acceptable modified Bishop Score.[6]

This study was therefore, undertaken at Maternal and Child health Center Unit II, PIMS, Islamabad, to determine the efficacy and safety among Pakistani women by comparing the outcomes among women with unfavorable cervical scores undergoing labour induction by the vaginal route with PGE2 3mg versus misoprostol 50ug at six hourly intervals. And to assess if misoprostol is an acceptable alternative to PGE2 especially, in a low resource setting.

Methodology

From 1st January to 30th June 2010, 249 women requiring induction of labour for varied indications at MCH, PIMS, were studied. The inclusion criteria were singleton pregnancy at gestational ages between 36 and 43 weeks with a modified Bishop score ≤ 6. Women with previous cesarean section and known allergy to prostaglandins were excluded. The women were assigned either to vaginal PGE2 or PGE1 group on the basis of lottery method (random allocation).

The women assigned to vaginal PGE2 received a 3mg pessary at 6 hourly intervals upto maximum of two doses in 24 hours followed by artificial rupture of

membranes (ARM) and oxytocin infusion. One women of PGE2 group whose Bishop Score failed to improve with this dose and ARM was not possible, a third dose of vaginal PGE2 3mg was inserted after 24 hours of the first dose. The women assigned to vaginal Misoprostol received 50ug at 6 hourly intervals upto maximum of three doses in 24 hours followed by ARM and oxytocin infusion. Oxytocin infusion was started at 5miu / minute and this rate was doubled every 30 minutes to a maximum rate of 40miu/min. Labour progress was recorded graphically on partogram after achieving 3 cm dilatation of the cervix.

The primary outcome measures were induction to delivery interval in hours, mode of delivery and neonatal admission to the special care baby unit (SCBU). The secondary outcome measured included the number of doses of vaginal preparations, tachysystole and postpartum hemorrhage. (For study purposes, tachysystole was defined as excessive uterine activity associated with non reassuring fetal heart rate pattern).[7]

The data was collected retrospectively from birth registers maintained in the Labour ward by the residents on duty. As this was a birth register based comparative study, departmental permission was taken for data collection and analysis. This was entered and analyzed on SPSS 17. Paired sample T test was applied to numerical data to compare the induction to delivery interval and number of doses. Chi-Square test was used to determine the significance of difference between categorical variables like mode of delivery, neonatal admission to SCBU, postpartum hemorrhage and tachysystole. Statistical significance was defined as $p<0.05$ *.

Results

A total of 249 women fulfilled the inclusion criteria. Vaginal misoprostol was given to 162 (65%) of the study population while 87(35%) women received PGE2 vaginally. Among these 249 women, there were 142 (57%) primigravidae and 107 (43%) multigravidae. The average gestational age of the study population was 39 weeks $\pm$ 1.46 weeks. The mean birth weight of the newborns was 3000 grams $\pm$ 580 g. There were no significant differences in these characteristics among women of the two groups. The mean age of women was 26 years with a range of 17-40 years. The mean age of women in PGE2 group was 27.2 years while it was 25.3 years in PGE1 and the p value was 0.02*(table 1).

Table I. Demographic Characteristics

Variable	PgE2	PGE1	p. value
Age (mean in years)	27.2	25.3	0.02*
Gestational Age(mean in weeks)	39.6	39.8	0.41
Birth weight (mean in grams)	3090	3080	0.92
Primiparas n (%)	46(52.8%)	90(55.5 %)	0.48
Multiparas n (%)	41(47.2%)	72(44.5 %)	

The commonest indication for labour induction was in the cases like post dates, 115 (46.2%), followed by prelabour rupture of membranes, 58 (23.3%), gestational hypertension, 24 (9.6%), non reassuring

fetal status on CTG, 15 (6%), intrauterine growth restriction, 3 (2.4%), gestational diabetes, 3 (2.4%), oligohydramnios, 6 (2.4%), prolonged latent phase, 4 (1.6%) and miscellaneous indications in 21 (8.4%) women. No difference was noted in the two groups in relation to indications of induction.

Efficacy: Induction to delivery interval was 12.38 hours for women receiving PGE2 and 13.26 hours in the misoprostol group. Among the total 249 women, 112(45%) delivered within 12hours of initiation of induction. Among those delivering within 12 hours PGE1 group had significantly more vaginal births than PGE2 (p=0.000*) Instrumental deliveries were required in 4 (4.7%) for PGE2 and in 11(6.9%) for PGE1 (p=0.34). Mode of delivery was Lower segment Cesarean section (LSCS) in 24 (25.9%) women for PGE2 and 42 (26.4%) for PGE1 (p=n.s). LSCS due to failed induction was done in 9 (4%) in PGE2 versus 23 (9%) in PGE1 with a p value of 0.06. The mean number of doses of vaginal preparations required was almost similar i.e 1.5 for PGE2 and 1.6 for PGE1 (Figure 1).

Adverse effects and safety: No episode of hyperstimulation or tachysystole was recorded in the labour room birth register and one episode of postpartum hemorrhage was noted in each group. The mean APGAR Scores at 5 minutes were 8.2 for PGE2 and 8 for PGE1 with a p value of 0.54. Neonatal admission to the special care baby unit in PGE2 group was 35% and in the misoprostol group was 39% with p value of 0.03*.

Discussion

For induction of labour, misoprostol is now a commonly used prostaglandin particularly in women with unfavorable cervices. It is increasingly replacing vaginal prostaglandin E2 in resource poor settings like Pakistan. In the present study, nulliparous as well as multiparous women were included for varied indications as in the majority of other studies.[8-12] The two groups of women in the current study were well matched for gestational age, parity and indication for induction of labour. However the mean age differ-

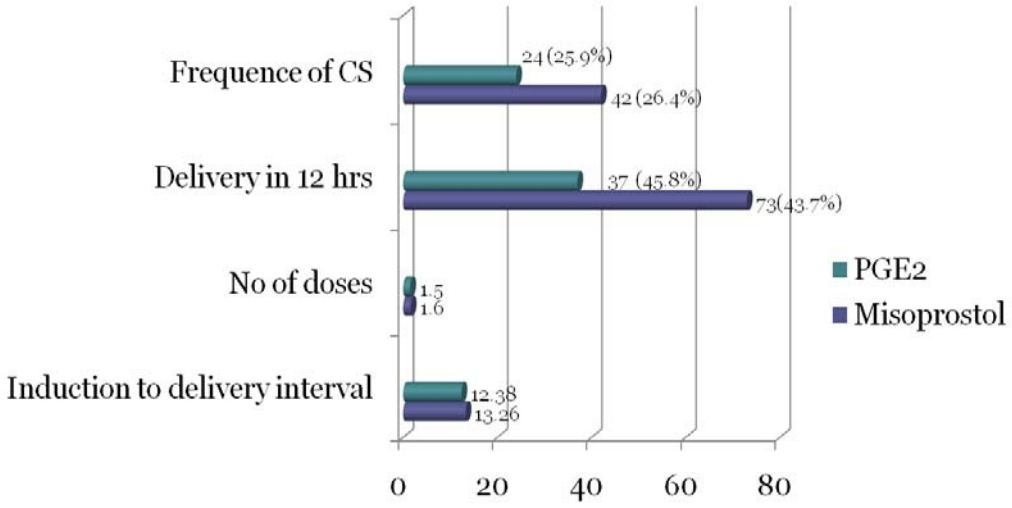

Figure 1. Outcome of IOL in misoprostol vsPGE 2

ence was 2 years which may be related to the reason that PGE2 being relatively expensive is often prescribed to affording women who may have been older due to later age at marriage or more education prior to marriage. However this could not be verified from the data in birth registers.

In the current study, the main indications for induction were post-dates gestation (46%), followed by prelabour rupture of membranes (23%) and gestational hypertension (9%). In the study by Van Gemund et al,[13] the indications had a significantly smaller number of post-dates gestation (25%) and significantly more cases of hypertension(26%). Others have restricted the study population on the basis of parity and gestation,[14] fetal viability[15] or indication of labour induction like premature rupture of membranes,[16] to remove confounding variables and have a homogenous study population.

Vaginal route of labour induction is the norm in our labour wards for more than two decades and misoprostol was used vaginally in the present study rather than the oral,[8] sublingual or buccal routes.[17,18] Indeed misoprostol was as well tolerated as the gold standard PGE2 vaginal pessary. However as the readily available tablet of misoprostol is 200ug, its division into four equal portions remains a bothersome issue.

No significant difference between misoprostol and PGE2 was found in the mean induction to delivery interval in our study. A study done in Lahore noted a significantly shorter mean induction to delivery interval in misoprostol of 13.3 hours compared to 18.5 hours in PGE2.[9] No difference in the rates of caesarean delivery between misoprostol and PGE2 groups was noted in the current study. There was a trend towards increased LSCS rate due to failed induction in Misoprostol group although it did not approach statistical significance. Among those delivering within 12 hours PGE1 group had significantly more vaginal births. This was also noted in a metanalysis by Crane et al in 2006[19] where a higher rate of vaginal delivery within 24 hours with PGE1 occurred when compared with PGE2. In contrast Calder et al[11] report higher rate of vaginal delivery within 12 hours in the PGE2 group.

A trend towards increased meconium staining was observed by Crane et al in 2006.[19] Although, infant APGAR scores were very similar, neonatal admission to the special care baby unit was significantly higher for misoprostol group 38% vs 35% in our population. Due to the limitation of retrospective nature of the study, we are unable to elaborate on the reasons. Wasim et al[9] found significantly increased meconium staining of amniotic fluid and fetal heart rate abnormalities in Misoprostol induction compared to PGE2, yet the increased neonatal admissions and reduced apgar scores in their population did not reach statistical significance. As reported in a previous meta analysis,[19] the risk of maternal adverse events like hyper stimulation and postpartum hemorrhage occurred at comparable frequencies in the two treatment groups of current study.

The number of doses of the two vaginal preparations was similar. Calder et al[11] state that in any study comparing the potency and efficacy of drugs, outcome measures may be influenced not only by the formulations being compared but also by the dosages and dosage intervals used in the study. Earlier meta analysis in 2005[8] found similar efficacy for oral and vaginal routes and recommended 50ug dose at 3-8 hourly interval in view of lack of well designed randomized control trial at that time. Currently WHO

guidelines 2011[1] recommend 25 ug misoprostol at 6 hourly intervals. The risk of not achieving vaginal birth in 24 hours is the same with high and low doses of misoprostol but the risk of uterine hyperstimulation with fetal heart rate changes is lower with the low dose misoprostol.

The lower dose of misoprostol was not practically possible due to availability of 200ug tablets which are divided into 4 portions of 50ug with a lot of difficulty, as these tablets are not scored. Using a 25ug dose is problematic because splitting a 100ug tablet into quarters with a free hand or commercial pill cutter does not provide a reliable 25ug dose. Previous studies have found that 42–74% of these one-quarter tablets (one-quarter of a 100 ug tablet) failed to provide misoprostol dose within 10% of the desired dose.[21]

Limitations of this study were that it was not randomized controlled or blinded thereby bringing an element of bias. Moreover the retrospective data retrieved from registers often has no information on minor side effects as well as lack of long term follow up of the mother and the newborn.

Conclusion

Vaginal misoprostol in the dose of 50 ug 6 hourly is an effective and safe pharmacological agent for induction of labour when compared to ProstaglandinE2, 3mg vaginal pessary. There is need for the national pharmaceutical industry to produce a 25 ug PGE1 preparation in our country. In the meantime dissolving the 200ug misoprostol tablet in water solution and administering 20 ug orally, 2 hourly as recommended by latest WHO guidelines should be considered to reduce the side effect profile.

References

1. Abdel-Aleem H. Misoprostol for cervical ripening and induction of labour: RHL commentary (last revised: 1 May 2011). *The WHO Reproductive Health Library*; Geneva: World Health Organization.
2. Induction of labour, NICE Clinical Guideline 70, 2008. www. nice.org.uk/CG070 .
3. Mazhar S.B, Alam K. Induced labour: Indications and outcome, PIMS Experience. Journal of Surgery 2001; 24: 31-34.
4. WHO model list of essential medicines: 16th list, March 2009. Geneva: World Health Organization 2009 (available at: http://www.who.int/medicines/publications/essentialmedicines/en/).
5. WHO Global Survey on Maternal and Perinatal Health. Induction of labour data. Geneva, World health Organization, 2010 (available at: http://www.who.int/reproductivehealth/topics/best_practices/global_survey).
6. Bishop EH. Pelvic scoring for elective induction: Obstst Gynecol 1964:24; 266-8.
7. Hofmeyr GJ, Gulmezoglu AM. Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2003;(4): Issue 1.
8. Hassan AA. A comparison of oral misoprostol tablets and vaginal prostaglandin E2 pessary in induction of labor at term. J Coll Physicians Surg Pak 2005;15:284-7.
9. Wasim T, Siddiq S. Comparison of prostaglandin E2 with misoprostol tablets for induction of labor at term. Professional Med J 2008;15: 344-9.
10. Begum A, Butt RM, Kouser S, Naqvi S. Comparison of dinoprostone (PGE2) and misoprostol (PGE1) for induction of labor. J Allama Iqbal Med Coll 2009;7: 20-4.
11. Calder A, Loughney A, Weir C, Barber J. Induction of labour in nulliparous and multiparous women: a U.K multicentre, open label study of intravaginal misoprostol in comparison to dinoprostone. BJOG 2008; 115:1279-88.
12. Tan TC, Yan SY, Chua TM, Biswas A, Chong YS. A randomized control trial of low dose misoprostol and dinoprostone vaginal pessaries for cervical priming. BJOG 2010;117:1270-7.

13. VanGemund N, Scherjon S, LeCessie S, Van Leeuwen JH, Van Roosmalen J, Kanhai HH. A randomized trial comparing low dose vaginal misoprostol and dinoprostone for labour induction. BJOG 2004;111:42–9.
14. Lokugamage AU, Forsyth SF, Sullivan KR, El Refaey H, Rodeck CH. Dinoprostone versus misoprostol: a randomized study of nulliparous women undergoing induction of labour. Acta Obstet Gynecol Scand 2003; 82: 133–7.
15. Week A, Alfrevic Z, Fandes A , Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labour with a live fetus. IJGO 2007;99: 194-97.
16. Lin MG, Nuthalapty FS, Carver AR, Case AS, Ramsey PS. Misoprostol for labour induction in women with term premature rupture of membranes: a meta analysis. Obstet Gynecol 2005; 6: 593–601.
17. Shetty A, Livingstone I, Acharya S, Rice PO, Danielian P, Templeton A. A randomized comparison of oral misoprostol and vaginal prostaglandinE2 tablets in labour induction at term. BJOG 2004; 111:436–40.
18. Muzonzine G, Hofmeyr GJ. Buccal or sublingual misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev 2004(4): CD004221,doi:10.1002/14651858. Art. No: CD004221, pub2.
19. Crane JM, Butler B, Young DC, Hannah ME. Misoprostol compared with prostaglandin E2 for labour induction in women at term with intact membranes and unfavorable cervix: a systematic review.BJOG 2006;113:1366-76.
20. Capilla MC, Bermejo VT. Efficacy and safety of misoprostol in obstetrics. Farm Hosp 2005; 29: 177-84
21. Williams MC, Tsibris JCM, Davis G, Baiano J, O'Brien WF. Dose variation that is associated with approximated one-quarter tablet doses of misoprostol. Am J Obstet Gynecol 2002;187: 615–9.

Plea!

It is urged that genuine research may be conducted on Pelvic Infective diseases, in concurrence with pregnancy, leading not only to pregnancy loss, particularly in mid trimester, but also to the continued aftermath of endometritis, all too often called the non specific type. More so, the recurrence of such infections in further pregnancies needs to be looked into. Invariably maltreated or ill-treated. A mention of their rational therapies, forming a part of the manuscript to be prepared, will be highly valuable and appreciable.

K A K Akhtar