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Comparison of the Safety and Efficacy of Intra-vaginal Misoprostol (prostaglandin E_1) with those of Dinoprostone (prostaglandin E_2) for Cervical Ripening and Induction of Labour in a Tertiary Level Hospital

SB CHOWDHURY[a], B NASRIN[b], S SHAMIM[c]

Summary :

To compare the efficacy and safety of intra vaginal misoprostol (prostaglandin E_1) with those of dinoprostone (prostaglandin E_2) for cervical ripening and induction of labour, a randomized controlled study was done on 74 pregnant women at term with unripe cervix, who had indication for induction of labour in the department of Obstetrics and Gynaecology of Bangabandhu Sheik Mujib Medical University (BSMMU) between the period from July 2002 to June 2003. Seventy-four cases were randomly assigned to receive either 50 µgm intra-vaginal misoprostol or 500 µgm dinoprostone intra-cervically. If labour was not initiated within 6 hours the same dose was repeated every 6 hours to a maximum of 150 µgm of misoprostol or 1.5 mg dinoprostone. The main outcome variables were induction delivery time, number of deliveries within 24 hours, mode of delivery, maternal and neonatal outcome. The mean induction delivery time was significantly shorter in misoprostol group compared with dinoprostone group 11.60±4.5 vs 18.07±. 5.9 hours (P<.0001). There was no difference in cesarean delivery rate between two groups. Uterine hyperstimulation and tachysystol occurred more frequently in misoprostol group than in dinoprostone (16.2% vs 2.7%, P<.05 and 29.7% vs 10.8%, P<.04) respectively. No statistically significant difference was noted between two groups regarding neonatal outcome. Compared to dinoprostone, misoprostol is more effective in cervical ripening and labour induction at term. The frequency of uterine hypercontractility associated with the use of misoprostol did not increase the risk of adverse intrapartum or neonatal outcomes.

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Introduction :

Unripe cervix is well known to cause failure of induction of labour and it is associated with an increased likelihood of prolonged labour and an increased incidence of cesarean delivery.[1] Prostaglandins have been shown to induce cervical ripening and stimulate uterine contraction and have been found to be effective in number of clinical trials at variety of doses and routes of administration[2-3]. Prostaglandin E_2 (dinoprostone) has been widely used for induction of labour[4]. They are most commonly administered intravaginally and in recent years intra-cervically. Intra-cervical approach of PGE_2 was found more effective than intra-vaginal one[5]. Although local application of prostaglandin E_2 (PGE_2) has been considered to be effective in cervical ripening and shortening of delivery time it is very expensive and also sometimes unavailable to obstetrician in developing and underdeveloped countries[6,7]. Misoprostol, a prostaglandin E, analogue, has the advantage of being inexpensive and stable at room temperature. There has been considerable interest in the use of misoprostol for both cervical ripening and labour induction in patients with Bishop score of <4[8-11]. Vaginal administration of misoprostol has been extensively studied and consensus exists as to its efficacy[12]. Safety is the main concern in all studies because of the occurence of extensive uterine contraction on dose related basis[13]. This study was designed to compare the safety and efficacy of intravaginal misoprostol with those of dinoprostone for cervical ripening and induction of labour.

Materials and Methods :

A randomized controlled study was performed on seventy-four pregnant women in department of Obstetrics and Gynaecology of Bangabandhu Sheikh Mujib Medical University who needed induction of

a. Dr. S B Chowdhury, Professor (Obs & Gynae), Department of Obstetric and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka
b. Dr. Begum Nasrin, Assistant Professor (Obs & Gynae), Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
c. Dr. Shayela Shamim, Assistant Professor (Obs & Gynae), Department of Obstetrics and Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka.
Address of Correspondence : Dr. S B Chowdhury, Professor (Obs & Gynae), Department of Obstetric and Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka

labour during the period from July 2002 to June 2003. Seventy four women were randomly assigned to receive either 50µgm intra-vaginal misoprostol or 500µgm dinoprostone intra-cervicaly. Inclusion criteria were singleton pregnancy at term (37-42 weeks), cephalic presentation, reassuring foetal heart rate monitor tracing and Bishop score ≤5. Patients were excluded if they had a known hypersensitivity to prostaglandin, history of cesarean section or myomectomy, premature rupture of membrane (PROM), cephalopelvic disproportion (CPD), polyhydramnios, severe oligohydramnios, multiparous women (para 4 or more) and cardiopulmonary disease. After selection for the study a written informed consent was obtained from each participant. For randomization a sequentially numbered sealed envelop were used before induction of labour. Assessment of cervix was done finally before application of medication and documented. The women were randomly selected for two different preparation of prostaglandin for cervical ripening and induction of labour. Tablet of 200µgm misoprostol were divided into 4 parts each part containing 50µgm. Women who were selected for vaginal misoprostol, an initial dose of 50µgm was applied in the posterior vaginal fornix. If labour did not establish within 6 hours subsequent doses of 50µgm were applied 6 hourly maximum up to 3 doses. Subjects who were assigned to receive dinoprostone 500µgm gel was applied intra-cervically. If needed subsequent dose was given every 6 hours maximum up to 3 doses. Study medication was given every 6 hourly until adequate contraction pattern developed (3 contraction in 10 minutes). Oxytocin augmentation if required was begun no sooner than 4 hours after the last dose of medication. Indications of oxytocin augmentation were a protracted or arrested cervical changes for at least 4 hours with inadequate uterine contraction. Following application of prostaglandin foetal cardiac activity was monitored by cardiotochograph (CTG) for at least 30 minutes. Continuous foetal and uterine monitoring was performed in all patients. For foetal heart rate monitoring CTG was done at frequent interval. Artificial rupture of membranes generally performed once cervix became 4 cm dilated. Entry characteristics for the study, including maternal age, parity, gestational age and Bishop score were compared between the treatment groups. Indications for labour induction, maternal and neonatal outcomes were also evaluated. Efficacy and safety were evaluated by the main outcome variables like induction delivery time, vaginal delivery within 24 hours of induction, maternal complications (hyperstimulation syndrome, tachysystol) and neonatal out-come (Apgar score in 5 minutes, admission in neonatal care unit for birth asphyxia or other labour complications).

In case of tachysystol (5 or more contractions in 10 minutes for two consecutive 10 minutes period) and hyper stimulation (tachysystol associated with an abnormal pattern of foetal heart rate tracing) vaginal tablet was removed, maternal position was changed to left lateral side and oxygen was given. Hyperstimulation and abnormal foetal heart rate tracing were indications to discontinue study drug.

Statistical analysis was performed with statistical package for social science (SPSS). For comparison we used unpaired t test and x^2 test. P<.05 was considered significant.

Result:

Total 74 patients were enrolled in this study with 37 patients randomized to each group. Demographic data presented in Table-I. There were no statistically significant differences in maternal age, parity, gestational age and Bishop score between two groups. In addition inductions for induction were similar between two groups (Table- II). Table-III compares intra-partum variables and maternal response to two different type of prostaglandin. Induction delivery time was significantly shorter in vaginal misprostol group than in dinoprostone group (11.60±4.5 hours vs 18.07±5.9 hours, P<.0001). In misoprostol group 64.86% patients delivered within 24 hours of induction compared to 40.54% of patients who received PGE2 for cervical ripening (P=.1). Significantly less patients in misoprostol group required oxytocin augmentation (51.53%) than in dinoprostone group (91.89%), P<.0001. The frequency of hyperstimulation syndrome (16.2% vs 2.7%, P<.05) and tachysystol (29.7% vs 10.8%, P<.04) were significantly higher in misoprostol group than in dinoprostone group. Mode of delivery and indications for cesarean section is compared in Table IV. More patients in misoprostol group (62.2%) delivered vaginally than in dinoprostone group (51.5%) but the difference was not statistically significant. 37.8% patients in misoprostol group and 48.6% patients in PGE2 group needed cesarean

Table I

Demographic Characteristics of the patients

Demographic Characteristics	Vaginal misoprostol	Dinoprostone (n=37)	Significance (n=37)
Maternal age (years) (mean±SD)	24.27 ±3.15	23.45 ±2.66	NS
Parity			
Nulipara	18(48.6)	19(51.4)	NS
Multipara	19(51.4)	18(48.6)	NS
Gestational age (weeks) (mean±SD)	40.13 ±1.45	40.43 ±1.16	NS
Bishop's score (mean±SD)	3.62 ±.79	3.51 ±.83	NS

(Percentage is within parenthesis)

Table-II

Indications of induction

Indications	Vaginal Misoprostol (n=37)	Dinoprostone (n=37)
Postdated pregnancy	24 (64.86)	26 (70.27)
Pregnancy Induced Hypertension (PIH)	8(21.62)	7(18.91)
Elective	3(8.1)	2(5.4)
GDM	2(5.4)	1(2.7)
Rh-isoimmunization	0	1(2.7)

(Percentage is within parenthesis)

Table-III

Maternal response to different Type of prostaglandins

Maternal response	Vaginal misoprostol (n=37)	Dinoprostone (n=37)	Significance
Induction delivery time (Hours) mean±SD	11.60±4.5	18.07±5.9	.0001
Delivery ≤ 24 hours	24(64.86)	15(40.54)	.1
Oxytocin augmentation	19(51.53)	34(91.89)	.0001
Hyperstimulation syndrome	6(16.2)	1(2.7)	.05
Tachysystol	11(29.7)	4(10.8)	.04

(Percentage is within parenthesis)

Table-IV

Mode of delivery and indications of cesarean section

Mode of delivery	Vaginal misoprostol(n=37	Dinoprostone (n=37)	Significance
Normal vaginal delivery	23(62.2)	19(51.5)	NS
Cesarean section	14(37.8)	18(48.6)	NS
Total	37	37	
Indications of cesarean section			
Fetal distress	10(71.4)	3(16.7)	.003
Arrested disorder	2(14.3)	7(38.9)	.23
Failed induction	214.3)	8(44.4)	.12

(Percentage is within parenthesis)

Table-V

Neonatal outcome

Neonatal outcome	Vaginal misoprostol (n=37)	Dinoprostone (n=37)	Significance
Birth weight (Kg) (mean±SD)	2.90±.42	2.88±.35	NS
5 minute Apgar Score <7	10(27)	5(13.5)	.12
Transfer to neonatal ward	7(18.9)	2(5.4)	.07

(Percentage is within parenthesis)

section. Significantly more patients of misoprostol group (71.4% vs 16.7%, P<.003) needed cesarean section due to foetal distress than in dinoprostone group.

Neonatal out-come is compared in table V. Regarding Apgar score it is observed that more neonates in vaginal misoprostol group had score < 7 at 5 minutes than in dinoprostone group (27% vs 13%, P=.12) but the difference was not statistically significant. More neonates of vaginal misoprostol group needed admission in neonatal ward (18.9% vs 5.4%, P=.07).

Discussion :

Labour induction in presence of cervical immaturity is a common indication for the use of prostaglandin particularly infra-cervical PGE_2[14-16]. However in the last 5 years there has been considerable interest in the use of misoprostol, a prostaglandin E_1 analogue for cervical ripening and labour induction[9-11].

In our study we compared the safety and efficacy of vaginal misoprostol with those of intra-cervical dinoprostone for cervical ripening and labour induction. In our result it is seen that vaginal misoprostol is more effective in cervical ripening and labour induction compared with dinoprostone. Induction delivery time was significantly shortened in vaginal misoprostol group (11.60 ± 4.5 vs 18.07 ± 6 hours, P<.0001). Our findings are consistent with previous studies done by Howard et al and Sanchez-Ramos et at[12-17]. In the present study the use of oxytocin was significantly less in vaginal misoprostol group than in dinoprostone group (51.53% vs 91.89%, P<.0001), the findings consistent with that of Fletcher et at and Majoko et al[18-19]. In this study more patients delivered vaginally within 24 hours of induction with misoprostol (64.86% vs 40.54%) but the difference was not statistically significant. When we consider safety of misoprostol uterine tachysystol

and hyper stimulation is the main concern. In this study, it is observed that the incidence of hyperstimulation (16.2% vs 2.7%, P<.05) and tachysystol (29.7 vs 10.8%, P<.04) was significantly more in vaginal misoprostol group than in dinoprostone group. Y.-K. Chang et al in 2003 reported in their study that significantly more patients developed hyper stimulation (18.6% vs 4.7%, P <.05) and tachysystol (25.6% vs 14.0%, P <.05) in misoprostol group than in dinoprostone group, which is consistent with our observation.[5] But in some randomized trial where efficacy and safety of vaginal misoprostol was compared with dinoprostone, it was reported that hyper stimulation was not different and there was no difference in neonatal and maternal out-come [20-22].

Regarding mode of delivery, in our study spontaneous vaginal delivery was more in vaginal misoprostol group (62% vs 51.5%) than in dinoprostone group but the difference was not statistically significant. On the other hand Filomena Nunes et al[14] and Y.-K. Chang et al[5] reported that misoprostol administration did not reduce cesarean delivery rate. In this study though the rate of cesarean section was not statistically different (37.8% vs 48.6%) between two groups, it is observe, that significantly more patients needed cesarean section due to foetal distress in vaginal misoprostol group, 10 out of 14 (71.4%) vs 3 out of 18 (16.7%), P<.003. This might to be due to higher incidence of tachysystol and hyper stimulation in vaginal misoprostol group.

Regarding neonatal out-come, more neonates had Apgar score less than 7 at 5 minutes in vaginal misoprostol group (27% vs13.5%, P=.12) than in dinoprostone group, though the difference was not statistically significant. More number of neonates in misoprostol group needed admission in neonatal ward, 7 out of 37 (18.9%) vs 2 out 37 (5.4%) than in dinoprostone group. Our findings are consistent with those of reported by Rokeya Begum et al[23] but not consistent with the findings reported by Y.-K. Chang et al[5] where no neonate in vaginal misoprostol group required intubation, resuscitation or admission in NICU.

Conclusion:

Administration of vaginal misoprostol appears to be more effective for cervical ripening and labour induction than intra-cervical PGE_2. Regarding safety in this study dinoprostone appears to be safer, as hyperstimulation and tachysystole was significantly less in this group. Close monitoring of labour, intra-partum CTG and maintenance of partogram is mandatory for using these preparations. Further large-scale study using different doses of misoprostol is necessary before one can advocate vaginal misoprostol for cervical ripening and induction of labour.

References :

1. Brindley BA, Sokol RJ. Induction and augmentation of labour: basis and methods for current practice. Obstet Gynecol Surve 1988; 43 :730-3
2. O'Brien WE Cervical ripening and labour induction: progress and challenges. Clin Obstet Gynecol 1995; 38 : 221-3
3. Keirse MJ. Prostaglandins in preinduction cervical ripening: meta-analysis of worldwide clinical experience. J Repord Med 1993; 38 suppl : 89-98.
4. Varaklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin E2 gel for induction of labour at term. Obstet Gynecol 1995; 86 (4 Pt 1) : 541-544.
5. Y.-K. Chang, W.-H. Chen, M.-H. Yu, H.-S. Liu. Intracervical misoprostol and prostaglandin E2 for labour induction. Int J Gynecol and Obstet 2003, 80 : 23-28.
6. Rayburn WE Prostglandin E2 gel for cervical ripening and induction of labour : a critical analysis. Am J Obstet Gynecol 1989; 160 (3) : 529-534.
7. Ulmsten U, Wingerup L, Ekman G. Local application of prostaglandin E_2 for cervical ripening or induction of term labour. Clin Obstet Gynecol 1983; 26(1) : 95-105.
8. Sanchez-Ramos L, Kaunitz AM, Del Valle GO, Delke 1, Schroeder PA, Briones Dk. Labour induction with prostagladin E1 methyl analogue misoprostol versus oxytocin: a randomized trial. Obstet Gynecol 1993; 81(3) : 332-336.
9. Fletcher HM, Mitchell S, Simeon D, Frederick J, Brown D. Intra vaginal misoprostol as a cervical ripening agent. Br J Obstet Gynaecol 1993;100 : 641-4
10. Margulies M, Perez GC, Voto LS. Misoprostol to induce labour. Lancet 1992; 339 : 64
11. Rodrigues R, Nunes F, Tiago D, Avillez T, Vieira A, Meirinho M. Induction of labour with intravaginal administration of misoprostol. Int J Obstet Gynecol 1998; 60 : 233-37

12. Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and induction of labour: A meta analysis. Obstet Gynecol 1997; . 89 : 633-42.

13. Wing DA, Paul RH. A comparison of different dosing regimens of vaginally administered misoprostol for preinduciton cervical ripening and labor induciton. Am J Obstet Gynecol 1996; 175 : 158-64.

14. Filomena Nunes, Rosalinda Rodrigues, Manuel Meirinho. Randomized comparison between intra-vaginal misoprostol and dinoprostone for cervical ripening and induction of labour. Am J Obstet Gynecol 1999; vol 181 : 626-629

15. Xenakis EMJ, Piper JM, Conway DL, Langer O. Induction of labour in nineties: conquering unfavourable cervix. Obstet Gynecol 1997; 90 :.235-39.

16. Orhue AAE. Induction of labour at term in primigravida with low Bishop's score: a comparison of three methods. Eur J Obstet Gynecol Reprod Biol 1995; 58 :119-25

17. Howard A. Blanchette, Sandhya Nayak, Sapna Erasmus. Comparison of the safety and efficacy of intra-vaginal misoprostol (prostaglandin E1) with those of dinoprostone (prostaglandin E2) for cervical ripening and induction of labour in a community hospital. Am J Obstet Gynecol 1999; vol 180 (6) : 1551-1556.

18. Fletcher H, Mitchell S, Frederick J, Simeon D, Brown D. Intra-vaginal misoprostol versus dinoprostone as a cervical ripening agent. Obstet Gynecol 1994; 83(2) : 244-247

19. Majoko F, Zwizwai M, Lindmark G, Nystrom L. Labour induction with vaginal misoprostol and extra-amniotic prostaglandin F_2 alpha gel. Int J obstet Gynecol 2002; 76(2) : 127-133

20. Gottschall DS, Borgida AF, MihaleK JJ, Sauer F, Rodis JF. A randomized clinical trial comparing misoprostol with prostaglandin E2 gel for pre-induction cervical ripening. Am J Obstet Gynecol 1997; 177 : 1067-70

21. Sanchez-Ramos L, Peterson DE, Delke 1, Gaudier FL, Kaunitz AM. Labour induction with prostagladin E1 misoprostol compared with dinoprostone vaginal insert: a randomized trial. Obstet Gynecol 1996; 91 : 401-5

22. Surbek DV, Boesiger H, Hoesli 1, Pavic N, Holzgreve W. A double -blind comparison of safety and efficacy of intr-vaginal misoprostol and prostaglandin E2 to induce labour. Am J Obstet Gynecol 1997; 177 : 1018

23. Begum R, Sultana A, Begum A. Misoprostol versus dinoprostone for induction of labour. Bang J obstet Gynecol 2003; vol 18(1) : 3-8