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Original Article

Misoprostol for term labor induction: A randomized controlled trial

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Abstract

Objectives: The aim of this study was to compare the efficacy of vaginal misoprostol with vaginal dinoprostone for term labor induction.
Material and Methods: It was a randomized controlled trial done in the Obstetrics Department, Shifa Community Health Centre, Shifa International Hospital (Teaching Hospital of Shifa College of Medicine, Islamabad). All pregnant women at term pregnancy coming for induction of labor were enrolled. 246 women fulfilled the inclusion criteria. Out of them 208 women consented to be part of the study. These women were then randomized to receive either Treatment A (vaginal misoprostol) or Treatment B (vaginal dinoprostone). Data were completed for 200 women. These included induction labor and induction-delivery interval, fetal and maternal complications, and baby apgar score.
Results: Out of 200 women in the study, 100 were in Group A and 100 in Group B. Labor commenced in a mean of 6.67 hours (±3.63) in Group A whereas it took a mean of 8.41 hours (±5.13) in Group B ($p = 0.00$). Actual induction to delivery (of the baby) interval was a mean of 11.68 hours (±4.55) for misoprostol and 15.37 hours (±5.30) for dinoprostone group ($p = 0.00$). There were no cases of uterine rupture in both groups; however, there were 10 cases of uterine hyperstimulation in Group A and 4 in Group B ($p = 0.09$).
Conclusions: It is time to re-evaluate the role of misoprostol for term labor induction. It is an efficacious and cost-effective alternative to the presently licensed treatment.

Keywords: Labor induction; Randomized controlled trial; Vaginal misoprostol

Introduction

Labor induction involves the stimulation of uterine contractions to produce delivery before the onset of spontaneous labor. This procedure has been commonly used since the synthesis of oxytocin in the 1950s and labor is currently induced in about 13% of live births in the United States [1]. Most labor inductions are for post-date pregnancy, which occurs in about 10% of live births [1]. Prostaglandin E2 (dinoprostone; Prepidil, Cervidil), administered intra-vaginally or intra-cervically, is the pharmacologic agent most widely used for ripening the cervix [2–4]. Its use is licensed by the United States Food and Drug Administration for cervical ripening. Misoprostol (Cytotec, Orthotec) has been extensively investigated in the past few years for use in cervical ripening and labor induction [5]. Marketed as a gastric cytoprotective agent, the drug is also an effective, safe, and inexpensive agent for cervical ripening and labor induction, although it is not food and drug administration United states (FDA)-labeled for that purpose [6–15]. The aim of this study was to compare the efficacy of vaginal misoprostol with vaginal dinoprostone for term labor induction and to assess whether it has the potential to replace the existing drug.

Material and methods

It was a randomized controlled trial. The sample size was calculated by using WHO software. Level of significance

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chosen was 5% and the power of the study was 90%. Sample size was separately estimated for each outcome including induction-delivery interval in hours (11.9 ± 0.6 hours for misoprostol and 15.6 ± 0.7 hours for dinoprostone), need for oxytocin (65.8% in misoprostol and 80.7% in dinoprostone group, $p < 0.05$), and fetal effects (1 minute apgar score < 7, 12.5% in misoprostol and 6% in dinoprostone group) [26]. The sample size calculated was 85 in each group. It was increased to 104 in each group to cover contingencies such as refusals during the trial, missing or incomplete data.

Approval of the study was taken from the 22-member ethical review board of the Shifa International Hospital, Islamabad, Pakistan, comprising religious scholars, bio-ethics and research specialists, doctors, and the dean of the institution. All pregnant women presenting in Shifa Foundation Community Health Centre (Shifa International Hospital, Pakistan) outpatient who were planned for induction of labor had their evaluation regarding inclusion criteria. Women with a parity of four or less and a gestation of 38 weeks or more with a single fetus in cephalic presentation and a Bishop score of 6 or less were enrolled, whereas women with previous cesarean delivery, transverse lie, active herpes, placenta previa & severe intra uterine growth restriction (IUGR) in present pregnancy, multiple pregnancy, breech presentation, bad obstetrical history/intrauterine growth restriction (less than 10th percentile), pre-eclampsia, poly- or oligohydramnios, and Bishop score 7 or more were excluded. All eligible women presenting at Shifa foundation antenatal outpatient fulfilling inclusion criteria and who had consented to be part of the study were enrolled. After evaluation, 246 women were found eligible for inclusion in the study. Out of these 208 women agreed to be part of the trial. Eight cases did not complete the trial protocol (refused drug administration as was required) and were dropped out of the analysis. Women included were explained about this clinical trial and their written informed consent was taken. Randomization was done by using computer software. Women were randomized to receive either Treatment A (vaginal misoprostol) or Treatment B (vaginal dinoprostone). Randomization was done in blocks of four to ensure equal number of women in each group. One hundred and four women were allocated to Treatment A and 104 women to Treatment B. According to generated randomization list 208 envelopes were prepared and the name of allocated treatment was placed in each envelope. These envelopes were then sealed. All the envelopes were serially numbered from 1 to 208 on the outside. When a woman was admitted for induction in labor ward, the first envelope was opened by the attending nurse under close supervision of the principal investigator. Principal investigator was there to ensure that the allocated treatment plan was adhered to. Once the treatment was allocated to a woman it was strictly adhered to. Neither the nurse nor the principal investigator could change the allocated treatment. The study was double blinded (neither the patient nor the outcome assessor knew about the type of allocation). Only the attending nurse and the principal investigator knew about treatment allocation. The outcome assessor was a separate physician who had no knowledge about the type of intervention given. After randomization, either 50 μg misoprostol or 3 mg dinoprostone was inserted in the posterior vaginal fornix of the patient by the labor ward nurse. The Bishop score at induction and the time of induction were clearly documented in patient's notes. The doctor in charge of the patient then recorded the progress of labor on the partogram. A 30-minute fetal cardiotocography (CTG) was performed 1 hour after insertion. Afterwards intermittent fetal heart auscultation was done. If the patient started complaining of labor pains, uterine contractions were recorded and examination was repeated to reassess Bishop score. In the absence of labor pains, a repeat Bishop score was done 6 hours after the first drug administration. Re-insertion of second tablet, if Bishop score was 6 or less, was preceded by a 20-minute pre-insertion CTG and then a 20-minute post-insertion CTG (1 hour after insertion of the second tablet). A maximum of three insertions were attempted in 6 hours with this protocol to induce labor. If the Bishop score was still poor after three tablets it was recorded as drug failure. If Bishop score improved up to 7 or more, artificial rupture of membranes was done and labor was followed as per regular protocol. Outcome in terms of mode of delivery, baby apgar scores, and possible complications (uterine tachysystole, uterine hyperstimulation, uterine rupture, post-partum hemorrhage, and fetal distress or fetal death) was recorded for each case.

Primary outcome measure was efficacy of misoprostol in comparison with dinoprostone for inducing labor. Whereas secondary outcome measures included feto-maternal complications, baby apgar scores, and possible complications like uterine tachysystole, uterine hyperstimulation, uterine rupture, post-partum hemorrhage, and fetal distress or fetal death, and cesarean rates. Five uterine contractions for 10 minutes persisting for 20 minutes was labeled as uterine tachysystole, whereas cutoff of a contraction persisting for 120 minutes was used to label the case as uterine hypersystole/hypertonus. CTG was assessed by the on duty trained labor ward doctor and abnormal CTGs were informed to the specialist obstetrician who re-evaluated them. Hence fetal heart rate changes such as late decelerations, persistent variable decelerations, persistent brady- or tachycardia, and decreased baseline variability were indicators used to label the CTG as abnormal [18].

Data entry and analysis were done in SPSS version 10 (SPSS Inc., Chicago, IL, USA). Intention to treat analysis was done for comparison of quantitative variables like induction labor and delivery interval by using independent sample t test. Pearson χ^2 test was applied for comparison of categorical variables (fetal and maternal complications). Level of statistical significance was $p < 0.05$.

Results

A total of 208 women were recruited. Complete data were available for 200 women, 100 in Group A and 100 in Group B. The two groups were matched for confounding factors such as age, gravidity, and Bishop score. The mean age of the women in the study group was 26.22 years. There was no statistical difference ($p = 1.00$) between the gestational age of women in both groups (Table 1) and the most common reason for induction of

Table 1
Descriptive statistics

	n	Mean ± standard deviation
Age (yr)	200	26.22 ± 3.40
Gravidity	200	2.20 ± 1.24
Gestational age	200	40.11 ± 1.37
Bishop score	200	3.12 ± 1.28

labor was post-date pregnancy in both groups. The mean Bishop score was poor 3.1 ± 95% confidence interval for misoprostol group than for dinoprostone group 3.1 ± 95% confidence interval though not statistically significant ($p = 0.6$).

Primary outcome measures including drug dose administered, induction labor interval, and induction-delivery interval for both the groups are shown in Table 2. When the two groups were compared regarding mode of delivery, there were 84 (54.2%) normal deliveries in the misoprostol group and 71 (45.8%) in the dinoprostone group. Instrumental deliveries were required in 39.4% women in the misoprostol group and 60.6% women in the dinoprostone group. It was noted that 25% women induced with misoprostol and 75% women induced with dinoprostone required cesarean section. But these differences did not reach statistical significance ($p = 0.06$). The results of secondary outcome measures like oxytocin use, uterine rupture, uterine hyperstimulation, post-partum hemorrhage, abnormal CTGs, meconium staining, and apgar scoring are given in Table 3.

Discussion

The main outcome was induction labor and induction-delivery interval. A statistically significant decrease in the induction to onset of labor interval was seen in the misoprostol group. The mean duration was 6.67 in misoprostol group and 8.40 in dinoprostone group ($p = 0.000$) with the additional benefit of a lesser dose of misoprostol [mean of 1.7 doses were required as compared to dinoprostone, where a mean of 2.1 doses used ($p = 0.003$)].

These results were in concordance with Neiger and Greaves who reported fewer doses and a shorter induction-delivery interval with misoprostol ($p = 0.007$) [7] and the same opinion was expressed by Chang et al in their study [8]. Danielian and Porter were of the opinion that more women delivered after only one dose (77% *vs.* 49%) of 50 μg vaginal misoprostol [11] and this was also concluded by Hassan [12].

Table 3
Results of secondary outcome measures

		Misoprostol	Dinoprostone	*p*
Use of oxytocin		36 (43.4)	47 (56.6)	0.114
Uterine rupture		0	0	
Uterine hyperstimulation		10 (71.4)	4 (28.6)	0.096
Post-partum hemorrhage		9 (36)	16 (64)	0.134
Abnormal CTG (% age within fetal complication)		14 (50)	14 (50)	
Meconium (% age within fetal complication)		0	7 (100)	
Apgar score	⩽6	8 (8)	15 (15)	0.36
	>6	92 (92)	85 (85)	

Data are presented as *n* or *n* (%).
CTG = cardiotocography.

The other main outcome was the induction-delivery interval. In our study, the mean induction to delivery interval was 3.68 hours ($p = 0.000$) shorter in the misoprostol group. Khoury also reported a shorter interval from induction to vaginal delivery in nulliparous women receiving misoprostol (21.3 hours *vs.* 27.2 hours) [15]. Chang and Chen concluded a significantly shorter induction-delivery interval (approx. 177 minutes) in their misoprostol group [8]. While in their review of trials of misoprostol used for term labor induction, Hofmeyr and Gulmezoglu found misoprostol to be associated with lower failure rates for achieving vaginal delivery compared to other prostaglandins [16].

In this study, vaginal deliveries were more in the misoprostol group as compared to dinoprostone. While out of 12 cesarean sections performed, 3 cases were from misoprostol and 9 from dinoprostone group. Ramos and Kaunitz in their review also felt that misoprostol was associated with a significantly lower overall rate of cesarean section (odds ratio 0.67) and a higher incidence of vaginal delivery (odds ratio 2.64) within 24 hours of insertion [13]. Whereas in a comparison between use of misoprostol in women at term (36 weeks of gestation) with control, misoprostol had a significantly increased rate of vaginal delivery compared to other methods [14]. On the contrary, Van Gemund and Scherjon found a longer median induction-delivery interval in misoprostol group compared with dinoprostone; however, the caesarean section rate was lower in the misoprostol group: 16.1% versus 21% [17].

Table 2
Results of primary outcome measures

	Mode of induction	*n*	Mean ± standard deviation	*p*	95% confidence interval	
					Lower	Upper
Number of doses	Misoprostol	100	1.77 ± 0.84	0.003	−0.565	−0.114
	Dinoprostone	100	2.11 ± 0.78	0.003	−0.565	−0.114
Induction labor interval	Misoprostol	100	6.67 ± 3.63	0.006	−2.971	−0.490
	Dinoprostone	100	8.40 ± 5.13	0.007	−2.972	−0.489
Induction-delivery interval	Misoprostol	97	11.69 ± 4.56	0.000	−5.105	−2.265
	Dinoprostone	91	15.37 ± 5.30	0.000	−5.111	−2.258

We found a greater need for later on use of oxytocin in dinoprostone group as compared to misoprostol. We used the Cochrane Database [18] definitions while evaluating uterine hyperstimulation, tachysystole, and CTG abnormalities. Abnormal CTGs were read by specialist obstetrician on call in labor ward, and abnormalities in terms of fetal heart rate changes such as late decelerations, persistent variable decelerations, persistent brady or tachycardia, and decreased baseline variability were indicators used to label the CTG as abnormal.

We found no case of uterine hyperstimulation or hypertonus but tachysystole occurred in 10 cases of misoprostol group and 4 patients of dinoprostone group. Our study was not powered to determine the statistical significance of this factor. An equal number of abnormal CTGs (14%) in both study groups was seen; however, meconium staining of liquor was present in seven cases of dinoprostone group and none of the misoprostol group.

The 1-minute apgar was less than 6 in 8% of misoprostol and 15% of dinoprostone group. The Cochrane Pregnancy and Childbirth Group trials register, comparing placebo to misoprostol concluded that misoprostol was associated with a reduced, failure to achieve vaginal delivery within 24 hours and there were no significant differences in the incidence of tachysystole, hypersystole, and hyperstimulation. No maternal and neonatal adverse effects were noted with misoprostol use [19].

International studies have found the incidence of uterine contraction abnormalities (tachysystole and hyperstimulation) and the incidence of abnormal CTG recordings similar for both misoprostol and dinoprostone [9]. Montvale, NJ reported less neonatal intensive care admissions (8.7%) in misoprostol versus (10.8%) in dinoprostone group [20]. No fetotoxic, teratogenic, or carcinogenic effects have been observed in animal studies, and no untoward direct effects on neonates have been noted so far in any of the clinical trials [6,21−25]. Khouri and Zhou were unable to find significant differences between misoprostol and dinoprostone groups in adverse maternal, fetal, or neonatal effects. And Danielian and Porter also concluded that misoprostol use was not related to any adverse neonatal outcomes. Results of Van Gemund and Scherjon also validated the fact that 'adverse neonatal outcome' was similar in both groups and fewer neonates were admitted to neonatal intensive care unit in the misoprostol group compared with dinoprostone 19% versus 26%. Other international data [24−28] also were consistent with the fact that misoprostol was more effective than dinoprostone without any serious increase in untoward effects. Since we had used vaginal route for administration of both the drugs, commonly encountered side effects, such as nausea, vomiting, and diarrhea were not seen. Another main advantage of misoprostol was the cost issue. Dinoprostone (Prostin) costs around $9 per tablet whereas misoprostol (Cytotec) is worth $0.20 per tablet. Prepidil and Cervidil cost $150 and $175 per insert, respectively, whereas a 100-μg Cytotec tablet costs $0.60 [20]. The issue of temperature stability further enhances the performance of misoprostol while making dinoprostone (which requires maintenance of cold chain) a less feasible option for countries with mainly warm climate all the year around.

Conclusion

We find misoprostol to be a more effective alternative to dinoprostone for induction of labor at term. Low cost and temperature insensitivity are its added benefits. No drug available in the market can be labeled as absolutely safe and good for all. The point we are trying to make is that poverty exists everywhere, but it is most cruel and debilitating in developing countries, where more than one person in five subsists on less than $1/day (World Bank Report—World Development indicators 2005). With the average rate of labor induction at term falling between 9% and 15% of the term pregnancies, can we not strongly recommended that international drug regulatory bodies including FDA, allow licensed use of misoprostol in low risk pregnancies for induction of labor at term to help doctors achieve cost-effective optimal treatment for their patients.

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