THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India March / April 2011 pg 153 - 160

Original Article

A Randomized Controlled Trial Comparing Low Dose Vaginal Misoprostol and Dinoprostone Gel for Labor Induction

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Abstract :

Objectives: To compare the safety and efficacy of low dose misoprostol and dinoprostone for cervical ripening and labor induction *Methods*: It was an open label randomized controlled trial conducted at department of Obstetrics & Gynecology, Dr TMA Pai Rotary Hospital, Karkala. The main outcome measure was induction-to-vaginal delivery interval. Secondary outcome measures were the labor characteristics, maternal complications and neonatal outcomes. *Results:* Out of 320 eligible women included for final analysis, 159 received misoprostol and 161 dinoprostone. There was no significant difference between the two groups in induction-to-vaginal delivery interval, mode of delivery, number of women delivering within 24 hours and neonatal outcomes. The efficacies of the two prostaglandins were similar. *Conclusion:* Low dose misoprostol is as efficient as dinoprostone in achieving active labor and delivering with in 24 hours. The maternal and neonatal outcomes associated with each group were similar. It is a cheaper alternative for labor induction.

Keywords: low dose, misoprostol, induction of labor, dinoprostone

Introduction

Situations arise in obstetrics where it becomes necessary to interrupt a pregnancy in the interest of mother or baby or both. Recently, elective inductions of labor at term have increased dramatically. Although dinoprostone gel is considered as the preferred method for labor induction, it is relatively expensive drug. The average maximum retail price is 230.50 per 0.5 mg dose of the endocervical gel (Cerviprime, AstraZeneca Pharma). Dinoprostone gel also requires refrigeration for storage which can cause significant problems for maternity units. There is a growing interest on misoprostol, a prostaglandin E1 analogue for labor induction which is much cheaper and stable at room temperature. A single 100 tablet costs 8.60, thus a low dose of 25 µg dose costs approximately 2.15 Replacing dinoprostone with misoprostol would allow considerable cost savings. A large body of data exists on misoprostol for use in cervical ripening and labor induction. Vaginal application of misoprostol has been reported in over 9000 women worldwide and seems to have safety profile similar to that of dinoprostone.[1, 2] The initial trials have used much higher dose of drug. But the American College of Obstetricians and Gynecologists (ACOG) recommends the use of low dose of 25 µg vaginal misoprostol every 3 to 6 hours.[3] At present, there is only limited information available on

Paper received on 31/03/2009 ; accepted on 01/11/2010

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low dose regimens (25 μg) of misoprostol for labor induction. With this background information the current trial was designed to compare the efficacy and safety of low dose of vaginal misoprostol with routinely used dinoprostone gel for induction of labor.

Material and Methods

This was a randomized controlled trial conducted from January 2006 to August 2008 at Dr TMA Pai Rotary Hospital, Karkala, a secondary level care hospital (an associated hospital of Manipal University, Manipal) in west coast of India. The objective was to compare the safety and efficacy of low dose of vaginal misoprostol with intracervical dinoprostone gel for induction of labor. The study was approved by the local institutional ethical committee. All eligible women with obstetrical or medical indication for labor induction with no contraindication for vaginal delivery were enrolled in the trial. The inclusion criteria were; singleton pregnancy, more than 37 weeks, cephalic presentation, Bishop score of five or less, amniotic fluid index of five or more, reactive fetal heart rate pattern, past dated pregnancy (period of gestation 40 weeks or more), membranes intact or ruptured. Women with following criteria were excluded from the study; para three or more, prior uterine scar (previous cesarean section and myomectomy), multiple pregnancy, estimated fetal weight more than 4000 or less than 2000 grams, abnormal fetal heart rate (FHR) tracings on non stress test (NST), placenta previa, hypersensitivity to prostaglandins, renal, hepatic or cardiovascular disease and severe asthma.

Sonography was performed to confirm the presentation expected fetal weight and amniotic fluid index. Prior to induction vaginal examination will be done to assign the Bishop's score and a NST will be routinely performed to evaluate the fetal well being. The envelopes were prepared before the start of the study. After written informed consent, women were randomized to receive either 25μg of misoprostol (quartering 100 μg tablets Cytolog, Zydus Cadila) in posterior fornix of vagina or 0.5 mg of l dinoprostone gel intracervically (Cerviprime, AstraZeneca Pharma). The dose was repeated if necessary every six hourly to a maximum of three doses in 24 hours.

The allocation of treatment was done by block randomization. Blocks of ten were prepared at the beginning of the trial and assignment was concealed by placement in consecutively numbered sealed envelopes. These were drawn in a consecutive order by the doctor, who was unaware of the agent to be allocated until the envelope was opened. The study was not placebo controlled therefore women and doctors were aware of the treatment allocated. Women lay down for at least 30 minutes after induction. Pelvic examination was repeated after six and twelve hours of insertion of drug or earlier when clinically indicated to assess the cervical score. Continuous electronic fetal heart rate monitoring was performed in all patients in active labor. Labor was augmented with oxytocin in patients with arrest of cervical dilatation due to poor contractions. Augmentation was delayed for six hours after administration of drug. Artificial rupture of the membranes was performed when clinically indicated.

Labor induction was considered successful if vaginal delivery occurred within 24 hours of induction. A primary outcome measure was the interval from first dose of drug to vaginal delivery. Secondary outcome variables included; change in Bishop score at six and twelve hours, time interval from induction to onset of adequate uterine contractions (three contractions per ten minutes), mode and route of delivery, indications for cesarean delivery, number of emergency cesareans performed for abnormal FHR pattern, number of doses of drugs used, oxytocin augmentation, incidence of adverse effects; uterine contraction abnormalities, pattern of FHR abnormalities. Specific prostaglandin side effects such as hyperpyrexia, vomiting and diarrhea, incidence of postpartum hemorrhage, cervical tears, and vaginal tears were recorded. The variables in neonatal outcome included birth weight, APGAR score at 1 and 5 min, incidence of meconium stained amniotic fluid, admission to neonatal intensive care unit. The patient's satisfaction of induction of labor was also recorded. Statistical analysis of data was performed using SPSS version 16. Variables were analyzed with chi-square test or Mann-Whitney's test, Fisher exact t test, and student *t*-test. The *P* value < 0.05 was considered as significant.

Results

Out of 320 eligible women included for final analysis 159 were received misoprostol and 161 dinoprostone. There was one incidence of violation of protocol, one woman inadvertently received dinoprostone instead of allocated 25μg misoprostol. No women were lost to follow up. The demographic characteristics of the women and indications for induction of labor in both groups were comparable (Table1). There is no

The Consort E-Flowchart for low dose misoprostol trial

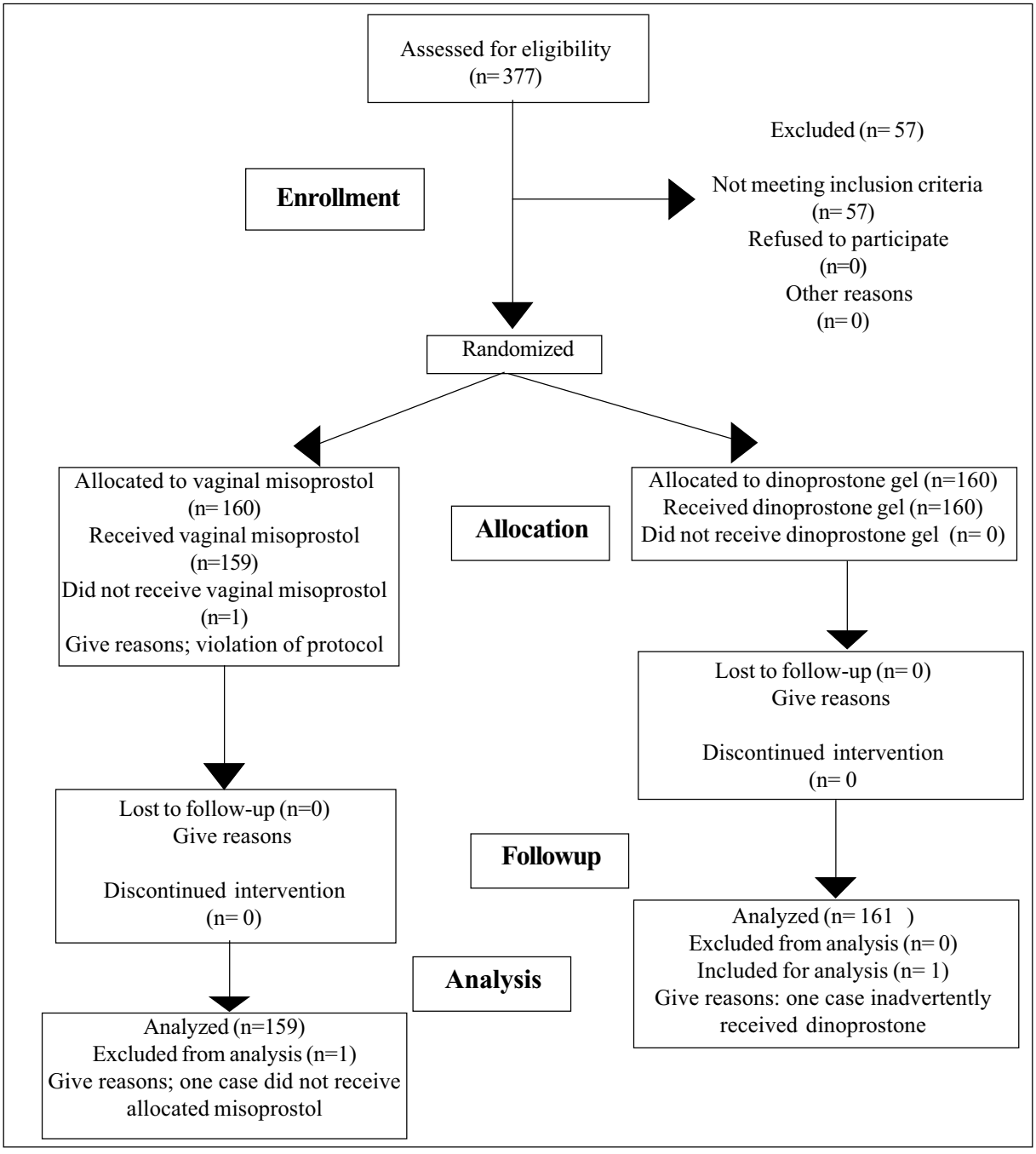

Table 1.
Maternal characteristics

Variables	Misoprostol (N=159)	Dinoprostone (N=161)	*P*
Age [a]	25 {19-37}	25{19-41}	0.578
Parity [c]			
Nulliparous (n)%	105 (66.04)	118 (73.3)	0.58
Multi (n)%	54 (34.96)	43 (26.70)	
Gestational age (weeks ± S.D) [b]	39.42 ± 1.09	39.43 ± 0.95	0.864
Initial Bishop score (mean ± S.D) [b]	3.06 ± 1.59	3.0 ± 1.48	0.770
Indications for labor induction [c]			
Past date	111 (69.8)	113 (70.2)	0.983
PROM	39 (24.5)	41 (25.5)	
Preeclampsia	7 (4.4)	5 (3.1)	
Patient's request	1 (0.6)	1 (0.6)	

PROM= premature rupture of membranes
[a] Mann-Whitney *U* test, Data represented as median {range}
[b] Student's *t*-test Data represented as mean ± SD or n (%)
[c] Chi square test

Table 2.
Change of Bishop score

Bishop score	Misoprostol (N=159)	Dinoprostone (N=161)	*P*-value
Initial Bishop score[b]	3.06 ± 1.59	3.0 ± 1.48	0.770
6 hours (n=250)[b]	5.22 ± 2.64	5.37 ± 2.84	0.678
12 hours (n=137)[b]	5.95 ± 2.64	5.95 ± 2.78	0.988

[b] Student's *t*-test, data represented as mean ± SD

significant difference in the initial mean Bishop score and change at six and twelve hours among groups (Table 2). With regard to out come of labor the median occurrence of active labor was similar in both groups (465 vs 457 minutes p=0.200). There was no significant difference in median induction to vaginal delivery in misoprostol and dinoprostone groups (684 vs 690, p=0.1).

The proportion of women delivering with in twenty four hours is similar among groups (98/119, 82.4% vs 106/119, 89.1% p=0.1947) The requirement of oxytocin augmentation is similar in misoprostol and dinoprostone group (34% vs 35%, p 0.786). There was no significant difference in the number of doses required among the groups. The intrapartum variables are presented in Table 3.

No difference was noted in the overall incidence of spontaneous vaginal deliveries, cesarean and instrumental deliveries among groups (vaginal delivery 68% vs 66%, forceps delivery 7% vs &.5%, cesarean delivery 25 % vs 26% p=0.959). As far as the newborn out come is concerned there were no significant differences in incidence of meconium (12.6 % vs 11.8%, p= 0.832) among groups. There was no significant difference in Apgar scores below seven at one and five minutes or admission to the neonatal unit. The mean

Table 3.
Intrapartum variables

Outcome	Misoprostol (N=159)	Dinoprostone (N=161)	*P*/ RR(95%CI)
Occurrence of active labor (min) [a]	465{0-4010}	457{15-3180}	p=0.439
Induction vaginal delivery interval [a]	684{138-6707}	690{60-5477}	p= 0.200
< 12 h(n, %)[c]	61/119 (51.3)	64/119 (53.8)	0.95[0.75,1.21]
12 - 24 h (n, %)[c]	37/119 (31.1)	42/119 (35.3)	0.88[0.61,1.26]
> 24 h (n, %)[c]	21/119 (17.6)	13/119 (10.9)	1.62[0.85,3.07]
Oxytocin augmentation [c]	54 (34)	57 (35.4)	0.96[0.71,1.30]
No of doses [c]			
1	61(38.36)	81(50.62)	0.76[0.59,0.98]
2	51(32.1)	41(25.5)	1.26[0.89,1.78]
3	47 (29.6)	39(24.2)	1.22[0.85,1.76]

[a] Mann-Whitney *U* test, Data represented as median {range}
[c] Chi-square test relative risk (95% CI)
Patients who underwent cesarean were excluded

Table 4.
Delivery method and fetal outcome

Outcome	Misoprostol (N=159) n %	Dinoprostone (N=161) n %	*P*/RR(95%)
Delivery [c]			
Spontaneous vaginal	108 (67.9)	107 (66.5)	1.02[0.88,1.19]
Forceps	11 (6.9)	12 (7.5)	0.93[0.42,2.04]
Cesarean section	40 (25.2)	42 (26.1)	0.96[0.66,1.40]
APGAR score [c]			
1 minute (<7)	15 (9.4)	8 (5)	p=0.1835
5 minute (<7)	3 (1.8)	1 (0.6)	p=6060
Meconium passage [c]	20 (12.6)	19 (11.8)	0.930[0.476.1.817]
Birth weight (grams) [b]	2997 ± 404	3006 ± 395	0.859
NICU admissions [d]	0 (0)	1 (0.6)	p=1.0000

[c] Chi-square test, [b] Student's *t*-test, [d] Fisher's Exact Test

birth weight is comparable in misoprostol and dinoprostone group (2997± 404 vs 3006± 395, p= 859). Table 4 summarizes the peripartum details. The indications for cesarean section are highlighted in Table 5.

Table 5.
Indications for cesarean delivery

Indications[c]	Misoprostol (N=159)	Dinoprostone (N=161)	RR(95%CI)
Fetal distress	14	21	0.68[0.36, 1.28]
Non progress of labor	10	8	1.27[0.51, 3.12]
Failed induction	16	13	1.25[0.62, 2.51]

[c] Chi-square test

Table 6.
Secondary outcome variables: complications

Variables	Misoprostol (n=159) n %	Dinoprostone (n=161) n %	*P/RR(95%)*
Uterine contraction abnormalities[d]	0	4 (2.5)	p=0.1226
Uterine tachysystole	0	0	0
Hypertonus	0	2 (1.2)	p=0.4984
Uterine hyperstimulation syndrome	0	2 (1.2)	p=0.4984
Abnormal cardiotocograph	20 (12.5)	23(14.3)	0.88[0.50,1.54]
Postpartum hemorrhage[d]	4 (2.5)	0	p=0.0597
Atonic	1 (0.6)	0	p=0.4968
Traumatic	3 (6.7)	0	p=0.1215

[d] Fisher's Exact Test

Potential adverse effects like nausea, vomiting, diarrhea, and fever were not noted in the study population. The incidence of abnormal cardiograph was 12.5% and 14.3% (p=0.931) in misoprostol and dinoprostone group respectively. Although there were four cases of uterine contraction abnormalities in dinoprostone group the difference was not statistically significant. Only one patient required subcutaneous terbutaline to counter the hyperstimulation. There were four incidences of maternal hemorrhage in misoprostol group and none in dinoprostone group (4, 2.5% vs 0% p=0.0597) (Table 6). Regarding the patient's satisfaction the information is available in 239 cases. More than 50% satisfaction of was observed in 107 (89.2%) mothers in misoprostol group and 109 (91.6%) which was not statistically significant p=0.6762.

Discussion

Although dinoprostone (PGE_2 gel),is the preferred method of pharmacologic method of induction of labor[4] because of its cost and storage requirement the search for an effective, easily stored, affordable labor inducing agent has led to the use of misoprostol. The efficacy of vaginal misoprostol for induction of labor was confirmed by many investigators since 1990s. The general concern in the use of intravaginal misoprostol for induction of labor was significant incidence of uterine tachysystole and hyperstimulation and potential of fetal jeopardy. The dose was titrated and lower doses of 25 µg were found to be effective while the hyperstimulation and meconium passage were found less frequently.[5]

In the present investigation of comparison of low dose of 25 µg misoprostol and dinoprostone for labor induction shows that there was no significant difference between the groups in terms of efficacy.

In our present study, administration of the two prostaglandins resulted in a similar induction delivery intervals confirming the results of previous investigators. [6,7] But there was conflicting reports by other investigators. Gemund van et al[8] in their study concluded that the median induction-to-vaginal delivery interval was approximately 6 hours longer in the misoprostol group (25 versus 19 hours, p = 0.008). Where as in an Indain study by Nanda et al[9] demonstrated that the mean induction to delivery interval is five hours shorter in misoprostol group (13.30±78.74 vs 18.53±11.33 p=0.011). Since Gemund van et al [6] has used pulverised misoprostol with cellulose in a capsule, it is possible, that the efficacy of the misoprostol may have been reduced.

Our data on secondary out come variables showed that there was no significant difference between groups for uterine contraction abnormalities. Although Nanda et al[9] reported that the increased efficacy of low dose of misoprostol, the uterine contraction abnormalities, abnormal fetal heart rate (FHR) pattern and meconium passage occurred more signiûcantly in the misoprostol group as compared with the dinoprostone group. A similar study by Prager et al[6] with Foleys catheter in the third arm in addition to the prostaglandin regimens observed that there was a tendency towards more frequent caesarean section in response to fetal distress among the women administered dinoprostone and more frequent dystocia in those receiving misoprostol.

Although, misoprostol is not licensed for use in pregnancy in the light of evidence of greater efficiency, the WHO manual 'Managing Complications in Pregnancy and Childbirth' recommends the use of misoprostol for induction of labor and places it in its list of 'essential drugs'.[10] Various factors influence the drug concentrations and availability which can potentially influence the efficacy and safety of misoprostol. The misoprostol oral tablets are available as unscored 100 µg and scored 200 µg tablets. The low dose tablets are not commercially available as this low dose is for off label use in pregnant women. The dose of 25 µg can only be obtained by cutting a 100 µg tablet in to four or by one-eighth of a 200 µg tablet or making up suspensions of the drug. But the exact dose of 25 µg cannot be guaranteed in individual pieces. Even now some hospital pharmacies decline to cut unscored tablets due to the inherent inaccuracy of dose. Moreover using an oral tablet vaginally results in a different pharmacological effect. Carlan and colleagues[11]suggest that this may be secondary to erratic and delayed absorption of the drug through the vaginal mucosa since the tablet is coated with cellulose matrix to give stability at room temperature.

However, in a Brazilian study[12] one-eighth of an oral 200 microgram tablet of misoprostol was found to be as effective in inducing labor and as safe as a new commercially available vaginal 25 microgram tablet. This new formulation was specifically developed to provide the precise dosage for vaginal administration and has been approved by the Brazilian Ministry of Health for use in obstetrics in Brazil.

The important message from our data is that low dose misoprostol and dinoprostone appear to have similar efficacy and safety profile for cervical ripening and labor induction. The additional beneûts of misoprostol are, its stability at room temperature, it costs approximately 300 times less per dose ease of administration. These beneûts make misoprostol comparable or even superior to dinoprostone for induction of labor especially in developing and tropical countries like India. There is a strong need for commercially available lower doses of vaginal misoprostol to allow further research. So that correct doses are available. This will be a valuable contribution to the safety of its use for cervical ripening and labor induction.

Acknowledgement

The authors thank Dr Sanjay Kumar, Assistant Professor for his valuable support in obtaining consent and counseling patients throughout the study. We would thank Dr Asha Kamath dept of Biostatistics for her advice and suggestions for statistical analysis. We would also thank Dr Avinash Shetty, Chief Medical Officer Dr TMA Pai Rotary Hospital Karkala for his valuable support and permitting us to use hospital and office facilities for this study.

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