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Original Article

Obstetrics and Gynaecology Section

Is Low Dose Vaginal Misoprostol Better Than Dinoprostone Gel For Induction of Labor: A Randomized Controlled Trial

MONIKA MADAAN[1], SWATI AGRAWAL[2], MANJU PURI[3], ARUNA NIGAM[4], HARVINDER KAUR[5], SHUBHA SAGAR TRIVEDI[6]

ABSTRACT

Objective: To compare the efficacy and safety profile of low dose vaginal misoprostol with dinoprostone gel for induction of labor in term pregnancies.

Methods: The study was conducted at Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital on 100 pregnant women with term pregnancy after application of inclusion and exclusion criteria. The women were randomized in 2 groups of 50 women each. Group I received misoprostol 25µg at every six hour vaginally for a maximum of five doses for induction of labor; while group II received dinoprostone gel 0.5 mg every six hourly for a maximum of three doses. Maternal outcomes such as mode of delivery and induction delivery interval; and fetal outcomes such as APGAR score and incidence of NICU admission were assessed in both the groups. Statistical analysis was done using student t-test and chi-square test.

Results: There was no significant difference in the mean induction to delivery interval in both the groups (14.32±0.13 hours in Group I and 14.92±0.18 hours in Group II, p=0.75), mode of delivery, indication of cesarean section and perinatal outcome. However, significant difference was observed in requirement of oxytocin augmentation in both the groups (32% in Group I and 68% in Group II, p=0.005).

Conclusion: Vaginal misoprostol in low doses is similar in efficacy and safety to dinoprostone gel for cervical ripening and labor induction in term pregnancy.

Keywords: Dinoprostone, Induction, Labor, Misoprostol

INTRODUCTION

In the past decades there has been an increase in the incidence of induction of labor. Data from WHO Global survey on maternal and perinatal health has shown that all over the world 9.6% of deliveries required labor induction [1]. In the developed countries the incidence of labor induction is as high as 25% [1].

Dinoprostone, a PGE2 analogue has long been used for cervical ripening and labor induction and is a very efficacious drug with a good safety profile. But it is costly and requires refrigeration for storage.

Misoprostol, a PGE1 analogue has also been shown to be effective in cervical priming and labor induction. It is inexpensive, can be stored at room temperature and has few systemic side effects. Although, originally approved for use in prevention and treatment of peptic ulcer, in April 2002 FDA finally approved a new label for use of misoprostol during pregnancy [2]. This revises the contraindication and the precaution that misoprostol should not be used in pregnant women by stating that the contraindication is only for pregnant women who are using the medication to reduce the risk of NSAID-induced stomach ulcers. Misoprostol is now a part of the FDA approved regime for use with mifepristone to induce abortion in early pregnancy and is also recognized for its use for induction of labor.

A large data exists in the literature regarding the use of misoprostol by oral, vaginal or sublingual routes for use in cervical ripening and labor induction in varied doses but there have been concerns about hyperstimulation, meconium and non reassuring fetal heart rates with the higher doses.

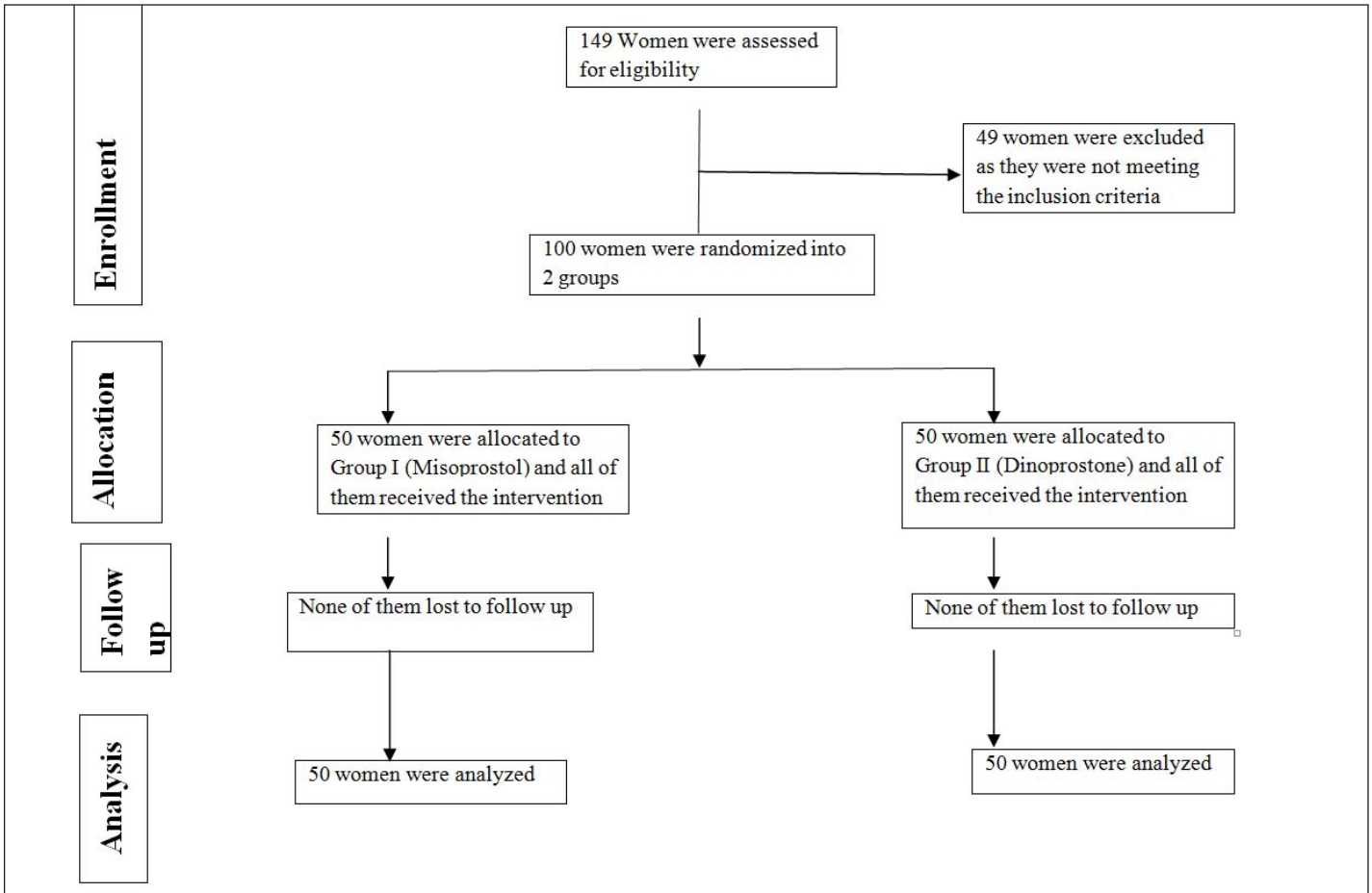
ACOG has recommended the use of vaginal misoprostol in doses of 25µg every 3 to 6 hourly [3], WHO has recommended it 6 hourly now [1].

Still the lowest effective dose of misoprostol and the optimal dosing interval that achieves a balance between high doses, which result in rapid delivery but frequent hyperstimulation and lower doses which take longer to achieve delivery but have a better safety profile is under investigation and people are using different protocols. With this background we designed the current study to compare the efficacy and safety profile of low dose vaginal misoprostol with dinoprostone gel for induction of labor in term pregnancies.

MATERIALS AND METHODS

The study was conducted in the Department of Obstetrics and Gynecology at Lady Hardinge Medical College and Smt. Sucheta Kriplani Hospital, New Delhi from October 2010 to May 2011. month. A total of 100 pregnant women with obstetrical or medical indication for induction of labor were enrolled in the study in accordance with the inclusion and exclusion criteria. The inclusion criteria were singleton pregnancy, cephalic presentation, period of gestation more than 37 weeks, bishop score of five or less, amniotic fluid index of five or more and a reactive non stress test. Women with previous uterine scar, multiple pregnancy, placenta previa, non reactive NST, severe IUGR, severe oligoamnios, estimated fetal weight more than 4000 grams or less than 2000 grams, chronic systemic disease or any hypersensitivity to prostaglandins were excluded from the study. The study was approved by the institutional ethical board.

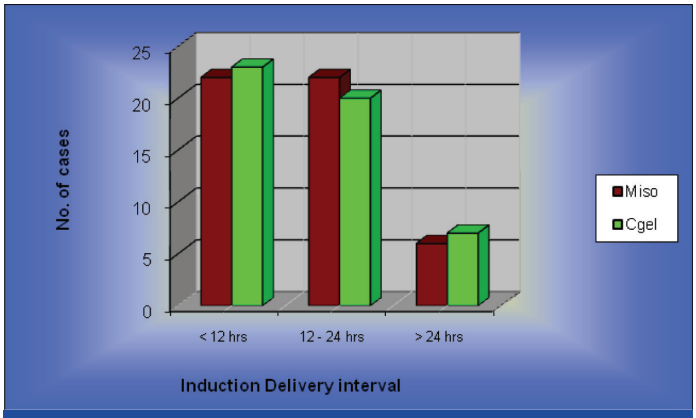
After a detailed history and examination, vaginal examination was done to assess the bishop score. NST was done in all cases prior to induction of labor. After written informed consent eligible candidates were randomized into two groups. The randomization was done according to the registration number/ admission number. Those with even registration number were allocated to Group I and with



[Table/Fig-1]: Consort flow diagram

	Group I (Misoprostol) N=50(%)	Group II (Dinoprostone) N=50(%)	p-value
Age (yrs)	25 (19-37)	24 (19-35)	0.68
Parity			
0	26 (52%)	23 (46%)	0.27
1	20 (40%)	17 (34%)	0.26
2	3 (6%)	7 (14%)	0.09
>2	1 (2%)	3 (6%)	0.15
Period of gestation (wks)	39.54±1.26	39.48±1.50	0.82
Mean Bishop score at induction	3.86±1.51	3.9±1.38	0.89
Indications for induction of labor:			
Postdated	31 (62%)	34 (68%)	0.41
Gestational Hypertension	6 (12%)	2 (4%)	0.07
Previous h/o IUD	2 (4%)	3 (6%)	0.32
Oligoamnois (mild)	3 (6%)	2 (4%)	0.32
Decreased Fetal	2 (4%)	1 (2%)	0.27
movements	3 (6%)	2 (4%)	0.32
PROM	3 (6%)	6 (12%)	0.08

[Table/Fig-2]: Demography and maternal characteristics



[Table/Fig-3]: Induction delivery interval in both the groups

odd no. were allocated to Group II. The women in Group 1 were induced with a 25 µg tablet of misoprostol placed in the vagina every six hourly upto maximum of five doses. The 25 µg dose was prepared by dividing the 100 µg tablet into four equal pieces and was placed in the vagina by the attending obstetrician. The women in Group II were induced with dinoprostone gel 0.5 mg instilled intracervically six hourly upto maximum of three doses.

The progress of labor was monitored as per the institutional protocol Fetal monitoring was done by intermittent auscultation every 15 minutes in the first stage and every 5 minutes in the second stage of labour.

Subsequent doses of the drugs were withheld if the woman went in established labor or ruptured her membranes as well as in cases with non reassuring fetal heart rate. The primary outcome measures assessed were mode of delivery and induction to delivery interval. Secondary maternal outcome measures assessed were requirement of oxytocin, number of doses of drug used, incidence of cesarean section for fetal distress, meconium stained liquor or failed induction and side effects like hyperstimulation, hyperpyrexia, vomiting, diarrhea, postpartum hemorrhage, cervical tears and vaginal tears. Fetal outcome was assessed in terms of birth weight, APGAR scores at one and five min and admission to neonatal intensive care unit. Statistical analysis was done using student t-test and chi-square test. P-value < 0.05 was considered as significant.

Power of the study: Previous studies had indicated around 85% normal deliveries in misoprostol group and 60% in dinoprostone group. With these percentages, the minimum required sample

	Group I (Misoprostol) N=50(%)	Group II (Dinoprostone) N=50(%)	P value
Oxytocin requirement	16 (32%)	29 (58%)	0.005
Number of doses			
1	11 (22%)	(60%)	0.00
2	19 (38%)	19 (38%)	1.00
3	13 (26%)	1 (2%)	0.00
4	4 (8%)	0 (0%)	0.02
5	3 (6%)	0 (0%)	0.03
Mode of delivery			
Vaginal delivery	41 (82%)	37 (74%)	0.16
Cesarean section	9 (18%)	12 (24%)	0.23
Forceps	0 (0%)	1 (2%)	0.15
MSL	11 (22%)	6 (12%)	0.092
Indication of Cesarean			
MSL	2	4	0.19
Fetal Distress	1	5	0.04
Failed induction	0	0	-
Arrest disorders	0	3	0.03
Complications			
Hyperstimulation	0	0	-
Fever	0	1(2%)	0.15
Perineal	0	1(2%)	0.15

[Table/Fig-4]: Intrapartum characteristics & Maternal outcome

	Group I (Misoprostol) N=50(%)	Group II (Dinoprostone) N=50(%)	P value
Birth weight (kg)	2.76±0.38	2.80±0.53	0.65
Apgar Score < 7			
1 min	5(10%)	2(4%)	0.23
5 min	0	1(2%)	0.15
7 min	0	0	-
Admission to NICU	2(4%)	3(6%)	0.53

[Table/Fig-5]: Fetal outcome

size with 80% power and 5% level of significance is 47 patients in each group. After initial enrollment and allocation, finally 50 women were analysed in each group. [Table/Fig-1] shows the consort flow diagram of the study.

RESULTS

There were 50 women enrolled in each group. Both the groups were comparable as regards demographic characteristics (age, parity and period of gestation), initial bishop score at admission and indications for induction of labor as shown in [Table/Fig-2]. There was no significant difference in the mean induction to delivery interval in misoprostol and dinoprostone groups (14.32±0.13 hours vs 14.92±0.18 hours, p=0.75). [Table/Fig-3] shows the distribution of two groups according to induction delivery interval. There was a significant difference in requirement of oxytocin augmentation in the two groups . In dinoprostone group 68% women required oxytocin augmentation as compared to 32% in the misoprostol group (p=0.005). However, the dose requirement was significantly less in the dinoprostone group as shown in [Table/Fig-4]. It also shows the various intrapartum characteristics, mode of delivery and the maternal outcome. There was no difference in the perinatal outcome in both the groups as is shown in [Table/Fig-5]. There was no perinatal mortality in the study population.

DISCUSSION

Thus, the results of the study show a comparable efficacy and safety profile of low dose vaginal misoprostol when compared with dinoprostone gel for induction of labor in term pregnancies. There was no significant difference in the rate of cesarean section in misoprostol and dinoprostone groups (9 vs 12, p= 0.23). Similar results were cited in a systematic review of 14 RCT's by Crane et al., in 2006 [4] and other studies [5,6].

In our study administration of the two prostaglandin regimens resulted in a similar induction to delivery interval as has been shown in an Indian study by Shivarudraiah G et al., [5] using the same dose regimens. However, in study by Nanda et al., [6] the mean induction delivery interval was shorter by five hours in the misoprostol group. But in that study misoprostol was used in the dose of 25µg every three hourly. Similarly a study by Wing et al., [7] and a systematic review by Crane et al., [4] have shown that misoprostol is more effective than dinoprostone. But since the dose schedules are different and involved higher doses, it is difficult to make direct comparisons.

As regards the outcome of secondary variables is concerned, our study showed slight deviations from the present available literature. The oxytocin requirement was significantly less in the misoprostol group which is consistent with other studies[4-6]. But the total dose of misoprostol required was significantly more in the misoprostol group. This is in contrast to studies where they concluded that there is no significant difference in number of doses required in misoprostol and dinoprostone groups [5,6].

There was no increased incidence of meconium and no increased incidence of cesarean section for non reassuring fetal heart found in the misoprost group in the present study. This is in contrast to other studies where the incidence of both meconium and cesarean section for non reassuring fetal heart is high in the misoprostol group [4,6]. This appears to be due to the fact that we used lesser dose of misoprostol at prolonged intervals than used in other studies. Even in a study by Papanikolaou where 50µg of misoprostol was used at intervals of nine hours, a higher incidence of both these abnormalities was found [8].

Cochrane review 2010 [9] including 121 trials has stated that compared with prostaglandin E2, vaginal misoprostol was associated with fewer failures to achieve vaginal delivery within 24 hours, more uterine hyperstimulation, lesser need for oxytocin augmentation but increased incidence of meconium-stained liquor. Lower doses of misoprostol compared to higher doses were associated with more need for oxytocin augmentation and less uterine hyperstimulation, with and without FHR changes.

A significantly increased incidence of cesarean section due to fetal distress and arrest disorders was observed in the dinoprostone group. This finding is in disagreement with most but not all studies. This could be attributable to the small sample size of the study population. However, a similar study by Prager et al., [10] 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.

There was no case of tachysystole in either of the group. The incidence of tachysystole and hyperstimulation are higher when 50 µg of misoprostol is used [4]. The adverse effects of misoprostol are dose related. Invitro effects of misoprostol were studied by Lyons et al., [11] in term pregnant rats. This study demonstrated that the EP3 receptor through which misoprostol acts is differentially expressed in the myometrium and cervix in response to misoprostol. This may account for the ability of misoprostol to stimulate the myometrium when administered for cervical ripening. Thus it seems reasonable to use lower doses of misoprostol at prolonged intervals i.e. six hours to reduce the risk of asynchrony between the myometrium

and the cervix thus avoiding complications like tachysystole and non reassuring fetal heart rate.

CONCLUSION

Low dose vaginal misoprostol (25µg six hourly) is similar in efficacy and safety to the routinely used dinoprostone gel for cervical ripening and labor induction in term pregnancy with unscarred uterus specially in developing countries due to its advantages of stability at room temperature and cost effectiveness.

REFERENCES

[1] WHO recommendations for Induction of labor. World Health Organization 2011. Available from: whqlibdoc.who.int/publications/2011/9789241501156_eng.pdf.

[2] ACOG committee opinion. New US Food and drug administration labeling of cytotec (misoprostol) use in pregnancy. *Int J Gynecol Obstet.* 2003;82:137-38.

[3] ACOG Practice Bulletin number 107, August 2009. Induction of Labor. *Obstet Gynecol.* 2009;114(2):386-97.

[4] Crane JM, Butler B, Young DC, Hannah ME. Misoprostol compared with prostaglandin E2 for labor induction in women at term with intact membranes and unfavourable cervix: a systematic review. *BJOG.* 2006;113:1366–76.

[5] Girija S, Manjunath A P. A Randomized Controlled Trial Comparing Low Dose VaginalMisoprostol and Dinoprostone Gel for Labor Induction. *J of Obstet Gynecol India.* 2011;61(2): 153 – 60.

[6] Nanda S, Singhal SR, Papneja A. Induction of labor with intravaginal misoprostol and prostaglandin E2 gel: a comparative study. *Trop Doct.* 2007;37:21–24.

[7] Wing DA, Gaffaney CA. Vaginal misoprostol administration for cervical ripening and labor induction. *Clin Obstet Gynecol.* 2006;49:627–41.

[8] Papanikolaou EG, Plachouras N, Drougia A, Andronikou S, Vlachou C, Stefos T, et al. Comparison of misoprostol and dinoprostone for elective induction of labor in nulliparous women at full term: a randomized prospective study. *Reprod Biol Endocrinol.* 2004;2:70–76.

[9] Hofmeyr GJ, Gülmezoglu AM, Pileggi C. Vaginal misoprostol for cervical ripening and induction of labor. *Cochrane Database Syst Rev*. 2010 ;(10):CD000941.

[10] Prager M, Eneroth-Grimfors E, Edlund M, et al. A randomised controlled trial of intravaginal dinoprostone, intravaginal misoprostol and transcervical balloon catheter for labor induction. *BJOG.* 2008;115:1443-50.

[11] Lyons C, Beharry K, Akmal Y, Attenello F, Nageotte MP: In vitro response of prostaglandin E2 receptor (EP3) in the term pregnant rat uterus and cervix to misoprostol. *Prostaglandins Other Lipid Mediat.* 2003; 70:317-21.

PARTICULARS OF CONTRIBUTORS:

1. Ex Assistant Professor, Department of Obstetrics and Gynecology, LHMC & SSKH (Lady Hardinge Medical College and Smt Sucheta Kriplani Hospital), New Delhi, India.
2. Assistant Professor, Department of Obstetrics and Gynecology, LHMC & SSKH, New Delhi, India.
3. Professor, Department of Obstetrics and Gynecology, LHMC & SSKH, New Delhi, India
4. Ex. Assistant Professor, Department of Obstetrics and Gynecology, LHMC & SSKH, New Delhi, India.
5. GDMO, Department of Obstetrics and Gynecology, LHMC & SSKH, New Delhi, India.
6. Director Professor, Department of Obstetrics and Gynecology, LHMC & SSKH, New Delhi, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Monika Madaan,
HOD and Specialist, ESIC Hospital, Manesar, Gurgaon, Haryana-122001, India.
Phone : 09891200166, E-mail : rmonikarajivgaur@gmail.com

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