The Role of Low Dose Misoprostol in Cervical Ripening and Induction of Labour Beyond the Age of Viability and its Effects on Maternal and Fetal Outcomes

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ABSTRACT

This study was conducted to compare the efficacy and safety of oral (50 µg) and vaginal (25 µg) misoprostol for cervical ripening and induction of labour. Two hundred patients with indications for labour induction randomly received either 50 µg oral misoprostol every 4 h (Group-I) or 25 µg vaginal misoprostol every 4 h (Group-II), for maximum of six doses. Mean induction to delivery time, delivery within 24 hrs, mode of delivery, oxytocin use, number of doses used, failed induction rate and maternal complication and fetal outcomes were compared for the two groups. Mean induction delivery time was significantly longer in Group-I (20.55±5.59 hrs) than in Group-II (16.70±7.12 hrs) (with mean difference of 3.85 and P-value of <0.001). Mean number of doses of misoprostol used for oral and vaginal misoprostol study populations were 2.61±0.94 and 2.37±1.20 respectively. Oxytocin augmentation was required in significantly more number of patients in oral group (80%) than in vaginal group (68%) with P-value of 0.027. There were 3 failed inductions in the oral and 4 in the vaginal group after a total of six doses of misoprostol. Incidence of maternal and fetal complications was similar between two groups. Our findings indicated that, 25µg vaginal misoprostol has the potential to induce labor as safely as, and more effectively than, 50 µg oral analogue. JMS 2017; 20(1):18-21

INTRODUCTION

Induction implies stimulation of contraction before spontaneous onset of labour. The primary condition that must be fulfilled to interfere with this natural process is that terminating pregnancy would benefit the mother and/or fetus. Since ages various methods for induction have been used. Prostaglandins (PGs) are nowadays often used for induction of labour. Expression of myometrial prostaglandin receptors increases in late gestation¹. PGE² analog dinoprostone is currently the only prostaglandin approved by United States Food and Drug Administration (US FDA) for cervical ripening and induction of labour. Disadvantages of dinoprostone are that it is expensive, requires strict refrigeration and cannot be used in patients with ruptured membranes.

There is a need for less costly and less temperature

sensitive alternatives. PGE1 analog misoprostol is the upcoming alternative. Use of prostaglandins followed by intravenous oxytocin is generally accepted to be the standard induction method for women with unfavorable cervix^{2,3}.

Advantages of misoprostol over dinoprostone are that it is not expensive, is easily stored, can be administered by more than one route and can be used in ruptured membranes. Several studies attest to efficacy of PGE¹ analog misoprostol in comparison to PGE² analog dinoprostone^{4,5}. WHO endorses the role of misoprostol by including it in WHO model list for essential medicines⁶.

For induction of labour misoprostol is mainly used by oral and vaginal routes. The ideal dose, route, and frequency of administration of misoprostol are still under investigation. There are several reports describing orally administered misoprostol for induction of labour⁷⁻⁹. Bennett et al found that orally administered misoprostol induced labour as effectively as vaginally administered misoprostol; however, the time interval from administration to vaginal

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birth was longer in orally administered group⁹. Advantage of oral administration of misoprostol is the ease of administration and its noninvasiveness. Orally 50–100 µg have been used in various studies¹⁰⁻¹².

Vaginal administration has advantages of decreasing systemic side-effects with profound effect on reproductive tract; also the bio-availability of vaginally administered misoprostol is more than twice that of orally administered misoprostol¹³. Time interval to delivery is decreased and a lower dose of drug is needed. Vaginally 25 µg or 50 µg misoprostol are used. The most common vaginal dose used has been 50 µg misoprostol, inserted once or administered every four to six hours. Inserting 25 µg misoprostol every six hours intra-vaginally has been associated with the fewest side effects^{14,15}.

METHODS

This study was conducted over a period of 2 yrs (Sep. 2012-Aug. 2014) in the Post graduate department of Obstetrics and Gynecology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir.

Pregnant women beyond the gestational age of viability, with a medical or obstetrical indication for induction of labour, were evaluated for participation in this study. Subjects with singleton pregnancy, longitudinal lie, cephalic presentation, reactive fetal heart rate, maternal age of 20-35 yrs, estimated fetal weight of more than 2 kg and less than 4 kg and parity of less than 3 were included. Exclusion criteria included patients in active labour, multiple pregnancy, malpresentation, estimated fetal weight ≥ 4 kg or < 2 kg, evidence of cephalo-pelvic disproportion, placenta previa or any other contraindication to vaginal delivery, history of uterine incision, evidence of chorioamnionitis, parity of more than three, signs and symptoms of fetal distress, herpes simplex (active) and contraindication to use of prostaglandins.

After admitting the patient, fully informed consent was taken. Detailed history was taken and a complete clinical examination was done. Cardiotocography and sonography was done in all patients. Subjects were randomly assigned to two groups (1:1). In one group 25 µg of misoprostol was put in posterior fornix of vagina, and in other 50 µg (25 µg two tablets) of misoprostol was given orally. Dose was repeated every four hours to a maximum of 150 µg (6 doses) in vaginal group and to a maximum of

300 µg (6 doses) for those who did not get adequate uterine contractions (3 in 10 min). Strict monitoring of fetal heart and uterine contractions was done.

Primary outcomes assessed were in terms of vaginal delivery within 24 hrs, induction to delivery time, change in Bishop's score and neonatal outcome. Secondary outcomes assessed included caesarean delivery, oxytocin use for augmentation, number of doses required, hyper stimulation syndrome, passage of meconium and tachysystole.

Induction was considered successful when delivery occurred within 24 hrs of induction. Augmentation with oxytocin was done when uterine contraction frequency was fewer than 2 in 10 minutes, failure to progress in active phase of labour (less than 1 cm in 1 hr), after adequate cervical ripening (dilatation of ≥ 3 cm or Bishops of ≥ 8) and failure to enter labour after maximum doses.

RESULTS

Two hundred women were enrolled for participation in this study, out of whom 198 were taken for final analysis as two women withdrew. These subjects were randomly assigned into two groups: Group-I included 98 women who were administered 50 µg of oral misoprostol 4 hourly to a maximum of 6 doses and Group-II included 100 women who were administered 25 µg of vaginal misoprostol 4 hourly to a maximum of 6 doses. The demographic characteristics and indications for induction of labour are shown in Table 1. The groups were similar in mean maternal age, gestational age, gravidity distribution, pre-induction Bishop's score and indication for induction (PIH and post-datism accounting for 59% patients in group I and 50% patients in group II).

Table 1:

Variable	Group I Oral Misoprostol Mean $\pm$ SD	Group II Vaginal Misoprostol Mean $\pm$ SD	P-value
Age (yrs)	28.07 $\pm$ 2.36	27.62 $\pm$ 2.50	0.194
Gestational Age (weeks)	39.23 $\pm$ 1.40	39.15 $\pm$ 1.26	0.660
Gravidity n (%)			
Primigravida	70(71.4)	66(66)	0.410
Multigravida	28(28.57)	34(34)	
Indication for induction			
PIH	32(32.65)	27(27)	0.857
Postdatism	26(26.54)	23(23)	
PROM*	18(18.36)	24(24)	
Oligohydramnios	14(14.28)	18(18)	
Rh—ve	6(6.12)	6(6)	

*Premature Rupture of Membranes

Mean induction delivery time (Graph 1) was significantly higher in Group-I than in Group-II. There was no difference in terms of delivery within 24 hrs, mode of delivery, incidence of maternal complications, neonatal complications and failed induction between the two groups (Table 2).

Graph 1

There was no difference in terms of mode of delivery; 18 % in both groups were delivered by LSCS, 2% in Group-I and 5% in Group-II had instrumental delivery. In terms of neonatal outcome both the groups had similar results; NICU admission and APGAR score were similar in two groups. There was no difference in incidence of meconium stained liquor.

Mean number of doses required were slightly higher in Group-I than in Group-II. But this difference was statistically insignificant. 81.63% of patients in Group-I and 68% in Group-II required oxytocin augmentation. This difference is statistically significant (Table 2).

Table 2:

Variable	Group I Oral Misoprostol Mean ±SD	Group II Vaginal Misoprostol Mean ±SD	P-value
Delivery Induction Time (Mean±SD)	20.55±5.59	16.70±7.12	<0.001*
Induction delivery time			
<24	63(64.29)	72(72)	0.244
>24	35(35.71)	28(28)	
Oxytocin Augmentation			
No	18(18.36)	32(32)	0.027
Yes	80(81.63)	68(68)	
NICU Admission			
No	88(89.80)	92(92)	0.590
Yes	10(10.20)	8(8)	
Maternal complications Tachysystole			
Hypertonus	2(2.04)	4(4)	0.625
Hyper stimulation	0	0	
Nausea/Vomiting	0	2(2)	
Diarrhea	5(5.10)	2(2)	
Postpartum hemorrhage	4(4.08)	1(1)	
	2(2.04)	2(2)	

DISCUSSION

Misoprostol is an efficacious agent for labour induction. Compared with dinoprostone nearly every measure of adequacy of labour induction was superior with misoprostol including induction to delivery time, lack of necessity of oxytocin, fewer doses, and delivery within 24 hours.^{3,6} Various studies attest to efficacy of PGE1 analog misoprostol in comparison to PGE2 analog dinoprostone². Our results showed that 25 µg vaginal misoprostol was more effective than 50 µg oral misoprostol for cervical ripening and induction of labour as mean induction to delivery time was lower in vaginal group. Similar results were seen in study conducted by Wing et al¹⁶ and Shetty et al¹⁷, although doses used by Shetty et al were 50µg vaginally. There was no difference in terms of delivery within 24 hrs between two groups and number of vaginal deliveries within 24 hrs. Similar results were seen in a study done by Rahman et al¹⁸.

Number of doses required in two groups were similar. There was no difference in mode of delivery. Neonatal outcome both the groups had similar results; NICU admission and APGAR score were similar in two groups. There was no difference in incidence of meconium stained liquor. These results were similar in a study done by Rahman et al¹⁸. In a study conducted by Kwon et al¹⁹ median doses required were higher in oral group (1-8) than in vaginal group (1-3) but doses used by them were 50 µg 6 hourly vaginally and orally.

In our study 81% patients in Group-I and 68% in Group-II required oxytocin augmentation. This difference is statistically significant. Similar to our results, Wing et al reported that Oxytocin administration was necessary in 75% and 59% of their patients who received oral and vaginal misoprostol respectively¹⁶. This difference was statistically significant. Uterine tachysystole developed in 2% and 4% of the women in Group-I and Group-II respectively. Hyper stimulation occurred in 3% patients in Group-II and none in Group-I. Nausea and/or vomiting occurred in 5.1% and 2.0% of patients in Group-I and Group-II respectively; diarrhea was reported by 4% and 2% of patients respectively. PPH (postpartum hemorrhage) occurred in 2% patients in each group. There was no statistically significant difference in incidence of maternal complications between two groups. Similar results were seen in a study done by Wing et al¹⁶.

CONCLUSION

Our study concluded that vaginal misoprostol 25µg 4 hourly is more effective than, and as safe as, oral misoprostol 50µg 4hrly for cervical ripening and induction of labour.

Larger studies are required to find out the least effective dose and the most favourable route for misoprostol in induction of labour.

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