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ORIGINAL ARTICLE

A Comparative Study of 25 mcg *vs* 50 mcg of Vaginal Misoprostol for Induction of Labor

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ABSTRACT

Objectives: To compare the efficacy and safety of 25 mcg intravaginal misoprostol *vs* 50 mcg misoprostol for induction of labor.

Material and methods: This study group consisted of 100 cases of low-risk singleton pregnancies attending the antenatal clinic of SAH and RC, or admitted to the antenatal ward. Study group included singleton pregnancy, Over 37 weeks of gestation with Vertex presentation, with unfavorable cervix (bishop score <4) and patients not in labor with reactive fetal heart rate pattern with intact membranes.

Women were randomized to either 25 mcg (n = 50) or 50 mcg (n = 50) of intravaginal misoprostol. The dose was repeated every 4 hours (maximum number of doses limited to 3 doses). The main outcome was induction vaginal delivery interval.

Results: Induction delivery interval was significantly less with 50 mcg misoprostol –9.45 hours in comparison to 25 mcg 14.2 hours (p-value <0.001), most cases delivered vaginally with 25 mcg misoprostol p value < 0.013, cesarean section rates were high in 50 mcg misoprostol group p-value <0.007, the proportion of women delivering vaginally with single dose of vaginal misoprostol was high in 50 mcg group, i.e. 64%, incidence of maternal complications like tachysystole and hyperstimulation was more with 50 mcg group.

Conclusion: In the present study, it is concluded that 25 mcg of misoprostol is safe and effective for labor induction.

Keywords: Labor induction, Misoprostol, Cervical ripening.

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INTRODUCTION

The spontaneous onset of labor is a robust and effective mechanism and should be given to operate on its own. We should only induce labor when we are sure that we can do better. Sir Alec Turnbull (1976)[10,11] Induction of labor is defined as an intervention intended to artifically initiate uterine contractions resulting in the progressive effacement and dilatation of the cervix.[12] Induction of labor is one of the most commonly performed obstetric intervention. Induction rate varies greatly between different countries from 4 to 40%.[10,12]

The success of induction will depend mainly on the parity and the state of the cervix at the begining of induction. State of cervix is evaluated using bishop's score. Labor induction in presence of unfavorable cervix is often prolonged, tedious and may lead to failed induction.

A number of methods are used for induction of labor both nonpharmacological and pharmacological. Misoprostol, an inexpensive and stable PGE 1 analouge which is registered for the treatment of NSAID induced ulcers, has in the last few years attracted attention in obstetrics and gynecology.

Misoprostol is effective in induction of labor whether it is given orally or vaginally. There is a shorter interval to vaginal birth with vaginal application. In this study, evaluation is done with regard to efficacy and safety of 25 mcg misoprostol in induction of labor compared to 50 mcg of misoprostol.

MATERIALS AND METHODS

This study was conducted in the department of obstetrics and gynecology at SAH & RC. This study group consisted of 100 cases of low-risk singleton pregnancies attending the antenatal clinic of SAH & RC, or admitted to the antenatal ward. Cases were selected on the basis of the simple random sampling technique.

The distribution of cases were matched with respect to their age and parity in all the cases, a detailed history was obtained and a thorough general physical and obstetrical examination was done.

Indications for induction—Term pregnancy, postexpected date of delivery pregnancy (postdatism), Post-term pregnancy, intrauterine death.

Patients with age 18 to 35 years, singleton pregnancy, over 37 weeks of gestation, vertex presentation, unfavorable cervix (bishop score <4) and patients not in labor, reactive fetal heart rate pattern, intact membranes, no contraindications to vaginal delivery are included.

Patients with previous uterine surgery, nonvertex presentation, abnormal fetal heart rate pattern, known allergy to prostaglandins, patients with bronchial asthma and glaucoma, multiple pregnancies, grand multipara are excluded.

After taking informed consent, patients were evaluated initially by modified bishop's score and NST for fetal well being. Fifty cases were selected at random to receive 25 mcg of misoprostol intravaginally and the other 50 cases, in a random selection received 50 mcg of misoprostol intravaginally. Misoprostol was placed in the posterior fornix after moistening the tablet with distil water. Second dose was repeated after 4 hours depending on the uterine contractions and cervical changes. After the drug insertion, patients were monitored for signs of labor, maternal vital signs, fetal heart rate and progress of labor. A partogram was maintained for all patients. Oxytocin

was started depending on the modified bishop's score and in the absence of adequate uterine contractions after 6 hours of last dose, or for augmentation of labor in case of arrest of dilatation. Oxytocin was started at a dose of 5 units in case of primigravida and 2.5 units in case of multipara dose titrated every 30 minutes based on uterine contractions.

Failed as been defined by Duff et al (1984) as failure to enter the active phase of labor after 12 hours of regular uterine contractions.[11] Tachysystole-more than six uterine contractions per 10 minutes without fetal heart rate changes, for 2 cosecutive 10-minute periods. Hyperstimulation-tachysystole resulting in nonreassuring FHR changes. Hypertonus-one contraction lasting for more than 2 minutes.

The data collected included maternal age, parity, booked or unbooked case, gestational age, indication for induction, modified bishop's score at the time of induction and 6 hours later, induction to delivery interval, oxytocin augmentation, mode of delivery, APGAR score of the baby, maternal and fetal complications.

The results obtained were subjected to statistical analysis by student t-test and p-value <0.05 was considered significant.

OBSERVATIONS

The age distribution between the two groups is fairly distributed. Maximum cases from both groups were in the age group 20 to 25 years, i.e. 58 and 44% respectively (Table 1). Most cases are booked cases in both groups accounting for 80 and 78% in both groups respectively. Maximum cases in both groups are primigravidae 76 and 56% respectively in both groups. Most cases in 25 mcg group were term pregnancies (64%) and in 50 mcg group postdated pregnancies (52%).[3] post-term cases in 25 mcg group and 8 in 50 mcg group. Oxytocin augmentation need in both groups is similar. Only 40 and 32% of cases needed oxytocin augmentation in both groups respectively. Vaginal deliveries are more with 25 mcg (72%) when compared to 50 mcg (50%). Cesarean section rate is more with 50 mcg (38%).

Table 2 shows induction delivery interval. In the present study, it was seen that the induction delivery interval with 50 mcg misoprostol was less than 12 hours in 19 cases (61%) and, in 25 mcg, it was in 13 cases (32%). In the present study, mean induction delivery interval was 14.5 hours with 25 mcg and 9.45 hours with 50 mcg, p-value < 0.001 statistically being

Table 1: Distribution of variables across the study group

	Parameters	*25 mcg*	*Percentage (%)*	*50 mcg*	*Percentage (%)*	
Age (years)	≤ 20	17	34	19	38	
	21-25	29	58	22	44	
	26-30	4	8	9	18	
Booked/unbooked	Booked	40	80	39	78	
	Unbooked	10	20	11	22	
Obstetric score	G2A1	-	-	3	6	
	G2P1	12	24	14	28	
	G3P1	-	-	3	6	
	G3P2	-	-	2	4	
	P	38	76	28	56	
Gestational age (weeks)	>37-40 wks	32	64	26	52	
	>40-42 wks	18	36	24	48	
Indication for induction	Term	27	54	20	40	
	Post-term	3	6	6	12	
	Post EDD	17	34	16	32	
	Intrauterine death	3	6	8	16	
Bishop's score before induction	1	11	22	9	18	
	2	15	30	35	70	
	3	11	22	3	6	
	4	13	26	3	6	
Number of doses required	1	32	64	41	82	
	2	18	36	9	18	
Oxytocin augmentation	Yes	20	40	16	32	
	No	30	60	34	68	
Modified bishop's score after 6 hours	1-3	1	2	2	4	p < 0.041
	4-6	14	28	10	20	
	7-10	35	70	38	76	
Mode of delivery	Vaginal	36	72	25	50	p < 0.013
	cesarian section	8	16	19	38	p < 0.007
	Vaginal instrumental	6	12	6	12	p > 0.50

Table 2: Induction delivery interval

No. of hours	25 mcg				50 mcg			
	Single dose	Percentage	Double dose	Percentage	Single dose	Percentage	Double dose	Percentage
<12	13	32	3	7	19	61	2	7
12-24	20	47	6	14	6	20	4	12
>24	-	-	1	4	-	-	-	-

p < 0.01

Table 3: Indication for cesarean section

Indication	25 mcg		50 mcg	
	No.	Percentage	No.	Percentage
Fetal distress	3	6	13	26
Failure to progress	5	10	1	2
Maternal distress			5	10

Table 4: Effects on mother

Effects on mother	25 mcg	50 mcg	Total	z-value	p-value
Antepartum hemorrhage	3	5	8	0.737	>0.33
TPPH	2	2	4	0	>0.5
Tachysystole		3	3	1.759	<0.040*
Hyperstimulation		2	2	1.429	>0.077
V	1	1	2	0	>0.5
F	1		1	1.01	>0.257
Total	7	13	20		

Note: *Significant at 5% level

significant. Most cases in 50 mcg group delivered vaginally within 12 hrs with single dose.

In 25 mcg group the total number of failed induction were 8 out of 50 patients giving an incidence of 16%. Majority of failed induction were due to failure to progress — 5 cases, 3 cases were due to fetal distress. In 50 mcg group the total number of failed induction were 19 out of 50 patients giving an incidence of 38%. Majority of failed induction were due to fetal distress — 13 cases, 1 case was due to failure to progress. 3 cases — tachysystole, 2 cases — hyperstimulation (Table 3).

Table 4 shows the effects on mother due to misoprostol. There was 26% incidence of side-effects in 50 mcg misoprostol group and 14% of incidence in 25 mcg group. Tachysystole and hyperstimulation were found only in 50 mcg group. This statistically significant p-value being less than 0.04.

The above table shows Apgar scores. One cases in 25 mcg group had scores of 3 at 1min and in 50 mcg group had 5 cases (Table 5).

Table 6 shows fetal complications. In 25 mcg group fetal distress was 6% when compared to 50 mcg group which was 26%.

NICU admissions were 6% in 25 mcg group, 12% in 50 mcg group.

Table 7 shows the incidence of meconium stained liquor. In 25 mcg group incidence of meconium stained liquor was 22% (both thick and thin). In 50 mcg group incidence of meconium stained liquor was 38% (both thick and thin).

DISCUSSION

Even though dose as high as 200 mcg have been reported in the literature, but most authors have used 25 or 50 mcg. The present study compares the efficacy and safety of 25 and 50 mcg misoprostol.

Most cases in our study belonged to 20 to 25 years age group similar to studies of fletcher et al and Louis Sanchez Ramos.[4,5] In the present study 76% were primigravida in 25 mcg group and 56% in 50 mcg group. In most studies, the sample under study were primigravida.

Most cases in the current study were booked cases and were between 40 and 41 weeks of gestation. Most cases belonged to postdatism group.[6]

Bishop score is one of important parameter in assessment of progress in delivary process. Initial bishop score was 2 to 3 cm (mean – 2.5 cm) in 25 mcg group and in 50 mcg

Table 5: Effects on fetus

Apgar Score	25 mcg				50 mcg			
	1 minute		5 minutes		1 minute		5 minutes	
	No.	%	No.	%	No.	%	No.	%
5	1	2.2	-	-	5	11.9	-	-
6-8	46	97.8	7	14.8	37	88.1	6	1404
9-10	-	-	40	85.2	-	-	36	85.96
Total	47	100	47	100	42	100	42	100

Table 6: Fetal complications

	25 mcg	50 mcg	Total	z-value	p-value
Fetal distress	3	6	13	1.048	>0.247
NICU admission	3	6	9	1.048	>0.247

Table 7: Color of liquor

Liquor	25 mcg	50 mcg	Total
Clear	39	31	70
Thick meconium	5	14	19
Thin meconium	6	5	11
Total	50	50	100

group it was 2 to 3 cm (mean – 2 cm). It was seen in our study that bishop's score after 6 hours was better with 50 mcg (7-10 cm: 76%) compared to 25 mcg (7-10 cm: 70%). Mean change in bishop's score was 8.76 cm in 50 mcg group when compared to 25 mcg group which was 7.82 cm. This indicates that 50 mcg misoprostol is efficient in the process of cervical ripening, similar with studies of Bugalho et al.[4,7,8]

In our study single dose was needed for labor induction in 32 cases (64%) in 25 mcg group and 41 cases (82%) in 50 mcg group. The proportion of women delivering vaginally with single dose of vaginal misoprostol was significantly greater in 50 mcg group. The number of doses required was significantly low with 50 mcg group. Twenty cases (40%) in 25 mcg group and 18 cases (32%) in 50 mcg group required oxytocin after 6 hours of last dose of misoprostol. The difference in both the groups is not statistically significant which is similar to study conducted by Sherbiny et al, Sanchez Ramos et al.[6,9]

Rate of vaginal deliveries was 72% in 25 mcg group when compared to 50 mcg group which was 50%. This being statistically significant, p-value — 0.013. Rate of instrumental delivery was similar in both the groups. Rate of cesarean section was higher in 50 mcg group — 19 cases (38%) compared to 25 mcg group — 8 cases (16%). With respect to mode of delivery, cause for cesarean section in 50 mcg group: 13 cases had fetal distress, of these seven cases had abnormal fetal heart rate findings, six cases had thick meconium stained liquor, one case was due to failure to progress, three cases had tachysystole, two cases had hypersystole in 25 mcg group three cases had fetal distress, five cases had failure to progress-similar to study conducted by Wing et al, Meydanli et al.[10-12]

With concern to induction to delivery interval, it is taken as a gold standard in studies of present kind. It denotes the success of achieving the final goal of delivery in shortest possible time and is an indirect measure of the efficacy of the drug in causing labor induction.

In the present study induction delivery interval with single dose of 25 mcg misoprostol was 14.3 hours and with 2 doses it was 18.5 hours, Mean induction delivery interval with 25 mcg misoprostol was 14.58 hours. where as in 50 mcg misoprostol group it was 8.2 hours and with 2 doses it was 14 hours, Mean induction delivery interval with 50 mcg misoprostol was 9.45 hours. This was consistent with study conducted by Wing et al, Sherbiny et al.[6,10] Thirteen cases (32%) in 25 mcg group delivered vaginally within 12 hours of induction. Twenty cases (47%) delivered within 24 hours. One case delivered after 24 hours. In 50 mcg group, 19 cases (61%) of cases delivered within 12 hours. Six (20%) cases delivered with in 24 hours.[6,11]

Significantly more women in 50 mcg group delivered vaginally within 12 hours of induction, where as there were significantly more women in the 25 mcg group who delivered within 12 to 24 hours. Zieman et al[13] reported that plasma concentration of misoprostol in women receiving misoprostol rose gradually, reached maximum levels within 60 to 120 minutes. It is plausible to expect misoprostol to reach a threshold concentration for initiating uterine activity when misoprostol is applied intravaginally. The potential direct effects of misoprostol on the uterine cervix in initiating physiological events must be taken into account. It is probable for the 50 mcg dose. Regarding to the potential direct effects on the cervix, the 50 mcg dose is expected to be more potent than the 25 mcg dose. In this background, it is not extraordinary to observe more women to be delivered vaginally within 12 hours of induction in the 50 mcg group when compared with 25 mcg group.

However, plasma misoprostol concentration was reported to decline to an average of 61% of the peak level at 240 minutes after vaginal administration.[14] Therefore, repeated doses of 25 mcg misoprostol 4 hours apart might constitute a cumulative plasma misoprostol concentration during a longer interval than the mcg dose, and might initiate uterine activity by reaching the threshold level at a later stage. The significantly greater number of women to be delivered vaginally within 12 to 24 hours of induction in the 25 mcg group can be explained on this basis.

Maternal adverse outcome is one of important factor to be considered. It was seen that 25 mcg group had very minimal side-effects. Three patients had atonic PPH and two patients had traumatic PPH and one patient had fever and one had vomiting. In 50 mcg group five cases had atonic PPH, two cases had traumatic PPH, three cases had tachysystole and two cases had hyperstimulation. This shows that 50 mcg misoprostol is associated with increased maternal complications. It most commonly associated with abnormal uterine contractions.[11,15] The mean birth weight and Apgar scores in both groups did not show any major difference. Fetal distress and NICU admission was less with 25 mcg group — 3 cases (6%). In 50 mcg group, 13 cases (26%) had fetal distress, seven cases had abnormal fetal heart rate pattern and six cases had meconium aspiration syndrome. In 50 mcg six cases needed NICU admission. This shows that 25 mcg of misoprotol is safe and associated with less neonatal complications when compared to 50 mcg similar to studies of Meydanli et al.[11,15]

CONCLUSION

Local application of misoprostol tablet in the posterior fornix is more convenient and easier procedure. Misoprostol offers benefits of reduced cost, temperature stability when compared to other prostaglandin preparation. Change in Bishop's score is good with both the groups, 50 mcg is proved to be a better cervical ripening agent statistically. Induction delivery interval is significantly less with 50 mcg group (9.45 hrs) in comparison to 25 mcg group (14.5 hours). A single dose of 50 mcg misoprostol is effective in culminating vaginal delivery within 12 hours. Rate of vaginal delivery is more with 25 mcg group in comparison to 50 mcg group. A 25 mcg dose was safer than 50 mcg dose when given every 4 hours, although the 50 mcg regimen resulted in faster delivery with less augmentation. The higher rate of uterine contractile abnormalities (tachysystole and Hyperstimulation), fetal distress with 50 mcg dose are of particular concern.

In the light of the available data and our findings we conclude that 25 mcg of intravaginal misoprostol 4 hours apart appears to be safe and effective for labor induction.

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