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Original Research Article

A comparative study of 25 mcg vs 50 mcg of vaginal misoprostol for induction of labour

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ABSTRACT

Background: The objectives of the current study were to compare the efficacy and safety of 25µg and 50µg of intravaginal misoprostol for induction of labor at term and to study the maternal and fetal outcome.
Methods: A Prospective Study was done on 50 cases with 25µg misoprostol and 50 cases of 50µg of misoprostol intravaginal, repeated every 6 hourly till adequate uterine contractions or maximum 5 doses. Total dose of induction, induction delivery interval, mode of delivery, maternal and fetal outcome were recorded.
Results: Mean induction delivery interval was 13.8±5.9 and 14.0±5.7 hours (P=0.9) with the 25µg and 50µg misoprostol respectively. The 25µg misoprostol group had a lower delivery rate with a single dose compared with the 50µg group (38% and 42% respectively). However, 25µg group had more deliveries than 50µg group with increasing number of misoprostol doses (36% vs. 38%, and 20% vs. 16% for 2 doses and 3 doses respectively). The need for oxytocin augmentation among participants was higher in the 25µg group (20%) than in 50 µg group (16%).This was however not statistically significant (P=0.603). At lesser initial bishop score, with 50µg misoprostol less doses are needed as compared to 25 µg and hence induction delivery interval decreases. The rates of caesarean section and operative vaginal delivery were similar in both groups. There was no significant difference in maternal side effects and neonatal outcomes among the women in the two groups.
Conclusions: The 25 µg of intravaginal misoprostol administered six-hourly appears to be as effective but safer than 50 µg for induction of labor. The use of 50 µg misoprostol may be recommended when there is a need to expedite vaginal delivery especially in cases of lesser initial bishop score.

Keywords: Bishop score, Induction of labor, Misoprostol

INTRODUCTION

Induction of labour is defined as intervention intended to artificially initiate uterine contractions resulting in the progressive effacement and dilatation of the cervix. Induction of labour is one of the commonly performed obstetric intervention. Induction rate varies greatly between different countries from 4 to 40%.[1] Approximately half of all women undergoing labour induction will have an unfavourable cervix, or low Bishop score, which will require ripening. This can be achieved with pharmacological and mechanical techniques. The search for an ideal agent, timing and dosage interval to convert an unfavourable cervix to one receptive to delivery is an ongoing process. The ideal induction agent would be one that is efficient, cost effective, easy to store, non-invasive, without side effects, and whose effects on mother and fetus can be readily monitored. Prostaglandins are often used for pharmacological cervical ripening. One of the benefits of prostaglandins over mechanical methods is that prostaglandins work not only to ripen the cervix, but also to stimulate myometrium contractility.[2,3] Misoprostol is a synthetic 15 deoxy 16 hydroxy, 16 methyl analogue of the naturally occurring prostaglandin E1 that was originally manufactured for prevention and treatment of

peptic ulcers diseases. Several studies have found that misoprostol is effective as an agent for cervical ripening and induction of labour. It is inexpensive, easy to store, and stable at room temperature. Despite many widely reported trials on misoprostol, several practical aspects of its administration are still yet to be well established and these include; the appropriate dosage, the dosing interval, and route of administration, with doses ranging from 25 µg to 100 µg.[4] The currently observed practice is that some obstetricians use 50 µg of misoprostol for induction of labor in nulliparous women and 25 µg in multiparous women, while others adhere to the ACOG recommendation of using 25 µg irrespective of parity.[5]

Minor maternal side effects include diarrhea, nausea, vomiting, abdominal pain, chills, shiver-ing and hyperthermia which are dose dependent. Uterine hyper stimulation and meconium stained amniotic fluid are also reported with higher dosage. This comparison was studied with the objective to whether by reducing the dosage, the side effects can be reduced and to study effectiveness.[6] It focused on comparison of two dosing regimens (25 µg versus 50 µg) of misoprostol for prelabour cervical ripening and induction of labour.

METHODS

A prospective study was carried out in the department of Obstetrics and Gynecology, Sri Guru Ram Das Medical College, Amritsar from January 2017 to August 2017. Women with singleton pregnancy ≥37weeks gestation with vertex presentation; intact membrane and reactive CTG were included after informed consent. Those with favorable cervix (modified bishop score ≥6), previous cesarean section or any other uterine surgery, gravida ≥5, any contraindication for vaginal delivery, any contraindication to the use of prostaglandins i.e. women with history of asthma, glaucoma, cardiac disease or any hypersensitivity to the use of prostaglandins. Total number of 100 cases meeting inclusion criteria were divided into Group A (25µg) and Group B (50µg). A complete history including maternal age, parity, gestational age and indication for induction of labor were noted. Abdominal examination was done to know the presentation, uterine tone and the fetal heart rate. Per vaginal examination was done to know the modified Bishop score and to rule out cephalopelvicdispro-portion. Cardiotocograph (CTG) and Obstetric scan were done to all the patients to ascertain the fetal well-being and confirm dating. An informed written consent was taken prior to induction. Following exclusion of uterine contractions or a non-reassuring CTG and confirmation of Modified Bishop score ≤5, patients received intravaginal misoprostol either 25µg (Group A) or 50µg (Group B), allotted alternatively till the patient gets adequate uterine contractions (3 contractions in 10 minutes) or cervical dilatation of ≥3 cms or a maximum of 5 doses are administered. If they do not respond to the above protocol (after receiving 5 doses of misoprostol), they were considered as failed induction. The progress of labor was monitored by partogram in active stage of labor. Labor was augmented with oxytocin if required. Total dose of induction, induction delivery interval, mode of delivery, oxytocin requirement, maternal side effects and fetal outcome like meconium stained liquor, FHR abnormalities, Apgar score, neonatal resuscitation and NICU admission were recorded. All the results were analyzed by appropriate statistical test.

RESULTS

A total of 100 Patient populations was divided into two groups; group A received 25 µg misoprostol pervaginally and group B received 50 µg after assessing for eligibility.

Above shows maternal demographic profile of the women included in the study. Both groups were comparable with respect to maternal age, parity, mean gestational age at the time of induction and Bishop's score at commencement of cervical ripening and labor induction. The mean age of patients in the 25 µg group was 25.28 ± 4.71, while the mean age in the 50 µ 25.39 ± 4.00, P=0.94; Nulliparity (40.0% vs.44.0%, P=0.685) and multiparity (60.0% vs. 56.0%) respectively for 25 µg and 50 µg were not statistically different. The mean gestational age (39.54 ± 1.92 vs. 39.27 ± 4.50, P=0.32); and initial Bishop's scores (3.14 ± 0.97 vs. 3.12 ± 1.06, P=0.12) were similar respectively for 25 µg and 50 µg groups (Table 1).

Table 1: Maternal characteristics of the study groups.

Characteristic	25µg Misoprostol n=50(%)	50µg Misoprostol	P-value
Age[a] (years) (Mean±SD)	25.28±4.71	25.39±4.00	0.94
Parity[b]			
Nulliparous	20(40)	22(44)	0.685
Multiparous	30(60)	28(56)	
Gestational age (weeks) (Mean±SD)	39.54±1.92	39.27±4.5	0.32
Initial bishop score (Mean±SD)	3.14±0.97	3.12 ±1.06	0.12

'[a]Student's t-test, [b]Chi square

The indication for induction was similarly distributed in the both groups. The Postdatism was single most common indication in both the groups accounting for more than 50 percent as shown (Table 2).

Majority of women in both groups delivered vaginally (80.0% in 25µg group and 82% in the 50 µg group). The 25 µg misoprostol group had a lower delivery rate with a single dose compared with the 50 µg group (38% and 42% respectively). However, 25 µg group had more deliveries than 50 µg group with increasing number of misoprostol doses (36% vs. 38%, and 20% vs.16% for 2

doses and 3 doses respectively). The need for oxytocin augmentation among participants was higher in the 25 µg group (20%) than in 50 µg group (16%). This was however not statistically significant (P=0.603).

Table 2: Indications for Induction.

Labour Induction[b]	25µg Misoprostol	50 µg Misoprostol	P-value
	n=50(%)		
Post date	30 (60)	28 (56)	0.685
Hypertensive disorder of pregnancy	10 (20)	12 (24)	0.629
IUFD	3 (6)	2 (4)	0.646
IUGR	3 (6)	2 (4)	0.646
GDM	2 (4)	2 (4)	1.0
Others	2 (4)	4 (8)	0.40

bChi square

There was no difference between the two groups with regard to the proportion of patients who had a successful induction. Eighty percent of patients allocated to 25 µg group and 80.1% of those in 50 µg group had vaginal delivery while 4% of participants had instrumental vaginal delivery in both groups.

Table 3: Intrapartum variables.

Variables	25µg Misoprostol	50 µg Misoprostol	P-value
	n=50(%)		
Number of Misoprostol doses[b]			
1	19 (38)	21(42)	0.68
2	18 (36)	19 (38)	0.836
3	10 (20)	8 (16)	0.683
4	3 (6)	2 (4)	0.646
Mean Induction vaginal delivery interval[a]	13.8±5.9	14.0±5.7	0.9
<12hours (n, %)[b]	15 (30)	18 (36)	0.523
12-<24hours (n, %)[b]	20 (40)	22 (44)	0.723
≥24 hours (n, %)[b]	15 (30)	10 (20)	0.248
Oxytocin augmentation[b]	10 (20)	8 (16)	0.603
Delivery[b]			
Vaginal	40 (80)	41 (82)	0.799
Instrumental	2 (4)	2 (4)	1.0
Ceasarean Section	8 (16)	7 (14)	0.779

[a]student t test;[b]Chi square test

The incidence of caesarean section was similar in the two groups, eight women (16.0%) in the 25 µg group and 7 women (14%) in the 50 µg required emergency caesarean delivery for one reason or the other (P=0.779). No differences were noted in the overall incidence of caesarean section (Table 3).

Above table shows that at lesser initial bishop score, with 50µg misoprostol less doses are needed as compared to 25 µg and hence induction delivery interval decreases. The mean interval between first dose of misoprostol and vaginal delivery is shorter in the 50 µg group (874 ± 345 minutes) than in the 25 µg group (985±545 minutes). If initial bishop score is good, then both doses are equally effective to achieve further cervical ripening (Table 4).

Table 4: Intrapartum variables.

Bishop Score	Doses of Misoprostol		Induction delivery Interval	
	25µg	50µg	25µg	50µg
1	4	2	≥24hour	18-24hour
2	3	2	20-24hour	12-24hour
3	3	1	18-20hour	12-20hour
4	2	1	12-20hour	12-18hour
5	1	1	6-12hour	6-12hour

As highlighted in above table there was no significant difference in the secondary outcomes variable such as neonatal outcomes and intrapartum complications. With regards to potential adverse effects, no patient in any group had nausea, vomiting, diarrhoea and fever in the study population. No case of hypertorus was recorded while a case of uterine tachysystole was seen in 50 µg group.

Table 5: Maternal and Fetal complications.

Complication[c]	25µg Misoprostol	50 µg Misoprostol	P-value
	n=50(%)	n=50 (%)	
Uterine contraction abnormalities	1 (1.1)	2 (4)	0.5
Uterine tachysystole	1 (1.1)	1 (2)	0.32
Uterine hyper stimulation Syndrome	-	1 (2)	1.0
Postpartum hemorrhage	-	2 (4)	0.90
Perineal laceration	-	2 (4)	0.90
Apgar score <7			
At 1 min	4 (8)	4 (8)	1.0
At 5 min	2 (4)	1 (2)	0.8
SCBU admission	2 (4)	2 (4)	1.0

[c]Fisher's exact test

The 50 µg misoprostol group recorded the highest number of cases with abnormal uterine contractions (4%) compared with misoprostol 25 µg group (1.1%). No significant differences were found in both groups regarding intrapartum stillbirth, Apgar scores of less than 7 at 5 minutes and the number of neonates admitted to the Special Care Baby Unit. Fetal distress requiring surgical intervention occurred in 12 patients.

In each of these patients, management was initially conservative using nasal oxygen, adequate hydration and nursing on the left side. Caesarean sections were done when these measures failed to correct the adverse fetal cardiac activity However, the observations were not significant statistically. Two women in the 50 µg group developed postpartum hemorrhage compared to none in the 25 µg group (P=0.90). No maternal death was recorded in the study. All results tended to be more favorable in 25 µg group but did not reach statistical significance (Table 5).

DISCUSSION

Misoprostol is increasingly being used for cervical ripening and induction of labour more than ever before. This was also observed in this study. The women in the study were homogenous in terms of age, gestational age and parity in both groups. The most common indication for cervical ripening and induction of labour was postdatism, accounting for 60%, followed by preeclampsia, accounting for 20%. This is similar to that obtained in a prospective study of labour induction.[6,7] These trends may be due to the fact that there is more postdated pregnancy now than before, probably due to better dating of gestational age and earlier booking. The results of this study indicate that 25 µg of intravaginal misoprostol every 6 hours was as efficacious as 50 µg for cervical ripening and labor induction. There was no statistical significant difference between the two misoprostol regimens in terms of clinical efficacy. Although the study found that induction delivery interval was similar among the two groups, other investigators 1 had demonstrated that it was shorter in the 50 µg group. In a meta-analysis comparing 25 µg with 50 µg misoprostol, the induction vaginal delivery interval was nearly five hours shorter in the 50 µg group.[6,8] This difference as against me may be due to inclusion of only post-dated pregnancies in Meydanli's study. Significantly more woman delivered vaginally with single dose and within 12 hours of induction in 50 mcg especially in case of lesser initial bishop score as seen in our study. The proportion of women delivering within the first twelve hours and next twelve hours of induction were similar among the groups, which is consistent with the finding by other investigators 9 while Meydanli et al reported more deliveries in 25 µg group which may be due to dose cumulative effect. There was no difference in the overall caesarean section delivery rates like other studies unlike increase in caesarean section rate in the 50 µg group reported by Has et al and Bharathi et al [1,2,3,4,8,9] In this study, there was no significant difference in occurrence of uterine contraction abnormalities among regimens, although some researchers have demonstrated an increase incidence of uterine contraction abnormalities in the 50 µg groups which may be related to dose interval, so 6 hrs. seems to be appropriate interval between next dose.[1,4,6] Although not statistically significant, the incidence of hemorrhage due to perineal laceration was more in the 50 µg group in this study. However, El-sherbiny et al reported significantly increased incidence of atonic postpartum hemorrhage in 50 µg group.[10] Even though higher dose misoprostol (50 µg) enhance cervical ripening and labor during induction in a more efficient way than lower dose (25 µg), concern persist with respect to intrapartum fetal wellbeing. The price for using a higher misoprostol dosage to achieve higher delivery rate is increased risk of hyper stimulation syndrome, abnormal fetal heart rate, meconium staining liquor and perinatal mortality and morbidity from asphyxia. In this study, though not statistically significant, the 50 µg misoprostol group accounted for a high number of cases with abnormal uterine contraction (1.1% vs.4.0%, Fisher exact test=0.375). However, the caesarean section for suspected fetal distress was not significant for both groups (10% vs.8%, P=0.821). This may be due to early detection of abnormal fetal heart rate and early corrections. The concern about safety of misoprostol is not limited to the fetus alone but extends to the mother. Statistical analysis comparing this effect showed no significant difference. Attempting an explanation for the aforementioned side effects in misoprostol use and taken into account other reports, it appears that the increase in clinically relevant adverse effects may be dose dependent rather than misoprostol related.

CONCLUSION

The 25 µg of intravaginal misoprostol administered six-hourly appears to be as effective but safer than 50 µg for induction of labor. The use of 50 µg misoprostol may be recommended when there is a need to expedite vaginal delivery especially in cases of lesser initial bishop score. It may also have appeared safe to suggest that WHO recommendation on the use of low dose 25 µg provided strict selection criteria are upheld. outcomes.

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