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A Study of Intravaginal Tablet Misoprostol (25µg) For Induction of Labour in Primigravida with Term Gestation

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Abstract: **This study evaluates the safety and efficacy of intravaginal low dose (25µg) of Misoprostol for cervical ripening and labour induction in primigravida with term gestation. Two hundred and forty seven patients with an indication for induction of labour in third trimester were included. The cervical score was assessed by using Bishop's score prior to prostaglandin induction. Patient's with Bishop's score <4 were induced with misoprostol (25µg) 4th hourly maximum of 4 doses. Data's were analyzed with student 't' test and P-value of >0.05 were considered not significant. Misoprostol was significantly more effective in inducing labour (98%) with the number of failed induction being 5 out of 247. 94% of Patients delivered within 24 hours. Mean time from start to delivery (including caesarean) was 12.97±6.34hours. Lesser number of patients required oxytocin augmentation i.e. 32%. Induction to vaginal delivery interval was 11.9±4.9 hours. Induction to vaginal delivery interval was significantly greater with Bishop's score ≤3 i.e. 12.53±5.7 hours compared to Bishop's score >3 i.e. 10.2+3.7 hours. 97.56% of patients delivered vaginally within 24 hours. 68.29% of patients delivered vaginally with single dose of Misoprostol with mean number of dose 1.34±0.52. Dystocia, non reassuring FHR with hyper stimulation and tachysystole were 2%, 4% and 4% respectively. Neonates with Apgar score of ≤7 at 1 minute and 5 minutes were 12% and 2% respectively. The incidence of thick meconium and neonatal intensive care unit admission being 14% & 12% respectively. Intravaginal low dose Misoprostol is effective and safe drug for induction of labour.**

Keywords: **Misoprostol, cervical ripening, induction, Bishop's score.**

1. INTRODUCTION

An induced labor is one in which the pregnancy is terminated artificially any time after 28 weeks of gestation by a method that aims to secure delivery per via naturalis.

In order to be successful, induction should result in uterine contraction and progressive dilatation of cervix leading to vaginal delivery. This aim must be achieved with a minimum of discomfort and risk to both mother and fetus.

The incidence of induction varies from 4% [1] to 40% (Mc. Naughton, 1980) in teaching institutions and as high as 55% in non teaching institutions [2].

A "ripe" soft yielding cervix requires a lower quantum of uterine work than an "unripe" hard and rigid one would [3]. An unripe cervix fails to dilate well in response to myometrial contractions. In patients with unripe cervix i.e., Bishop's score <5, if measures are not taken to improve cervical status before induction, oxytocin infusion alone may be relatively ineffective resulting in prolonged induction, induction failures, unacceptable rate of caesarean sections (>40%), prolonged hospital stays and an overall increase in maternal and fetal morbidity.

Misoprostol is a synthetic analogue (15 deoxy 16 hydroxy 16 methyl) of natural PGE1, with a molecular weight of 382.54. The utero tonicity of this in pregnant women was first described in 1987. The use of Misoprostol for cervical softening and term labor induction was first reported by Marguilies et al in 1992. Misoprostol acts as a myometrial

stimulant of the pregnant uterus by selectively binding to prostaglandin E2 sensitive receptor subtypes EP-2 and EP-3 [4]. It can be used orally as well as vaginally.

Misoprostol is affordable, easily stored at room temperature. Dispersion in hydroxyl propyl methyl cellulose (1:100) enhances the stability of misoprostol. Therefore the conventional tablets of misoprostol can be produced with a shelf life of several years.

In this study, efficacy and safety of intravaginal low dose (25µg) misoprostol for cervical ripening and labor induction is evaluated in primigravida with term gestation.

2. MATERIALS AND METHODS

The study was done at KSHEMA & Sahara Hospital in Mangalore.

The Criteria for inclusion in the study were

- Singleton pregnancy
- Cephalic presentation
- Unfavourable cervix (Bishop's score ≤ 4)
- Clinically adequate pelvis
- No history of any uterine scar
- Patients not in labor
- Patients with no fetal distress.

Two hundred and forty seven patients with an indication for induction of labor in third trimester and who gave informed consent were studied. After the recruitment to study, patients identification, data, history, physical examination, findings were noted in the designed pro forma. Pelvic examination was carried out to note the inducibility of cervix prior to the induction and during the course of labor to assess the progress of labor. Inducibility of cervix was assessed by Bishop's score (1964).

All patients enrolled in the study received Misoprostol 25µg 4th hourly placed digitally in the posterior vaginal fornix under aseptic precaution for maximum of four doses. The second dose was withheld, if patients were having three or more regular uterine contractions in 10 minutes lasting for 30-60 seconds.

Oxytocin was started if Bishop's score was more than 6 in the absence of adequate uterine contractions after 4 hrs of last dose; or for augmentation of labor in case of arrest of dilatation. Oxytocin was started at the dose of 2mU/min. with increments of 2mU/min. every 30 minutes. Membranes were ruptured, when the cervix was completely effaced with a cervical dilatation of ≥ 3 cms.

The data collected included indication for induction, maternal age, parity, gestational age on entry into the study, insertion to delivery interval, duration of labour, number of patients delivered within 24 hrs, the occurrence of spontaneous labour, route and type of delivery, mean number of doses until delivery, number of patients delivered after a single dose, number of patients requiring oxytocin augmentation, maternal complication and neonatal complication, neonatal birth weight and Apgar scores at 1 and 5 minutes, etc.

Student't' test was used for data analysis and P value of <0.05 was considered significant.

3. RESULTS

TABLE -1 Patients' Characteristics

Sl. No	Patients' Characteristics	n=247
1.	Age (years)	23.96±3.62
2.	Gravidity	1.42±0.7
3.	Gestational age (weeks)	39.86±1.22
4.	Bishop's score ≤3 >3	 193 (78%) 54 (22%)

(Values are in mean ±SD or in percentages)

The indication for induction in primigravida with term gestation is shown in Table 2.

TABLE -2 Indications for induction

Sl. No.	Indications	n= 247 %.
1.	Post dates	46%
2.	Hypertensive disorders	14%
3.	Gestational Diabetes mellitus	8%
4.	IUGR	6%
5.	Oligohydramnios	6%
6.	PROM	4%
7.	Decreased fetal movement	12%
8.	Rh Negative Pregnancy	4%
9.	Others	-

The most common indication for induction of labor was post dated pregnancy i,e,. 46%.

Total vaginal deliveries were 82% out of which 93% were spontaneous deliveries and 7 % being operative vaginal deliveries. Out of total operative vaginal deliveries 67% were vacuum extractions and 33% outlet forceps.

Indications for operative vaginal deliveries were non-reassuring fetal heart rate in late first stage of labour, hyperstimulation with fetal distress and failure of secondary forces during second stage of labour. Incidence of caesarean deliveries was 18%.

TABLE -3 Indications for caesarean section

Sl. No.	Indications	%
1	fetal distress	78
2	Dystocia	11
3	failed induction	11

Indications for caesarean section was fetal distress (78%) dystocia (11%) failed induction (11%). Misoprostol was significantly more effective in inducing labour (98%) with the number of failed induction being 5 out of 247. 94% of patients delivered within 24 hrs. Mean time from start to delivery including caesarean section was 12.97$\pm$6.34.

Significantly lesser number of patients required oxytocin augmentation (32%).

Induction to vaginal delivery interval was 11.9$\pm$4.69hrs. 97.56% of patients delivered vaginally within 24 hrs. 68.29% of patients delivered vaginally with single dose of Misoprostol with mean number of dose being 1.34$\pm$0.52.

TABLE-4 Complications during Labor

Sl. No	Complications	n=247 %
1	Non reassuring FHR: with hyperstimulation with dystocia with dystocia and hyperstimulation without dystocia or hyperstimulation	 4% 0 0 18%
2	Dystocia	2%
3	Tachysystole	4%
4	Vomiting	2%
5	PPH	2%

Fetal distress occurring in the late 1st stage or 2nd stage of labour either delivered spontaneously (10%) or by vacuum (10%) or forceps (10%) whereas those occurring in the early stage of labor delivered by caesarean section (70%).

2% of patients had vomiting during second stage of labour treated with IV fluids and anti emetics. 5 patients had Post Partum Haemorrhage requiring blood transfusion. Out of this 2 had atonic PPH responded to oxytocics and 1 unit of blood transfusion. 3 patients had traumatic PPH (Colporrhexis) requiring 2 units of blood transfusion and suturing under general anaesthesia.

4. DISCUSSION

The earliest studies of the use of misoprostol for cervical ripening and labour induction were done by South American investigators [5]. Results of our study are discussed under the following headings.

Response to treatment, uterine response, operative delivery rate, maternal side effects, neonatal outcome.

Response to treatment:

a. Success Rate: In various randomized trials labor induction was considered successful if the patient were delivered vaginally within 24 hrs of initiation of misoprostol.

The rate of successful induction in our study group was 97.56%. This is consistent with the studies of [6, 7, 8] who had success rate of 91%, 95% and 100% respectively.

TABLE-5 Selected Randomized Controlled Trials of Misoprostol for labour induction

Authors (year)	No. of Patients	Regimen	Success Rate
1. Sanchez-Ramos et al (1998)	223	PGE_1=50µg Intravaginally every 3hrs	71.3%
2. Kramer et al (1997)	130	PGE_1=100µg Intravaginally every 4hrs	80%
3. Wing & Paul (1996)	522	PGE_1=25µg Intravaginally every 3hrs PGE_1=25µg Intravaginally every 6hrs	63.9% 55.4%
4.Sanchez- Ramos et al (1993)	129	PGE_1=50µg Intravaginally every 4hrs	91%
5. Gottschall et al (1997)	75	PGE_1=100 µg Intravaginally single dose	95%
6. Farah et al (1997)	399	PGE_1=25 µg Intravaginally every 3hrs PGE_1=50 µg Intravaginally every 6hrs	82% 84%
7.Wing et al (1994)	135	PGE_1=50 µg Intravaginally every 3hrs	70.6%
8.Marguilies et al (1992)	64	PGE_1=50 µg Intravaginally single dose	79%
9.Chuck & Huffaker et al (1995)	99	PGE_1=50 µg Intravaginally every 4hrs	100%
Present study	**247**	**PGE_1=25 µg Intravaginally every 4hrs**	**97.56%**

The time taken from the stimulation of labor to its successful completion is the induction delivery interval. In our study induction to vaginal delivery interval was 11.9±4.9 hours. This is comparable to other studies shown in the table 5 except in a study [9] where they used 25µg of misoprostol every 3 hrly. Neonates with Apgar score of ≤7 at 1 min., 5 min. and incidence of thick mechonium were 12%, 2%, 14% respectively. There was 1 still birth in a patient with severe PIH associated with IUGR at 38 weeks of gestation.

In one of the studies [10], 399 patients received either 25µg or 50 µg of misoprostol intravaginally every 3hrs. There was significant difference between nulliparous and multiparous in both the groups. Multiparous patients receiving 50 µg. had short induction delivery interval (547 ± 362 minutes Vs 706 ± 442) compared to 25 µg.

Patients with low inducibility rating had lower success rate, longer induction time and higher total dose of misoprostol.

b. Failed induction:

In our study there was 5 (2%) failed inductions treated with caesarean section

Uterine response:

Hypertonus was defined as a single contraction lasting for at least 2 minutes. Tachysystole was defined as at least 6 contractions in 10 minutes for 2 consecutive 10 minutes period.

Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with fetal tachycardia, late decelerations and/or loss of beat to beat variability.

In our study we had 4% incidence of tachysystole compared to incidences reported in literatures which varies from 4.2% [11] to 36.8% [9].

The Incidence of tachysystole was significantly decreased in the 25 µg group (7.4%) compared with the 50 µg group (36.8%) and 100 µg group (72%) but no adverse events reported as a consequence of tachysystole in any of the misoprostol studies [12].

The incidence of hyperstimulation syndrome in our study was 4%. No difference in the incidence of hyperstimulation syndrome was noted between 50 µg and 25 µg group which is 7.3% and 5.8% respectively [9].

Operative delivery rat:

Misoprostol induction resulted in 7% operative vaginal delivery in our study. Caesarean section was 18% compared to [6] 21.9%, [11] 3.1%, [9] 14.7%, [13] 20.3%, [14] 22.2%, [8] 20.4%.

Meta analysis [15] revealed that subjects receiving misoprostol had a lower caesarean rate than the control (15.6% Vs 21.5%; $P < 0.02$).

Maternal side effects:

Gastrointestinal side effects were uncommon in our study group. Diarrhoea, fever, and chorioamnionitis were not seen. <3% incidence of pyrexia has been reported during labour after misoprostol administration for induction of labor [16]

2% of our patients had PPH which is comparable to other studies i.e., [14] $PGE_{1=}$ 25 µg/3hrs 2.1% and PGE_1=50 µg/3hrs 1.9%, [8] PGE_1=50 µg q 4hrs 2%, [6] PGE_1=50 µg q 4hrs 1.6%.

Miscellaneous side effects:

1. Tachycardia [11]
2. Sensation of warmth in the vagina after placement of drug is uncommon [9].
3. Amniotic fluid embolism caused maternal death in one case probably related to prior amnioinfusion. [17].
4. Uterine rupture may occur in multipara even with lower dose of misoprostol (25 µg)[13].

These side effects were not seen in our study.

Neonatal outcome

Incidence of neonates with Apgar score of $\leq$7 at 5 minutes was 2%. 12% neonates were admitted to intensive care unit in our study compared to 4.7% [6], 19.1% [9], 12.3% [18] and 8.7% [8].

Meta analysis found no difference in incidence of 5 minutes Apgar scores and admission to NICU between the misoprostol and control groups [6].

Neonatal outcome was similar in both the groups (PGE_1 and PGE_2 groups). Cord blood acid base analysis did not differ between the groups. No neonate met the ACOG criteria for birth asphyxia [13].

Complications like hyperbilirubinemia and mechonium aspiration syndrome were not seen in our study compared to [9, 19, 15] i.e., 0.8% and 6.1%, 6.0% and 4.4%, 13.1% and 1.0% respectively

5. CONCLUSIONS

Misoprostol is an inexpensive drug. It is stable at room temperature and has got a long shelf life. It is easy to administer, safe and convenient for patients because they do not require bed rest, they can sit or move around freely and even carry out their routine activities at home until the beginning of labour. It holds a great promise for the developing and tropical countries like ours.

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