Section: Obstetrics and Gynecology

Original Research Article

A STUDY OF EFFICACY OF INTRAVAGINAL MISOPROSTOL IN MEDICAL INDUCTION OF LABOUR AND COMPARISON WITH THE EFFICACY OF OTHER AGENTS LIKE INTRAVENOUS OXYTOCIN AND TRANSCERVICAL PROSTAGLANDINE E2GEL

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Received : 28/02/2024
Received in revised form : 13/04/2024
Accepted : 29/04/2024

Keywords:
Intravaginal Misoprostol, Induction, Intravenous Oxytocin and Transcervical Prostaglandine E2gel

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DOI: 10.47009/jamp.2024.6.4.227

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (4); 1141-1146

Abstract

Background: For effective induction of labour oxytocin and prostaglandin E2 gel is being used in clinical practice for a long time. A newer drug misoprostol, (synthetic analogue of prostaglandin E1) has got uterotonic and cervical ripening actions used in clinical practice. It shows better efficacy over the other agents. Search is still on for an ideal drug for medical induction, and therefore, this comparative study may help in finding the ideal agent for induction of labour and substantiate the ongoing studies worldwide. **Materials and Methods:** The present study was conducted on those patients admitted at Dept. of Obstetrics and Gynaecology, JLNMCH Bhagalpur, for delivery beyond 28 weeks of gestation who needed termination of pregnancy by medical induction. A total number of 100 patients were selected in the study between January 2020 to June 2021. There were 3 groups of patients according to the induction. **Result:** The overall success rate was 90% with intravaginal misoprostol, 84% in oxytocin and 80% in prostaglandin E2 gel group irrespective of gravidity. However study group shows highest success rate. In primigravida with Bishop Score 6-7 success rate was higher in misopostol group (88.46%) than oxytocin group (81.82%) and prostaglandin E2 group (76.92%). In multigravida with Bishop Score 6-7 success rate was almost similar in study group (87.5%) and oxytocin (85.71%) group. In multigravida with Bishop Score 8-10, number of cases from both the groups were small (9) and all delivered vaginally? **Conclusion:** Pervaginal misoprostol, intravenous oxytocin infusion, transcervical E2 gel all are good inducing agent though the overall success rate of intravaginal misoprostol is slightly higher than others, particularly in Bishop Score 6-7 group.

INTRODUCTION

The onset of labour in humans is a complex biological phenomenon controlled by multiple regulatory mechanisms which remain largely unknown to us. A cascade of biochemical, physiological and physical processes modulated by neuroendocrine pathways, steroids and local hormones seems to be involved in the initiation of labour.[1]

Although most pregnant women experience spontaneous onset of labour, sometimes there is a need for labour induction in the obstetric conduct. Induction of labour means deliberate termination of pregnancy beyond 28 weeks (period of viability) of gestation by any method which aims at initiation of labour and a vaginal delivery. Whether the intention is fulfilled or not, the definition is not altered.[2]

Timely induction plays an important role where spontaneous onset of labour does not occur or there is increased foetal and/or maternal danger if the pregnancy is allowed to continue though it has not passed the expected date of delivery. It may obviate many unnecessary caesarean sections.[3]

Traditionally there are surgical and medical methods of labour induction. For medical methods oxytocin is being used for many years. It is seen that at term concentration of oxytocin receptor increases in the myometrium. But in maternal blood oxytocin level does not increase before or during labour. It is argued that the striking increase in oxytocin receptors in myometrium late in pregnancy is so great that oxytocin action is effected with only subtle or

ISSN (O): 2687-5365; ISSN (P): 2753-6556

perhaps no changes in the level of oxytocin in maternal blood.[4]

Prostaglandins as inducing agents are new. Prostaglandin level is found to increase in the amniotic fluid during labour. They activate the proteolytic enzyme, which causes breakdown of the collagen fibres, and bring about changes in the glycosaminoglycans in the cervix resulting in its ripening culminating in effacement and dilation during the progress of labour. Various routes have been tried to prime the cervix. Prostaglandins have been administered through intravaginal, end cervical and oral route.[5]

Previously the cervix was considered only to be a passive structure and greater significance was given to the contractility of the uterus. But the last two decades have shown that the cervix is a dynamic organ and the role of cervix during labour has been established by numerous scientific investigations.[6]

Cervical ripening, whether physiological or pharmacological, is the conversion of the rigid cervical "sphincter" associated with the maintenance of pregnancy to a compliant and readily dilating structure. The objective of the pharmacological induction of a physiological process is to attempt to mimic the natural process as close as possible.[7]

For effective induction of labour oxytocin and prostaglandin E2 gel is being used in clinical practice for a long time. A newer drug misoprostol, (synthetic analogue of prostaglandin E1) has got uterotonic and cervical ripening actions used in clinical practice. It shows better efficacy over the other agents. Search is still on for an ideal drug for medical induction, and therefore, this comparative study may help in finding the ideal agent for induction of labour and substantiate the ongoing studies worldwide.

MATERIALS AND METHODS

The present study was conducted on those patients admitted at Dept. of Obstetrics and Gynaecology, JLNMCH Bhagalpur, for delivery beyond 28 weeks of gestation who needed termination of pregnancy by medical induction. A total number of 100 patients were selected in the study period between January 2020 to June 2021.

There were 3 groups of patients according to the inducing agent.

Group – I: 50 patients on whom induction was done by misoprostol (study group).

Group – II: 25 patients on which induction was done by intravenous oxytocin (control 1).

Group – III: 25 patients on which induction was done by transcervical prostaglandin E2 gel (control 2).

Induction by intravaginal misoprostol (Group – I)

During history taking any history of, heart disease, renal disease etc. were excluded. After checking vital sign, FHS and Bishop score misoprostol tablets of 100 □gm were divided into fraction of 25 □gm. An initial dose of 25 □gm was applied in the posterior fornix. The dose was repeated every 4 hours until adequate uterine contraction were achieved (at least 3 contractions in 10 minutes and duration of each contraction about 40 seconds). If the labour pain was not established within 12 hours, the induction was discontinued.

Induction by intravenous oxytocin infusion (Group – II)

Because of erratic response of the uterus to a particular dose the oxytocin infusion was started with a low dose – 2 mU/min. Then dose was escalated at 30 minutes intervals, doubling the close each time until a maximum of 32 mU/minute was achieved or regular contractions were occurring of adequate duration and frequency (3 contractions in 10 minutes and each contraction lasting for about 40 seconds). When labour started with desired uterine contraction, both in duration and frequency, the dose was maintained. After labour became well established progress of labour was noted by abdominal examination and pervaginal examination monitored with maintenance of partogram just like in misoprostol group – oxytocin drip was continued fill delivery and at least 30 – 60 minutes beyond that. Failure to initiate the active phase of labour after 12 hour was called failed induction.

Induction by Prostaglandin E2 gel (Group – III)

PGE2 (DINOPROSTONE) intracervical gel was instilled with a 12 cm long x 3 cm thick nylon catheter under strict aseptic conditions. Care was taken to see that the nozzle does not go beyond the internal os. The catheter was kept in situ for 2 minutes to decrease regurgitation. The patients were kept in bed for one hour following application of the gel. Blood pressure, pulse rate, respiratory rate, temperature, uterine activity & foetal heart rate were monitored initially every 15 minutes for one hour, then 30 minutes for two hours and then one hourly. The onset of the uterine contractions was noted from the zero hour. Contractions were considered to be optimum when 3 contractions came in 10 minutes, each lasting for at least 45 seconds.

After 12 hours – if there was no improvement of Bishop's score – another dose of PGE2 gel was instilled. A reassessment was done 6 hrs after the repeat instillation and if no improvement in Bishop score had occurred – it was taken as failed induction.

RESULTS

In my study, total number of cases were hundred (100); of which in the study group fifty (50) cases were induced with intravaginal misoprostol tablet and in the control group of fifty (50) cases, twenty five (25) received intravenous oxytocin infusion and remaining twenty five (25) were induced by transcervical prostaglandin E2 gel.

In the study group, 34 (68%) patients were primigravida and 16 (32%) patients were multigravida. In the control group, 36 (72%) patients were primigravida and 14 (28%) patients were

ISSN (O): 2687-5365; ISSN (P): 2753-6556

multigravida. The commonest indication of induction group was postdated pregnancy (50%), followed by pregnancy induced hypertension (24%) and premature rupture of membranes (21%), and Rh incompatibility (4%).

Table 1: Distribution of cases according to inducing agents and gravidity.

Inducing agent	Primigravida	Multigrarvida	Total
Tab misoprostol	34 (68%)	16 (32%)	50
Oxytocin Infusion	18 (72%)	7 (28%)	25
Prostaglandin E2 gel	18 (72%)	7 (28%)	25

Table 2: Success rate of inducing agents in different indication of induction.

Indication of induction	Misopostol		Oxytocin		Prostaglanding E2 gel	
	Number	Success	Number	Success	Number	Success
Post dated pregnancy	26	24 (92.30%)	12	10 (83%)	12	10 (83%)
Pregnancy induced hypertension	12	11 (91.66%)	6	5 (83%)	6	5 (83%)
Premature rupture of membranes	10	8 (80%)	6	5 (83%)	5	3 (60%)
Rh incompatibility	2	2 (100%)	1	1 (100%)	2	2 (100%)

Table 3: Mean induction and onset labour interval according to modified Bishop score

Modified Bishop score	Misoprostol tablet	Oxytocin infusion	Pprostagladin E2 gel
6 – 7	210 minutes	60 minutes	480 minutes
8 – 10	190 minutes	40 minutes	400 minutes

Table 4: Maternal side effects

	Misoprostol	Oxytocin	Prostaglandin E2 gel
Nauaea and Vomitting	4(8%)	-	1(4%)
Diarrhoea	3(6%(	-	-
Bronchospasm	-	-	1(4%)
Uterine hyperstimalation	2(4%)	1(4%)	1 (4%)
Maternal pyrexia (transient) and shivering	2(4%)	1(4%)	-
Neonatal death	1(2%)	1(4%)	-

In the study group misoprostol tablet (25 g) was placed into the posterior fornix 4 hourly until adequate uterine contractions were achieved. If labour pain was not established within 12 hours, the induction was discontinued. Intravenous oxytocin infusion was started with 1 unit in 500 ml of Ringer Lactate at a rate of 15 drops/minute (2 mU/min). The dose was escalated at 30 minutes interval, doubling the dose each time until desired uterine contraction or a maximum 32 mU/minute was achieved. For induction with prostaglandin E2 gel 0.5 mg was placed trans-cervically. If there was no improvement of Bishop score after 12 hours another dose was instilled. If even no improvement in Bishop score 6 hours after repeat installation – it was taken as failed induction.

The overall success rate was 90% with intravaginal misoprostol, 84% in oxytocin and 80% in prostaglandin E2 gel group irrespective of gravidity. Considering primigravida success rate in the study group was 88.24% followed by oxytocin 83.33% and prostaglandin E2 gel (77.78%) group. In multigravida success rate was high in all groups. However study group shows highest success rate. In primigravida with Bishop score 6-7 success rate was higher in misopostol group (88.46%) than oxytocin group (81.82%) and prostaglandin E2 group (76.92%). In multigravida with Bishop score 6-7 success rate was almost similar in study group (87.5%) and oxytocin (85.71%) group. In multigravida with Bishop score 8-10, number of cases from both the groups were small (9) and all delivered vaginally.

According to gestational age, success rate between 38-40 weeks and above 40 weeks was high in all groups. Success rate in less than 38 weeks of gestation was also good in misoprostol group, but less number of cases was studied with gestation less than 38 weeks. Caesarean section delivery was 10% cases in misoprostol group, 16% cases in oxytocin and 20% case in prostaglandin E2 gel group. Caesarean section rate was high in primigravida particularly with prostaglandin E2 gel group followed by oxytocin group. Foetal distress was the commonest indication of caesarean section in misoprostol (4 out of 5). Non progress of labour and foetal distress cases were of equal number as indication for LUCS in both oxytocin and prostaglandin E2 gel group.

Only in one case, failed induction was the indication of Caesarean section in prostaglandin E2 group.

The dose needed for induction and delivery was different in primigravida and, multigravida. It differs in different Bishop score also. Considering together, average requirement of misopostol was 51.50 gm. So most of the delivery in this group occurs with the second dose. Mean oxytocin requirement was 5080 mU but the group with Bishop's score 8-10 delivered mostly with 4000 mU oxytocin. Only one patient in prostaglandin E2 group (Bishop score 6) needed repeat instillation. 11 patients in misoprostol group were delivered after single dose (25 gm).

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Gastro intestinal side effect like nausea, vomiting, and diarrhoea occurred in misoprostol group, a few more than prostaglandin E2 gel group. No case of bronchospasm was noted in misoprostol group but it occurred in one case 4 hours after prostaglandin E2 gel instillation. In primigravida incidence of foetal distress was more in misoprostol than control group. Meconium staining of the liquor was also more in misoprostol group than control group, but incidence of Apgar score at 5 minutes <7 was almost similar in all groups. One neonatal death because of birth asphyxia occurred in study and oxytocin group. One case of post partum haemorrhage developed from all group and prostaglandin E2 gel group. Manual removal of plaenta was required in one multigravida mother in prostaglandin E2 gel group. All the methods were well accepted by most of the mothers. Only one mother had unfavorable acceptability of prostaglandin E2 gel due to its cost.

DISCUSSION

In my study, in the study group misoprostol tablets were given 25 gm pervaginally into the posterior fornix. The dose was repeated 4 hourly until adequate uterine contractions were achieved (at least 3 contractions in 10 minutes and duration of each contraction about 40 seconds).

In a randomized study at El-Sherbiny Hospital, Demietla, Egypt in 2001 has shown 50 gm pervaginal dose 4 hours interval resulted in a significantly shorter induction delivery interval than 25 gm. per vaginal dose but the 50 gm dose was associated with an increased risk of developing uterine contractile abnormalities. So a regime using 25 gm of misopostol every 4 hourly can induce labour safely and effectively.

In 2002, a randomized study at University of Istanbul, Turkey has shown the rate of caesarean section due to non-reassuring foetal status was higher in the 50 gm intra vaginal administered misoprostal group than 25 gm intravaginal administered group.[8]

A, comparison study of various routes and dosages of misoprostol for labour induction at University of Cincinnati Olf, USA has shown that percentage of women who achieved vaginal delivery with in 24 hours was highest in the vaginally administered misoprostol (25 gm) group compared with oral plus vaginal (25 gm each route) and the oral (25 gm) group.

In a randomised study at Queen's University, Kingston General Hospital, Ontario, Canada has made conclusion that, compared with oral misoprostol, vaginal misoprostol for induction of labour at term results in a shorter induction to delivery time, with fewer doses required per patient.[9]

So from the above studies 25 gm misoprostol pervaginally 4 hourly was most effective dose and route of administration of misoprostol for successful labour induction.

In my study oxytocin was started with 2 mU/minute. The dose was escalated at 30 minutes intervals, doubling the dose each time until a regular uterine contraction (3 contraction in 10 minutes and each contraction lasting for about 40 seconds) or a maximum 32 mU/minute was achieved.

Foster and co-worker 1988 showed that increasing dose of oxytocin at 15 minutes and 30 minutes interval and caesarean section and induction delivery interval were similar but infusion was stopped more often in first group due to hyperstimulation.[10]

Stain et al (1994) also found that 20 minutes internal was associated with more hyperstimulation but fewer caesarean section for dystocia when compared to 40 minutes interval protocol.[11]

Orhae (1993) showed that increment at 30 minutes interval was superior to 15 minutes interval protocol in reducing the incidence of hyperstimulation.[12]

Xenakis and colleagues (1995) reported a starting dose with 4 mU/minute had significantly decreased duration from induction to second stage labour and from induction to delivery time. Nulliparous in this group had a trend toward a higher caesarean delivery rate compared with those in the starting dose less than 4 mU/minute.[13]

So most of the above studies show initiation of labour with low dose (2 mU/Min) and titration of the dose at 30 minutes interval associated with higher success rate and less side effects.

Both prostaglandins F2 and prostaglandins F2 have been used for cervical priming as well as labour induction. Initially pintravenous route was used and Karim et al (1968) were the first to use intravenous prostaglandin F2 for induction of labour. Prostaglandins E2 is more potent than prostaglandin F2. Intravenous prostaglandins have not found wide clinical acceptance because of associate gastrointestinal side effects and local phlebitis.

In a study at University of Nebraska Medical Center, Omaha has shown prostaglandin E2 gel (0.5 mg) is safe in uncomplicated post dated pregnancy and was found to significantly changes the Bishop's score, enhance the onset of labour, minimize the need for oxytocin administration, and encourage a spontaneous vaginal delivery.

Minaretzis et al (1993) evaluated a .5 mg prostaglandin E2 gel transcervically was associated with less incidence of caesarean section and better neonatal outcome on higher dose.

So most of the above study had shown transcervical prostaglandin E2 gel 0.5 mg is the ideal dose. In my study this dose was used for induction of labour by prostaglandin E2 gel.

In Bernstein (1987) study, postdatism (61.5%) was the most frequent indication. In the present study also the postdatism was the most common indication (50%).

Ferguson (1988) reported PIH as the commonest indication (46%). This was same for Trofatter et al. who reported 60% incidence of PIH in their study.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

In the study conducted by Shashikala et al (1994), postdatism and PIH were the two most common indications for induction. This was also the same in the present study.

In my study vaginal delivery after induction with misoprostol was 45 out of 50 patients. So success rate was 90%. Among this success rate in primigrvida was 88.24% and in multigravida it was 93.75%.

Overall success rate in oxytocin and prostaglandin E2 gel group was 82%. Among primigravida success rate was 83.33% in oxytocin group and 77.78% I prostaglandin E2 gel group. In multigravida success rate in both the control group was (85.71%) less than misoprostrol group (93.75%).

In a study in 2000 at University Hospital of Puerto Real, Spain was shown success rate was higher induction with Misoprostal group than prostaglandin E2 gel group. Occurrence of failed induction were higher in prostaglandin E2 gel group (9% versus 1%).[14]

In the year 2002, a rendomized, double marked study at University of Virginia School of Medicine, Charfottesvilley USA shows labour abnormalities were more common in oxytocin group than misoprospol group (26% vs 16%).

A double blind comparison of the safety and efficacy of intravaginal misoprostol and prostaglandin E2 gel to induce labour, studied by Department of Obstetrics and Gynaecology, University Hospital, Basel, Switzerland has shown caesarean section rate was slightly more (12% vs 14%) in prostaglandin E2 gel group.

By intravenous oxytocin Embrey in 1975 shows 84.6% success rate. Foster and co-workers (1988) reported 83% success rate. Jina et al (1994) shows 80%, Bhatle et al (1998) shows 85.7% Sondher et al 1995 shows 85% success rate by intravenous oxytocin.

In this study induction-onset of labour interval was 210 minutes, and 190 minutes in misoprostol group, 60 minutes and 40 minutes in intravenous oxytocin group, 480 minutes, 400 minutes in prostaglandin E2 gel group having modified Bishop's score 6-7, and 810 respectively. In primigravida it was 220 minutes, 58 minutes and 494 minutes for misoprostol, oxytocin and prostaglandin E2 gel respectively. For multigravida induction onset of lbour interval for misoprostol, oxytocin and prostaglandin E2 gel was 173 minutes, 35 minutes and 390 minutes respectively.

In prospective randomised study at University of Hong Kong, Queen Plary Hospital has shown that labour starts with in 60 minutes after oxytocin infusion and with 240 minutes of intravaginal misoprostol (25 □gm) in 90% of cases.

Rayburn et al (1989) reported a 83% rate of labour onset with in 6 hour of prostaglandin E2 gel administration in patients with Bishop score >6.[15]

So the induction-onset of labour interval is comparable to my study and previous studies.

In my study in primigravida induction delivery interval was 1026 minutes, 712 minutes and 1160 minutes in misoprostol, oxytocin and prostaglandin E2 gel group respectively. In multigravida induction delivery interval for misoprostol was 580 minutes. Same for oxytocin and prostagtandin E2gel was 490 minutes and 857 minutes respectively.

Gastrointestinal side effect: In the present study nausea and vomiting occurred in 4 (8%) patients in misoprostol group and 1 patient (4%) in prostaglandin E2 gel group. No such side effect in induction with oxytocin.

In a study at Khon Kaen University, Thailand has shown that nausea and vomittins1 hour after vaginal misoprostol administration were 6.8%.

Nimrod (1984) reported 3.3% gastrointestinal side effects where as Umsten 1983 repoted on incidence of 1% in induction with progtaglendin E2 gel.

In my study neonatal death was 2% in misoprostol group and 4% in oxytocin group because of birth asphyxia. No neonatal death was observed in prostaglandin E2 gel group.

In my study, there was no maternal mortality study.

CONCLUSION

Pervaginal misoprostol, intravenous oxytocin infusion, transcervical E2 gel all are good inducing agent though the overall success rate of intravaginal misoprostol is slightly higher than others, particularly in Bishop score 6-7 group.

Induction delivery interval of misoprostol is greater because of induction onset of labour interval is longer in this group than oxytocin group. Actual time taken from onset of labour to delivery for primigravida in oxytocin group is less than misoprostol group, but in multigravida duration of labour is less in misoprostol group. Duration of 2nd stage and 3rd stage are almost equal in oxytocin and misoprostol group. Both the interval (induction-onset of labour and induction delivery) is longer with prostaglandin E2 gel.

Oxytocin infusion as an inducing agent has advantages that it is cheap, available in our hospital has shorter induction delivery interval than other inducing agent and also efficacy is high particularly with Bishop's score 8-10. Induction with misoprostol although has got longer induction delivery interval can be used instead of oxytocin in both primi and multigravida with Bishop score 6-7 because of its higher success rate than oxytocin and comparable side effects.

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