

DOI: <http://dx.doi.org/10.18203/2320-1770.ijrcog20201778>

Original Research Article

A comparative study of misoprostol oral versus vaginal route for induction of labour

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Received: 09 July 2019

Revised: 08 March 2020

Accepted: 20 March 2020

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ABSTRACT

Background: Induction of labour at term is a common obstetric intervention. Prostaglandin E2 has been the agent of choice for pre-induction of cervical ripening for several decades. In recent time, prostaglandin E1 analogue (misoprostol) is a preferred new agent for pre-induction cervical ripening and labour induction owing to inexpensive, stable in room temperature, administrable through several routes. The ideal dose, route, and frequency of administration of misoprostol are still under investigation.

Methods: A double blind parallel group placebo control randomized clinical trial was done in the department of obstetrics and gynecology of Agartala Govt. Medical College among 130 pregnant women those required induction of labour. In this clinical trial, the women were allocated by lottery to receive oral misoprostol (25 µg) and vaginal placebo (same dosage) or vaginal misoprostol (25 µg) and oral placebo (same dosage). Both active and placebo drug (25 mcg) were repeated at 4 hours interval till the parturient reached active labour (not exceeding 5 doses). Both primary (induction delivery interval) and secondary outcomes (failed induction, vaginal/caesarean delivery rate, maternal and foetal complications) were statistically analyzed.

Results: The mean induction delivery interval (primary outcome) differences were insignificant among both groups (oral versus vaginal). Success rate of induction (56.9% versus 75.4%), mean dosage (misoprostol 90.5 mcg versus 96 mcg) requirement, maternal and foetal complications was indifferent among two groups. The rate of vaginal delivery (within 24 hours of induction) was significantly higher when misoprostol was used through vaginal route. Caesarean section rate trends to be higher when misoprostol was administered orally.

Conclusions: Low dose of misoprostol (25 mcg) offer an additional statistically significant clinical advantage in successful vaginal delivery when used vaginally.

Keywords: Induction of labour, Labour, Misoprostol, Oxytocin, Prostaglandin, Vaginal delivery rate

INTRODUCTION

Induction of labour is the intentional initiation of labour before spontaneous onset, for delivery of the fetoplacental unit.¹ Induction of labour at term is a common obstetric intervention and cervical ripening in these cases is of importance. Systematic review and meta-analysis have shown there are advantages in using vaginal

prostaglandins when compared with oxytocin alone in the presence of an unripe cervix, with regards to shorter induction of delivery time and lower operative delivery rate.²

Prostaglandins were first discovered in 1935 and in 1968; Karim and colleagues were the first to report the use of prostaglandin for labour induction. Since then, the

use of prostaglandins, in different varieties and forms of administration, has become a common method of labour induction⁴. Prostaglandin E2 has been the agent of choice for pre-induction of cervical ripening for several decades and is one of the pharmacologic agents approved by the United States Food and Drug Administration for this indication. However, it has several disadvantages: it is expensive, requires continuous refrigeration, and is not widely available.

Misoprostol (prostaglandin E1 analogue) is a comparatively new agent for pre-induction cervical ripening and labour induction. It has several potential advantages: stable at room temperature, is relatively inexpensive and can be administered by several routes (oral, vaginal, sublingual and buccal).² These properties make it a useful agent for induction of labour particularly in a setting in which prostaglandin E2 is not possible because of lack of availability, lack of facilities for storage, or financial constraints. The ideal dose, route, and frequency of administration of misoprostol are still under investigation. Most clinical trials have used doses ranging from 25 mcg to 100 mcg and inserted intra-vaginal into the posterior fornix. The most common vaginal dose used has been 50 mcg, inserted once or administered every 4-6 hours; inserting 25 mcg every 6 hours intra-vaginal has been associated with the fewest side effects.

Although vaginal application of misoprostol has been validated as a reasonable means of induction, there is patient resistance to repeated digital examination necessary for the placement of the agent. There is also a risk of ascending infection because of repeated vaginal examinations. Oral misoprostol is well tolerated when used for the management of upper gastrointestinal tract dysfunction. For this reason, oral administration of misoprostol has been introduced for cervical ripening and labour induction.

In the trials assessing the efficacy and tolerability of oral misoprostol for induction of labour, although the efficacy was high at higher doses, there was significantly higher incidence of abnormal uterine activity, non-reassuring foetal heart rate tracing and meconium stained amniotic fluid. The advantages of oral route include, ease of administration and the ability to administer repeated doses without internal examinations and without increasing the risk of bacterial contamination in women with ruptured membranes.³ The advantage of the vaginal route is that the bioavailability is more than twice that of orally administered misoprostol.⁵

The dose of 25 mcg of misoprostol is chosen because this dose has been shown to be effective with the least complication and is also recommended by the ACOG for induction of labour.⁶ In view of uncertainty regarding the preferred doses and routes of administration of misoprostol for induction of labour, this study is designed to assess and compare the efficacy and safety of 25 mcg

of misoprostol orally and vaginally for induction of labour at term. The results obtained will be subjected to a statistical analysis to find out if there is any significant value of clinical importance.

METHODS

The study was conducted in the department of obstetrics and gynecology, Agartala Government Medical College and G. B. Pant Hospital from November 2017 to April 2018. Pregnant women booked or unbooked who were admitted at the department of obstetrics and gynecology, Agartala Government Medical College and GB Hospital, Agartala, fulfilling the inclusion criteria were studied.

Age group of 18 years to 30 years pregnant women.

In reference to Feitosa FEL et al, 31 with vaginal delivery rate at 57% in the sublingual group and 69% in the vaginal group with an error of 5% and by using this data in PS software the minimum sample size were 126.⁷ Now, considering the minimum sample size to be 126, the study was done on 130 numbers of pregnant women.

Pregnant women for induction of labour were enrolled as per criteria. Induction by oral or vaginal misoprostol was done on working days as per department protocol.

This study was a double blind parallel group placebo control randomized clinical trial was done. Randomization was done by lottery. All the participants and researchers were blinded.

Subjects recruited from outpatient department, labour room and obstetrics ward, Agartala Government Medical College and GB Pant Hospital.

Inclusion criteria

- A live singleton pregnancy with vertex presentation at a gestational age of >37 week for obstetric or medical indication for induction
- Bishop score <5 with intact membrane without previous stripping.

Exclusion criteria

- Suspected cephalo-pelvic disproportion
- Previous caesarean section or history of uterine surgery
- Multiple gestations
- Malpresentation
- Any contraindication for vaginal delivery or prostaglandin administration and suspected chorioamnionitis
- Suspected foetal jeopardy
- Placenta previa
- Drug allergy (allergy to prostaglandins)

- Grand multigravida.

In this double blind randomized clinical trial, the women were allocated by lottery to receive oral misoprostol (25 µg) and vaginal placebo or vaginal misoprostol (25 µg) and oral placebo. In total 130 envelopes were prepared by a third person for the study. Each brown coloured envelope had two small white colour packet containing active misoprostol and placebo tablets of similar size, shape and colour. Out of 130 envelopes 65 contained oral misoprostol and placebo vaginal tablets and in the other 65 envelopes there was vaginal misoprostol and oral placebo tablets. The blinding of investigators was done by the third person by numbering the brown envelopes and keeping the records appropriately. The allocation was done by opening brown opaque envelope.

The route of administration of the drugs was mentioned over the white colour packets, such as oral and vaginal and they contained 5 numbers of tablets each. The on duty medical officer introduced one of the tablets from the white envelope marked vaginal in the posterior vaginal fornix and the women was instructed to take orally from the other the packet. A 25 µg dose of misoprostol along with placebo was repeated by both routes every 4 hours to a maximum number of 5 doses if required. Foetal heart rate, uterine contraction and cervical dilation were observed prior to every dose. Medicine from the envelop of the study was stopped at the onset of labour pain. When the parturient is in active labour artificial rupture of membrane was done, and acceleration of labour was observed for 30 minutes. When no effective uterine contraction was observed oxytocin, augmentation was done.

When the women did not go into labour or the cervix is not favourable enough for artificial rupture at the end of five doses and after waiting for eighteen hours, it was categorized as failed induction. When complications were observed during the study (uterine tachysystole, rupture uterus, foetal distress etc.), it was managed according to the department protocol.

Primary outcome measures

- The time interval from induction to vaginal delivery.

Secondary outcome measures

- Rate of vaginal delivery within 24 hours

- Caesarean section rate
- Uterine tachysystole (more than five contractions in 10 min for two consecutive 10 min segments)
- Neonatal outcome (Apgar score at one minute, admission in NICU).

Statistical analysis

It was done in computer using SPSS 17 version. Descriptive statistics (mean, standard deviation), and other suitable statistical tests ('t' test, Chi-square test) is applied as per applicability.

RESULTS

This double-blind placebo control study was carried out at Agartala Government Medical College and GBP Hospital from November 2017 to April 2018 and 130 numbers pregnant women included after taking history, clinical examination and with a Bishop score of less than and equal to five. After decoding 65 numbers of women had received 25 microgram misoprostol vaginally and 65 numbers orally. There was no significant difference in terms of maternal age, height, weight and parity. The indications for induction of labour are grouped in total of six groups. The commonest indication for induction is prolonged pregnancy (72.3 %). There were four expectant mothers who requested for elective induction (Figure 1).

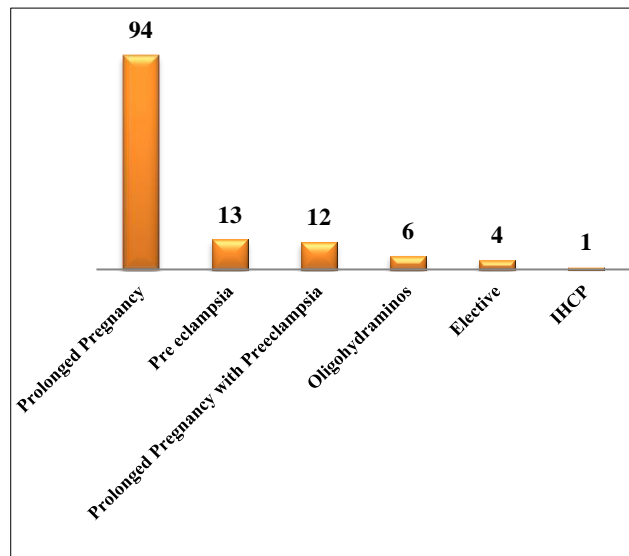


Figure 1: Indication for induction of labour.

Table 1: Successful induction according to route of administration.

Route of drug administration	Induction of labour		Significance
	Successful n (%)	Failed n (%)	
Oral	37 (56.9%)	28 (43.1%)	p=0.026
Vaginal	49 (75%)	16 (24.6%)	

Data indicated that similar number of women received oral and vaginal misoprostol when the pre-induction cervical score was grouped. There was no statistical significance between the two routes of administration regarding induction delivery interval. Women who received the drug vaginally had a higher percentage of successful induction compared to the oral route and this is statistically significant (Table 1). Most of the mothers who received drug orally for induction of labour took more time to deliver in comparison to those who received the drug vaginally (Figure 2). Fairly large number of women had successful induction of labour and delivered within 24 hours of start of induction in both groups. There was no significant difference in number of doses required in both the groups for induction of labour. Among 130 pregnant women who had induction of labour, 30.8% of them had to undergo caesarean section, the commonest indication was labour dystocia (52.5%), second being intra-partum foetal distress. The indications of caesarean section were not related to the route of drug administration as per statistical analysis. The caesarean section rate was high in the study group those received oral misoprostol for induction of labour in comparison to

vaginal group. The p value was 0.02 which indicates statistical significance (Table 2).

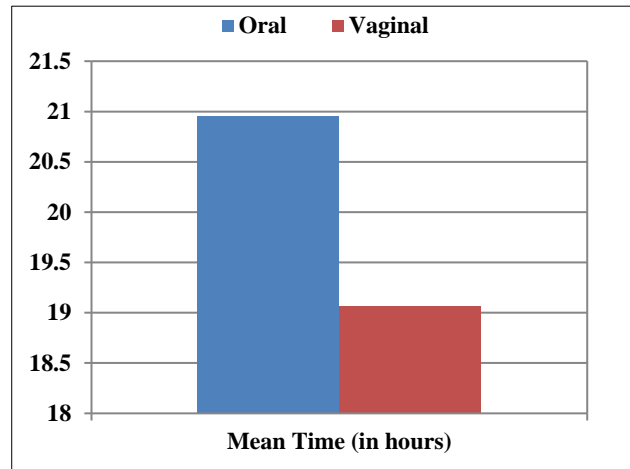


Figure 2: Comparison of time since induction of labour to delivery according to route of drug administration.

Table 2: Mode of delivery according to route of administration of misoprostol.

Route of drug administration	Vaginal delivery, n (%)	Caesarean section, n (%)	Significance
Oral	39 (60%)	26 (40%)	p=0.02
Vaginal	51 (78%)	14 (21.5%)	

Table 3: Induction of labour and mode of delivery by bishop score.

Induction of labour and mode of delivery	Bishop's score		Significance
	1-3, n (%)	4-5, n (%)	
Induction of labour			
Successful	28 (32.6 %)	58 (67.4 %)	p=0.015
Failed	24 (54.5 %)	20 (45.5 %)	
Mode of delivery			
Vaginal	30 (33.3%)	60 (66.7 %)	p=0.02
Caesarean	22 (55 %)	18 (45 %)	

Only one mother had developed uterine tachysystole after receiving the drug orally which is statistically insignificant. There was no uterine contraction abnormality amongst the mothers who received vaginal misoprostol. The uterine contraction abnormalities were diagnosed based on clinical judgment not by electronic devices. There was evidence of a greater number of patients with non-re-assuring foetal heart rate in case of oral administration of drug, but this was statistically insignificant.

There were no statistically significant major and minor maternal adverse effects noticed in both the study groups regarding route of drug administration. Presence of intra-

partum meconium was more (16.9%) in case of vaginal drug receivers but this is statistically insignificant. There was no statistical difference in Apgar score of new born and NICU admission in both groups. The response to inducing agent and successful vaginal birth was significantly higher in the study group that had pre-induction cervical score of 4 (Table 3).

The relation between pre-induction bishop score and induction failure was also statistically significant. That is a greater number of women had induction failure when the bishop score was less <3. Women with low Bishop's score had more induction failure and increased caesarean section rate (Table 3).

DISCUSSION

One thirty pregnant women with obstetric and non-obstetric indication for induction of labour were randomized and assigned for oral (65 patient) and vaginal (65 patient) use of 25 mcg of misoprostol. The study was carried out at Agartala Government Medical College and GBP Hospital, in the department of obstetrics and gynecology from 1st November 2017 to 30th April 2018. The purpose of the present study was to compare the efficacy and safety of novel minimum dose (25 mcg) of oral and vaginal misoprostol in the background of its known complications of mother and the unborn foetus.

Multiple clinical trials support misoprostol is an effective agent for cervical ripening and labour induction. It is being used for the above-mentioned reason for the last few years because of its low cost, effectiveness and due to its stability at room temperature.

Studies of misoprostol pharmacokinetics demonstrate a route depending pharmacokinetic profile that seem to show different bioavailability of the agent.

There have been different published reports of misoprostol used through different routes (oral, vaginal, rectal) and in varying doses. Misoprostol and transcervical foley catheter are both considered appropriate induction agents by ACOG.⁶ However, despite the data supporting its use there is still controversy regarding misoprostol as an induction agent.

Maternal demographic profile

The demographic characteristics of the study population are shown in Table 1. The groups were similar in mean maternal age, height, weight and gravidity. Pregnant women with similar demographic profiles were also noted by Rahaman H et al.⁵

Pre-induction data

The indication for induction of labour is shown in Figure 1. In this study more than two third of pregnant women (68.5%) were in gestational age of 40-42 weeks. Interestingly there were two expectant mothers who requested for elective induction at term. The pre-induction cervical score (Bishop's Score) were similar in both the groups. Prolonged pregnancy was also common indication for induction in studies done by Rahaman H et al; van Gemund et al, Gregson S et al, Hall R et al.^{3,5,8,9}

Primary outcome

Many clinical trials support the efficacy of vaginal misoprostol for cervical ripening and induction of labour. In this study successful induction with 25 microgram vaginal misoprostol was higher (75.4% versus 56.9%) and it was statistically significant. Successful induction (52.72%) was also observed by Rahaman H et al, after 25

microgram misoprostol by vaginal route.⁵ Similarly, higher rates of successful induction (77%) were also observed by Hall R et al after 25 microgram misoprostol through vaginal route.⁹ Cheng et al noted induction failure in 10.4% of women receiving 25 microgram misoprostol by vaginal route and there was no induction failure in the titrated 20 microgram oral misoprostol group.¹⁰ Successful induction with 25 microgram misoprostol by vaginal route was also observed by Sheikher C et al.¹¹ Jindal P et al reported successful induction with 50 microgram vaginal misoprostol (90.38% versus 74.51%) as compared to oral route.¹² Barik S et al also reported lower failure (2.4% versus 6.76%) with 50 micrograms vaginal misoprostol.¹³

The mean induction delivery interval was similar in vaginal and oral misoprostol (20.45 hours versus 19.06 hours) in this study. Similar observation was made by Rahman H et al, with 25 microgram misoprostol intra-vaginal and 50 micrograms orally (20.15 hours versus 21.22 hours).⁵ Interestingly, Cheng et al noted a mean induction delivery interval of 17.6 hours versus 8.2 hours after 25 microgram misoprostol vaginally and titrated 20 microgram misoprostol solution every one hour by oral route.¹⁰ Hall R et al and Sheikher C et al also observed less induction delivery time interval (17.9 hours, 22.05 hours 10.3 hours) after vaginal administration of 25 microgram misoprostol.^{9,11} Bano K et al also showed mean induction delivery interval were similar in both the groups after reported induction with 50 micrograms vaginal (9.09±3.4 hours) and 50 micrograms oral (9.81±4.43 hours).¹⁴ Several other researchers found that initial 50 microgram oral misoprostol is less effective and associated with longer induction delivery interval presumably because of "first pass effects".^{2,9}

Secondary outcome

As vaginal misoprostol is absorbed rapidly and eliminated slowly from body making it available to act for a longer time as compared to oral resulting in rapid progression of labour leading to greater number of women delivering within 24 hours of induction (69.5% versus 56.4%).^{2,8,9}

In this study there is no statistical difference between the two study groups regarding time of delivery since induction of labour. But large number of women delivered successfully within 24 hours of induction of labour (76.5% in vaginal and 74.3% in the oral group). In a study by Rahman H et al pregnant women who delivered within 24 hours were similar with 50 micrograms oral and 25 micrograms vaginal (49.1% versus 52.72%) groups with no difference in caesarean section rate and neonatal outcome.⁵ Cheng et al, reported 94.1% of women delivered within 24 hours after oral administration of titrated 20 microgram misoprostol and 53.8% with 25 microgram misoprostol vaginally.¹⁰ Kundodyiwa et al, in a systemic review reported 57.70% successful delivery after oral low dose 20-25 microgram

misoprostol.¹⁵ Higher rate of vaginal delivery was also reported by Sheikher C et al (65.5% and 86.61%).¹¹ Caesarean section rate in this study was higher in oral compared to vaginal group (40% versus 21.5%) and this is statistically significant.

The caesarean section rate was more due to labour dystocia and foetal distress in the oral group. Though, Cheng et al reported a caesarean section rate of 4% after titrated 20 microgram misoprostol solution compared to 17% in the vaginal group.¹⁰ Kundodyiwa et al in a meta-analysis of 5 studies found 20.20% after low dose 20-25 microgram oral misoprostol.¹⁵ Similar observation was reported by Jindal P et al, with a higher caesarean section rate in the oral group (25.49% versus 9.62%) as compared to vaginal group.¹² Excessive uterine contraction and uterine rupture especially in scared uterus is the main fear with this drug. Barik S et al, and Paungmora N et al, have also reported occurrence of tachysystole and uterine hyper stimulation in women receiving 50 micrograms of vaginal misoprostol.^{13,16} Uterine tachysystole was observed by Cheng et al 15% but Rahaman H et al, reported only 5.45% in women receiving 25 microgram misoprostol by the vaginal route.^{5,10} Though foetal heart rate changes were higher in the vaginal group, meconium stained liquor, Apgar score and NICU admission was found to be similar in both the groups. In this study uterine tachysystole occurred in only one pregnant woman (1.5%) in the oral and no uterine contraction abnormality was observed in the vaginal misoprostol group.

There was also no case of uterine rupture in either group during the study period. Foetal distress was also higher in oral group compared to vaginal misoprostol group, but they were found to be not significant. Similarly, Ngai SW after extensive investigation regarding doses regimen of misoprostol for induction suggested 25 microgram doses vaginally was associated with lower incidence of tachysystole and uterine hyper stimulation.¹⁷ In this observation there is no significant difference in meconium stained liquor, Apgar score and NICU admission between oral and vaginal groups. Similar observations were also reported by Jindal P et al.¹²

ACKNOWLEDGMENTS

Authors would like to thank to manufacturing unit of CIPLA Pt. Company Ltd., India for providing the placebo.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: DebBarma AM, Baidya JL, Ray D. A comparative study of misoprostol oral versus vaginal route for induction of labour. Int J Reprod Contracept Obstet Gynecol 2020;9:1907-13.