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A Comparative Study of Efficacy of Oral Misoprostol versus Vaginal Misoprostal in Induction of Labour after 34 Weeks Gestation to 40 Weeks Gestation

Dr. CH Jyothi, Dr. G. Sushma*, Dr. Vamshee Priya P, Dr. L. Rani kumari

Assistant Professor, Department of Obstetrics and Gynaecology, Gandhi Medical College, Secunderabad, Telangana, India

Corresponding author: Dr. G. Sushma, Assistant Professor, Department of Obstetrics and Gynaecology, Gandhi Medical College, Secunderabad, Telangana, India

ABSTRACT

Background and Objective: In modern obstetrics, around 30% of cases require induction of labour for various reasons. Misoprostol is gaining popularity as a pharmacological inducing agent, though the route and dosage of administration is not standardised. The objective of the study is to compare the safety and efficacy of the two routes of Misoprostol administration - Oral (25 µ gm 4th hourly) and Vaginal (25 µ gm 4th hourly), for induction between gestation age 34-40 weeks.

Methods: In this randomized trial, 100 women having crossed the expected date of delivery without going into spontaneous labour were considered for labour induction and were divided into two equal groups. Group A received 25 µ gm Misoprostol orally 4th hourly and Group B received 25 µ gm Misoprostol vaginally 4th hourly. Labour characteristics and maternal and foetal outcome were compared.

Results: The mean induction to delivery interval was longer in oral group (oral 22.40 hrs vs. vaginal 16.26 hrs, $p<0.001$). More cases required Oxytocin augmentation in oral group (oral 70% vs. vaginal 80% cases, $p=0.01$). Fewer cases delivered vaginally in oral group (oral 88% vs. vaginal 92% cases), though the results were statistically insignificant ($p=0.67$). Mean number of doses of Misoprostol required for induction of labour was more in oral group (oral 3 vs. vaginal 2, $p <0.0001$). Higher rate of uterine Hyperstimulation was associated with vaginal group, though the difference was statistically insignificant ($p >0.05$). Vaginal group had higher rate of meconium stained amniotic fluid (vaginal 30% vs. oral 26% cases, $p =0.346$) and NICU admissions (40% vaginal vs. oral 86% cases had respiratory distress and LBW, meconium 14% oral vs. 50% vaginal), and they differed statistically between the groups ($p=0.00001$). Bishop Score improvement after 1st dose of Misoprostol was better in vaginal group and could be attributed to the direct action of Misoprostol on uterus and cervix in vaginal administration. Oral group witnessed three cases of failed induction, which was nil in the vaginal group. Oral group witnessed more number of c-sections mainly because the failure of induction was more in oral group. Maternal complications, such as Uterine Hyperstimulation were seen only in vaginal group.

Conclusion: Vaginal Misoprostol administered every 4 hours is more effective for induction of labour than oral Misoprostol administered every 4 hours. Vaginal Misoprostol has statistically significant better efficacy whereas oral Misoprostol seems to be safer in terms of maternal and foetal outcome. The limitation of the present study is small sample size, studies with larger samples in different zones of the country will help us to establish the efficacy of oral Misoprostol.

Keywords: Pregnancy, Induced Labor, Misoprostol, Oxytocin.

INTRODUCTION

Induction of labour at term with unfavorable cervix is associated with increased risk of failed induction and caesarean section. Convention methods for cervical ripening [oxytocin, Foleys catheter] being used, but have their own merits and demerits. Hence there is a need for more efficient inducing agent with fewer limitations. There are various methods of induction of labour falling in two broad categories: non-pharmacological and pharmacological. The aim of the obstetrician should be to select the ideal method of induction which is safe, reliable, cheap, easily applicable, readily available, and which results in good maternal and foetal outcome.

Prostaglandins as pharmacological agents have always fascinated the obstetrician for induction of labour as well as cervical ripening agent. Recently, Prostaglandin E1 (Misoprostol) tablets as an inducing agent of labour by various routes e.g. vaginal, oral, rectal etc have received huge attention. As it is cheap, easily available, has long shelf life and easily administrable, it is fast gaining popularity. In Parkland Hospital, Misoprostol is the Prostaglandin of choice for induction of labour. The American College of Obstetricians and Gynaecologists (2000,2003) has reaffirmed the use of Misoprostol as a drug for induction of labour because of its proven safety and efficacy [1-2].

Prostaglandins are the new drugs of interest in this field. Out of all prostaglandins, PGE1 and PGE2 have been tried for induction of labour. As PGE2 is being used in gel and tablet form has the advantage of being 1 intracervical or vaginal. But it is expensive and need refrigeration. PGE1 synthetic analogue, misoprostal originally used as a gastroprotective

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drug and it is used as cervical ripener and labour inducer. It has the advantage of being cheap, stable at room temperature and easy to be administered by various routes i.e. vaginal, oral, sublingual, rectal, hence it is necessary to study the efficacy of oral misoprostal versus vaginal misoprostal in induction of labour after 34 weeks gestation to 40 weeks gestation.

AIMS & OBJECTIVES

- To compare the efficacy of oral versus vaginal misoprostol in induction of labour after 34 weeks of gestation.
- To find out any variation in the maternal and fetal outcome.
- To evolve a protocol based in this study.

MATERIALS AND METHODS

Source of Data

A Randomized Control Trial will be carried out in the Department of Obstetrics and Gynaecology, Gandhi Medical College, Secunderabad, Telangana, India for the period of one year, from April 2022 to March 2023.

In the present study 100, antenatal women who are more than 34 weeks gestation and who need induction of labour will be selected for the study. To calculate the EDD, following method was adopted

• Patient should be sure of her Last Menstrual Period
• Previous cycles should be regular
• Pt should have at least one USG report in 1st or 2nd trimester
• EDD is calculated using Naegele's Formula

Inclusion criteria:

- Singleten pregnancy, vertex presentation gravida (1-3), adequate pelvis bishopscore less than 4.
- Pre-Eclampsia, Eclamsia
- Prolanged pregnancy, premature rupture of membrane.
- Antepartum eclamsia, oligohydramnios & intra uterine death

Exclusion criteria:

- Placenta previa, abruption.
- Previous lower segment caesarean section, previous history of myomectomy
- Asymmetrical IUGR, grand multipara
- Diabetic mellitus, maturity onset DM, precious pregnancy
- Cardiac and renal disease

RESULTS

Following section provides a summary of data collected and results obtained in the present study. The Master Charts for the data is represented in Annexure I and II

Indication for Induction

The indication for labour is crossing of Expected Date of Delivery without going into spontaneous labour.

In oral group

• Mean gestational week for induction of labour was 39 weeks, 2 days
• Minimum gestational week for induction of labour was 34 weeks, 4 days
• Maximum gestational week for induction of labour was 40 weeks

In vaginal group

• Mean gestational week for induction of labour was 39 weeks, 1 days
• Minimum gestational week for induction of labour was 34 weeks, 4 days
• Maximum gestational week for induction of labour was 40 weeks.

Table 1: Indication for Induction –Pregnancies between 34 weeks to 40 weeks gestation

Dose groups	N	Mean Gestational Age	SD	Minimum	Maximum	t value	p value
Oral	50	39.3weeks	1.88	34 weeks 4 days	40 weeks	0.307	0.759
Vaginal	50	39.14weeks	1.33	34 weeks 4 days	40 weeks		

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Parity

A total of 57 women were primigravida while 43 were multigravida.

For oral group
• 29 cases (58%) were primigravida
• 21 cases (42%) were multigravida

For vaginal group
• 28 cases (56%) were primigravida
• 22 cases (44%) were multigravida

Table 2: Distribution According to Parity

Dose	Parity		Total N(%)
	Primi N(%)	**Multi** N(%)	
Oral	29 (58.0%)	21 (42.0%)	50(100.0%)
Vaginal	28(56.0%)	22 (44.0%)	50(100.0%)
Total	57 (57.0%)	43 (43.0%)	100(100.0%)
	χ^2 : 0.02	**p-value: 0.88**	**df : 1**

Number of Doses of Drug Required for Delivery

Of the total women enrolled, majority of the cases were on 2 doses (38%) followed by 3 doses (31%), 1 dose (17%), 4 doses (9%) and 5 (5%).

For oral group
• Minimum number of dose required was 1 (4% of cases)
• Maximum number of dose required was 5 (10% of cases)
• Majority of cases (46%) required 3 doses
• 24% of cases required 2 doses and the rest (16%) required 4 doses

For vaginal group
• Minimum number of dose required was 15 (30% of cases)
• Maximum number of dose required was 1 (2% of cases)
• Majority of cases (52%) required 2 doses
• Rest of the cases (16%) required 3 doses

Table 3: Number of Doses of Drug Required for Delivery

Dose	Number of doses					Total N(%)
	1 N(%)	2 N(%)	3 N(%)	4 N(%)	5 N(%)	
Oral	2 (4.0%)	12 (24.0%)	23 (46.0%)	8 (16.0%)	5 (10.0%)	50 (100.0%)
Vaginal	15 (30.0%)	26 (52.0%)	8 (16.0%)	1 (2.0%)	0 (0.0%)	50 (100.0%)
Total	17 (17.0%)	38 (38.0%)	31 (31.0%)	9 (9.0%)	5 (5.0%)	100 (100.0%)

Fisher exact test value : 59.02
p-value : <0.001
degrees of Freedom : 4

Response to Drug in terms of Bishop Score
Bishop score, which is one of the important determinants for induction of labour was measured: First at the time of dose administration, next after 4 hours and then before every repeat dose.

For oral group
• The mean pre-induction score was 2.80
• Mean bishop score was 5.10 after 4 hours.
• Minimum pre-induction Bishop score was 1 and maximum was 4

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For Vaginal group
• The mean pre-induction score was 3.12
• Mean bishop score was 5.72 after 4 hours.
• Minimum pre-induction Bishop score was 1 and maximum was 4

Table 4: Response to Drug in terms of Bishop Score

	Groups	N	Mean	SD	Minimum	Maximum	t- value	p- value
Pre-induction Bishop Score	Oral	50	2.82	1.26	1	5	1.32	0.19
	Vaginal	50	3.12	1.17	1	5		
4 Hours Bishop Score	Oral	50	4.40	1.71	2	9	**10.27**	**0.002***
	Vaginal	50	5.72	1.75	3	10		

Augmentation with Oxytocin
Of the total, 45% of the cases were on Oxytocin while remaining was not.
For Oral Group
• 27 cases (54%) required augmentation with Oxytocin
• Rest 23 cases (46%) did not require any augmentation

For Vaginal Group
• 18 cases (36%) required augmentation with Oxytocin
• Rest 32 cases (64%) did not require any augmentation

Table 5: Requirement of Augmentation with Oxytocin

Dose	Augmentation with Oxytocin		Total N(%)
	Yes N(%)	No N(%)	
Oral	27 (54.0%)	23(46.0%)	50 (100.0%)
Vaginal	18 (36.0%)	32 (64.0%)	50 (100.0%)
Total	45 (45.0%)	55 (55.0%)	100 (100.0%)

FISHER Exact Test Value : 5.58
p-value : 0.01
Degrees of Freedom: 1

Induction to Delivery Interval
In oral group
• Mean induction to oral delivery interval was 24.40 hours
• Minimum induction to oral delivery interval was 10 hours
• Maximum induction to oral delivery interval was 30 hours

In vaginal group
• Mean induction to vaginal delivery interval was 16.26 hours
• Minimum induction to vaginal delivery interval was 8 hours
• Maximum induction to vaginal delivery interval was 26 hours

Table 6: Induction to delivery interval

Groups	N	Mean induction to delivery interval (Hrs)	SD	Minimum	Maximum	t - Value	P - Value
Oral	50	24.4	3.31	10	30	11.32	**<0.0001**
Vaginal	50	16.26	3.86	8	26		

Failed Induction
In the study group, nearly 3% of the cases failed induction.
In Oral group
• Failed induction incidence was in 2 cases (4%).
In Vaginal group
• There was no failure of induction.

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Table 7: Failed Induction

Dose	Failed Induction		Total
	Yes N(%)	No N(%)	
Oral	3 (6.0%)	47 (94.0%)	50 (100.0%)
Vaginal	0 (0%)	50(100.0%)	50 (100.0%)
Total	3 (3.0%)	97(97.0%)	100(100.0%)

FISHER Exact Test Value : 4.92
p-value : 0.038
Degrees of Freedom: 1

Mode of delivery
Among the studied cases, 75% of the cases had normal delivery, 12% showed vaccum delivery followed by C section (10%) and 3% cases had forceps delivery.

For oral group
• 70% (35 cases) proceeded for normal delivery
• 12% (6 cases) required LSCS intervention
• 4% (2 cases) required forceps application for delivery
• 14% (7 cases) required vacuum application for delivery

For vaginal group
• 80% (40 cases) proceeded for normal delivery
• 8% (4 cases) required LSCS intervention
• 2% (1 case) required forceps application for delivery
• 10% (5 cases) required vacuum application for delivery

Table 8: Mode of delivery

Dose	Mode of delivery				Total N(%)
	Normal N(%)	C-Section N(%)	Forceps N(%)	Vaccum N(%)	
Oral	35 (70.0%)	6(12.0%)	2(4.0%)	7(14.0%)	50(100.0%)
Vaginal	40(80.0%)	4(8.0%)	1(2.0%)	5(10.0%)	50(100.0%)
Total	75(75.0%)	10(10.0%)	3(3.0%)	12(12.0%)	100(100.0%)
	χ^2 : 1.53	**p-value: 0.67**	**df : 3**		

Indications for Emergency LSCS
For Oral Group
• Of the 6 cases
o 17% (1 case) was taken for LSCS due to DTA
o 50% (3 cases) were taken for LSCS due to Failed Induction
o 33% (2 cases) was taken for LSCS due to Thick Meconium

For Vaginal Group
• Of the 4 cases
o 25% (1 case) was taken for LSCS due to DTA
o 75% (3 cases) was taken for LSCS due to Thick MSAF
o No cases were taken for LSCS due to induction failure

Table 9: Indication for Emergency LSCS

Dose	Remark			Total N (%)
	DTA N(%)	Induction Failure N(%)	Thick MSAF N(%)	
Oral	1(17.0%)	3(50.0%)	2(33.0%)	6(100.0%)
Vaginal	1(25.0%)	0(0.0%)	3(75.0%)	4(100.0%)
Total	2(20.0%)	3(3.0%)	5(50.0%)	10(100.0%)

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FISHER Exact Test Value: 65.75
p-value :<0.0001
Degrees of Freedom : 2

Liquor Characteristic
79% of the cases had clear liquor, 10% showed Thin MSAF while the remaining 11% had Thick MSAF.

For Oral group
• 80% (40 cases) exhibited clear liquor
• 8% (4 cases) exhibited thin MSAF
• 12% (6 cases) exhibited thick MSAF

For Vaginal group
• 78% (39 cases) exhibited clear liquor
• 12% (6 cases) exhibited thin MSAF
• 10% (5 cases) exhibited thick MSAF

Table 10: Characteristics of liquor

Dose	**Liquor**			**Total N(%)**
	Clear N(%)	Thin MSAF N(%)	Thick MSAF N(%)	
Oral	40(80.0%)	4(8.0%)	6 (12.0%)	50 (100.0%)
Vaginal	39 (78.0%)	6 (12.0%)	5 (10.0%)	50 (100.0%)
Total	79(79.0%)	10(10.0%)	11(11.0%)	100(100.0%)
	χ^2 : 0.502	**p-value: 0.77**	**df : 2**	

Maternal Complication

For Oral group
• 98% (49 cases) encountered no maternal complication
• 0% (0 cases) mothers developed diarrhoea
• 2% (1 case) mothers developed fever
• No case of tachysystole
• 0% (0 case) of mothers experienced uterine hyperstimulation

For Vaginal group
• 96% (48 cases) encountered no maternal complication
• No case of diarrhoea
• 2% (1 case) mothers developed fever
• 0% (0 cases) mothers experienced tachysystole
• 2% (1 cases) of mothers experienced uterine hyperstimulation

Table 11: Maternal Complication

Dose	**Maternal Complication**					**Total N(%)**
	Diarrhoea N(%)	Fever N(%)	Trachy Systole N(%)	Citerine hyperstimulation N(%)	No complication N(%)	
Oral	0(0%)	1(2.0%)	0(0%)	0(0%)	49(98.0%)	50(100.0%)
Vaginal	0(0%)	1(2.0%)	0(0%)	1(2.0%)	48(96.0%)	50(100.0%)
Total	0(0%)	2(2.0%)	0(0%)	1(1.0%)	97(97.0%)	100(100.0%)

FISHER Exact Test value: 0.252
p-value: 0.49
Degrees of Freedom: 2

APGAR score
APGAR score of the neonate was recorded at 1 minute and 5 minutes after birth

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For Oral Group
• Minimium 1 minute apgar score was 4/10 which proceeded to be 6/10 after 5 minutes
• Maximum 1 minute apgar score was 7/10 which proceeded to be 9/10 after 5 minutes
• Mean 1 minute score was 7.42
• Mean 5 minutes score was 8.62
• 5 neonates (10% cases) had APGAR score < 6 at 1 minute
• 0 neonate (0% cases) had APGAR score 6 at 5 minutes

For Vaginal Group
• Minimium 1 minute apgar score was 5/10 which proceeded to be 9/10 after 5 minutes
• Maximum 1 minute apgar score was 7/10 which proceeded to be 9/10 after 5 minutes
• Mean 1 minute score was 7.28
• Mean 5 minutes score was 8.56
• 6 neonates (12% cases) had APGAR score < 6 at 1 minute
• None of the neonates had APGAR < 6 at 5 minutes

Table 12: APGAR score at 1 and 5 minute

APGAR	Group	N	Mean	SD	Minimum	Maximum	t-value	P - Value
1 minute	Oral	50	7.42	1.11	4	8	0.63	0.53
	Vaginal	50	7.28	1.12	5	9		
5 minute	Oral	50	8.62	0.78	6	9	0.39	0.69
	Vaginal	50	8.56	0.76	7	9		

Neonatal Complications
For Oral Group
• 26% (13 cases) of neonates required NICU admission due to neonatal complication
For Vaginal Group
• 30% (15 cases) of neonates required NICU admission due to neonatal complication

Table 13: Neonatal Complications

Dose	Neonatal Complications		Total
	Yes N(%)	No N(%)	N(%)
Oral	7(14.0%)	43(86.0%)	50(100.0%)
Vaginal	10(20.0%)	40(80.0%)	50(100.0%)
Total	17(17.0%)	83(83.0%)	100(100.0%)
	χ^2 : 0.88 p-value: 0.346 df : 1		

Neonatal Outcome in terms of NICU admissions

Oral group
• Of the 7 NICU admissions
- 6 were admitted for Respiratory Distress and low birth weight (86%)
- 1 case for Thick Meconium (14%)

Vaginal group
• Of the 10 NICU admissions
- 4 were admitted for Respiratory Distress and Low Birth Weight 4 (40%)
- 5 cases for Thick Meconium (50%)
- 1 case was kept for observation (10%)

Table 14: Indication to NICU Admission

Dose	Neonatal Complication Reason			Total
	Respiratory distress + LBW	Observation	Meconium	
Oral	6(86.0%)	0(0%)	1(14.0%)	7(100.0%)
Vaginal	4(40.0%)	1(10.0%)	5(50.0%)	10(100.0%)
Total	10(59.0%)	1(6.0%)	6(35.0%)	17(100.0%)

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FISHER Exact Test Value: 43.31
p-value: <0.0001
Degrees of Freedom: 2

DISCUSSION

100 women were checked for the eligibility criteria and enrolled for the study. They were divided into two groups:
Group A: 50 women for oral administration of 25 microgram Misoprost every 4th hourly for induction of labour
Group B: 50 women for vaginal administration of 25 microgram Misoprost every 4th hourly for induction of labour

None of the women from either of the groups withdrew from the study. There was no statistically significant difference in baseline characteristics as age, height and weight in both groups. The indication for induction of labour in both the groups was crossing of EDD without going into spontaneous labour, where EDD was calculated by Naegele's formula.

Indication for Induction – Post dated pregnancies

Mean gestational age for Oral group was 39 weeks 2 days and that for Vaginal group was 39 weeks 1 days. The mean gestational age did not differ between the groups and the p value was statistically insignificant (p= 0.76)

Parity

Primigravidas predominated in both the groups and is often considered as one of the known aetiological factor [3]. 29 cases (58%) were primigravida in oral group while 28 cases (56%) were primigravida in vaginal group. The frequencies of primigravidas and multigravidas did not differ between the groups and the p value was statistically insignificant (p value 0.88).

Number of Doses of Drug Required for Delivery

Majority of cases in the oral group needed 3 doses for induction of labour. Only two cases delivered after 1 dose. In vaginal group, majority required only two doses for induction of labour whereas 15 cases (30%) delivered after 1 dose of Misoprost. Our findings are consistent with the observations made by Shetty Ashalatha etal., in the year 2001 [4]. 46% of cases in oral group required 3 doses for induction and in vaginal group nearly 52% required 2 doses for induction. A study by Kwon *et al*, 2001 [5] showed similar results with mean number of doses required was more in the oral group as compared to the vaginal group.

This is of most importance because pharmacokinetics varies with the mode of induction of Misoprostol whether administered oral or vaginal. For oral administration, the onset of action is 8 mins, Tmax is 30 mins and duration of action is 2 hours. For vaginal administration, the onset of action is 20 mins, Tmax is 70 mins and duration of action is 4 hours. It is clear by the pharamcokinetics, vaginal Misoprostol remains effective for longer time and hence lesser dosage is required for induction of labour.

Response to Drug in terms of Bishop Score

Before induction of labour, cervical scoring was done by Bishop's score and for both the groups, followed by next cervical scoring after 4 hours. Before administrating the next dose of Misoprost, PV examination was done. If the patient had already gone into active labour, further Misoprost administration was withheld. Mean pre-induction bishop score for Oral group was 2.80 ± 1.26 and the vaginal group was 3.12 ± 1.17 which was statistically insignificant (p = 0.19). After 4 hours, the bishop score for oral group had a mean of 4.40 ± 1.71 and for vaginal group, was 5.72 ± 1.75, which was also statistically significant (p=0.02).

Table 15: No. of Doses, comparison with previous studies

Study/Year	Oral				Vaginal			
	No. of Cases	Mean no. of Doses	No. of Cases requiring		No. of Cases	Mean no. of Doses	No. of Cases requiring	
			1 Dose	>1 Dose			1 Dose	>1 Dose
Shetty [4] Ashalatha *et al*., 2001	92	NA	47 (50.1%)	45 (48.9%)	95	NA	74 (77.8%)	21 (22.2%)
Know S. J *et al*., 2001[5]	78	2.21	NA	NA	82	1.39	NA	NA
Uludag *et al*., 2005[6]	99	2.17	NA	NA	99	1.91	NA	NA
Rasheed R *et al*., 2007[7]	165	2.52	NA	NA	145	1.93	NA	NA
Abbassi RM *et*	40	NA	24 (60%)	16 (40%)	40	NA	31	9(22.5%)

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al., 2008[8]							(77.5%)	
Akhtar *et al*., 2010[9]	50	2.1	NA	NA	50	2.4	NA	NA
Deshmukh *et al*., 2013[10]	100	2.73	NA	NA	100	2.26	NA	NA
Rezaie *et al*., 2016[11]	NA	1.2	NA	NA	NA	1.7	NA	NA
Present Study	50	3.04	2 (4%)	48 (96%)	50	1.9	15 (30%)	35 (70%)

Requirement of Augmentation with Oxytocin

In the present study, it was found that 27 (54%) cases in oral group and 18 (36%) cases in vaginal group required augmentation with Oxytocin. The difference was statistically significant (p = 0.01) indicating that oral administration of Misoprostol for induction of labour requires additional methods of labour augmentation, such as Oxytocin drips. A study by Deshmukh *et al*., 2013 also demonstrated lesser requirement of Oxytocin augmentation in vaginal group compared to oral [10]. In a study by Mesomeh *et al*., 2016, induction with oxytocin was performed in 36.7% of the 100µg Oral group, 55% of the 50 µgm Oral group, and 51.7% of the 25 mcg vaginal group. The three groups did not differ in terms of induction frequency (p= 0.66) [11]. The findings of this study are in accordance with the findings of previous studies given in the table below. All the studies mentioned below, demonstrated increased frequency of cases in oral group that required augmentation with Oxytocin compared to vaginal group for delivery.

Table 16: Augmentation with Oxytocin, comparision with previous studies

	Oral		**Vaginal**	
Study/year	**No. of Cases**	**Cases requiring augmentation**	**No. of Cases**	**Cases requiring augmentation**
Kwon S. J. *et al*, (2001)[5]	78	61 (78.2%	82	
Shetty A. *et al*, (March 2001)[4]	122	71(52.2%)	123	48(39%)
How, (2001)	110	81(74%)	110	41(37%)
Rasheed R. *et al*, (2007)[7]	165	89(53.9%)	145	65(44.8%)
Abbassi R.M et al, (2008)[8]	40	Reported to be less	40	Reported to be more
Sheikher C. *et al*, (2009)[12]	30	17(56.6%)	30	7(23.3%)
Akhtar *et al*.2010[9]	50	68%	50	21%
Sreelatha.S *et al*., 2013 [13]	50	24(48%)	50	17(34%)
Present Study	50	30(60%)	50	16(32%)

Induction to Vaginal Delivery Interval

The induction to delivery interval is one of the primary outcomes of the present study. In Oral group, the mean interval was 24.40 hours and the same in vaginal group was 16.26 hours. The difference is statistically significant (p < 0.001), indicating that vaginal route of administration leads to lesser induction to delivery interval as compared to the oral route. Also, in vaginal group, the maximum induction to delivery interval was 26 hours, i.e. all the cases delivered within 26 hours of induction of labour. The same measure was 30 hours in the oral group.

This finding corroborates the pharmacokinetics of oral and vaginal route of administration of Misoprostol, since vaginal route has longer duration of action than oral route. It could be explained on the basis that there is greater Oxytocic effect of Misoprostol on uterus via vaginal route due to direct access to myometrium via cervical canal. [1] [14][2][15] [16] According to Mishra *et al*., 2007 the systemic bio-availability of vaginally administered Misoprostol is 3 times greater than that of oral Misoprostol.[14] The findings of the present study coincided with the earlier ones outlined in the table below. In all the studies, including the present one, the IDI in oral group was longer than that of vaginal group.

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Table 17: Induction to Delivery Interval, comparison with previous studies

Study/Year	Oral			Vaginal		
	No. of Cases	Dosage	IDI	No. of Cases	Dosage	IDI
Shetty A *et al*., 2001[4]	92	50 ug 4th hr	27.9±16.2	95	50 ug 4th hr	17.8±13.5
Know S. J *et al*., 2001 [5]	78	50 ug 6th hr	27.3±18.8	82	50 ug 6th hr	19.3±11.9
Rasheed R. *et al*, (2007)[7]	NA	50 ug 6th hr	20.6	NA	50 ug 6th hr	13.5
Ratna khatri *et al* 2007[17]	50	25 ug 4th hr	15.5	50	25 ug 4th hr	15.03
Abbassi R.M *et al*, (2008)[8]	32	50 ug 6th hr	7.5±4.3	38	50 ug 6th hr	6.7±4.4
Sheikher C. *et al*, (2009)[12]	17	50 ug 4th hr	15.05	26	25 ug 4th hr	10.35
Mehrotra *et al*., 2010 [18]	NA	50 ug 4th hr	14.6	NA	50 ug 4th hr	22.5
Komala *et al*., 2011 [19]	86	50 ug 4th hr	12.92	74	25 ug 4th hr	14.04
Sreelatha.S *et al*. 2013[13]	50	25 ug 4th hr	12.0	50	25 ug 4th hr	18.0
Deshmukh *et al*., 2013[10]	100	50 ug 6th hr	15.24	100	50 ug 6th hr	12.74
Ambika H.E *et al*., 2017[20]	100	50 ug 4th hr	15.0	100	50 ug 4th hr	12.90
Present Study	50	25 ug 4th hr	24.40	50	25 ug 4th hr	16.26

Failed Induction

In the present study, 3 cases (6%) in oral group failed to proceed to active labour, while there was only no (0%) failure of induction in the vaginal group, though the difference was statistically insignificant (p = 0.038). Increased frequency of induction failure in oral group could be attributed to:

- More 1st pass metabolism of oral Misoprostol
- Less bio-availability of the drug
- Less direct access to uterine myometrium in case of oral administration

In five cases, even after 5 doses (maximum considered) of Misoprostol orally, there were minimal improvement in bishop's score even after 24 hours of induction. Hence, these cases were declared as failure of induction and were taken for emergency LSCS. However, the perinatal outcome of all the five cases was good. Most of the comparative studies of different routes of administration have not reported failed induction as a separate outcome of interest. Those who have reported it have shown oral groups to have more failure to induction.

Table 18: Failure of Induction, comparison with previous studies

Study/Year	Oral Group		Vaginal Group	
	No. of Cases	Failed Induction	No. of Cases	Failed Induction
Shetty A. *et al*, (March 2001)[4]	122	8 (6.7%)	123	3 (2.4%)
Uludag *et al*., 2005[6]	99	4%	99	2.5%
Sheikher C., (2009)[12]	30	5 (16.6%)	30	0
Komala *et al*., 2011[19]	86	6%	74	2%
Present Study	50	2 (4%)	50	1 (2%)

Mode of Delivery after Induction

In the oral group, 35 cases (70%) proceeded for unassisted vaginal delivery. Remaining 30% cases required assistance in terms of LSCS, vacuum and forceps. Of these, 6 (12%) required LSCS, 7 cases (14%) required vacuum extraction and

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remaining 2(4%) required Forceps delivery. In vaginal group, 40 (80%) cases proceeded to unassisted vaginal delivery and 6 (12%) cases required assistance in terms of vacuum and forceps. 4 cases (8%) required LSCS intervention. Majority of the assisted vaginal deliveries were meant to cut short the second stage of labour as these cases had meconium stained liquor. In a study by Sultana *et al*., 2006, only nulliparous women in oral group took longer time to deliver than vaginal group though it was not statistically significant and the mode of delivery also did not differ significantly similar to our findings [21]. There was no difference in the mode of delivery, analgesic requirements or neonatal outcomes in the two groups. According to Akhtar *et al*., 2010 [9] and Mehrotra *et al*., 2010 [9] there was no statistical difference between the groups with respect to mode of delivery and neonatal outcome. Jindal *et al*., 2011 [22] demonstrated that the overall incidence of vaginal births is significantly greater in vaginal group 47/52 vs. 38/51 than oral group (p=0.0462) however cesarean section rate was significantly more in oral group (25.49% vs. 9.62% p=0.0462).

Table 19: Mode of Delivery, comparison with previous studies

Study/Year	Oral group			Vaginal Group		
	No. of cases	Vaginal Delivery	C Section	No. of cases	Vaginal Delivery	C Section
Shetty A et al., March (2001)[4]	122			123	95(77.2%)	28(22.8%)
Iris *et al*., 2005[23]	93	NA	18(19.4%)	111	NA	36 (32.4%)
Rasheed R. *et al*, (2007)[7]	165	Reported to be similar to vaginal group	Reported to be similar to vaginal group	145	Reported to be similar to oral group	Reported to be similar to oral group
Abbassi R.M *et al*, (2008)[8]	40	32 (80%)	8 (20%)	40	38 (95%)	2 (5%)
Sheikher C. *et al*, (2009)[12]	30	17 (56.6%)	8 (26.6%)	30	26 (86.6%)	4 (13.3%)
Present Study	50	35 (70%)	6 (12%)	50	40 (80%)	4 (8%)

Indication for Emergency LSCS

In oral group, a total of 6 cases (12%) required emergency LSCS. Failed induction was the main reason for LSCS in oral group (3 cases, 50%) was failed induction, Of them, 17% (1 case) are due to DTA and 33% (2 cases) are due to thick meconium. In the vaginal group one DTA (25%) and 3 (75%) had thick MSAF. The difference in requirement of LSCS in two groups was statistically significant. Previous studies were contradictory to our findings [4,5]. Detailed breakup of reasons for emergency LSCS could not be obtained from previous studies.

Characteristic of Liquor

In the present study, in oral group, 80% of the cases had clear liquor. Of the remaining 10 cases, 6(12%) had thick MSAF and 4 (8%) had thin MSAF. In the vaginal group, 78% (39 cases) had clear liquor. Of the remaining 11, 6 cases (12%) had thin MSAF and remaining 5 cases (10%) had thick MSAF. Thin MSAF had no adverse effect on any of the neonates in both the groups.

In vaginal group, neonatal outcome was good in case of thin MSAF. In Vaginal group, all the 6 cases of thin MSAF had good neonatal outcome. All such cases delivered vaginally in which 3 required vacuum delivery and the rest 3 delivered unassisted. [9]

MSAF incidences in present study are more when compared with previous similar studies. It can be contributed to smaller body surface area and smaller BMI of the patients in south Asian population in which the study was conducted. Similar findings were reported by Khatri R. *et al* for a study conducted in Nepal [17]. This comparison shows that oral route is safer in terms of neonatal outcome on account of lesser number of MSAF and foetal distress.

Table 20: Characteristic of Liquor, comparison with previous studies

Study/ Year	Oral Group			Vaginal Group		
	No. of cases	Clear Liquor	Stained Meconium	No. of cases	Clear Liquor	Stained Meconium
Shetty A. *et al*, (March 2001)[4]	122		19 (13.4%)	123		16 (12.2%)
Wing A. D. *et al*, (2000)[24]	121		15 (12.4%)	113		15 (13.3%)

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Khatri R. et al,(2009)[17]	50	44 (88%)	6 (12%)	50	20 (40%)	30 (60%)
Present Study	50	40 (80%)	10 (20%)	50	39 (78%)	11 (22%)

Maternal Complication

Common side effects of Misoprostol for induction of labour are nausea, vomiting, watery diarrhoea, uterine cramps, uterine hyperstimulation, fever, tachycardia and chest pain. [16] In Oral group, a total of 1 (2%) cases developed some kind of maternal complication and had pyrexia while in vaginal group, maternal complication developed in 2 (4%) cases. Of these, 1 developed pyrexia and the other witnessed uterine hyperstimulation.

According to the findings of Sreelatha *et al*,2013, Maternal Effects Oral group 3(6%) had diarrhoea, 2(4%) fever, 3(6%) nausea and vomiting, 1(2%) shivering. Vaginal group had diarrhoea, 2(4%) fever, 3(5%) nausea & vomiting, 2(4%) shivering [13].

However, this finding was found to be statistically insignificant. There is a higher trend of maternal complication in vaginal route, which concerns the safety of this route as compared to oral group. Data available with the previous studies show no statistically significant differences in maternal outcome between oral and vaginal groups. However, there is a higher trend of maternal complication in vaginal group. Present study also indicates the same pattern and is consistent with previous studies.

Apgar score at 5 minutes

In oral group, no case resulted in Apgar score < 6 at 5 minutes and the vaginal group also did not have any such case. These differences were statistically insignificant (p = 0.375).

The one case in oral group was a forceps assisted vaginal delivery and the baby was admitted to NICU for respiratory distress. The birth weight of the neonate was 2.7 kg. Previous studies in conjunction with the present one show that there is no significant difference in neonatal outcome in terms of APGAR score between oral and vaginal administration.

Mesomeh Rezaie *et al*, 2016 demonstrated a statistical significant difference in First minute Apgar Score of the groups (p =0.0001). However, the Apgar score at 5 minutes there were no statistically significant differences between three groups (p=0.06).

Table 21: Apgar Score at 5 mins, comparison with previous studies

Study/Year	**Oral Group**		**Vaginal Group**	
	No. of cases	**No of cases with APGAR score <=6 at 5 min**	**No. of cases**	**No of cases with APGAR score <=6 at 5 min**
Shetty A. *et al*, (March 2001)[24]	122	0	123	0
Kwon S. J. et al, (2001)[25]	78	0	82	2 (2.4%)
Sheikher C. et al, (2009)[1]	30	1 (3.33%)	30	0
Present Study	50	0	50	0

Neonatal Outcome in terms of NICU admissions

In the present study, in oral 7 cases developed neonatal complications. Of these, 6 (86%) required NICU admission for pre term complication such as respiratory distress, low birth weight and 1 (14%) for Thick meconium aspiration syndrome.

In vaginal, 20% (10 cases) neonates had to be admitted to NICU. Of these 4 (40%) cases were admitted due to respiratory distress and low birth weight, 5 (50%) had meconium aspiration syndrome and 1(10%) was kept for observation. In previous studies NICU admissions were more because of associated comorbid condition of the neonate.

According to the findings of Sreelatha *et al*., 2013, 12(20%) had meconium aspiration in oral group and 11(22%) in vaginal group. NICU Admission 4(8%) required NICU admission in oral group and 5(10%) in vaginal group.

The findings of Uludag *et al*., 2005 reported no significant differences for intrapartum complications and neonatal

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outcomes between the oral and vaginal misoprostol groups (p>0.05) [6] According to Rasheed *et al*., 2007, a higher incidence of neonatal intensive care unit (NICU) admission in the vaginal group was mainly due to respiratory distress syndrome (RDS) [7].

In a study by Ratna khatri *et al* 2007 in Katmandu, transfers to NICU were statistically significant in oral and vaginal groups. In the oral misoprostol group 44 (88%) babies were directly given to mother, 6 (12%) babies were taken to NICU for stomach wash and observation but none of the babies had to be admitted. In the vaginal misoprostol group 28 (56%) babies were handed over to mother,20 (40%) babies were taken to NICU for stomach wash and observation out of which 2 (4%) cases had to be admitted in NICU [17].

CONCLUSION

The indication for induction of labour in present study was ranging between gestation age 34-40 weeks. The number of primigravidas was more compared to multigravidas in both the groups. The maximum number of doses required in oral group was 3 where as in vaginal group it was 2. Favourability of the cervix was ascertained using Bishop Score. Bishop Score improvement after 1st dose of Misoprostol was better in vaginal group and could be attributed to the direct action of Misoprostol on uterus and cervix in vaginal administration. Vaginal group required less Oxytocin augmentation for delivery. It is proved by pharmacokinetics that the peak onset of action and duration of action is more in vaginal route as compared to oral route, i.e. when Misoprostol is given by vaginal route, it remains in circulation for longer time, hence the Oxytotic effect is more prominent.

The mean induction to delivery interval was significantly shorter in vaginal group, the cause of which could be longer duration of action, no first pass metabolism and direct action of vaginal Misoprostol on uterus and cervix. The number of doses required for induction of labour was more in oral group. In vaginal group, all the cases which delivered vaginally, delivered in less than ours from the time of induction. Oral group witnessed three cases of failed induction, which was nil in the vaginal group.

Oral group witnessed more number of c-sections mainly because the failure of induction was more in oral group. Majority of the cases in vaginal group witnessed Thin MSAF. Maternal complications, such as Uterine Hyperstimulation were seen only in vaginal group. Emergency LSCS in oral group is mainly due to induction failure.Gastro-intestinal side effects were more in oral group, which could be attributed to more number of doses required for induction in this group. None of the neonates had APGAR score <6 at 5 minutes. In vaginal group, there were more cases of thin meconium-stained liquor, though it did not have much effect on neonatal outcome and seemed to be an insignificant finding. Neonatal complications were higher in the vaginal group than oral group. Cases of thick MSAF leading to NICU admission was higher in vaginal group compared to oral group.

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