



INDUCTION OF LABOR WITH LOADING ORAL MISOPROSTOL FOLLOWED BY MAINTENANCE VAGINAL MISOPROSTOL – A RANDOMIZED CONTROL STUDY

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ABSTRACT Since decades many trails for induction of labor have been done using different methods with different regimes to try to find the ideal induction regime which is both safe and effective. The present study was conducted among 126 participants who presented in the Department of Obstetrics & Gynecology, School of Medical Sciences & Research, Sharda University, Greater Noida. It was a randomized control trial conducted over the span of 2 years with the aim to evaluate the effectiveness and safety of loading oral misoprostol with maintenance vaginal misoprostol administration on induction of labor in nulliparous women. In the case group loading oral misoprostol followed maintenance vaginal misoprostol was given. In control group only vaginal misoprostol was given. Total number of doses given in case group is less than control group with significant p value. This shows that a lesser number of doses were required in case group for induction of labor, correlating with lesser duration from induction to first contraction, to active phase and to vaginal delivery in case group than control group. Oxytocin augmentation was similar in both case and control group. Total 80 participants achieved vaginal delivery and 46 participants had emergency caesarean section. Although p value between groups is not significant but proposed regime had lower caesarean rate. Maternal and fetal complication had insignificant difference between the two groups.

KEYWORDS : Labor, induction of labor, loading misoprostol, maintenance misoprostol

INTRODUCTION

The most crucial phase during pregnancy is labor. It starts with the onset of regular uterine contractions and ends with the fetal delivery and placental expulsion.¹

Induction of labor means artificial initiation of labor before its spontaneous onset. It is sometimes a life saving measure that is indicated in various situations to reduce maternal, perinatal and neonatal morbidities & mortalities. The aim of labor induction is to attain vaginal delivery which is safe for both mother and fetus. Induction of labor is considered till patient enters active phase (cervical dilatation=6cm) of labor.¹

Labor induction helps in reducing the increasing rates of caesarean section all over the world. It gives a choice against caesarean section in cases where there is a need for delivery of fetus before natural onset of labor due to maternal or fetal causes. Recent studies (ARRIVE trial) have shown that as compared to expectant management elective induction at 39 weeks are associated with lower caesarean rates.²

Labor induction rates have steadily raised in last two decades. Current incidence of induction of labor is 9.6% worldwide and about 10% in India.³

Induction of labor can be done by various methods. Methods could be mechanical or pharmacological. Mechanical methods like balloon catheter, artificial rupture of membranes (ARM). It can also be done using various drugs like oxytocin, dinoprostone. One such wonder drug for induction of labor is synthetic PGE₂ analogue, Misoprostol.

Misoprostol is a prostaglandin E₁ analogue. As it is a prostaglandin analogue, it also has an effect on uterine contractions but for long it was not used by obstetrician due to fear of having strong contractile effect on uterus. Many trials till 1999 have been conducted to see its effectiveness in induction of labor in viable pregnancies through various routes which showed that misoprostol can be used for labor induction in viable pregnancy. Following that various trials have been done using different route and different dose of misoprostol for induction of labor. Although approval is not given by FDA and Government of India but still it's been recommended by various institution for use in labor induction^{4,5}.

Misoprostol has effects on cervical ripening and stimulation of uterine contraction which helps in induction of labor. Induction with Misoprostol is highly effective and safe with minimal side effects. It is

heat stable, cost effective and user friendly.

It can be used through various routes like oral, vaginal, sublingual, buccal and rectal. Each route has its own pharmacokinetics and acts differently. Different routes and regime have been studied to find out most suitable regime for induction of labor.

The regime of loading oral misoprostol is based on pharmacokinetics of oral route of misoprostol that after oral misoprostol uterine tone increases rapidly due to high and faster plasma peak levels but are not followed by sustained uterine contractions due to rapid fall in plasma levels. For sustained uterine contractions maintenance vaginal misoprostol dose is added. After vaginal misoprostol uterine tone increases slowly due slow and slightly lower plasma peak levels but have sustained uterine contraction for long time due to slower decline of plasma levels⁹⁻¹². Therefore, in this study oral misoprostol is given for rapid peak plasma values for start of initial contraction and vaginal misoprostol is given for sustained contractions.

Till date, only comparative studies between different routes and combination of mechanical method with one route of misoprostol are available. This study being unique as it is going to be the first of its kind, which has combined two different routes of misoprostol that is loading dose 50microgram (mcg) of oral misoprostol followed by maintenance dose of 25mcg of vaginal misoprostol to achieve induction of labor. This was studied by comparing the effectiveness, safety and efficacy of the proposed regimen with conventional regimen of 25mcg of vaginal misoprostol.

AIM

To evaluate the effectiveness and safety of loading oral misoprostol with maintenance vaginal misoprostol administration on induction of labor

MATERIALS AND METHOD

This study was conducted in Department of Obstetrics and Gynecology of Sharda hospital Greater Noida. It is Randomized control study with 126 participants done from Nov 2020 till Nov 2022. The participants were recruited from the Labor Room and OPD. A total of 126 subjects were taken who were randomly divided into 2 groups of 63 each. Half of the subjects were taken under case group and other half under control group.

Inclusion Criteria

- Nulliparity

- POG ≥ 39 weeks of gestation with no associated complication
- POG ≥ 34 weeks of gestation with appropriate indication for termination of pregnancy
- Singleton pregnancy
- Cephalic presentation
- Assuring fetal heart rate pattern
- Intact membranes
- Adequate pelvis

Exclusion Criteria

- Multiparity
- Gestational age < 34 weeks
- Multiple pregnancies
- H/O any uterine surgery
- Any known hypersensitivity to misoprostol
- Non reassuring NST
- Ruptured membranes (PROM) & Chorioamnionitis
- Mal-presentation
- Patient refusal
- Any other obstetrical, gynecological and medical contradiction to vaginal delivery

After taking informed consent from patients and ethical clearance from Ethical committee.

Initial Assessment Of Patients At Time Of Recruitment

- Detailed history
- Complete antenatal examination and investigation
- Pelvic assessment
- Non-Stress Test at the time of Admission

If the patient fulfils all the inclusion criteria after initial assessment, then she was considered for the study and will be managed in labor room. After taking the consent, patients were assigned to group (study group or control group) by opening a sequentially numbered opaque envelope only at time of induction. Envelopes contained the group (study group or control group) which prepared by staff not associated with this study using computer generated random number tables.

Pelvic examination was done and Modified Bishop scoring was given just prior to induction. Following this misoprostol was given according to assigned regimen (Figure 1).

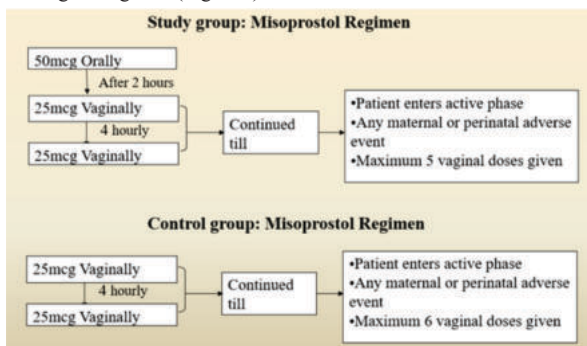


Figure 1: Misoprostol Regimen In Study And Control Group

All patients were monitored by continuous electronic monitoring of fetal heart rate and uterine contractions. Labor was monitored with WHO Partogram 2000. Next dose was given only after assessing uterine contraction and pelvic examination. After entering active phase of labor those patients requiring oxytocin were given oxytocin only after 4 hours of last dose of misoprostol given to the patient.

Mode of delivery (vaginal/instrumental/caesarean) was noted. New born assessment was done by APGAR score and admission to NICU. Any maternal or fetal complication was noted down.

All the demographic data between two groups is included and compared. Data entry is done with case group as group A and control group as group B. Data analyser is blinded. Data analysis is done according to descriptive statics. Statistically significant p value is less than 0.5.

RESULT

All of the participants were given at least 1 dose of their allotted regime and none of the participants withdraw their consent during the study. Demographic data between two groups is given in Table 1.

Table 1: Demographic Distribution Among The Study Groups

Variable	Case		Control		p value
	N	%	N	%	
Age					0.38
19-20	9	14.29	7	11.11	
21-25	36	57.14	43	68.25	
26-30	14	22.22	40	15.87	
>30	4	6.35	3	4.76	
Mean $\pm$ SD	24.02 $\pm$ 3.27		23.87 $\pm$ 2.91		
Gravida					0.82
Primigravida	55	87.30	58	92.06	
History of previous abortion	8	12.7	5	7.94	
Period of gestation					0.35
37-39	35	55.56	40	63.49	
39-41	26	41.34	21	33.41	
>41	2	3.1	2	3.1	
Mean $\pm$ SD	39.12 $\pm$ 2.16		39.13 $\pm$ 1.23		
Residence					0.85
Urban	23	36.5	22	34.9	
Rural	40	63.5	41	65.1	
Religion					0.78
Hindu	49	77.78	46	73.02	
Muslim	14	22.22	17	26.98	
Socio-economic status					0.52
Lower	60	95.2	63	100	
Lower middle	3	4.8	0	0	
Booked	48	76.2	37	58.7	0.036*
Unbooked	15	23.8	26	41.3	
High risk pregnancy					
GDM	2	3.2	1	1.6	0.55
HDP	8	12.7	8	12.7	1
Hypothyroidism	5	7.9	1	1.6	0.94
IHCP	5	7.9	13	20.6	0.041*
Oligohydramnios	4	6.3	1	1.6	0.17
Rh neg	3	4.8	6	9.5	0.29
Total	28	44.4	20	31.7	
Indications					
Elective	34	53.9	29	46	0.37
GDM	2	3.2	1	1.6	0.55
HDP	8	12.7	8	12.7	1
IHCP	5	7.9	13	20.6	0.041*
Oligohydramnios	4	6.3	1	1.6	0.17
Post dated	10	15.9	11	17.5	0.81

*: statistically significant

Some of the participants had some other medical or obstetrical conditions due to which their pregnancies were high risk. Most common condition was intrahepatic cholestasis of pregnancy (IHCP) with significant p value.

Elective induction at 39 weeks was the most common indication in the study with total of 63 participants (50%). p value between both group is insignificant.

Before giving the first dose of designated induction regimen all the participants were examined (Table 2). At start of induction on abdominal examination uterine tone and fetal head position was noted down. On vaginal examination modified bishop score was calculated. Mean modified Bishop score is 3.73 in case group and 3.75 in control group. p value between two groups is 0.96 which is insignificant.

Table 2: Pre Induction Evaluation

Variable	Case		Control		p value
	N	%	N	%	
Uterine tone					0.33
Irritable	8	12.7	12	19	
Relaxed	55	87.3	51	81	
Head Position					0.34
2/5	4	6.35	3	4.76	
3/5	49	77.78	55	87.30	
4/5	10	15.87	5	7.94	

Modified bishop score					
1-5	47	25.40	51	19.06	0.96
>5	16	74.60	12	80.94	
Mean with SD	3.73	1.79	3.75	1.50	

Peripartum outcomes is given in Table 3. Total number of doses given in case group is 3.87 whereas in control group it is 4.41. p value between 2 group is 0.037 which is significant. This shows that a lesser number of doses were required in case group as compared to control group for induction of labor. Oxytocin requirement between two groups have not significant p value of 0.58.

Table 3: Peripartum Outcomes

Variable	Case		Control		p value
	Mean	SD	Mean	SD	
Total Dose	3.87	1.26	4.41	1.59	0.037*
Oxytocin use					0.58
No	46	73	49	77.8	
Yes	17	27	14	22.2	
Mode of delivery					0.26
Caesarean section	20	31.7	26	41.2	
Vacuum	3	4.8	0	0	
Delivery					
Vaginal	40	63.5	37	58.7	
Delivery					
Time duration (hours)					
Duration from induction to first contraction	5.77	4.83	6.48	3.63	0.17
Duration from induction to active phase	12.02	7.47	12.44	6.17	0.76
Duration from induction to vaginal delivery	14.74	8.06	15.16	6.56	0.63
APGAR Score at 5 min					
5-7	13	20.6	12	19	0.82
8-9	50	79.4	51	81	0.57
Mean $\pm$ SD	8.1 $\pm$ 1.97		8.4 $\pm$ 1.74		

*: statistically significant

Total 80 (63.4%) participants had vaginal delivery. Out of 80 vaginal deliveries 3 were vacuum assisted delivery. All 3 vacuum assisted delivery were seen in case group. Total 46 (36.5%) had delivery by caesarean section. In case group 40 participants had vaginal delivery, 3 participants had vacuum assisted delivery and 20 participants had caesarean section. In control group 37 participants had vaginal delivery and 26 participants had caesarean section. p value (0.26) between 2 groups is insignificant.

Indication for the caesarean section done is listed in Table 4. Overall, fetal distress was the most common indication for caesarean section. p value between 2 groups is not significant in all the indication.

Table 4: Indication For Caesarean Section Among The Study Groups

Indications	Case		Control		p value
	N	%	N	%	
NPOL	1	1.6	2	3.2	0.56
Failed Induction	5	7.9	10	15.9	0.17
MSL with poor bishop score	4	6.3	2	3.17	0.40
Fetal Distress	10	15.9	12	19	0.63

Average duration from first dose of assigned regime till first contraction perceived by the patient, till active phase and till delivery is given in Table 3. Although the p value between groups is not significant but in the case group it has taken less time as compared to control group.

Average baby weight in case group was 2.89kg and control group was 2.78kg with p value of 0.14. Mean APGAR score of case group was 8.1 and of control group was 8.4 with p value of 0.57.

Maternal and fetal complications are listed in Table 5. No participants had tachysystole or uterine rupture. Failed induction was seen in 5 participants in case group and 10 participants in control group. p value between groups is insignificant. Meconium staining of liquor and fetal distress due to fetal hypoxia between two groups had insignificant p value. NICU admission after delivery also had insignificant p value of 0.54. No fetal or neonatal death is seen in this study.

Table 5: Maternal And Fetal Complication Among The Study Groups

Outcome	Case		Control		p value
	N	%	N	%	
Tachysystole	0	0	0	0	1
Tocolytic use	0	0	0	0	1
Uterine rupture	0	0	0	0	1
NPOL	1	1.6	2	3.2	0.56
Failed Induction	5	7.9	10	15.9	0.17
MSL	10	15.9	8	12.7	0.61
Fetal Hypoxia	10	15.9	12	19	0.63
Fetal Death	0	0	0	0	1
NICU admission	15	23.8	18	28.5	0.54

DISCUSSION

This is a novel randomized control study done in single centre over the span of two years combining two routes of misoprostol for labor induction in nulliparous women. As no study using loading oral misoprostol and maintenance vaginal misoprostol has been done before so there is no data to compare the result of this study.

Total dose given in case group is lesser than the total dose given in control group with statistically significant p value which means lesser number of doses of proposed regime is required for labor induction as compared to control group regime. This correlates with lesser duration from induction to first contraction lesser duration, to active phase and to vaginal delivery in case group than control group although the p value is not significant. This is due to faster action of oral misoprostol which is added in case group as compared to control group. In randomized control trial by David C Young et al comparing misoprostol by oral and vaginal route for labor induction, mean duration from induction to vaginal delivery in oral misoprostol was 22.6 hours and in vaginal misoprostol was 25.5 hours which shows that with oral misoprostol vaginal delivery is achieved faster than with vaginal misoprostol¹³. This result correlates with current study where group with additional oral misoprostol has lower induction delivery interval as compared to only vaginal group.

After ARRIVE trial elective induction at 39 weeks is preferred in pregnancies to reduce maternal and neonatal morbidities and caesarean section rates². Hence in this study, labor induction was most commonly done electively in around 50% of participants.

Total 80 participants (63.4%) achieved vaginal delivery and 46 participants (36.5%) had emergency caesarean section. Although p value between groups is not significant but proposed regime had lower caesarean rate.

Fetal distress was the most common indication for caesarean section. Although p value of failed induction between two group is not statically significant but number of participants is double in control group as compared with case group. This indicates that proposed regime of loading misoprostol by oral route with maintenance misoprostol by vaginal route is more effective in inducing labor than only misoprostol by vaginal route.

In current study meconium-stained liquor was seen more in case group (15.8%) than in control group (12.6%), it could be due to the effect of misoprostol of increased gut motility. It is more seen after oral misoprostol than vaginal misoprostol due to higher plasma levels after oral misoprostol than vaginal misoprostol¹⁴. In Cochrane review in 2015 on oral misoprostol for labor induction similar results of meconium-stained liquor after oral misoprostol as compared with vaginal misoprostol was seen¹⁴. In trial by David C young et al meconium-stained liquor was seen 22.2% in oral misoprostol group and 22.7% in vaginal misoprostol group which is higher than the current study result¹³.

In trial by David C young et al oxytocin use was more in group in which oral misoprostol was given (70%) than group in which vaginal

misoprostol was given (57%)¹³. In current study oxytocin use was seen in 27% in case and 22.2% in control group which is much lower than the trial¹³. This could be due to the use of epidural analgesia which was not used in current study but was given in study by David C young. Use of epidural analgesia during labor increases need for oxytocin use as patient is not able to bear down properly¹. In current study use of oxytocin was seen more in case group as compared to control group, this finding correlates with findings of trial.

In trial by David C Young et al tachysystole was seen in 21.7% in oral misoprostol group and 29.8% in vaginal misoprostol group and tachysystole with fetal heart changes was seen in 4.8% oral misoprostol group and 9.4% in vaginal misoprostol group¹³. This result is completely different from current study as no cases of tachysystole or hyperstimulation is seen in current study. This could be due to smaller sample size in current study as compared to randomized control trial.

LIMITATION

Triple blinded studies are the best type of study as they are free of any type of bias. This study is not a blinded study; hence they are chances of observer bias and reporting bias.

As only nulliparous women are included in this study and the labor graph of both nulliparous and multiparous women are different, the universal nature of proposed regime cannot be commented upon.

Sample size of current study is a smaller size to comment about the universal application of proposed regime.

CONCLUSION

The proposed regime of loading oral misoprostol 50 micrograms followed by maintenance vaginal misoprostol of 25 micrograms requires lesser number of doses than only vaginal misoprostol 25 micrograms regime for induction of labor with statistically significant result. Duration interval from induction to first contraction, from induction to active phase and from induction to delivery is lesser in proposed regime.

Proposed regime had higher vaginal delivery rates with lower caesarean rate. Other maternal and neonatal complication were similar in both proposed and control regime. The proposed regime is seeming to be efficient in labor induction in nulliparous women with comparable safety with already available regime.

Due to smaller sample size, non-blinded study and exclusion of multiparous more studies with proposed regime can be done in future.

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