

## PROSPECTIVE STUDY COMPARING EFFECTIVENESS OF SINGLE AND MULTIPLE DOSE 25 MICROGRAMS INTRAVAGINAL MISOPROSTOL FOR INDUCTION OF LABOUR AT TERM

Arati Achamma IPE<sup>1</sup>, Anoj Kattukaran<sup>2</sup>

<sup>1</sup>Senior Resident, Department of Obstetrics & Gynaecology, Amala Institute of Medical Sciences, Thrissur.

<sup>2</sup>Professor, Department of Obstetrics & Gynaecology, Amala Institute of Medical Sciences, Thrissur.

### ABSTRACT

#### OBJECTIVES/PURPOSE

To compare two dosing regimens of the same 25 mcg misoprostol with respect to Induction delivery interval, successful vaginal delivery and its associated maternal and neonatal outcomes.

#### METHODS

Prospective study was conducted among 300 low risk pregnant patients at 40 weeks' gestation, attending labour room in the Dept. of OBG, Amala Institute of Medical sciences, comparing, A-single dose 25 mcg misoprostol in 24 hours Vs. B-multiple dose 25 mcg misoprostol (4 hourly up to 3 doses) intravaginally for its effectiveness.

#### RESULTS

Statistically significant difference was obtained in the number of deliveries within 24 hours in group A and B (36.6% Vs. 63.4% with p value 0.002). The induction delivery interval between primigravidae and multigravidae were statistically significant (12.5  $\pm$  3.9 Vs 11.08  $\pm$  4.3 with p value 0.035) but not significant between groups A and B. There was no statistical difference in other maternal and neonatal outcomes. Incidence of MSL and foetal distress were higher in primigravidae after single dose itself. Serious adverse outcomes like MAS, NND, APGAR <7 at one minute and uterine rupture were not encountered in this study.

#### CONCLUSION

Around 65% of women delivered with a single dose of misoprostol in 24 hours. Most multigravidae delivered vaginally with a single dose in 24 hours. It appears that in multigravidae a single dose induction is adequate; however, in primigravidae multiple doses of 25 mcg misoprostol is best to achieve delivery within 24 hours.

#### KEYWORDS

Induction of Labour, Misoprostol, Induction Delivery Interval.

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**INTRODUCTION:** More than 22.5% of all gravid women undergo induction of labour.<sup>(1)</sup> Since time immemorial man has tried to induce labour with various mechanical and pharmacological methods. As the effectiveness of the agents grew, the pendulum shifted to the other side leading to more reasons and indications for labour induction.

A considerable amount of research has been directed towards the ideal dose and route of misoprostol which is safest and most effective for induction. But the controversy still continues and different protocols of misoprostol are practised in different parts of the world and it is logical since one particular regimen may not be appropriate for women of all population.

A retrospective study done at Amala Institute of Medical Sciences, analysing data over last eight years showed that 80% women delivered with single dose misoprostol. This study is an effort to compare two dosing regimens of the same 25 mcg misoprostol with respect to induction delivery interval, successful vaginal delivery and its associated maternal and neonatal outcomes.

**METHODS:** A prospective study was conducted from Jan 2012 to June 2013 (18 months), among 300 low risk pregnant patients at 40 weeks' gestation attending our labour room at Dept. of OBG, Amala Institute of Medical sciences, comparing the effectiveness and outcomes of two dosing regimens of same 25 mcg misoprostol for induction of labour at term. An informed consent was taken from all 300 subjects included in the study after explaining the indication, agent and method used for induction and the possible need for repeat induction and LSCS (caesarean section). Only women meeting the following criteria were included in the study.

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*Corresponding Author:*  
 Dr. Arati Achamma IPE,  
 Department of Obstetrics & Gynaecology,  
 Rajagiri Hospital, Alwaye.  
 E-mail: aarthiipe@gmail.com  
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**Inclusion Criteria:**

1. Singleton live pregnancies.
2. Primigravida/Multigravida (G2P1L1).
3. Term gestation/40 weeks.
4. Cephalic presentation.
5. Bishop's score  $\leq$  6.
6. Absence of uterine contractions.

All high risk cases including maternal medical conditions, foetal compromise, premature rupture of membranes and multigravidae who have delivered more than once were excluded from the study.

**The subjects included were equally divided into two groups as follows:**

**Group A:** Received 25 mcg single dose intravaginal misoprostol once in 24 hours. If required two more doses were repeated 24 hourly.

**Group B:** Received multiple dose 25 mcg intravaginal misoprostol every four hours for a maximum of three doses if required, on the same day.

A thorough history and clinical examination followed by per vaginal examination to assess the Bishop's score and pelvis was done and NST (Nonstress test) was recorded prior to induction.

The patient was reassessed four hours after initial dose. And if necessary, further doses were repeated at four-hour intervals for maximum three doses in group B and after 24 hours for the next two days in group A. Further doses were withheld if subject started having uterine contractions or leaking per vaginam. Those patients who went into labour were monitored in labour room for uterine contractions and FHR (Foetal heart rate). ARM (Artificial rupture of membranes) was done in active labour and partogram was maintained. Oxytocin augmentation was started at least four hours after the last dose of misoprostol in cases with unsatisfactory progress of labour irrespective of the groups.

The management of uterine tachysystole and abnormal CTG (Cardiotocograph) tracing includes maternal repositioning, oxygen supplementation, discontinuation of oxytocin (If any). In case of persistent tachysystole or FHR abnormalities caesarean section was done. Induction was considered to have failed if cervix remains unfavourable or having no contractions even after three doses in both groups. Delivery by LSCS was proceeded in case of failed induction and any other obstetric indications.

Any patient refusing further doses when indicated were excluded from the study.

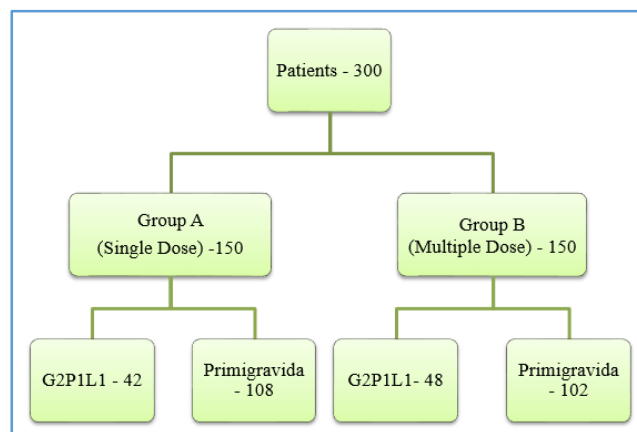
**The primary outcome measured was Induction delivery interval. The secondary outcomes were; Percentage of successful vaginal delivery within 24 hours:**

1. Percentage of successful cervical ripening (favourable Bishop's score) with single dose.
2. Uterine hyperstimulation/tachysystole.
3. Uterine rupture.
4. Failed induction.

5. Mode of delivery-vaginal/ abdominal.
6. PPH (Postpartum haemorrhage).
7. MSL (Meconium staining of liquor).
8. Foetal distress.
9. MAS (Meconium aspiration syndrome).
10. APGAR $<$ 7 at one minute.
11. NND (Neonatal death).

**STATISTICAL ANALYSIS:** Analysis was done using Spss software. To verify the statistical difference between the groups, the chi-square and student t test were used respectively for categorical or continuous variables.

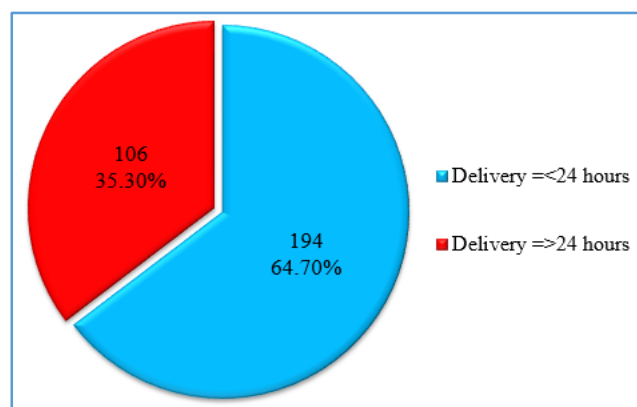
**RESULTS:** Out of total 300 subjects, there were 210 primigravidae and 90 multigravidae in both groups. (Fig. 1)



**Fig. 1**

There were no dropouts and no woman discontinued for any reason after enrolment to the study.

194(64.70%) delivered within 24 hours of induction in both groups. (Fig. 2). In that only 36.60% (71) belonged to Group A and the majority 63.40% (123) was in Group B. This is found to be statistically significant as the p value is 0.002. (Table. 1). Out of 71 patients in group A, 62% (44) were primigravida and 38% (27) were multigravida. Similarly, out of 123 patients in Group B 63.40% (78) were primigravida and 36.6% (45) were multigravida.



**Fig. 2**

Group	Multigravida		Primigravida		Total
	Number	Percentage	Number	Percentage	
A	27	38%	44	62%	71
	37.5%		36.1%		36.6%
B	45	36.6%	78	63.4%	123
	62.5%		63.9%		63.4%
Total	72	37.1%	122	62.9%	194
	100%		100%		100%

**Table 1: Delivery within 24 hours on the Basis of Group in Multigravida and Primigravida**

Among 90 multigravidae, 72 (80%) have delivered within 24 hours in both groups. But only 122 (58%) out of 210 primigravidae delivered within 24 hours. Even though the numbers seem to be relevant this was not found to be statistically significant (0.962). Probably because of confounding factors due to higher number of primigravidae in the study.

The induction delivery interval between primigravidae and multigravidae was found to be statistically different as expected.  $12.52 \pm 3.98$  Vs  $11.08 \pm 4.39$  with p value 0.035. (Table. 2).

	No. of Patients	Mean	Std. Deviation	Std. Error Mean
Multigravida	71	11.0813	4.39777	0.52192
Primigravida	80	12.5299	3.98041	0.44502

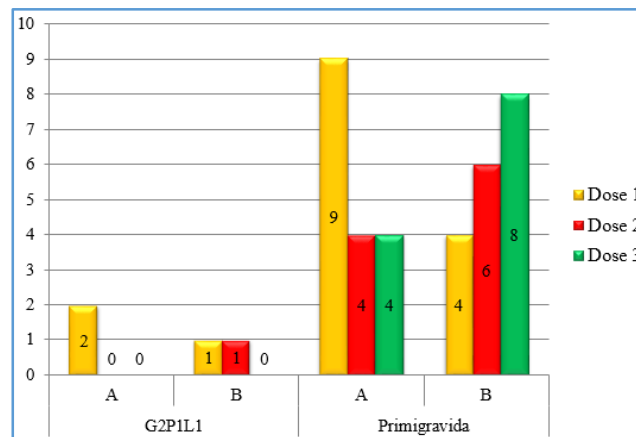
**Table 2: Induction Delivery Interval According to Parity**

After excluding the women who had caesarean section, induction to vaginal delivery interval in the two groups were compared. The induction delivery interval did not significantly differ between single (A) and multiple dose (B).  $12.22 \pm 4.0$  hrs. Vs  $11.7 \pm 4.6$  hours with p value 0.41.

Those who had not gone into active labour even after 3 doses, were considered as failed induction. Of the total, 20 (6.70%) had failed induction. 45% (9) in Group A and 55% (11) in Group B. These findings did not appear to be statistically significant. All failed induction occurred in primigravida and none in multigravida.

78 subjects from the study underwent caesarean section which forms 26% of the total. Majority of the cases were in primigravida 97.4% (76). Only two multigravidae underwent caesarean and that too in Group A. The caesarean rate is not found to be statistically significant. Among the indications for CS, most were done for MSL (31) followed by failed induction (20) and foetal distress (11).

39 (13%) were found to have MSL. 19 in group A and 20 in Group B which was statistically not significant. The grade of meconium was not assessed. Interestingly most cases occurred after the first dose itself in Group A, 11 out of 19 (57.9%). Majority were in primigravida, 9 out of 11. Only two multigravida cases were found to have MSL. Not much difference was observed in the dose wise incidence of MSL in Group B. (Fig. 3).



**Fig. 3: Dose wise Incidence of Meconium Stained Liquor**

There were 14(4.7%) cases of foetal distress, and all were in primigravidae. No cases of foetal distress occurred in multigravidae. 11 had caesarean section for foetal distress. Group A had 9 cases 64.3% and Group B had 5 cases 35.7%. Four cases were associated with MSL and one with Tachysystole.

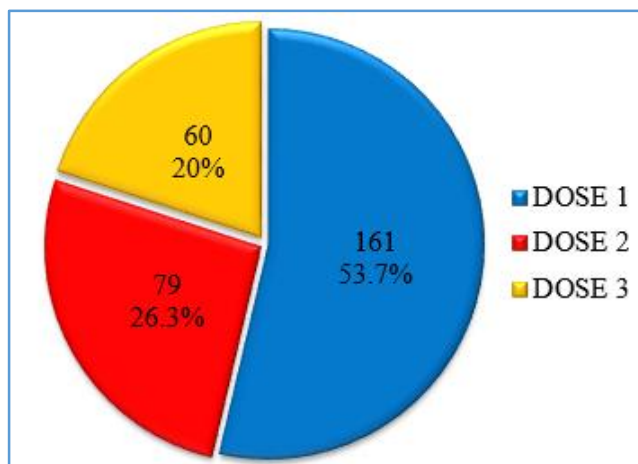
There was only one case of Tachysystole/Hyperstimulation which occurred in a primigravida of group A. There were only 3 cases (1%) of PPH and all occurred among primigravidae in single dose Group A.

**The following outcomes were not encountered in this study;**

- MAS.
- NND.
- APGAR < 7 at one minute.
- Uterine rupture.

Larger studies are needed to assess rare adverse events such as those mentioned above including PPH and tachysystole.

53.7% needed only one dose for cervical ripening. Cervix is considered to have ripened when the Bishop score is equal to or more than six. (Fig. 4)



**Fig. 4: Dose for Cervical Ripening**

**DISCUSSION:** Statistically significant difference was found in the number of patients delivered within 24 hours with single and multiple dose. It appears that for primigravidae multiple doses of 25 mcg misoprostol are needed to achieve substantial rate of vaginal delivery in 24 hours while for multigravidae single dose 25 mcg seemed appropriate.

But the mean Induction Delivery Interval in those who had delivered vaginally within 24 hours was not statistically significant. The mean induction delivery interval obtained is similar to that in various studies using misoprostol which ranges from 9 - 14 hours. Fatemah V et al compared 25 mcg misoprostol with Foley catheter and reported shorter delivery interval for misoprostol group which was  $11.08 \pm 5.6$  hrs. Vs  $13.6 \pm 16.9$  hours.<sup>(2)</sup> The shorter intervals obtained in this study could be attributed to low body weight and body surface area of our patients than those in western countries. Looking at some of the Indian studies, Nigam A et al compared 25 and 50 mcg misoprostol for induction and got no significant difference in induction delivery interval  $12.52 \pm 7.05$  Vs.  $11.72 \pm 6.74$  hours. Also the rate of vaginal delivery within 24 hours was found to be similar between the two groups 83.3% Vs. 71.6% (p value > 0.0).<sup>(3)</sup>

Chander Sheikar et al compared 50 mcg oral and 25 mcg vaginal misoprostol with intracervical Foleys. They reported shortest induction delivery interval with 25 mcg vaginal PGE1 10.35 hours. It was concluded that prolonged interval has adverse effect on labour outcome resulting in higher Caesarean section and failed induction.<sup>(4)</sup> With regards to outcome 86.6% had successful vaginal delivery.

The variability in criteria for the definition of failed induction is evident even in randomised trials depending upon the inducing agent. In this study, only primigravidae had failed induction probably those who are unlikely to

respond even with higher or more number of doses and needed caesarean section anyway.

Among the adverse foetal outcomes, foetal distress and meconium stained liquor was observed more commonly among primigravidae belonging to single dose groups after the first dose itself though not statistically significant.

In the systemic reviews by Hofmeyr GJ and Gulmezoglu AM,<sup>(5)</sup> the occurrence of complications does appear to be dose dependent. But contrary to the common expectations the dose wise statistics proved majority cases of foetal distress occurred after the single dose itself, six out of nine in Group A 66.67%. But this did not have a similar adverse effect in the neonatal outcome.

Rather than the number of doses it appears that the exposure and duration of exposure to misoprostol is associated with more adverse events; more often in primigravidae. Probably attributable to their longer induction delivery interval than multigravidae, but larger studies are required to prove the same.

**CONCLUSION:** Around 65% delivered with a single dose of misoprostol in 24 hours. Most multigravidae delivered vaginally with a single dose in 24 hours. It is noted that in multigravidae, a single dose induction is adequate; however, in primigravidae, multiple doses of misoprostol is best to achieve delivery within 24 hours.

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