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Indian Journal of Obstetrics and Gynecology Research

Journal homepage: www.ijogr.org

Original Research Article

A comparative interventional study on fixed-dose versus titrated- dose oral misoprostol solution for induction of labour at term gestation in a tertiary care centre of Eastern Uttar Pradesh

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ARTICLE INFO

Article history:
Received 03-12-2023
Accepted 03-02-2023
Available online 11-05-2024

Keywords:
Fixed- dose oral misoprostol
Titrated- dose oral misoprostol
Induction of labour
Modified Bishop's score

ABSTRACT

Background: Induction of labor entails the deliberate initiation of uterine contractions before the spontaneous onset of labor, irrespective of whether the amniotic membranes have ruptured or not. The Modified Bishop's score of six or higher indicates that the cervix is ripe, or "favorable" – when there is a high likelihood of spontaneous labor or responsiveness to interventions designed to induce labor. Misoprostol being cost-effective, easily available and stable at room temperature makes itself a promising agent in future for induction of labour if the feto-maternal safety concerns are proved with evidence. The aim of our study was to compare the efficacy of titrated versus fixed dose oral misoprostol solution regimen as inducing agents and the effects on fetomaternal outcome.

Materials and Methods: A comparative interventional study was conducted for one year and study population consisted of term pregnant women admitted to the labour room of the hospital. A total sample size of 150 was deemed necessary, with 75 participants required per group. Following allocation into groups, induction of labor was carried out using either oral titrated-dose misoprostol solution or fixeddose misoprostol solution.

Result: Successful induction of labour was higher in fixed -dose group (Group F) (80%) as compared to 65.53% in titrated-dose group (Group T), the difference was statistically significant (p=0.0439). The need for augmentation was lower in group F (30.67%) than in group T (56%). Statistically, this difference was significant (p = 0.0017). Uterine hyper stimulation and atonic post-partum haemorrhage were noted more in group T but this difference was not significant (p = 0.1461; p = 0.3108). Requirement of newborn resuscitation was observed higher in group T [34 (45.34%)] than group F [16(21.33%)]. Statistically, this difference was significant [p=0.0081]. NICU admissions were more in group T (21.34%) than group F (13.33%), but difference was not significant (p = 0.0574).

Conclusion: This study concludes that both fixed- dose and titrated-dose oral misoprostol solution regimens are effective in induction of labour but fixed-dose regimen has an advantage of less mean total dose of misoprostol administered, reduced induction to delivery interval, less uterine hyperstimulation, atonic postpartum hemorrhage and better fetomaternal and neonatal safety profile.

1. Introduction

Induction of labor refers to the deliberate initiation of uterine contractions (after the period of viability) prior to the natural onset of labor for the purpose of vaginal

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https://doi.org/10.18231/j.ijogr.2024.049

delivery of fetus.[1] Multiple feto-maternal and obstetric indications require labor induction, common indications being premature rupture of membranes, hypertensive disorders of pregnancy, intrauterine fetal growth restriction, oligohydramnios, post-term pregnancy and certain maternal medical conditions such as diabetes & cholestasis of pregnancy. Conversely, contraindications for labour induction include cephalopelvic disproportion, abnormally implanted placenta, fetal macrosomia, malpresentation, and non-reassuring fetal heart rate.[2] The Modified Bishop's score is a collection of metrics based on the station, dilation, effacement (or length), location, and consistency of the cervix that are obtained during a vaginal examination. A score of six or higher indicates that the cervix is ripe, or "favourable" - when there is a high likelihood of spontaneous labour or responsiveness to interventions designed to induce labour.[3] Various techniques are available for labor induction, encompassing mechanical methods such as Foley's catheter, pharmacological methods involving oxytocin and prostaglandins (such as misoprostol and dinoprostone), as well as procedures like amniotomy or stripping of membranes.

Misoprostol, an analog of prostaglandin E1, is frequently employed for labor induction. American college of obstetrics and gynaecology (2003) states that off – level use of misoprostol for cervical ripening is safe and effective. Its advantage over PGE2 preparations being stability at room temperature and low- cost. It can be administered through diverse oral, vaginal, sublingual, buccal, and rectal routes. The pharmacokinetic properties of each route exhibit variability. Oral administration facilitates rapid and nearly complete absorption from the gastrointestinal tract, with peak concentration attained in approximately 30 minutes.[4–7] Vaginal administration yields gradual absorption, reaching the highest concentration after 70-80 minutes. Sublingual administration features the shortest time to peak concentration, highest peak concentration, and greatest absorption. Buccal administration manifests absorption patterns akin to vaginal administration, albeit with lower serum drug levels. Rectal administration showcases a comparable absorption curve to vaginal administration, albeit with a reduced area under the curve.[8] Each route presents distinct advantages and considerations, necessitating further research to compare their efficacy. Misoprostol can also be administered to nursing mothers; however, its concentration in breast milk amounts to only one-third of that found in plasma.[9] The consequences of brief exposure to low levels of misoprostol on the fetus remain unknown. Misoprostol's uterotonic and cervical-softening effects are deemed therapeutic in obstetrics and gynecology.[10–12] Vaginal administration of misoprostol has demonstrated higher efficacy to oral administration in inducing uterine contractions.[13,14]

Our study aimed to compare the efficacy and safety of titrated versus fixed dose oral misoprostol solution for induction of labor. The primary objective was to determine which approach was more effective in initiating labor. Safety assessments focussed on the well-being of pregnant women and their foetuses. A secondary objective was to compare the rate of vaginal deliveries within 24 hours of administration. The study intended to provide a piece of evidence for obstetric practice in selecting the more effective and safer approach of oral misoprostol induction.

2. Materials and Methods

This comparative interventional study was conducted in Labor Room of the Department of Obstetrics and Gynecology at Nehru hospital, Baba Raghav Das Medical College in Gorakhpur, Uttar Pradesh from 01 /07/2021 to 30/06/2022. The study included pregnant women at term who were admitted to the department, required labour induction, met the inclusion criteria and gave the consent. Inclusion criteria were women at term gestation, singleton pregnancy with cephalic presentation with unfavorable cervix (Modified Bishop's score 6 or less) and requiring induction of labour for either fetomaternal or obstetric indications. Exclusion criteria were contraindications to vaginal delivery, hypersensitivity to misoprostol and active labour.

Misoprostol 200 mcg tablet was dissolved in 200 ml of drinking water (constituting 1mcg of misoprostol in 1 ml solution) and then solution was used in 24 hrs.

In fixed- dose regimen, Induction was started with 25 ml of oral solution (25 mcg of drug) repeated 2 hourly till regular uterine contractions started or for 24 hours maximum. So a total of 12 doses (300mcg) given.

In titrated-dose regimen, Induction was started with 20ml of solution orally (20mcg of drug) and repeated 1 hourly for 6 hours, then titrated to 40 ml (40mcg) every 1 hourly for next 6 hours and then again titrated to 60 ml(60 mcg) every 1 hourly for next 6 hours. So a maximum of 18 doses (720 mcg drug) given in 18 hours.

In both the regimens, oral solution was continued till regular uterine contractions started or for 24 hours maximum in fixed-dose regimen and 18 hours maximum in titrated-dose regimen; failing which no further misoprostol solution was given and alternative method of induction was used. In case of feto-maternal complications like uterine hyper stimulation or non- reassuring fetal heart rate, the methods were immediately abandoned.

In order to determine the appropriate sample size, a calculation was performed utilizing the formula: $n = 2 \times f(\alpha, \beta/2) \times \pi \times (100 - \pi) / d^2$. The value of π denoted the true percentage of "success" within both the fixed misoprostol group and the titrated misoprostol group. Additionally, $f(\alpha, \beta)$ represented $[\varphi^{-1}(\alpha) + \varphi^{-1}(\beta)]^2$, wherein φ^{-1} symbolized the cumulative distribution function of a standardized

normal deviate. The significance level (α) was set at 5%, while the power (1 - β) was established at 80%. Considering a percentage "success" of 94.1% within both the control and experimental groups and an equivalence limit (d) of 10%, the sample size required per group was determined to be 75. Hence, a total sample size of 150 was deemed necessary. The methodology employed in the study involved conducting a comprehensive evaluation of indications and contraindications for labor induction through patient history and examination in a pre -structured working proforma. Both maternal and fetal outcomes were assessed, encompassing side effects directly associated with misoprostol induction as well as those unrelated to the induction process.

3. Results and Observations

All the patients were randomly divided into two groups, i.e., Group-T (n=75; Titrated dose of [5]oral misoprostol solution) and Group-F (n=75: Fixed dose of oral misoprostol solution).

Normal BMI was observed to be higher in group F [45(60.00%)] as compared to group T [37(49.33%)]. Overweight women were more in group T [19(25.33%)] as compared to group F [15(20.00%)] while obese women were also more in Group T [18 (24.00%)] as compared to group F. The upper, upper lower, and lower class was observed to be higher in group T [12(16.00%)], [14(18.67%)], [19(25.33%)] as compared to group-F [5 (6.67%)], [13(17.33%)], [17(22.67%)] respectively. Primigravida women were more in group -T as compared to group F [46(61.33%)] and number of Multigravida was observed higher in group F [29 (38.67%)] as compared to group T [27(35.99%)]. Hypertension was comparable between the groups. Hypothyroidism and GDM was observed higher in group T [9 (12.00%)], [5(6.67%)] as compared to group F [5 (6.67%)], [2(2.67%)] respectively. Other medical history were observed higher in group F [12(0.00%) as compared to group [9(1.33%)]. The mean bishop score < 3 was noted more in group T [32(42.67%)] compared to group F [21(32.31%)] while the bishop score 4-6 was almost comparable in women of both groups (Table 1).

The mean Induction to delivery time was higher in group F [11.83±4.15] hrs as compared to group T [10.49±4.09] hrs and the difference was significant [p=0.0482]. The number of women delivering in <12 hrs time was more in group T [33(67.34%)] than group F [37(61.66%)] while the women delivering in ≥12 hr time was more in group F [23(38.33%)] than group T [16(32.65%)]. Induction failure was higher in group T [26(34.6%)] compared to group F [15(20%)], but difference was non- significant [P=0.2168]. Total dose of misoprostol used was more in group T (248.80+_150.35mcg) than group F (131.60+_51.06mcg) and this difference was statistically significant (p<0.0001). Need for labour augmentation was higher in group T [42(56.00%)] than group F [23(30.67%)]. Statistically, it was a significant difference [p=0.0017]. Successful induction was observed higher in group F [60 (80.00%)] than group T [49 (65.53%)]. Statistically, this difference was significant [p=0.0439] (Table 2).

The fixed dose group had a higher rate of vaginal delivery (78.67%) compared to titrated dose group(61.33%). The number of assisted vaginal deliveries was more in Group T (4.00%) than in Group F (1.33%) & caesarean deliveries were also higher in Group T (34.67%) than Group F (20.00%). However, these differences were not statistically significant (p=0.0620) No uterine rupture occurred in either group in our study. Uterine hyper stimulation and atonic post-partum haemorrhage were noted more in group T but this difference was not significant (p = 0.1461 ; p = 0.3108). (Table 3).

Regarding specific indications for caesarean section, Group T had higher rates of non- reassuring fetal heart rate (3.85%), uterine hyperstimulation (11.54%), meconium-stained liquor (38.46%), and non-progression of labor (38.46%) compared to Group F, where the respective rates were 0.00%, 1(6.67%), 4(26.67%), and 8(53.33%). The incidence of caesarean section for obstructed labour was comparable between both groups. However, these differences were statistically not significant (p=0.7385). (Table 4)

Both the groups had all live births in our study. APGAR score (At 1 min) was comparable in both groups and non-significant (p=0.0950), Reduced APGAR score <8 at 1 min & 5 min was observed more in group T [26(34.67%); 18(24.00%)] compared to group F [19 (25.33%); 11(14.67%)] while APGAR score ≥8 at 1 min & 5 min was observed more in group F [56(74.67%); [64(85.33%)] compared to group T [49(65.33%); 56(74.67%]. Statistically, this difference was non-significant [p=0.2123]. Requirement of newborn resuscitation was observed higher in group T [34 (45.34%)] than group F [16(21.33%)]. Statistically, this difference was significant [p=0.0081]. NICU admissions were more in group T (21.34%) than group F (13.33%), but difference was not significant (p = 0.0574). (Table 5)

4. Discussion

The results of our study showed no significant differences between both groups in terms of mean time from starting of induction to onset of labor. These findings are consistent with previous studies by Abbas et al.,[15] and Souza et al.[16] However, it is important to note that time intervals reported in these studies varied. For example, Abbas et al.[15] reported a mean time of 10.70 hours. The variability in these results may be attributed to differences in patient populations, protocols, and methodologies. Induction to delivery interval within 12 hours, was slightly higher in the titrated

Table 1: Sociodemographic and clinical profile of the study subjects

S. No .	Variables		Group-T (N=75) (Titrated Dose)		Group-F (N=75) (Fixed Dose)	
			n	%	n	%
1	**Age in years**	19-29	63	84.00	65	86.67
		30-40	12	16.00	10	13.33
2	**BMI**	Underweight <18.5	1	1.33	0	0.00
		Normal 18.5-22.9	37	49.33	45	60.00
		Overweight 23-25	19	25.33	15	20.00
		Obese >25	18	24.00	15	20.00
3	**Socioeconomic status**	Upper	12	16.00	5	6.67
		Upper Middle	19	25.33	21	26.67
		Lower Middle	11	14.67	19	25.33
		Upper Lower	14	18.67	13	17.33
		Lower	19	25.33	17	22.67
4	**Gravida**	Primigravida	48	64.00	46	61.33
		Multigravida	27	35.99	29	38.67
5	**Medical History**	Hypertension	14	18.67	14	18.67
		Hypothyroidism	9	12.00	5	6.67
		GDM	5	6.67	2	2.67
		Others	9	1.33	12	0.00
6	**Modified Bishop Score**	< 3	32	42.67	21	32.31
		4-6	43	57.33	44	67.69
7	**Indication of Induction of labour**	Post-dated pregnancy	2	2.67	1	1.33
		PROM	27	36.00	21	28.00
		Intra uterine growth restriction	2	2.67	2	2.67
		Oligohydramnios	13	1	19	25.33
		Preeclampsia/GHTN	25	33.33	27	36.00
		GDM/DM	5	6.67	3	4.00
		Other Medical Conditions	1	1.33	2	2.67

Table 2: Association of induction-related outcome between Group-T and Group-F

	Group-T (Titrated Dose)	Group-F (Fixed Dose)	P-value
Induction			
Time interval b/w 1st dose given to active phase of labor (hour)	8.31±3.31	8.99±3.78	t=1.172 p=0.2430
Successful induction	49(65.54%,)	60(80%)	X=4.061 p=0.0439
Failed induction	26(34.46%)	15(20%)	
Induction to delivery time (hour)	10.49±4.09	11.83±4.15	t=1.992 p=0.0482*
<12 hr	33(67.34%)	37(61.66%)	X=3.057 p=0.2168
≥12 hr	16(32.65%)	23(38.33%)	t =6.392 p <0.0001
Total dose of misoprostol used (mcg)	248.80+_150.35	131.60+_51.06	
Need for Augmentation			
Yes	42(56.00%)	23(30.67%)	X=9.801
No	33(44.00%)	52(69.33%)	p=0.0017*

Table 3: Distribution and association of mode of delivery and obstetric complications

Mode of Delivery	Group-T (N=75) (Titrated Dose)		Group-F (N=75) (Fixed Dose)		P-value
	n	%	n	%	
Vaginal	46	61.33	59	78.67	X=5.561 p=0.0620
Assisted	3	4.00	1	1.33	X = 2.113 p =0.1461
Caesarean section	26	34.67	15	20.00	X = 1.027 p = 0.3108
Obstetric Complications Uterine rupture Uterine hyper stimulation	0 6	- 8.00	0 2	- 2.67	
Atomic post-partum haemorrhage	3	4.00	1	1.33	

Table 4: Distribution and association of indication of caesarean section between both the groups

Indication of caesarean section	Group-T (N=75) (Titrated Dose)		Group-F (N=75) (Fixed Dose)		P-V alue
	n	%	n	%	
Non-reassuring fetal heart rate	1	3.85	0	0.00	X=1.985 p=0.7385
Uterine Hyperstimulation	3	11.54	1	6.67	
Meconium-Stained Liquor	10	38.46	4	26.67	
Non-progression of labour	10	38.46	8	53.33	
Obstructed labour	2	7.69	2	13.33	
Grand Total	**26**	**100.00**	**15**	**100.00**	

X= Chi-square value

Table 5: Association of fetal outcome in between both the groups (N=150)

Fetal Outcome	Group-T (N=75) (Titrated Dose)		Group-F (N=75) (Fixed Dose)		P -value
	MEAN/n	MEAN/%	MEAN/n	MEAN/%	
Live birth	75	100	75	100	
APGAR score (At 1 min)	7.31	1.06	7.57	0.82	t=1.680 p=0.0950
<8	26	34.67	19	25.33	X=1.556 P=0.2123
≥8	49	65.33	56	74.67	
APGAR score (At 5 min)	9.33	1.05	9.60	0.80	t=1.771 p=0.0786
<8	19	24.00	11	14.67	X=2.216 P=0.1366
≥8	56	74.67	64	85.33	
Resuscitation					
No	41	54.66	59	78.67	X=7.843 p=0.0081
Yes	34	45.34	16	21.33	
Still birth	0	0.00	0	0.00	–
Birth weight					
< 2.5 kg	21	28.00	17	22.7	X=0.5639
≥ 2.5 kg	54	72.00	58	77.33	p=0.4527
Nicu Admission					
No	59	78.66	65	86.67	X =10.71 p
Yes	16	21.34	10	13.33	=0.0574

X= Chi-square value, t= Unpaired t-Test value

group(67.34%) compared to the fixed group (61.66%). However, this difference was not statistically significant. These findings are consistent with Souza et al.,[16] who also reported vaginal delivery within 12 hours that did not differ significantly between the two groups. On the other hand, Varsha et al.[17] reported a higher rate of vaginal delivery within 24 hours (80.5%) in the titrated group, indicating that the efficacy of induction may vary depending on the time frame considered. Regarding obstetric complications, our results showed no significant differences between the two groups. This finding is consistent with previous studies conducted by Rouzi et al.,[14] Souza et al.,[16] and Alami Harandy et al.[18] These studies suggest that dosing of misoprostol administered in both groups (titrated vs. fixed) does not significantly impact obstetric complications. In terms of neonatal outcomes, the need for neonatal intensive care unit (NICU) care was slightly higher in the titrated group (21.34%) compared to the fixed group (13.33%), but this difference was not statistically significant. These findings align with the study by Rouzi et al.,[14] which also did not find a significant difference in the need for NICU care between the two groups. It is important to note that the overall rates of NICU care were relatively low in both groups, indicating favorable neonatal outcomes. The majority of indications for induction of labor in our study were PROM, oligohydramnios, and pre-eclampsia/gestational hypertension. These findings are consistent with the study conducted by Rouzi et al.,[14] which reported similar indications for induction in their study population. Comparing our findings with other studies, Jane M. Bendix et al.[19] suggested that implementing a low dosage oral misoprostol solution protocol resulted in decreased time of labor induction and reduced requirement for additional induction methods compared to a previous high dosage procedure. In our study, induction to delivery interval was slightly longer in fixed-dose group but similarly lesser need for augmentation & caesarean deliveries than titrated-dose group was noted. Similarly, Baradwan et al.[20] demonstrated a significant association between titrated oral misoprostol and a higher caesarean delivery rate compared to static oral misoprostol. In contrast, Aduloju et al.[21] reported comparable rates of vaginal delivery between an hourly titrated misoprostol dose and a 2-hourly static misoprostol dose. These findings suggest that the effectiveness of induction may not be significantly influenced by the dosing regimen, although it is important to consider other factors such as sample size and specific study protocols. In terms of adverse effects, our study observed a higher incidence of drug-related side effects in the fixed group compared to the titrated group. However, these differences were not statistically significant. The use of fixed-dose regimen of misoprostol solution resulted in significantly reduced total dose required for induction compared to the titrated dose. This finding is consistent with the study by Amporn Thaisomboon et al.[13] which reported a higher total dose of misoprostol used in the titrated oral group, despite similar clinical efficacy.

This comparative study shows that both fixed-dose and titrated-dose oral misoprostol solution regimens are safe & effective in labour induction at term. Fixed-dose regimen inspite of taking slightly longer induction to delivery interval, offers an advantage of less mean total dose of drug administered, higher chances of vaginal delivery, reduced incidence of uterine hyperstimulation, dysfunctional labour and meconium-stained liquor, fewer newborns requiring resuscitation and NICU admissions.

5. Source of Funding

None.

6. Conflict of Interest

None.

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Cite this article: Kumari S, Aditya V, Malik N, Saxena A, Tiwari HC. A comparative interventional study on fixed-dose versus titrated- dose oral misoprostol solution for induction of labour at term gestation in a tertiary care centre of Eastern Uttar Pradesh. *Indian J Obstet Gynecol Res* 2024;11(2):249-255.