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Original Research Article

A randomized control study of titrated and oral misoprostol solution for induction of labor at term

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ABSTRACT

Background: Quest for an induction method with safety, efficacy, feasibility, low cost, and patient preference is a constant pursuit for all obstetricians. Oral misoprostol is one such method which has been shown to be effective in achieving vaginal birth and has been recommended by WHO (2011) and FIGO (2012) for induction of labor. This study aimed to evaluate effectiveness and safety of hourly titrated oral misoprostol solution in comparison with two hourly static-dose oral misoprostol solution for induction of labor at term.
Methods: Single centre interventional single-blinded randomized controlled trial conducted in a tertiary care centre in Ludhiana. 264 term pregnant women were randomly given titrated (group A) or static oral misoprostol solution (group B) till the onset of active labor. Induction to delivery time was the primary outcome measure while the secondary outcome measures pertained to efficacy and safety of the regimens.
Results: 268 women were randomized, 4 patients were excluded from analysis because of drop out, leaving 264 women for intention to treat analysis. The mean interval between induction and delivery was 16.19±10.48 hours in group A and 15.28±8.34 hours in group B ($p>0.10$, NS). 71 women (53.8%) in group A and 72 women (54.5%) in group B had vaginal delivery within 24 hours ($p>0.10$, NS). 40.9% women in group B required more than 8 hours to receive the required number of doses as compared with 8.3% women in dose group A ($p<0.01$, SS). Oxytocin requirement was significantly higher in group A (76.5%) as compared to group B (59.8%) ($p<0.05$, SS). Incidence of fetal and maternal complications, rate of cesarean section and instrumental delivery was comparable between the two groups ($p>0.10$, NS).
Conclusions: Titrated oral misoprostol, considering its efficacy, safety and time saving is comparable to WHO recommended static oral misoprostol.

Keywords: Oral misoprostol solution, Static, Titrated

INTRODUCTION

Induction of labor is a commonly practiced obstetric intervention to artificially initiate the process of labor when benefits to either mother or fetus outweigh those of pregnancy continuation. The incidence for labor induction dramatically varies between 8-44% and has shown a gradual increase in recent years.[1]

Adopting safe and effective method of labor induction at appropriate gestational age can greatly decrease complications and morbidity of pregnancy and fetus. Various methods of induction of labor include administration of pharmacological agents like oxytocin, prostaglandin analogues, smooth muscle stimulants such as herbs or castor oil, mechanical methods such as digital stretching of the cervix and sweeping of the membranes, hygroscopic cervical dilators like laminaria tents, extra-amniotic balloon catheters and artificial rupture of membranes.

Presently prostaglandins, such as dinoprostone (PGE_2) and misoprostol (PGE_1), are used as most potent and acceptable methods for cervical ripening and labor induction. Oral misoprostol has been shown to be as effective as vaginal misoprostol and has the advantage of

being more acceptable to women and can be self-administered.[4]

In 2012, the International Federation of Gynecology and Obstetrics (FIGO) recommended an oral dose of 25 mcg misoprostol solution every 2 hours to induce labor, citing the 2011 World Health Organization (WHO) recommendations for labor induction.[1,2] The WHO strongly recommended this regimen, rating the quality of evidence as moderate using the data from the 2006 Cochrane review by Alfirevic.[3]

Absorption of "misoprostol" by oral route is known to be more rapid and predictable with terminal half-life of 20-40 minutes.[4] Peak concentrations are achieved in 34 minutes followed by a rapid decline to low levels during the period of 120 minutes, and no drug accumulation phenomenon. Thus the administration of oral misoprostol in titrated doses may provide a steady drug serum level with better efficacy in less time with improved clinical outcome of induction as compared to two hourly dosing.

Our objective in this study was to evaluate effectiveness and safety of titrated oral misoprostol solution (OMS) in comparison with static-dose oral misoprostol solution (OMS) for induction of labor at term.

METHODS

Study design

This comparative randomized study was conducted in the Department of Obstetrics and Gynecology, Christian Medical College and Hospital, Ludhiana for a period of one year from 1st December, 2017 to 30th November, 2018. The study group comprised of all antenatal women admitted in labor room at term for induction of labor. Informed consent was taken for all selected women. Women were subjected to detailed history taking, a complete physical examination including per vaginum examination (to calculate modified bishop's score and to rule out cephalopelvic disproportion), investigations and a NST. Gestational age was established by the first date of the last menstrual period and confirmed by first trimester ultrasound. Presentation was confirmed by palpation and third trimester ultrasound.

Inclusion criteria

Singleton live pregnancy; ≥37 weeks gestation; cephalic presentation; reactive NST; modified Bishop's score ≤6.

Exclusion criteria

Hypersensitivity to misoprostol; uterine scar due to previous cesarean section or other uterine surgery; grand multipara; multiple gestations; high risk pregnancies, preeclampsia with severe features, significant maternal cardiac, renal, liver disease; any contraindication to induction and vaginal delivery e.g. cephalopelvic disproportion, malpresentation, fetal compromise and ante partum haemorrhage; Intrauterine fetal demise

Randomization

Women were randomized (1:1) into the treatment groups A) titrated-dose OMS group B) static dose OMS group; using computer generated number sequence. Allocation concealment was carried out by using opaque envelopes that were distributed by the obstetrics nurse. Whereas study investigators and attending care teams were aware of the allocated arm, patients were kept blinded to the allocation. Study investigators and outcome assessors could not be blinded as the data collection and analysis included outcome measures like timing of oral misoprostol solution doses.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of our research.

Study interventions

Women after randomization were allocated into two groups after informed consent. The first group (A) was induced with hourly titrated oral misoprostol regimen and the second group (B) received two hourly static oral misoprostol regimen. Once labor had started, vital signs, fetal heart rate (FHR) and uterine activity were closely monitored during first stage of labor according to institutional protocols. Per vaginum examination was done 4-hourly or as indicated.

Procedure was ceased at any time when one of the following criteria was reached: 1) regular uterine contractions every 3-5 minutes and lasting 60 seconds or more; 2) dilatation of cervix reached 2.0 cm; 3) uterine tachysystole; 4) non-reassuring fetal status 5) completed dose regimen. If contractions subsequently become inadequate, artificial rupture of membranes was done and/or oxytocin was started ≥2 hours after the last misoprostol dose according to the discretion of the attending consultant.

Method of preparation of oral misoprostol solution: Based on the WHO labor induction recommendation, and for the purpose of achieving precise oral misoprostol dosage, one misoprostol tablet (200 µg) was pulverized and dissolved into 200 ml water. Thus 1 ml of solution had 1 µg of misoprostol. This misoprostol solution could be preserved at room temperature and remained active for 24 hours.

Method of administration

Titrated OMS group: All the women enrolled into the group A were given oral misoprostol solution according to the regimen described by Wang et al.[10]

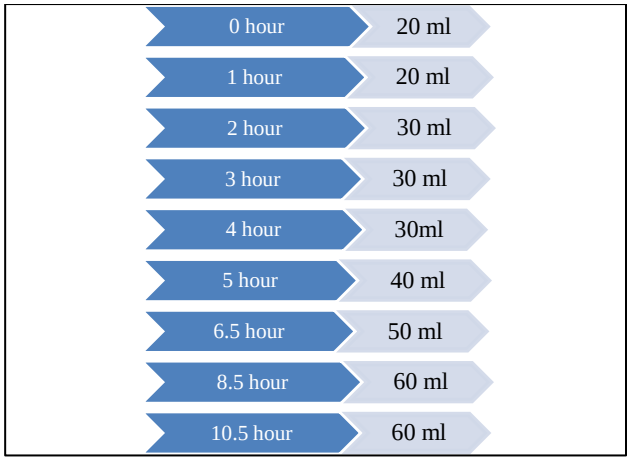

Figure 1: Dosage regimen of misoprostol.

Static OMS group: In group B, the recommended FIGO regimen was used. Oral misoprostol solution 25 µg (25 ml) was administered every 2 hours for a maximum of 12 doses or until the onset of regular uterine activity.

Study outcome

Primary outcome was induction to delivery time.

Secondary Outcomes were major maternal and fetal complications which pertained to safety and efficacy of regimens.

Efficacy

This included mean gestational age, indication of induction of labor, mean change in Bishop's score, total number of misoprostol doses required, time taken to complete doses, mean total dose of misoprostol required, indication for stopping drug regimen, mean interval from induction to onset of labor, mode of delivery, indication for LSCS, oxytocin augmentation.

Maternal morbidity

This included incidence of tachysystole, fever-intrapartum and postpartum, puerperal sepsis, uterine rupture.

Neonatal parameters

Neonatal parameters such as incidence of meconium-stained liquor, APGAR scores at 1, 5 minutes and NICU stay.

Sample size calculation

The sample size by using the clinical data was 132 for each group. Required sample size of 264 for the study was calculated using the formula:

Sample size= $(r+1)\ (p^*)(1-p^*)(Z1-\alpha/2+Z1-\beta)\ 2\ /r^*(p_1-p_2) \times 2$

Where,

$Z1-\alpha/2=1.96$, is standard normal deviate at type 1 error $\alpha=0.05$,

$Z1-\beta=0.84$ is standard normal deviate at 80% power,

r is ratio of cases, in case of equal number it is 1,

p^* =average proportion exposed = (proportion of exposed cases in group 1 + proportion of exposed cases in group 2)/ 2 p_1 is proportion in case 1 and p_2 is proportion in case 2,

p_1-p_2= Effect size or difference in proportion expected based on previous study.

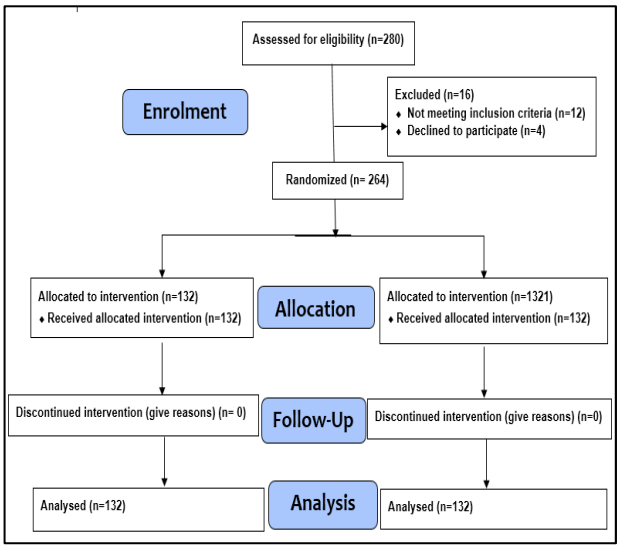

Figure 2: CONSORT 2010 flow diagram.

Statistical analysis

Data was entered in the Microsoft excel and analyzed by SPSS version 21. Frequency, proportions, mean, mode, standard deviation were calculated. 't'-test, ANOVA and Chi square test were the tests of significance. P value <0.05 was considered significant.

RESULTS

Our study population in both the groups had similar demographic profile with no significant differences with regards to maternal age, parity and gestational age. The mean gestational age of the patients at the onset of study was 38.65±1.19 weeks in the hourly titrated dose group and 38.83±1.12 weeks in the two hourly static dose group of patients (p>0.10, NS). The most common indication for induction in both the groups was elective induction with 32.6% (n=43) in group A and 29.6% (n=29) in group B

followed by prelabor rupture of membranes (17.4% and 12.1% respectively) (p>0.10, NS).

Table 1: Trial profile and outcomes.

Variable	Hourly misoprostol	2 hourly misoprostol	P value
Age, years	27.39±3.56	27.40±2.83	>0.10
Gestation, weeks	38.65±1.19	38.83±1.12	>0.10
Nulliparous	60.6%	56.8%	>0.10
Bishop score ≤3 before induction	18.2%	22%	>0.10
Change in modified bishop score	3.51±1.14	3.52±1.14	>0.10
Total misoprostol dosage	144.47±89.86	110.23±52.14	<0.05 Significant
Mean number of doses	4.95±2.19	4.39±2.09	>0.10
Delivered vaginally in ≤24 hours	53.8%	54.5%	>0.10
Cesarean section	34.8%	32.6%	>0.10
Oxytocin			
Yes	76.5%	59.8%	<0.05 Significant
No	23.5%	40.2%	

The mean change in modified Bishop's Score was 3.51±1.14 in the hourly titrated-dose group and 3.52±1.14 in the two hourly static dose group which was not significant statistically. Most of the women were given 5 doses in the hourly titrated-dose group and 4 doses in the two hourly static dose group with a mean of 4.95±2.19 in group A and 4.39±2.09 in group B (p>0.10,NS). However, 44.7% of women in group A took 4 hours to receive required number of doses to go into labor as compared to 18.2% women in group B (p<0.01,SS). A significantly higher number of women took 9-12 hours to receive required number of doses in group B (26.5 %) than women in group A (8.3%) (p<0.01, SS). Maximum time of 10.5 hours (9 doses) was taken by 8.3% women in group A. In group B, 14.4% women took more than 12 hours to complete the required number of doses and 1 woman required maximum dose (12 doses) taking 24 hours.

Oral misoprostol was stopped when 30.3% women in the hourly titrated-dose group had regular uterine contractions as compared to 38.6% women in the two hourly static dose group (p>0.10,NS). 8.3% women in group A required complete dose regimen as compared to 0.8% women in group B (p<0.01,SS). The mean total dosage of misoprostol received was 144.47±89.86 µg (range between 70-340 µg) in group A which was significantly more than the dosage 110.23±52.14 µg (range between 75-300 µg) received by women in group B (p<0.05, SS).

Table 2: Distribution of cases according to time taken to give required doses.

Time taken to give required doses (hours)	Hourly misoprostol		2 hourly misoprostol		P value
	N	%	N	%	
1-4	59	44.7	24	18.2	<0.01 significant
5-8	62	47	54	40.9	>0.10
9-12	11	8.3	35	26.5	<0.01 significant
≥13	0	0	19	14.4	<0.01 significant
Total	132	100	132	100	

The mean interval between induction and onset of labor was 7.96±6.76 hours in group A and 7.10±5.26 hours in group B (p>0.10, NS). Oxytocin augmentation was required in most of the patients with maximum dose of 12 mU/minute. 76.5% women in the hourly titrated dose group required oxytocin as compared to 59.8% in the two hourly static dose group (p<0.05,SS).

Table 3: Maternal morbidity.

Variable	Hourly misoprostol	2 hourly misoprostol	P value
Uterine hyperstimulation/ tachysystole	1.5%	0	>0.10
Intrapartum fever	1.5%	0	>0.10
Postpartum fever	6.1%	6.8%	>0.10
Puerperal sepsis	0	0	>0.10
Uterine rupture	0	0	>0.10

86 women (65.2%) in the hourly titrated-dose group had vaginal delivery as compared to 89 women (67.4%) in the two hourly static dose group (p>0.10, NS). The mean interval between induction and delivery was 16.19±10.48 hours in group A and 15.28±8.34 hours in group B (p>0.10, NS). 36 women (41.9%) delivered vaginally within 12 hours, 35 women (40.7%) in 12-24 hours and 15 women (17.4%) took more than 24 hours to deliver with titrated regimen. In group B with static regimen, 32 women (36.0%) had vaginal delivery in 12 hours, 40 women (44.9%) in 12-24 hours and 17 women (19.1%) took more than 24 hours. (p>0.10, NS). Remaining 46 women (34.8%) in group A and 43 women (32.6%) in group B had LSCS. The most common indication for caesarean section in titrated dose group was MSAF in early labor in 13 women (28.3%) while in group B it was secondary arrest of dilatation in 14 women (32.6%) (p>0.10, NS). Overall incidence of meconium stained amniotic fluid was noted in 17 women (12.9%) in group A as compared to 15 women (11.4%) in group B with no significant difference (p>0.10, NS).

Table 4: Fetal parameters.

Variable	Hourly misoprostol	2 hourly misoprostol	P value
Non-reassuring fetal heart rate	1.5%	0	>0.10
Meconium-stained fluid	12.9%	11.4%	>0.10
Intrauterine pneumonia	0	0.76%	>0.10
Birth weight, gm	3049.6±422.4	3037.6±441.7	>0.10
Apgar score <7 at 1 minute	0	0.76%	>0.10
Apgar score <7 at 5 minutes	0	0.76%	>0.10
NICU admission	3.8%	3.8%	>0.10

No incidence of puerperal sepsis and uterine rupture and was seen in both the groups. The only complications noted were intrapartum fever, postpartum fever and uterine contraction abnormality. Intrapartum fever and uterine contraction abnormality was seen in 1.5% in hourly titrated dose group. 6.1% had postpartum fever in hourly titrated dose group as compared to 6.8% in two hourly static dose group (p>0.10, NS). NICU stay was required in 5 (3.8%) cases in both the groups. 0.76% cases had APGAR score <7 in group B. There was no significant difference observed in neonatal outcomes in the two groups.

DISCUSSION

Hourly titrated regimen of oral misoprostol solution can decrease the time and drug dosage required for induction of labor as compared to static two hourly regimen, thereby decreasing the time taken from induction to delivery. In this study, titrated oral misoprostol dose regimen has been found to have comparable efficacy to static oral misoprostol dose regimen. 71 (53.8%) women in group A and 72 (54.5%) women in group B had vaginal delivery within 24 hours. There was no statistically significant difference found with respect to outcomes like time taken from induction to onset of labor, time taken from induction to delivery time, number of doses required and change in modified Bishop score in our study.

The median total misoprostol dosage requirement was noted to be higher in the titrated group than the static group. Incidence of cesarean section was similar in both the groups in our study (34.8% and 32.6%) (p>0.10).

Need for augmentation by oxytocin was also higher in titrated group as compared to static oral misoprostol group. Intrapartum fever and uterine contraction abnormality were seen in 2 women (1.5% each) in group A and postpartum fever was seen in 8 women (6.1%). Incidence of postpartum fever in group B was 6.8% (9 women). Incidence of meconium stained amniotic fluid was also found to be similar in both the groups. It is thus be noteworthy that the incidence rates for all adverse outcomes associated with titrated and static oral misoprostol dose regimens were of similar magnitude.

Comparison with other studies

Hourly titrated regimen of oral misoprostol solution can decrease the time and drug dosage required for induction of labor as compared to static two hourly regimen, thereby decreasing the time taken from induction to delivery. In our study, titrated oral misoprostol dose regimen has been found to have comparable efficacy to static oral misoprostol dose regimen. Vaginal delivery was achieved in a total of 86 women (65.2%) with hourly titrated dose regimen and in 89 (67.4%) women with two hourly static regimen. 71 (53.8%) women in group A and 72 (54.5%) women in group B had vaginal delivery within 24 hours. These observations were comparable to a study by Rouzi et al in which 64.4% women in the hourly titrated dose group and 65.8% in the two hourly static dose group delivered vaginally within 24 hours.[6] 78.7% had vaginal birth in hourly group and 80% in two hourly static group in a study by Aduloju and colleagues which was higher than present study.[8] Similarly, it was noted that a significantly higher number of women (79.7%) delivered vaginally within 24 hours with titrated oral misoprostol in a study conducted by Aalami-Harandi and colleagues.[11] Study reported by Cheng and colleagues also noted higher vaginal delivery rate of 96.0% with titrated oral misoprostol regimen out of which 94.1% delivered within 24 hours.[9] There was no statistically significant difference found with respect to outcomes like time taken from induction to onset of labor, time taken from induction to delivery time, number of doses required and change in modified bishop score in our study.

The median total misoprostol dosage requirement was noted to be higher in the titrated group than the static group. Aduloju and colleagues also reported greater misoprostol requirement in titrated group as compared to static group with median dose of 180 µg (range 60-720 µg) and 150 µg (range 25-275 µg) in each group respectively.[8] Similar dosage was observed in studies by Rouzi et al, Aalami-Harandi and colleagues and Cheng with higher misoprostol requirement by women in titrated group.[6,9,11] Number and overall misoprostol dose requirement in both titrated and static groups were higher in all these studies as compared to the present study.

Incidence of cesarean section was similar in both the groups in our study (34.8% and 32.6%) (p>0.10). A lower caesarean delivery rate of 21.3% in titrated group and 20.0% in static group was observed by Aduloju and colleagues.[8] Cheng and colleagues had earlier reported even lower caesarean delivery rate in their study in 2008 with titrated group.[9] The caesarean section rate of 23.2% in titrated group was comparable to our study. Rouzi et al had also reported lower cesarean section rates as compared to our study (23.2% and 8.2% respectively).[6] Need for

augmentation by oxytocin was also higher in titrated group as compared to static oral misoprostol group. Oxytocin requirement was also higher in hourly titrated dose group (76.5%) as compared to two hourly static dose group (59.8%) ($p<0.05$). This was similar to the higher oxytocin requirement noted in 72.2% women in hourly titrated group and 75% in two hourly static group by Rouzi et al in 2017.[6] Lesser number of women (31%) required oxytocin infusion in study conducted by Deshmukh and colleagues.[7] Similarly, Aduloju and collegues in had reported lower oxytocin requirement in both hourly titrated group (32%) and two hourly static group (30.7%).[8] Cheng and colleagues had observed lowest oxytocin requirement by women in titrated group (10.9%).[9]

Strengths and limitations of this study

Prospective recording of the data contributed to the strength of our study. Randomization of participants led to minimal allocation and selection bias with greater data reliability. Number of women enrolled in the study also helped to get high quality data. Nonetheless, the data was not extrapolated with respect to the parity of women and the results should therefore be interpreted with caution. We restricted the analysis to women at term without any co-morbid conditions limiting the possibility of confounding by these factors.

CONCLUSION

Although misoprostol fell into disrepute in view of effects like uterine contraction abnormality, non-reassuring fetal heart rate pattern and neonatal outcome with respect to meconium staining of amniotic fluid, however our study showed none of these effects to be significant. Shorter time interval is required to administer hourly titrated oral misoprostol regimen as compared to two hourly static oral misoprostol regimen to achieve similar results. To conclude, titrated oral misoprostol, considering its efficacy, safety and time saving is comparable to WHO recommended static oral misoprostol.

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