Original Article

Titrated Misoprostol Versus Dinoprostone for Labor Induction

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ABSTRACT

Background: Misoprostol is as effective as dinoprostone for labor induction with low cost and temperature stability. **Aim:** This study designed to compare titrated misoprostol regarding its safety and efficacy with dinoprostone for induction of labor. **Subjects and Methods:** Women with a single pregnancy, above 37 weeks' gestation, cephalic presentation, modified Bishop's score <8, and not in labor with reassuring fetal heart rate, admitted for labor induction enrolled in this randomized controlled study. Studied women were randomized into; Group I: received oral misoprostol titrated in sterile water (200 μg tablet was dissolved in 200 ml sterile water [1 μg/ml]), starting dose of 20 μg misoprostol required, given every 2 h, and stopped if adequate contractions obtained and Group II: received vaginal dinoprostone tablet maximum two doses followed by augmentation of labor by oxytocin ± amniotomy if there is no uterine contractions after two doses of dinoprostone. In Group I, if the contractions were inadequate after two doses of oral titrated misoprostol (20 μg [20 ml]), the starting dose increased to 40 μg (40 ml), escalating the dose from 5 to 10 ml (45–50 μg), and 20 ml (60 μg) maximum ± amniotomy. If the uterine contractions were adequate, the next dose of misoprostol or dinoprostone was omitted. Statistical analysis done using Student's *t*-test for quantitative data and Chi-square test for qualitative data. **Results:** Induction-to-delivery time was significantly longer in misoprostol than dinoprostone group (975 vs. 670 min, respectively), (P = 0.01). About 20.2% (21/104) of women in misoprostol group did not deliver vaginally within 24 h compared to 7.4% (8/108) in dinoprostone group (significant difference, P = 0.01). Augmentation of labor was significantly high in dinoprostone (37.96% [41/108]) compared to misoprostol group (10.6% [11/104]) (P < 0.01). **Conclusion:** Titrated misoprostol for induction of labor seems to be associated with significantly longer induction-to-delivery time, low incidence of vaginal birth within 24 h, and less need for augmentation of labor compared to vaginal dinoprostone.

KEY WORDS: Dinoprostone, labor induction, titrated misoprostol

INTRODUCTION

Induction of labor defined as artificially initiating uterine contractions, prior to their spontaneous onset, with progressive cervical dilatation and subsequent delivery of the baby.[1]

Prolonged gestational age is the most common cause for induction of labor in obstetrics practice. Induction of labor may be difficult or unsuccessful with subsequent cesarean delivery and prostaglandins is used in obstetrics practice for cervical ripening before labor induction.[2,3]

Prostaglandins registered for induction of labor are expensive and unstable in room temperature.[4] Cervical ripening is associated with an increase in cyclooxygenase enzyme, which leads to increase local prostaglandins production in the cervix with subsequent more cervical ripening.[5]

Misoprostol is a prostaglandin E1 analog, and it is as effective as dinoprostone with low cost and temperature stability. Uterine hyperstimulation associated with misoprostol is

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dose-dependent and related to the route of misoprostol administration.[6]

Previous studies concluded that misoprostol is effective as cervical ripening agents and reported that the challenge is to administer misoprostol accurately while maintaining the ability to discontinue the medication when needed. Recent coworkers utilized a misoprostol delivery system that controls misoprostol release and rapid removal.[7,8]

Most researchers used misoprostol vaginally, while oral administration of misoprostol is easier, more convenient, and has several advantages. Recorded peak of oral misoprostol was 227 pg/ml after 34 min compared with 165 pg/ml after 80 min for vaginal misoprostol, and oral route of misoprostol is characterized by short half-life.[9]

This study designed to compare titrated misoprostol regarding its safety and efficacy with dinoprostone for induction of labor.

SUBJECTS AND METHODS

This randomized controlled study conducted from June 2013 to August 2014 after approval of the Institute Ethical Research Committee of Ain Shams University, Cairo, Egypt. After thorough explanation, women included in this study had to sign written consent explaining the purpose and procedures of this study. Women with a single pregnancy, >37 weeks' gestation (from the 1st day of last menses and confirmed by ultrasound done at 20 weeks' gestation), cephalic presentation, modified Bishop's score <8, and not in labor with reassuring fetal heart rate by cardiotocography (CTG) (basal fetal heart rate 120–160 beats/min, with good variability and accelerations of fetal heart beats 15 beats/min in response to fetal movements without decelerations) for 20–30 min on the day of induction admitted for labor induction enrolled in this study.

Women with premature rupture of fetal membranes, previous uterine scar, fetal malpresentation, multiple pregnancies, significant antepartum hemorrhage, uncontrolled diabetes, severe preeclampsia or eclampsia, and women who have contraindications to receive the induction medications (allergy, history of severe asthma) excluded from this study. Studied women were randomized into; Group I: 104 women included and received oral 200 μg misoprostol in 200 ml water titrated over 12 h and Group II: 108 women included and received vaginal dinoprostone tablet (3 mg) maximum two doses.

Randomization performed using a computer-generated randomization system. A plan of interventions was sealed in closed envelopes, numbered in accordance with the randomization tables, and opened before the induction process. Packing, sealing, and numbering were all performed by two independent doctors other than the investigator.

Women included in this study subjected to thorough history, general and local vaginal examination with evaluation of modified Bishop's score.

Studied women monitored by the external CTG continuously through labor induction process to assess uterine contractions and fetal heart rates and examined vaginally 4 hourly to assess the progress of induction process.

In Group I: Misoprostol available tablets is 200 μg tablet misoprostol (Sigma Pharmaceutical Industries, Cairo, Egypt) was dissolved in 200 ml sterile water (1 μg/ml), shaking the solution well before each administration. A prepared solution made up freshly for each woman admitted for induction of labor and the same bottle used till finished (maximum 12 h). For induction of labor, a starting dose of 20 μg misoprostol required, given every 2 h, and stopped if adequate contractions obtained (three contractions in 10 min each lasting 40–60 s with progressive cervical changes). If the contractions were inadequate after two doses of oral titrated misoprostol (20 μg [20 ml]), the starting dose increased to 40 μg (40 ml), escalating the dose from 5 to 10 ml (45–50 μg), and 20 ml (60 μg) maximum ± amniotomy.

In Group II: Dinoprostone 3 mg tablet (Alexandria Pharmaceuticals Co. Cairo, Egypt) was inserted in vaginal fornix and repeated 6 hourly if contractions were inadequate (maximum two doses). If the uterine contractions were inadequate after two doses of dinoprostone, augmentation of the active phase of labor attempted by oxytocin infusion ± amniotomy.

If the uterine contractions were adequate, the next dose of misoprostol or dinoprostone was omitted.

Primary outcome measures; induction delivery time (time from the start of induction medication until delivery). Secondary outcomes measure the duration of the first and second stages of labor, maternal complications, side effects of induction agents, mode of delivery, and neonatal outcome.

Sample size justification

The required sample size was calculated using G* power software version 3.17 for sample size calculation (*Heinrich Heine Universität; Düsseldorf; Germany), setting α-error probability at 0.05, power (1-β error probability) at 0.95%

and effective sample size (w) at 0.3, and data from previous study,[8] which concluded that vaginal misoprostol in doses above 25 μg four hourly was more effective than conventional methods of labor induction but with more uterine hyperstimulation and lower misoprostol doses were similar to conventional methods in effectiveness and risks. The effective size (*w*) was calculated as follows: $w=\sqrt{\chi^2}/N$, where χ^2 is the Chi-square test and *N* is the total sample size.

Statistical analysis

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 20 (Chicago, IL, USA). Data were presented as mean and standard deviation if it was numerical data and number (n) and percentage (%) if it was categorical data. Student's *t*-test for quantitative data analysis and Chi-square was used for qualitative data analysis.

RESULTS

Two hundred and twenty-three women recruited in the beginning of this study and it was completed with 212 women. One hundred and four women in Group 1 or titrated oral misoprostol (seven women dropped due to; missed notes, spontaneous rupture of membranes, and spontaneous onset of labor) and 108 women in Group II or vaginal dinoprostone tablet (four women dropped due to; spontaneous rupture of membranes and spontaneous onset of labor) [Figure 1].

Maternal age, gestational age, parity, body mass index, and indications of induction of labor were similar in both studied groups with no statistical difference. Moreover, there was no difference between two studied groups regarding; initial modified Bishop's score assessment [Table 1].

The induction-to-onset of contraction interval and the whole induction-to-delivery time were shorter in Group II (vaginal dinoprostone group) compared to Group I (titrated oral misoprostol), while the active phase of the first stage and the second stage of labor were significantly shorter in Group I compared to Group II [Table 2].

Need for epidural analgesia and rate of uterine hyperstimulation during induction of labor were similar in the two studied groups with no statistical difference.

Augmentation of labor was significantly high in dinoprostone (37.96% [41/108]) compared to misoprostol group (10.6% [11/104]) ($P < 0.01$). Mode of delivery, rate of operative vaginal delivery for intrapartum fetal compromise or protracted second stage of labor and rate of cesarean delivery for intrapartum fetal compromise, and protracted labor or failed induction of labor were similar

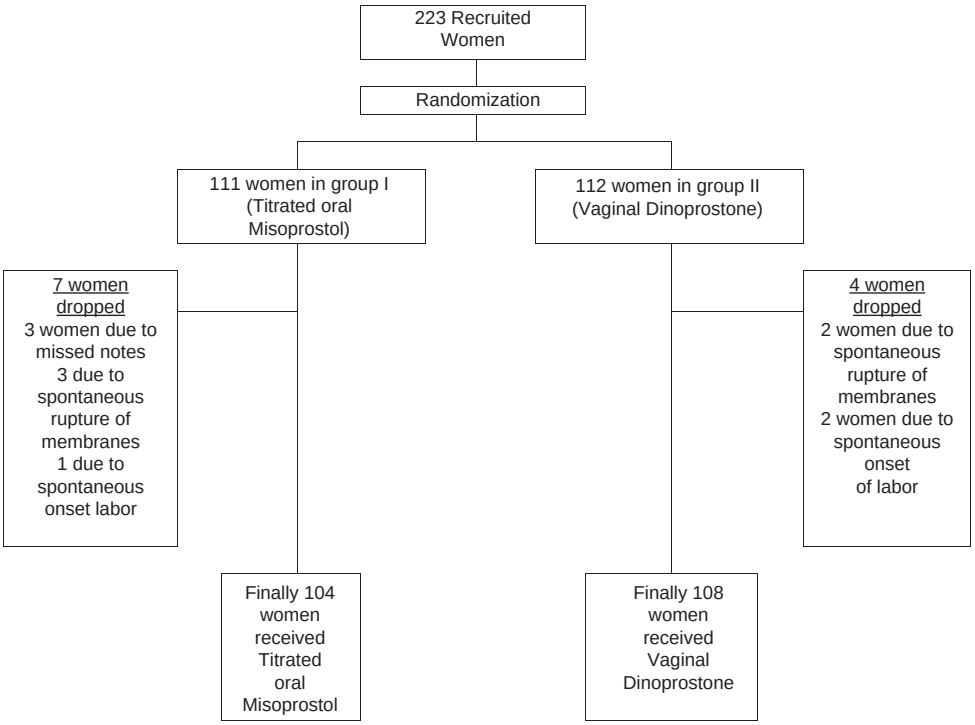

Figure 1: Flow diagram of the studied women

without statistical difference between two studied groups. Complications of inductions and side effects of induction agents were similar without statistical difference between two studied groups [Table 3].

Fetal birth weight, 5 min Apgar score, and rate of Neonatal Intensive Care Unit (NICU) admission were similar without statistical difference between two studied groups [Table 4].

Table 1: Demographic data, indication of induction of labor, and initial modified Bishop's score in both studied groups

Variables	Group I (titrated oral misoprostol) (*n*=104)	Group II (vaginal dinoprostone) (*n*=108)	*P*, significance
Age (years)			
Mean (SD)	26.13 (5.6)	26.5 (5.2)	0.2*
Parity			
Median (IQR)	0 (0-2)	0 (0-2)	1**
Parity			
Nulliparous (*n* and %)	52 (50)	60 (55.6)	0.6**
Multiparous (*n* and %)	52 (50)	48 (44.4)	1**
BMI (kg/m^2)			
Mean (SD)	31.47 (3.07)	32.21 (3.39)	0.9*
Gestational age (weeks)			
Mean (SD)	40.58 (1.18)	40.61 (1.2)	0.5*
Indications of induction of labor decreased			
Diminished fetal movements (*n* and %)	36 (34.6)	46 (42.6)	0.4**
Prolonged pregnancy (*n* and %)	41 (39.4)	40 (37)	0.8**
Hypertensive disorders (*n* and %)	15 (14.4)	13 (12)	0.6**
Diabetes mellitus (*n* and %)	12 (11.5)	9 (8.3)	0.4**
Initial Bishop's score			
Median (IQR)	6 (5-7)	6 (5-7)	1**

*Analysis using independent Student's *t*-test, **Analysis using Chi-square test. *n* and %=Number and percentage, SD=Standard deviation, IQR=Interquartile range, BMI=Body mass index, FHR=Fetal heart rate

Table 2: Duration of phases of labor, induction-to-onset of contractions, and induction to delivery intervals in both studied groups

Variables	Group I (titrated oral misoprostol) (*n*=104)	Group II (vaginal dinoprostone) (*n*=108)	*P*, significance
Induction-to-onset of contractions interval (min), median (IQR)	480 (330-720)	330 (260-435)	<0.01
Duration of latent phase of the first stage of labor (min), median (IQR)	360 (300-420)	330 (240-420)	0.4
Duration of active phase of the first stage of labor (min), median (IQR)	90 (60-180)	135 (97.5-232.5)	0.05
Duration of the first stage of labor (min), median (IQR)	480 (360-800)	464 (360-592.5)	0.6
Duration of the second stage of labor (min), median (IQR)	30 (15-50)	60 (40-107.5)	0.01
Induction-to-delivery interval (min), median (IQR)	975 (760-1405)	760 (720-1095)	0.01

Analysis using Chi-square test. IQR=Interquartile range

Table 3: Use of epidural analgesia, augmentation of labor and rate of uterine hyperstimulation, mode of delivery, and complications of induction of labor in both studied groups

Variables	Group I (titrated oral misoprostol) (*n*=104) (%)	Group II (vaginal dinoprostone) (*n*=108) (%)	*P*, significance
Use of epidural analgesia	7 (6.7)	4 (3.7)	0.3
Artificial rupture of the membranes	94 (90.4)	102 (94.4)	0.8
Need for augmentation of labor	11 (10.6)	41 (37.96)	<0.01
Uterine hyperstimulation			
With FHR changes	1 (1.0)	1 (0.9)	1
Without FHR changes	1 (1.0)	1 (0.9)	1
Mode of delivery			
Vaginal delivery	101 (97.1)	102 (94.4)	0.3
Cesarean delivery	3 (2.9)	6 (5.6)	0
Forceps-assisted delivery for intrapartum fetal compromise	1 (1)	1 (0.9)	1
Forceps-assisted delivery for protracted second stage	2 (1.9)	1 (0.9)	0.5
Maternal side effects			
Shivering	4 (3.8)	0 (0)	0.1
Diarrhea	6 (5.8)	3 (2.8)	0.3
Pyrexia	3 (2.9)	3 (2.8)	1
Maternal complications			
Retained placenta	1 (1)	1 (0.9)	1
Atonic postpartum hemorrhage	1 (1)	0 (0)	0.2

Data presented as number and percentage. *Analysis using Chi-square test. FHR=Fetal heart rate

Table 4: Fetal birth weight, 5 min Apgar score, and rate of Neonatal Intensive Care Unit admission in both studied groups

Variables	Group I (titrated oral misoprostol) (*n*=104)	Group II (vaginal dinoprostone) (*n*=108)	*P*, significance
Birth weight (g)			
Mean (SD)	3231.7 (445.3)	3151.9 (461.9)	0.6*
5-min apgar score <7 (*n* and %)	5 (4.8)	4 (3.7)	0.9**
NICU admission			
TTN (*n* and %)	1 (1)	2 (1.9)	0.9**
Congenital pneumonia (*n* and %)	1 (1)	0 (0)	0.9**

*Analysis using independent Student's *t*-test. **Analysis using Chi-square test. NICU=Neonatal Intensive Care Unit, TTN=Transient tachypnea of the newborn, *n* and %=Number and percentage

DISCUSSION

Two hundred and twelve women were included in this study to compare titrated misoprostol regarding its safety and efficacy with dinoprostone for induction of labor; 52.8% of studied women were nulliparous and 47.2% were multiparous.

While, indications of labor induction were prolonged pregnancy (50.6%), hypertensive disorders (29.4%), diminished fetal movements (15.6%), and 4.4% for other causes (4.4%) in Patil *et al*. study.[10]

In this study, the induction-to-delivery time was significantly longer in misoprostol group versus dinoprostone group.

Dodd *et al*. compared titrated misoprostol versus vaginal dinoprostone for labor induction, and they found that the induction-to-delivery time was significantly longer in titrated oral misoprostol versus dinoprostone group (21.2 h vs. 18.4 h, respectively).[11]

Hofmeyr *et al*. randomized 695 women to receive either titrated misoprostol solution or dinoprostone 2 mg, for labor induction, and they found that the induction-to-delivery time was longer in misoprostol versus dinoprostone group (17.1 vs. 14.25 h, respectively).[6]

On the other hand, Patil *et al*.[10] found that the induction-to-delivery time shorter in oral misoprostol group (11.68 ± 4.49 h) compared to intracervical dinoprostone (14.83 ± 7.08 h).

This difference between this study and Patil *et al*.[10] study regarding induction-to-delivery time is due to the different dose and route regimens of both oral misoprostol and dinoprostone used in this study compared to Patil *et al*. study.[10]

In this study, 20.2% of women in misoprostol group did not deliver vaginally within 24 h compared to 7.4% in dinoprostone group.

Although Sheela *et al*. found that 35% women in misoprostol group did not deliver vaginally within 24 h compared to 13% in the vaginal dinoprostone group (high significant difference).[12]

Hofemyr *et al*. found that 38% of women in misoprostol group did not deliver vaginally within 24 h compared to 36% in the vaginal dinoprostone group (no significant difference).[6]

In addition, Dällenbach *et al*. found no significant difference in the percentage of women who did not deliver vaginally within 24 h between misoprostol group compared to dinoprostone group (44% vs. 38%, respectively).[13]

Prolonged labor was observed in this study in titrated oral misoprostol group, while labor duration was same in misoprostol and dinoprostone groups in Hofemyr *et al*.[6] and Dällenbach *et al*.[13] studies. This may be due to wide scale usage of epidural analgesia in other studies, which causes prolonged labor and prolonged second stage.[14]

Percentage of cesarean section was similar with no difference between two studied groups; 2.9% in oral misoprostol group versus 5.6% in vaginal dinoprostone group. Cesarean sections were done in oral misoprostol group due to fetal distress (1.9%) and failed induction (1% [1/104]), while cesarean sections were done in vaginal dinoprostone group due to failed induction (3.7%), protracted labor (0.9%), and fetal distress (0.9%).

Patil *et al*. found no significant difference between oral misoprostol group and intracervical Dinoprostone group regarding the percentage of cesarean section; however, the indications for cesarean section in the two studied groups were different.[10]

Cesarean sections indicated in oral misoprostol group due to fetal distress, meconium stained liquor, hypertonic contractions not responding to pharmacologic drugs, and failure to progress, while cesarean sections indicated in vaginal dinoprostone group due to failed induction, fetal distress, and meconium stained liquor.[10]

Hofemyr *et al*. found that the rate of cesarean section was less in titrated oral misoprostol group (16%) versus vaginal dinoprostone group (20%), and this difference was statistically insignificant.[6]

Alfirevic *et al*. concluded that oral misoprostol as an induction agent is effective in achieving a vaginal birth. It is more effective than placebo, as effective as vaginal misoprostol and results in fewer cesarean sections than vaginal dinoprostone or oxytocin.[15]

In addition, Alfirevic *et al*. concluded that the evidence supported the use of oral misoprostol over vaginal regimens and suggested a dose of oral misoprostol should be 20–25 mcg in solution.[15]

Aalami-Harandi *et al*. concluded that misoprostol is a safe and effective drug with low complications for the induction of labor and cesarean sections are less frequently indicated with misoprostol as compared to oxytocin.[16]

In addition, Ho *et al*. concluded that labor augmentation with titrated oral misoprostol or intravenous oxytocin resulted in similar rates of vaginal delivery within 12 and 24 h.[17]

Epidural analgesia used in 6.7% of women in oral misoprostol group compared to 3.7% in vaginal dinoprostone group in this study (no significant difference).

The need for augmentation of labor was significantly high in vaginal dinoprostone (37.96%) compared to oral misoprostol group (10.6%).

Hofemyr *et al*. found that 30% of women in misoprostol group managed by artificial rupture of membranes versus 33% in vaginal dinoprostone group (this may be attributed to the inclusion of women with rupture of membranes in their study).[6] In addition, Hofemyr *et al*. found that augmentation of labor was needed in 33% of women in vaginal dinoprostone group compared to 17% in titrated oral misoprostol group.[6]

Uterine hyperstimulation recorded in 0.94% of both studied groups and one case (0.47%) of them was associated with fetal heart rate changes with no significant difference between two studied groups.

Hofemyr *et al*. found that 4% of uterine hyperstimulation with fetal heart rate changes was recorded in misoprostol group versus 3% in vaginal dinoprostone group with no significant difference.[6]

Dodd *et al*. found that 1.6% of uterine hyperstimulation with fetal heart rate changes recorded in dinoprostone group compared to 0.8% in misoprostol group.[11]

Randomized trials comparing titrated oral misoprostol with placebo, other interventions (oxytocin, other prostaglandins), or no treatment for labor augmentation conducted by Vogel *et al*.[18]

Vogel *et al*. concluded that low-dose titrated misoprostol may offer a better alternative to an uncontrolled oxytocin infusion to avoid hyperstimulation.[18]

In addition, Souza *et al*. concluded that the oral solution of misoprostol was effective and safe for the induction of labor. However, further randomized controlled trials are needed to compare this new formulation with misoprostol administered by the vaginal route.[19]

Souza *et al*. in another study concluded that a titrated oral misoprostol solution was as effective and safe for labor induction as vaginal misoprostol tablets.[20]

Birth weight, 5 min Apgar score <7, and rate of NICU admission were similar with no significant difference between two studied groups.

Hofemyr *et al*. found that the 5 min Apgar score <7 was 3% in misoprostol group versus 4% in Dinoprostone group and 2% NICU admission in misoprostol group versus 3% in dinoprostone group.[6]

Zvandasara *et al*. concluded that titrated oral misoprostol suspension is as effective and safe as vaginal misoprostol for induction of labor even in poor resource countries where intrapartum monitoring is inadequate.[21]

Cheng *et al*. concluded that titrated oral misoprostol solution is a promising method of labor induction for both nulliparous and multiparous women.[22]

The strength of this study is coming from the comparative nature of the study and proper statistical analysis, while women refused to participate in this study and technical difficulties preparing placebo for both misoprostol solution and vaginal dinoprostone were limitations faced during conduction of this study.

Low titration dose of misoprostol used in this study explains the vaginal birth achieved after 24 h in titrated misoprostol group. Further clinical studies are needed to reach proper titration dose for oral misoprostol and to encourage the availability of this dose in markets for safe use in labor induction.

CONCLUSION

Titrated misoprostol for induction of labor seems to be associated with significantly longer induction-to-delivery time, low incidence of vaginal birth within 24 h, and less need for augmentation of labor compared to vaginal dinoprostone.

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Conflicts of interest

There are no conflicts of interest.

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