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Titrated oral misoprostol as a safe route for induction of labour at term (a clinical trial)

Abstract

Objective: To assess safety and efficacy of induction of labour at term by low doses of oral misoprostol in the form of titration versus the standard regimen of vaginal misoprostol in the term of induction delivery interval, operative interventions and fetal outcome.

Methods: Clinical comparative study was carried out for a period of one year from November 2008 to October 2009 at Zagazig university hospital. The study protocol was approved by the ethics committee of our hospital. One hundred women at term with indication of labour and Bishop score less than or equal 5, no either Obstetric or maternal contraindications for induction of labour were randomly assigned to receive oral (titrated) or vaginal misoprostol for induction of labour. The oral group received a basal of 20ml misoprostol solution (1mcg/ml) every hour for four doses and then were titrated according uterine response individually, the vaginal group received 25mcg every 4hours(maximum number of doses limited to six) until cervix became more favorable. The induction delivery interval, oxytocin need, mode of delivery, frequency of side effects and neonatal and maternal outcome were assessed. Chi-square or Fisher exact test, Student's T-test and Wilcoxon rank sum test were used for analysis the data statistically.

Results: The oral misoprostol group had 50 women (50%) and was given it in the form of titrated oral solution and vaginal misoprostol group had 50 women (50%). Vaginal delivery occurred within 12hours in 38 women (76%) in oral group and in 12 women (24%) in vaginal group. The median interval from starting induction by misoprostol to vaginal delivery was significantly shorter in oral titrated misoprostol group (7.5h) compared with vaginal misoprostol group (16.1h) with P value <0.01.The incidence of hyper-stimulation in oral group was 0.0% compared with 12% in vaginal group with P value <0.01 which is significantly different. More women had nausea 8% in oral group but fewer infants had Apgar score less than 7 at 1minute in oral group than in vaginal group.

Conclusion: Oral misoprostol in the form of titration is associated with lower incidence of uterine hyper-stimulation and lower cesarean delivery rate, better fetal outcome than vaginal misoprostol for labour induction at term in patients with unripe cervix.

Keywords: misoprostol, induction of labour, hyper-stimulation

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Introduction

Induction of labour is to start uterine contraction prior to their spontaneous onset accompanied with cervical dilatation, effacement and descent of fetal presenting part.[1] Induction of labour is frequently indicated for a variety of obstetric and medical problems to achieve benefit to the health of mother and/or baby which must exceed that to be gained by continuing the pregnancy.[2] It is carried out in over 20% of pregnancy in developed countries.[3] As prenatal mortality and fetal compromise increase progressively with gestation beyond 37weeks. Induction of labour between 37weeks and 41weeks has the potential to improve neonatal outcome.[4]

Induction of labour at term in the presence of an unfavorable cervix is associated with an increased risk of failed induction and caesarean section. Therefore, cervical ripening for induction should be assessed before a regimen is selected. Assessment is accomplished by calculating Bishop score.[5] Although the indications of induction of labour have clearly changed during the past 200years from a need to expel a dead fetus to reduce the threat to fetal or maternal health, effective and safe methods of achieving delivery must always be the primary objectives. Among the more old common approaches for induction of labour are frequent walking, vaginal intercourse, consumption of laxative, spicy food or herbal tea, nipple stimulation and administration of an enema.[6] During the past 40years, labour induction had mostly involved combining the recognized advantages of physical manipulation with a pharmacological myometrial stimulant. Prostaglandin preparations with or without oxytocin infusion is widely recognized and accepted as standard method of labour induction.[7] Prostaglandins remain the single most effective means of achieving cervical ripening and inducing labour when combined with a timed amniotomy, providing good clinical effectiveness. Prostaglandin E2 is registered for labour induction in many countries. However it is expensive in developing countries and because it is sensitive to temperature changes, it needs to be kept under refrigeration so they are inconvenient to use.[8] Thus, there is a need for less costly and less temperature-sensitive alternative. Misoprostol, a prostaglandin E1 analogue, is an alternative agent for induction of labour. It is less expensive than dinoproston and requires

no special storage arrangement.[9] Misoprostol is an oral prostaglandin compound, structurally related to prostaglandin E1 and manufactured as treatment for peptic ulcer disease.[10] Though unlicensed for this indication, it is being used increasingly in induction of labour with vaginal or oral administration.[1]

A number of randomized controlled trials support the effectiveness of misoprostol administration at term for cervical ripening and induction of labour.[11] Some studies suggest that vaginal administration of misoprostol is more effective than oral but there is significant increase in tachysystol and hyper stimulation with the use of vaginal misoprostol compared to oral use.[12] Oral misoprostol has some advantages in comparison with vaginal misoprostol like ease of administration and avoidance of repeated vaginal examination to insert it.[13] Based on pharmacokinetic findings, it was found that peak serum concentration after oral administration is 34minutes and half-life of 20-40minutes. Peak serum concentration is 60-80minutes for vaginal misoprostol and this level is sustained for up to 4hours.[14] So, the shorter half-life of the oral misoprostol, delivery may be safe in the event of uterine hyper stimulation although vaginal one has advantageous direct local effect in cervical ripening.[15] There are different recommendations about ideal dose of either vaginal or oral administration of misoprostol. In this study; the objective was evaluation of safety and efficacy of using repeated small doses of oral misoprostol by titration in comparison to vaginal administered vaginal misoprostol in induction of labour at term.

Material and methods

This randomized clinical study was carried out between November 2008 to October 2009 in obstetric Department at Zagazig University Hospital. The study protocol was approved by the ethics committee of Zagazig University hospitals. The randomization was performed using a computer-generated random number table. An informed consent was obtained from the selected women. Sample size was 100 pregnant women at or beyond term were scheduled for induction of labour due to an obstetric or medical indication. Inclusion criteria were: singleton pregnancy, cephalic presentation, gestational age of 37-42weeks confirmed by menstrual dates and first ultrasound, Bishop score ≤5. Exclusion criteria were: Previous uterine scar, parity more than four, non reassuring fetal heart pattern, mal presentation, multiple pregnancy, placental abruption and known allergy to prostaglandins. Fifty cases were allotted to either group of two groups. Group (1) was oral (titration) misoprostol and Group (2) was vaginal misoprostol. After complete history and clinical examination, a reassuring fetal heart tracing was confirmed with cardiotocography. Vaginal examination was performed to assess Bishop score. Women of the vaginal group received 25mcg every 4hours into the posterior fornix of vagina until cervix became more favorable (Bishop score ≥7 or adequate uterine activity; more than or equal to 3 contractions in 10minutes or entering active labour, the maximum number of doses limited to six. Women of the oral (titrated) misoprostol group were started induction with a basal unit of 20ml misoprostol solution (1mcg\ml) every one hour prepared by dissolving one tablet of misoprostol 200mcg in 200ml distilled water in medicine bottle[16] until adequate uterine contractions were achieved. If contractions did not occur after four doses of those before, the dosage was increased to 40mcg and repeated every hour until uterine contractions were achieved, with a maximum of four more doses. If the uterine activity still remained weak, the dosage was increased to 60 mcg per hour until adequate response. Once that occurred no more misoprostol was given. If uterine activity subsequently became insufficient, again hourly doses of misoprostol solution were started with 10mcg and could be increased to 20mcg and could be 40mcg according to uterine response. The misoprostol solution was used completely within 24hours after preparation or discarded. Fetal well being was confirmed by cardiotocography and Bishop Score was assessed prior to every dose of misoprostol either given vaginally or orally. Fetal heart rate and uterine activity were continuous monitored throughout labour induction. If diagnosis of labour was made or the Bishop`s score was 8 or more the woman was transferred to labour room and artificial rupture of membrane could be formed if it had not occurred. The use of oxytocin as supplementation if uterine activity were insufficient when entering the active phase due to weak response to misoprostol, was according to protocol of the hospital and was not started less than 4hours after the last dose of misoprostol either orally or vaginally. It administrated through an infusion with an initial dose of 1mu\min to a maximum of 32mu\min. A partogram recording the progress of labour was maintained. Induction failure was clear as not entering into active phase after 24hours of misoprostol conduct. Cesarean delivery was presented to those patients had failed induction or prolonged active phase. If uterine hyper stimulation occurred, intravenous magnesium sulfate in the dose of 4g through 30minutes was given. Adequate uterine contraction in the study was defined as occurance of it every 2-3minutes and lasting 60-90seconds. Hypertonus was defined as a single contraction lasting more than 2minutes. Tachysystol as the presence of at least six contractions in 10minutes over at least two 10minutes windows. Hyper stimulation was defined as tachysystol or hypertonus with non reassuring FHR changes like; late deceleration, severe variable deceleration, prolonged deceleration, tachycardia or reduced FHR variability need intervention by tocolytics or delivery. Induction failure was defined as not entering into the active phase after 24hours of misoprostol treatment. The primary measures used to evaluate efficacy were: The interval from the first misoprostol dose to vaginal delivery and percentages of women delivered vaginally within 12hours and 24hours of induction. The primary measures used to evaluate safety were the frequency of tachysystol, hypertonus, nonreassuring FHR and\or uterine hyper-stimulation. The secondary measures accustomed to evaluate efficacy or safety included total dosage of misoprostol, rate of women given oxytocin, cesarean delivery and induction failure, neonatal outcomes counting lower Apgar score <7 at 5minutes, need positive pressure ventilation, intubation or admission to neonatal intensive care unit. Statistical analysis was performed with the use of Chi-square or Fisher exact test for discontinuous variables such as parity, mode of delivery, Apgar score and the number of complications. Student's t-test was used to analyze group differences in maternal age. The interval between use of misoprostol to delivery, and total dosage of used misoprostol with Wilcoxon rank test. P value of <0.05 was considered statistically significant.

Results

One hundred women were incorporated in this study. 50 women (50%) received oral misoprostol in the form of titrated solution and 50 women (50%) received vaginal misoprostol. The demographic characteristics of them were shown in Table 1, There were no statistically significant differences in maternal age, parity or initial Bishop score. The indications of induction of labour were shown in Table 2. The two groups were similar in most of those indications. The primary outcomes of induction were shown in Table 3. The median interval from the first dose of misoprostol to delivery was 7.5hours

in the oral titrated group and 16.1hours in vaginal group (P<.01). There were significantly more women who delivered vaginally in the oral group within 12hours (76%) and in 24hours (96%) compared to vaginal group who within 12hours (24%) and within 24hours (64%). There were no significant differences between both groups in occurrence of hypertonus. Tachysystol developed in 3(6%) women in oral titrated group and 8(16%) in vaginal group. When tachysystol happened in oral titrated group misoprostol was stopped immediately in this group. So hyper stimulation did not occur in oral titrated group but happened in 6 women (12%) in vaginal group (Table 3). Non reassuring FHR patterns that need urgent delivery was renowned in one (2%) woman in oral titrated group and in 6(12%) women in the vaginal group. The median total dosage of misoprostol was 190 mcg in oral titrated group and 50 mcg in the vaginal group (P<.01). About oxytocin augmentation 4(8%) women only need it in oral titrated group but in 23(46%) women in vaginal group so there were significant differences between the two group (Table 4). The mode of delivery differed significantly between the both groups; Six (12%) women in the vaginal group underwent cesarean section compared with two (4%) women only in oral titrated group. About maternal adverse effects; there was significant difference between two groups in nausea, it happened in 4 (8%) and vomiting in two (4%) in the oral titrated group and no patients had nausea or vomiting in vaginal group. No significant difference between both group in occurrence of shivering, pyrexia or diarrhea (Table 5). There were significant difference in neonatal outcomes according to Apgar score in 1minute (Table 6) as more newborn with Apgar score less than 7 at 1minute in vaginal group. Two newborn need resuscitation and were admitted to neonatal intensive care unit in the same group.

Table 1 Characteristics of women of study

Character	Oral titrated misoprostol n=50	Vaginal misoprostol n=50	P
Age	23.2 ± 3.2	24.7 ± 3.6	0.4
Gestational age	39.3 ± 1.2	39.8 ± 1.4	0.3
Bishop score ≤5	50100%	50100%	0.5
Nullipara	2448%	2652%	0.1
Multipara	2652%	2448%	0.1

Data are presented as mean±standard deviation. n=number.

Table 2 Indications for induction

Indications	Oral titrated misoprostol n=50	Vaginal misoprostol n=50	P
Postterm	26(52%)	24(48 %)	0.65
Premature rupture of membranes	15(30%)	16(32%)	0.1
Hypertension	3(6%)	3(6%)	0.1
Diabetes	2(4%)	2(4%)	0.35
Social causes	4(8%)	5(10%)	0.67

Data of indications are (%) with no significant differences

Table 3 Primary induction outcomes

Outcome	Oral titrated misoprostol n=50	Vaginal misoprostol n=50	P
Starting dose to vaginal delivery (h)	7.5 (QR 5.1)	16.1 (QR 17.5)	<0.01
Vaginal delivery in12h	38 (76%)	12 (24%)	<0.01
Vaginal delivery in24h	48 (96%)	32 (64%)	<0.1
Non reassuring FHR	1 (2%)	6 (8%)	0.6
Tachysystole	3 (6%)	8 (16%)	0.7
Hypertonus	0 (0%)	0 (0%)	1
Hyper stimulation	0 (0%)	6 (12%)	<0.01
Repture uterus	0 (0%)	0 (0%)	1
Use of tocolysis for hyper tstimulation	0 (0%)	6 (8%)	0.05

QR, quartile range; Data are median, or (%); FHR, fetal heart rate

Table 4 Secondary outcomes of labour induction

Outcome	Oral Titrated Misoprostol n=50	Vaginal Misoprostol n=50	P
Total dosage (mcg)	190(QR 200)	50(QR 25)	<0.01
Oxytocin augmentation	4(8%)	23(46%)	<0.01
Vaginal delivaries	48(96%)	44(89%)	<0.01
Cesarean section delivaries	2(4%)	6(12%)	<0.01
Induction failure	0(0%)	5(10%)	<0.01

QR, quartile range; Data are median or (%).

Table 5 Maternal adverse effects

Adverse Effects	Oral titrated misoprostol n=50	Vaginal misoprostol n=50	P
Nausea	4(8%)	1(2%)	<0.01
Vomiting	2(4%)	0(0%)	<0 .01
Diarrhea	1(2%)	0(0%)	< 0.5
Shivering	1(2%)	1(2%)	1
Pyrexia	0(0%)	1(2%)	0.5

Data are (%).

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Table 6 Neonatal outcomes

	Oral titrated misoprostol n=50	Vaginal misoprostol n=50	P
1 min Apgar score <7	0%	5(10%)	0.03
5 min Apgar score <7	0%	3(6%)	0.18
Need for PPV	0%	2(4%)	0.16
Need for intubation	0%	2(4%)	0.16
NICU admission	0%	2(4%)	0.16

NICU, neonatal intensive care unit; PPV, positive pressure ventilation

Discussion

In recent years, there has been significant interest in the use of misoprostol for cervical ripening and induction of labour. Misoprostol administrated either vaginally or orally.[1] Different doses of misoprostol were studied but the most widely used was 25mcg every 4hours as accompanied with least number of complications and accepted as the most effective[(17)]. The aim of this study to assess clinical outcome and compare the efficacy and safety of new dosing regimen of oral titrated misoprostol in comparing it with the widely used regimen of vaginal misoprostol every 4hours. Vaginal rout of misoprostol is associated with Uterinetachysystol and hyperstimulation as probable disadvantages. Furthermore, the risk of introducing ascending infection.[2] Thus, oral rout may be a better alternative. In this study, It was tried to use oral misoprostol in small, frequent doses in titration to avoid uterine hyper stimulation and shorten time of labour induction to vaginal delivery. Measures used to assess efficacy were the interval from the first dose of misoprostol to vaginal delivery, the percentages of women who delivered vaginally within 12 and 24hours of labour induction and induction failure. It was found that the median interval from first dose to vaginal delivery was significantly shorter in oral titrated group (7.5hours) in comparing to vaginal group (16.1hours). Also there were more women delivered vaginally within 12hours (76%) and within 24hours (98%) in oral titrated group in comparing to vaginal group. Therefore these results hold that the efficacy of oral titration misoprostol is better than vaginal rout of misoprostol. The measures used to assess safety in this study were incidence of tachysystol, hypertonus, uterine hyper stimulation, and neonatal outcomes. In spite of occurrence of tachysystol in (6%) of women in oral titrated group, the oral titrated solution was stopped immediately until uterine contractions decreased so, no woman had developed hyper stimulation. These results proposed that small dosage with continuous adjustment according to response is superior way to reduce incidence of uterine hyper-stimulation. The median total dosage in oral titrated group was 190mcg which was more than three times that of vaginal group, but the need of oxytocin augmentation was less in oral titrated group as misoprostol has both uterotropic and uterotonic effects. These findings agreed with Shi-Yann et al.[17] who found that titrated oral misoprostol was associated with a lower incidence of uterine hyper stimulation than vaginal misoprostol for labour induction in patients with unfavorable cervix. In this study, the percentage of cesarean section in the women received oral titrated misoprostol was significantly lower than in vaginal group and this suggests that the repeated small oral doses of misoprostol ripened cervix and enhanced the vaginal delivery in term pregnancy with unfavorable cervix. The maternal adverse side effects of misoprostol were more frequent in oral titrated group but less than those recorded in other studies like study of Shetty et al.[13] as they used high oral doses. Neonatal outcome in oral titrated group were better than vaginal group as regard Apgar score assessment at 1minute also no one need admission to neonatal intensive care unit in comparing to vaginal group.

Conclusion

This study suggests that oral misoprostol in small, repeated doses in the form of titration has more efficacy and safety and associated with a low incidence of uterine hyper-stimulation and low cesarean delivery rate than vaginal misoprostol for induction of labour at term with unripe cervix.

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None.

Conflict of interest

The author declares no conflict of interest.

References

1. Alfirevic Z, Weeks A. Oral Misoprostol for induction of labour. *Cochr ne Database Syst Rev*. 2006;(2):CD001338.
2. Beigi A, Kabiri M, Zarrinkoub F. Cervical ripening with oral misoprostol atterm. *Int J Gynaecol Obstet*. 2003;83(3):251–255.
3. Mealing NM, Roberts CL, Ford JB, et al. Trends in induction of labour, 1998-2007: a population-based study. *Aust N Z J Obstet Gynaecol*. 2009;49(6):599–605.
4. Smith GC. Life-table analysis of the risk of perinatal death at term and post term in single tone pregnancies. *Am J Obstet Gynecol*. 2001;184(3):489–496.
5. Hofmeyr GJ. Induction of labour with an unfavorable cervix. *Best Pract Res clin Obstet Gynaecol*. 2003;17(5):777–794.
6. Schaffir J. Survey of folk beliefs about induction of labour. *Birth*. 2002;29(1):47–51.
7. Kelly AJ, Kavanagh J, Thomas J. Vaginal Prostaglandins for induction of labour at term. *Cochrane database sys Rev*. 2003;(4):CD003101.
8. Bartusevicius A, Barcaite E, Krikstolaitis R, et al. Sublingual compared with vaginal Misoprostol for labour induction. *Br J Obstet Gynaecol*. 2006;113(12):1431–1437.
9. Gregson S, Waterstone M, Norman I, et al. A randomized controlled trial comparing low dose vaginal Misoprostol and dinoprostone vaginal gel for inducting labour at term. *BJOG*. 2005;112(4):438–442.
10. Hofmeyr GJ, Gülmezoglu AM. Vaginal Misoprostol for cervical ripening and labour induction in late pregnancy. *Cochrane Database Syst Rev*. 2003;(1):CD000941.
11. Sanchez-Ramos L, Kaunitz AM, Wears RL, et al. Misoprostol for cervical ripening and labour induction: a meta-analysis. *ObstetGynecol*. 1997;89(4):633–642.
12. Fisher SA, Mackenzie VP, Davies GA. Oral versus vaginal misoprostol for induction of labour : a double-blind randomized controlled trial. *Am J Obstet Gynecol*. 2001;185(4):906–910.
13. Shetty A, Mackie L, Danielian P, et al. Sublingual compared with oral misoprostol in term labour induction: a randomised controlled trial. *BJOG*. 2002;109(6):645–650.

14. Zieman M, Fong SK, Benowitz NL, et al. Absorption kinetics of misoprostol with oral or vaginal administration. *Obstet Gynecol*. 1997;90(1):88–92.

15. Danielsson KG, Marions L, Rodriguez A, et al. Comparison between oral and vaginal administration of misoprostol on uterine contractility. *ObstetGynecol*. 1999;93(2):275–280.

16. Hofmeyr GJ, Alfirevic Z, Matonhodze B, et al. Titrated oral misoprostol solution for induction of labour: a multi-centre, randomised trial. *BJOG*. 2001;108(9):952–959.

17. Cheng SY, Ming H, Lee JC. Titrated oral compared with vaginal Misoprostol for labour induction. *Obstet Gynecol*. 2008;111(1):119–125.

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