Original Article

Oxytocin versus sublingual misoprostol for induction of labour in term prelabour rupture of membranes: A randomized controlled trial

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ABSTRACT

Background: Induction of labor is one of the most common interventions practiced in modern obstetrics. In the developed World, the ability to induce labor has contributed to the reduction in maternal and perinatal mortality and morbidity**.**

Aim: This study aimed to evaluate the effect of pre-labour administration of sublingual misoprostol versus oxytocin in term PROM on maternal and fetal outcomes.

Materials and Methods: In a randomized single-blind controlled trial at department of obstetrics and gynecology, Menoufia University between September 2018 and October 2019. A total of 100 pregnant women who had spontaneous rupture of membrane and unripe cervix were enrolled. The group A underwent Oxytocin infusion according to low-dose standard protocol and the group B received 50 microgram sublingual Misoprostol every 6 hours.

Results: There was a significant reduction in induction duration hours between Misoprostol group than Oxytocin group ($p<0.001$). Second stage of labour was significantly shorter in misoprostol group. Although, some maternal side-effects were non-significantly higher in misoprostol group. There was no significant difference between Oxytocin and Misoprostol groups regarding neonatal condition.

Conclusion: pre-labour administration of sublingual misoprostol in patients with singleton term pre-labour rupture of membranes shorten duration of both active phase and second stage of labour significantly in comparison with oxytocin administration.

Key Words: Induction, misoprostol, oxytocin, pre-labour rupture of membranes

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INTRODUCTION

Prelabour rupture of membranes (PROM) is defined as the rupture of membranes before the beginning of uterine contractions. This event occurs in about 8–10% of pregnancies and about 60% of these cases are term pregnancies[1].

The increase in time interval between rupture of membranes and onset of labour pains is associated with increase in the incidence of complications such as chorioamnionitis, endometritis, chronic abruption, cord compression, neonatal morbidity and neonatal sepsis[2].

Misoprostol is a synthetic prostaglandin E1 analogue was developed for gastric ulcer prevention but commonly used in reproductive health because of its uterotonic and cervical priming action[3].

Misoprostol is usually used vaginally for cervical ripening and induction of labour, even in PROM cases. However, meta-analyses of randomized trials have not demonstrated any clear benefit with the use of any type of prostaglandin in women with PROM, including in women with an unfavorable cervix[4].

The effectiveness of sublingual misoprostol in labour induction of PROM patients is not evaluated in any of these studies[5].

Oxytocin is a neurohormone secreted by the posterior pituitary. It stimulates the myometrium to contract, Since the discovery and use of the posterior pituitary extract in 1948, followed by its synthesis 5 years later, oxytocin is one of the most commonly used drugs in the United States[6].

AIM OF THE STUDY

The objective of this study was to evaluate the effect of pre-labour administration of sublingual misoprostol versus oxytocin in term PROM on maternal and fetal outcomes.

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PATIENTS AND METHODS

In a single-blind, randomized, controlled trial conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Menoufia, Egypt, 100 women undergoing induction of labour by sublingual misoprostol versus oxytocin, between September 2018 and October 2019 were enrolled. Written informed consent was obtained from each eligible participant.

During the study period, women with pre-labour rupture of membranes were initially counseled about the available treatment options.

A total of 100 women were included in this study. They were randomly allocated in two groups; Group A received oxytocin (50 patients) and group B received misoprostol (50 patients).

Those randomized to group A received intravenous oxytocin (syntocinon, Novartis Pharmaceutical Limited) by continuous infusion following a low-dose protocol starting with 2mU/min and increasing 2mU/min each 20 minutes using an infusion pump until adequate contractions were achieved. Whereas, those allocated to group B received a pre-prepared sealed opaque packet containing 50 µg of misoprostol (Cytotec-misoprostol tablet G.D. Searle LLC Division of Pfizer Inc; 1 tablets of 200 µg).

Baseline demographic data comprising age, parity, body mass index (calculated as weight in kilograms divided by the square of height in meters), gestational age, parity and Bishop Score were recorded.

The inclusion criteria of the study were as followed singleton pregnancy, PROM between 37 and 41 weeks of gestation, cephalic presentation, no history of hypersensitivity to prostaglandins, no contraindication of vaginal delivery (like placenta previa, abruption placenta, previous uterine scar, non-reassuring fetal hear pattern), reassuring fetal heart rate patterns by CTG and Bishop scores less than 6. Exclusion criteria were abnormal fetal heart rate patterns by CTG, patient's refusal for being in the study and cephalopelvic disproportion (CPD).

The followings were done for all patients included in the study; detailed history taking, gestational age was calculated based on the first day of last menstrual period (LMP) or the first trimester ultrasonography, general examination was done and vital data was recorded, abdominal and pelvic examination, obstetric US was done, fetal monitoring was recorded continuously by CTG, labour progress was recorded on WHO modified partographic tracing and the total duration from start of induction to delivery was recorded.

Patients with PROM were diagnosed via vaginal speculum examination in order to determine the amniotic fluid leakage. Bishop score was determined by assessing cervical dilation, effacement, station, position and cervical consistency.

One hundred women were randomly assigned to receive either sublingual misoprostol (Cytotec) microgram every 6 hours (to a total of four doses or until the patient entered active phase of labour) or intravenous oxytocin (syntocinon) by continuous infusion following a low-dose protocol starting with 2mU/min and increasing 2mU/min each 20minutes (using an infusion pump) until adequate contractions will be achieved (3 contractions every 10 minutes) or reaching 12 hours from starting oxytocin induction.

The baseline demographic characteristics of the women was recorded. Fetal heart rate (FHR) was continuously monitored during the induction of labour to diagnose any potential abnormality, and appropriate treatment was initiated according to FHR category tracing if needed. Conservative management was the first option for these abnormalities (left lateral positioning, O2 therapy, discontinuation of oxytocin infusion, hydration with 500cc Ringer lactate for 30 minutes). If the abnormalities did not improve with conservative management, our next steps were determined by the FHR abnormality category. Prophylactic antibiotics were administered to prevent neonatal sepsis in cases in which PROM was more than 18 hours or if body temperature was 38 C and it was suspected to represent chorioamnionitis.

The primary outcome measure was the number of women delivering vaginally within 24 hours of the first dose or start of oxytocin.

Secondary outcome measures were the interval from induction to vaginal delivery, the number of misoprostol doses given, mode of delivery, uterine hyperstimulation and maternal satisfaction.

The study was done after approval of ethical board of Menoufia University and an informed written consent was taken from each participant in the study.

STATISTICAL ANALYSIS:

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013.

Descriptive statistics were done for quantitative data as minimum and maximum of the range as well as mean ± SD

(standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using independent t-test in cases of two independent groups with normally distributed data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher's Exact test for variables with small expected numbers. The level of significance was taken at *P value < 0.05* is significant, otherwise is non-significant.

RESULTS

In this study, there were no significant differences between the studied groups regarding maternal characteristics (mean age 25.2 vs 26.1) (mean BMI 25.2 vs 25.7) (mean bishop score 3.9 vs 3.8). Nulliparous women in oxytocin group were 32% vs 26% in misoprostol group, while multiparous women were 68 % in oxytocin group vs 74 % in misoprostol group (Table 1).

In this study, induction duration was significantly longer among oxytocin group than among misoprostol group (mean duration was 8.2 hours in oxytocin group vs 6.8 hours in misoprostol group) (Table 2).

In this study, CS delivery was non-significantly more frequent among misoprostol group than among oxytocin group (26% in oxytocin group vs 14 % in misoprostol group) (Table 3). Failed induction and arrest of labor were non-significantly more frequent among oxytocin group than among misoprostol group (23.1% vs 57.1% and 23.1 % vs 28.6 %, respectively). However, non-reassuring CTG pattern was non-significantly more frequent among misoprostol group than among oxytocin group (53.8 % vs 14.3%).

In the current study, second phase duration was significantly shorter among misoprostol group than among oxytocin group (mean duration was 39.7 minutes vs 42.3 minutes) (Table 4).

Tachysystole and hyperstimulation were non-significantly less frequent among oxytocin group than among misoprostol group (8% vs 2% and 6 % vs 2% respectively). Moreover, nausea, vomiting and fever were non-significantly less frequent among oxytocin group than among misoprostol group (Table 5).

According to neonatal condition among the studied groups, there were no significant differences between oxytocin and misoprostol groups regarding neonatal condition (mean APGAR 5 minutes was 8.3 vs 8.4) (Table 6).

However in this study, mean NICU admission was 6 % vs 4 % in misoprostol and oxytocin, respectively, and this was consistent with Pourlail *et al.* 2018 who found that two neonates in each group were admitted to NICU and there was no statistical difference between the two groups.

Table 1: Demographic characteristics among the studied groups

Variables		Oxytocin (N=50)	Misoprostol (N=50)	*P*
Age (years)	Mean±SD	25.2±4.2	26.1±4.5	^ 0.290
	Range	19.0–36.0	19.0–36.0	
BMI (kg/m2)	Mean±SD	25.2±2.1	25.7±2.4	^ 0.327
	Range	20.8–30.5	21.6–31.5	
GA (weeks)	Mean±SD	38.9±1.2	38.7±1.0	^ 0.417
	Range	37.0–41.0	37.0–41.0	
Bishop score	Mean±SD	3.9±0.9	3.8±0.8	^ 0.478
	Range	3.0–5.0	3.0–5.0	
Parity	Nulliparous	16 (32.0%)	13 (26.0%)	# 0.509
	Multiparous	34 (68.0%)	37 (74.0%)	

Table 2: Induction duration (hours) among the studied groups

Variables	Misoprostol (N=50)	Oxytocin (N=50)	^*P*
Mean±SD	6.8±1.8	8.2±1.9	<0.001*
Range	4.1–10.9	4.8–11.5	
	Value of Misoprostol over Oxytocin		
Phase		Mean±SE	95% CI
Induction duration reduction		1.4±0.4	0.6–2.1

P value -0.002

Table 3: CS delivery and its indications among the studied groups

	Misoprostol (N=50)	Oxytocin (N=50)	*P*	RR (95% CI)
CS	13 (26.0%)	7 (14.0%)	#0.134	1.86 (0.81–4.26)
Indications of CS				
Failed induction	3 (23.1%)	4 (57.1%)	§0.174	0.40 (0.12–1.32)
Arrest of labor	3 (23.1%)	2 (28.6%)	§1.000	0.81 (0.17–3.75)
Non-reassuring CTG pattern	7 (53.8%)	1 (14.3%)	§0.158	3.77 (0.57–24.78)

Table 4: Second stage duration (minutes) in cases underwent vaginal delivery among the studied groups

Variables	Misoprostol (N=37)	Oxytocin (N=43)	^*P*
Mean±SD	39.7±3.1	42.3±2.7	0.001*
Range	32.0–46.0	37.0–48.0	
	Value of Oxytocin over Misoprostol		
Stage		Mean±SE	95% CI
Second stage shortening		2.3±0.7	1.3–3.8

Table 5: Maternal adverse effects among the studied groups

Effects	Misoprostol (N=50)	Oxytocin (N=50)	§P	RR (95% CI)
Tachysystole	4 (8.0%)	1 (2.0%)	0.362	4.00 (0.46–34.54)
Hyperstimulation	3 (6.0%)	1 (2.0%)	0.617	1.50 (0.26–8.60)
Nausea	5 (10.0%)	1 (2.0%)	0.204	5.00 (0.61–41.28)
Vomiting	2 (4.0%)	1 (2.0%)	1.000	2.00 (0.19–21.36)
Fever	5 (10.0%)	2 (4.0%)	0.436	2.50 (0.51–12.29)
PPH	1 (2.0%)	2 (4.0%)	1.000	0.50 (0.05–5.33)

Table 6: Neonatal condition among the studied groups

Indications		Misoprostol (N=50)	Oxytocin (N=50)	*P*	RR (95% CI)
APGAR1	Mean±SD	7.2±0.9	7.1±0.9	^ 0.912	--
	Range	4.0–9.0	4.0–9.0		
APGAR5	Mean±SD	8.4±1.0	8.3±1.1	^ 0.637	--
	Range	5.0–10.0	4.0–10.0		
Birth weight (kg)	Mean±SD	3.2±0.2	3.2±0.3	^ 0.779	--
	Range	2.9–3.6	2.9–3.6		
NICU admission		2 (4.0%)	3 (6.0%)	§1.000	0.79 (0.27–2.36)

DISCUSSION

Pre-labour rupture of membranes (PROM) is defined as the rupture of membranes before the beginning of uterine contractions. This event occurs in about 8-10% of pregnancies and about 60% of these cases are term pregnancies[1].

The increase in time interval between rupture of membranes and onset of labour pains is associated with increase in the incidence of complications such as chorioamnionitis, endometritis, chronic abruption, cord compression, neonatal morbidity and neonatal sepsis[2].

The goal of labor induction is to stimulate uterine contractions before the spontaneous onset of labor, resulting in vaginal delivery[7].

Misoprostol is a prostaglandin E1 methyl ester that stimulates myometrial contractions. Initially introduced for early pregnancy termination, in lower doses it is found to be effective for labour induction[8].

Oxytocin is a peptide hormone that has various effects on both the brain and peripheral systems during and after birth. It is produced in the magnocellular nuclei of the supraoptic nucleus (SON) and paraventricular nucleus (PVN) of the hypothalamus, and it is stored in and released into circulation from the posterior pituitary gland[6].

A total of one hundred women were included in the study. The patients were allocated randomly into two groups; group A received oxytocin (50 patients) and group B received misoprostol (50 patients).

In this study, there were no significant differences between the studied groups regarding maternal characteristics (mean age 25.2 vs 26.1) (mean BMI 25.2 vs 25.7) (mean bishop score 3.9 vs 3.8).

Nulliparous women in oxytocin group were 32% vs 26% in misoprostol group while multiparous women were 68 % in oxytocin group vs 74 % in misoprostol group.

In this study, induction duration was significantly longer among oxytocin group than among misoprostol group (mean duration was 8.2 hours in oxytocin group vs 6.8 hours in misoprostol group).

This was consistent with[9] who noted that the time between the induction of labour and the active labour was shorter in the misoprostol group than in the oxytocin group, but the difference was not statistically significant. According to Pouralil *et al.*, duration between start of labour induction to achieve active labour between misoprostol group and oxtocin group was 248.96 ± 197.51 minutes, 229.54 ± 166.88 minutes, respectively[9].

This was also consistent with Ameen[10] who found that the interval from the start of induction to vaginal delivery was significantly shorter in sublingual misoprostol group 14 + 3.7 hours compared with oxytocin group 18 + 4.2 hours[10].

This was also consistent with[11] which used 100 microgram oral misoprostol every 6 hours versus intravenous oxytocin demonstrated a significantly shorter time period between labour induction and active labour in the misoprostol group[11].

In this study, CS delivery was non-significantly more frequent among misoprostol group than among oxytocin group (26% in oxytocin group vs 14 % in misoprostol group).

Failed induction and Arrest of labor were non-significantly more frequent among oxytocin group than among misoprostol group (23.1% vs 57.1% and 23.1 % vs 28.6 %, respectively), while non-reassuring CTG pattern was non-significantly more frequent among misoprostol group than among oxytocin group (53.8 % vs 14.3%).

This also was inconsistent with[9] who found that 24 cases were delivered by caesarean section in each group; CS indications in misoprostol group were foetal distress (70.8%), arrest of descend (25%), dilatation arrest (4.2%) and in oxytocin group were foetal distress (54.2%), failed induction (20.8%), dilatation arrest (16.7%) and arrest of descend (8.3%)[9].

In the current study, the active phase duration was significantly shorter among misoprostol group than among oxytocin group (mean duration was 5.2 vs 5.6).

This was consistent with[9], who noted that the mean duration of active labour was significantly shorter in the misoprostol group Median (IQR) 480 (330-705) minutes while was 600 (390-795) minutes in oxytocin group[9].

In the current study, second phase duration was significantly shorter among misoprostol group than among oxytocin group (mean duration was 39.7 minutes vs 42.3 minutes).

This was consistent with[9] who found that mean second stage duration was 48.43 ± 27.84 minutes in misoprostol group and 56.99 ± 26.46 minutes in oxytocin group[9].

In the current study according to maternal adverse effects among the studied groups, tachysystole and

hyperstimulation were non-significantly less frequent among oxytocin group than among misoprostol group (8% vs 2% and 6 % vs 2%, respectively), also nausea, vomiting and fever were non-significantly less frequent among oxytocin group than among misoprostol group.

This was consistent with[9] who found that the most prevalent side effects attributable to labour augmentation in the misoprostol group were nausea and vomiting (22.5%), postpartum haemorrhage (10.8%), fever (5.8%) and diarrhoea (1.7%). These complications were present in 0.8%, 20% and 1.7% and 0% of those in the oxytocin group and according to Monte Carlo statistical test there was a significant difference between the two groups in terms of these complications.

According to neonatal condition among the studied groups, there was no significant differences between oxytocin and misoprostol groups regarding neonatal condition (mean APGAR 5 minutes was 8.3 vs 8.4).

This was inconsistent with[9] who found that the median 5-minute Apgar score was significantly better in the misoprostol group. The median 5-minute Apgar scores in the misoprostol and oxytocin groups were 9.75 ± 0.58 and 9.27 ± 0.66, respectively.

However in this study, mean NICU admission was 6 % vs 4 % in misoprostol and oxytocin, respectively, and this was consistent with[9] who found that two neonates in each group were admitted to NICU and there was no statistical difference between the two groups.

CONCLUSION

This study concluded that pre-labour administration of sublingual misoprostol in patients with singleton term pre-labour rupture of membranes shorten duration of both active phase and second stage of labour significantly in comparison with oxytocin administration. No major complications were associated with use of either drug.

CONFLICT OF INTEREST

There are no conflicts of interests.

REFERENCES

1. Dare MR, Middleton P, Crowther CA, Flenady V, Varatharaju B.(2006): Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more). Cochrane Database of Systematic Reviews, Issue 1.
2. Horvath B, Grasselly M, Bodecs T, Boncz I, Bodis J. (2012 Aug). Histological chorioamnionitis isassociated with cerebral palsy in preterm neonates. Eur J Obstet Gynecol Reprod Biol. 1; 163(2):160-4.
3. Laura J. Frye, Meagan E. Byrne & Beverly Winikoff (2016): A crossover pharmacokinetic study of misoprostol by the oral, sublingual and buccal routes.
4. Hofmeyr GJ, Gulmezoglu AM, Pileggi C. (2010): Vaginal misoprostol for cervical ripening and induction of labour. Cochrane Database Syst Rev; 10:CD000941.
5. Thomas J, Fairclough A, Kavanagh J, Kelly AJ. (2014): Vaginal prostaglandin (PGE2 and PGF2a) for induction of labour at term. Cochrane Database of Systematic Reviews 2014:CD003101.
6. von Bohlen und Halbach, Oliver and Dermietzel R. (2002). Neurotransmitters and neuromodulators: Handbook of receptors and biological effects. Ballantyne D, editor. Weinheim: Wiley-VCH Verlag GmbH.
7. Saeed GA, Fakhar S, Nisar N, Alam AY (2011). Misoprostol for term labor induction: a randomized controlled trial. Taiwan J Obstet Gynecol.; 50(1):159-.
8. Weeks A, Alfirevic Z, Faundes A, Hofmeyr GJ, Safar P, Wing D. Misoprostol for induction of labour with a live fetus. Int J Gynaecol Obstet. 2007 Dec; 99 Suppl 2:S1947-.
9. Pourali, Leila, *et al*. (2018): "Induction of labour in term premature rupture of membranes; oxytocin versus sublingual misoprostol; a randomised clinical trial." Journal of Obstetrics and Gynaecology 38.2 (2018): 167-171.
10. Ameen S. (2014): "Labour induction; use of sublingual misoprostol versus oxytocin in case of ruptured membranes at term." Professional Medical Journal 21.5 (2014).
11. Al-Hussaini T, Abdel-Aal S, Youssef M. (2003): Oral misoprostol vs. intravenous oxytocin for labor induction in women with prelabor rupture of membranes at term. International Journal of Gynaecology and Obstetrics 82:73–75.