Oral Misoprostol Versus Oxytocin for Induction of Labor in Premature Rupture of Membranes at Term

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Abstract: Background: Premature rupture of membranes is one of the most common complications of pregnant women. Induction of labor is important to reduce the risk of maternal infection (chorioamnionitis). **Objective:** This study aims to compare the effect of oral misoprostol versus intravenous oxytocin drip in the induction of labour in premature rupture of membranes at term. **Methods:** 60 pregnant women with (PROM) requiring labour induction were divided randomly into three groups from Dec.2016 to Dec.2018 One group received the Titrated oral misoprostol solution 20 ml (1µg/ml, 20µg total) every hourly until adequate contractions were achieved. Another group received Oxytocin IV infusion with the maximum dosing rate of 20 milliunits/min. The third group is a group control which not received misoprostol nor oxytocin. **Results:** This study showed that oral misoprostol was not only as successful as oxytocin for labor induction in women presenting with PROM at term but also has arole in cervical ripening which reduce the duration of labor. **Conclusion:** Titrated oral misoprostol solution is as efficacious as IV oxytocin infusion for labour augmentation. It is safe, inexpensive and easy to use. Induction to-delivery interval is very much reduced with the use of titrated oral misoprostol solution and the incidence of caesarean sections is comparable to the IV oxytocin group.

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1. Introduction

Premature rupture of membranes (PROM) refers to a patient who is beyond 37 weeks' gestation and has presented with rupture of membranes (ROM) prior to the onset of labor. Spontaneous preterm rupture of the membranes (SPROM) is ROM after or with the onset of labor occurring prior to 37 weeks. Prolonged ROM is any ROM that persists for more than 24 hours and prior to the onset of labor **(Yaqub,*2015*)**.

The major maternal risk is infection, namely chorioamnionitis, which occurs in about 35%; abruption, which occurs in 19%; and sepsis, which is rare and occurs in less than 1% ***(Waters TP, Mercer BM, 2009).***

In 1906, Dale observed that extracts from the infundibular lobe of the pituitary gland caused myometrial contractions. Three years later, Bell reported the first experience with the use of a pituitary extract for labor induction. With the introduction of pituitary extract as a hormonal method of labour induction in 1913, the use of this method gained acceptance among obstetricians. However, due to the use of large doses, numerous adverse effects were reported. Gradually, as the number of reported cases of uterine rupture increased, pituitary extract became discredited in many centers **(Leng et al., 2016).**

Hence adoption of the policy of "Active management of labour" use of prostaglandins (PG's) and / or oxytocin resulted in shorter labors with better obstetric outcome and a lowering of the rates of cesarean section **(Rossen, 2017)**.

Induction of labor is an obstetrical intervention to stimulate uterine contractions before spontaneous onset of labor. It commonly includes two steps: cervical ripening by prostaglandins or mechanical methods and stimulation of contractions by use of oxytocin. **(*Society of Obstetricians and Gynecologists of Canada, 2013).***

Misoprostol is a stable, synthetic form of prostaglandin E1 analogue. It was originally developed in the 1970s for the prevention of non-steroidal anti-inflammatory drugs (NSAIDS)-induced peptic ulcers. It was initially used to treat peptic ulcers caused by prostaglandin synthetase inhibitors. In April 2002, the U.S. Food and Drug Administration revised the original labeling of misoprostol and approved it for use in pregnancy ***(Chiong et al., 2010).***

Misoprostol is absorbed, and undergoes rapid de-esterification to its free acid, which is responsible for its clinical activity and, unlike the parent compound, is detectable in plasma. The alpha side chain undergoes beta oxidation and the beta side chain undergoes omegaoxidation followed by reduction of the ketone to give prostaglandin F analogs ***(Glaser et al., 2010).***

Pharmacokinetic studies also showed a lack of drug interaction with antipyrine and propranolol when these drugs were given with misoprostol. Misoprostol given for 1 week had no effect on the steady state pharmacokinetics of diazepam when the two drugs

were administered 2 hours apart. The serum protein binding of misoprostol acid is less than 90% and is concentration-independent in the therapeutic range ***(Ambuja and Rani, 2016)***.

The oral route has the most rapid uptake, but the shortest duration. The rectal route has slow uptake but prolonged duration. The buccal or sublingual route has rapid uptake, prolonged duration and greatest total bioavailability ***(Ambuja and Rani, 2016).***

The longer time to reach peak levels of misoprostol (20–30 minutes) than syntocinon (3 minutes) may account for more early blood loss with misoprostol. This does not exclude that misoprostol may have an effect on more persistent bleeding ***(Mukharya et al., 2017).***

Misoprostol has been used extensively for its cervical softening effect before induction of labor and surgical evacuation of the uterus. Studies have demonstrated that less force is required for mechanical dilatation of the cervix if misoprostol, it is used more likely to be due to the direct effect of misoprostol on the cervix. **(Mahajan et al, 2018**).

Syntocinon® (oxytocin) is a synthetic, (1-6) cyclic nonapeptide. Chemically, oxytocin is designated as Glycinamide, L-cysteinyl-L-tyrosyl-L-isoleucyl-L-glutaminyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucy1-, cyclic (1-6)-disulfide **(Fonseca et al., 2010).**

Carcinogenesis, Mutagenesis, Impairment of Fertility There are no animal or human studies on the carcinogenicity and mutagenicity of this drug, nor is there any information on its effect on fertility **(Saccone and Berghella, 2015)**.

2. Patient and Methods:

This prospective controlled randomized study included 60 pregnant women presenting with PROM at term in the period from December 2016 to December 2018. After obtaining approval from ethical committees, all women were informed about the nature of the study and they signed an informed consent before starting the study.

The inclusion criteria were as follow: singleton living fetus, gestational age of at least 37 weeks, cephalic presentation, rupture of membranes, normal fetal heart rate. The exclusion criteria were as follow: history of CS, placenta previa, any contraindication to misoprostol or oxytocin, and any condition that contraindicated vaginal delivery.

Examination was performed to determine the fetal presentation, gestational age and fetal cardiac activity. Then women were assigned to three groups.

First group:

The titrated oral misoprostol group (n =20cases).

The titrated oral misoprostol group, misoprostol is manufactured as a water-soluble oral tablet. One 200-microgram tablet of misoprostol was completely dissolved in 200 mL of tap water with stirring bar in a medicine bottle by the duty nurse. The misoprostol solution was stored in this medicine bottle at the nurses' station and used completely within 24 hours after preparation or discarded. Women were given one basal unit of 20 ml of misoprostol solution (1 microgram/ml, 20 micrograms total) prepared as described above. It can be expected that the pharmacokinetics of misoprostol may not change when it is given after onset of spontaneous labor.

Second group:

The titrated I.V oxytocin group (n =20 cases).

The titrated I.V oxytocin group, we gave oxytocin via the intravenous route initially set to deliver 1 milliunit/min for 20 minutes, until adequate uterine contractions attained.

Third group:

Control group (n=20 cases)

Statistical analysis:

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non parametric distribution.

3. Results

The result of this study showed that there was no significant difference between the study groups in demographic and antepartum variables. Maternal age, height and maternal weight were similar in the three group as shown in Table (1).

There was no statistically difference between the 3 groups in the gestational age as shown in table (2).

Two patients (10%) in the misoprostol group showed gastrointestinal tract complications in the form of nausea and vomiting. Other two patients (10%) in this group showed increase in the body temperature (pyrexia) as a complication of misoprostol. On the other hand there are no complications in the oxytocin and control groups. These results were showed in the Table (3).

One patient (5%) in the misoprostol group were received an additional dose (40mcg) after four hours, on the other hand no patient in the oxytocin group were received any additional dose as showed in the table (4).

Three patients (15%) in the oxytocin group experienced acervical tear, no cases of cervical tear were detected in the misoprostol or control group as showed in Table (5).

The indication for cesarean section in the misoprostol group was one case (5%) because of fetal

distress and uterine hyperstimulation. There was no indication for cesarean section in oxytocin group, but four cases in control group were indicated for cesarean section due to failure of uterine contraction. These results showed in Table (6) and Table (7).

Table (7) shows that there was no statistically significant difference in fetal distress and episiotomy regarding studied groups but there was statistically significant increase inmisoprostol and oxytocin in comparison to control group with uterine contraction.

Table (1): Comparison between misoprostol, oxytocin & control group as regards demographic data.

	Misoprostol		Oxytocin		Control group		One way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P- value
Age	24,15	2,52	24,20	2,48	24,40	3,59	0,041	0,960
Height	162,10	2,38	161,45	1,54	160,80	1,85	2,210	0,119
Weight	79,70	7,24	80,40	7,60	80,95	7,82	0,137	0,872
Post hoc test								
	Misoprostol VS Oxytocin		Misoprostol VS control		Oxytocin VS control			
Age	0.957		0.787		0.829			
Height	0.298		0.040		0.298			
Weight	0.771		0.603		0.819			

This table (1) shows that there was no statistically significant difference in demographic data regarding studied groups. In post hoc test there was statistically significant in height in comparison between Misoprostol VS control group.

Table (2): Comparison between misoprostol, oxytocin & control group as regards gestational age

	Misoprostol		Oxytocin		Control group		One way ANOVA	
	Mean	SD	Mean	SD	Mean	SD	F	P- value
Gestational age	38,85	0,60	38,58	2,39	39,00	0,40	0,445	0,643
Post hoc test								
	Misoprostol VS Oxytocin		Misoprostol VS control		Oxytocin VS control			
Gestational age	0.556		0.735		0.355			

This table (2) shows that there was no statistically significant difference in gestational age regarding studied groups.

Table (3): Nausea, vomiting, pyrexia and shivering

		Misoprostol	
		No	%
Nausea	Negative	19	95,0%
	Positive	1	5,0%
Vomiting	Negative	19	95,0%
	Positive	1	5,0%
Pyrexia	Negative	18	90,0%
	Positive	2	10,0%
Shivering	Negative	20	100,0%
	Positive	0	0,0%

This table (3) shows that there were 5% of patients have nausea, 5% have vomiting and 10% have pyrexia

Table (4): Comparison between misoprostol, oxytocin & control group as regards dose and additional dose

		Misoprostol		Oxytocin		Chi square	
		No	%	No	%	X^2	P value
Dose	Negative	19	95,0%	20	100,0%	1.026	0.311
	Positive	1	5,0%	0	0,0%		
Additional dose	Negative	19	95,0%	20	100,0%	1,026	0.311
	Positive	1	5,0%	0	0,0%		

This table (4) shows that there was no statistically significant difference in dose and additional dose regarding studied groups.

Table (5): Comparison between misoprostol, oxytocin & control group as regards cervical tear

		Oxytocin		Control group		Chi square	
		No	%	No	%	X^2	P value
Cervical tear	Negative	17	84,2%	20	100,0%	3.421	0.064
	Positive	3	15,8%	0	0,0%		

This table (5) shows that there was no statistically significant difference in cervical tear regarding studied groups.

Table (6): Comparison between misoprostol, oxytocin & control group as regards MOD

		Misoprostol		Oxytocin		Control group		Chi square	
		No	%	No	%	No	%	X^2	P value
Mode of delivery	Negative	19	95,00%	20	100,00%	16	80,00%	5,673	0,059
	Positive	1	5,00%	0	0,00%	4	20,00%		

This table (6) shows that there was no statistically significant difference in mode of delivery regarding studied groups.

Table (7): Comparison between misoprostol, oxytocin & control group as regards fetal distress, uterine hyperstamulation and episiotomy

		Misoprostol		Oxytocin		Control group		Chi square	
		No	%	No	%	No	%	X^2	P value
Fetal distress	Negative	19	95,00%	20	100,00%	20	100,00%	2,034	0,362
	Positive	1	5,00%	0	0,00%	0	0,00%		
Uterine hyperstamulation	Negative	0	0,00%	0	0,00%	4	20,00%	8,571	0,014
	Positive	20	100,00%	20	100,00%	16	80,00%		
Episiotomy	Negative	1	5,00%	2	10,00%	4	20,00%	2,264	0,322
	Positive	19	95,00%	18	90,00%	16	80,00%		

This table (7) shows that there was no statistically significant difference in fetal distress and episiotomy regarding studied groups but there was statistically significant increase inmisoprostol and oxytocin in comparison to control group with uterine contraction.

4. Discussion

This study compared the efficacy of titrated oral misoprostol solution with intravenous oxytocin infusion for labor induction when inadequate uterine contractions occurred. There were no significant differences between the two groups that delivered vaginally within 12 or 24 hours. Side effects and neonatal outcomes also did not differ between the two groups.

Cesarean birth rates are greater than 20% in many developed countries ***(Betra´n et al., 2007).*** The main diagnosis contributing to the high rate in nulliparous women is dystocia or prolonged labor. Early induction of labor after ruptures of membranes with oxytocin administration for the prevention of delay in labor progress is associated with a modest reduction in the rate of cesarean births ***(Cheng et al., 2008).***

There is no significant difference in cesarean delivery rate, neonatal outcome, and maternal outcome between the low and high doses of oxytocin on labor induction except for labor induction interval ***(Jamal et al., 2004).*** However, oxytocin administration through the intravenous route needs to be under the control. Multiple trials have shown that misoprostol is an effective agent for cervical ripening and labor induction. The study of orally administered misoprostol compared with titrated intravenous oxytocin for labor induction in women with favorable cervical condition.

Because titrated oral misoprostol solution is easier to administer than titrated intravenous oxytocin, we found it worth conducting this randomized controlled trial to examine the optimal treatment regimen for labor induction. Parameters used to assess efficacy included the interval from the start of induction to vaginal delivery, the percentage of women who delivered their newborns vaginally within

12 and 24 hours of augmentation, and rate of failure to progress.

According to the pharmacokinetics, the onset time and administration route of oxytocin is better than that of misoprostol. In this study, it was expected that the titrated intravenous oxytocin would be more effective than titrated oral misoprostol in terms of the interval of augmentation to vaginal delivery. However, the difference of these intervals is not significant in actual clinical practice. Vaginal delivery within 12 or 24 hours is the more important clinical factor. We found that there were no significant differences between the groups in the percentages of women who delivered their newborns vaginally within 12 or 24 hours of induction and in the rate of failure to progress.

Therefore, labor induction with titrated oral misoprostol solution is an effective alternative method. The parameters used to assess adverse outcomes in this study were incidence of tachysystole, hypertonus and uterine hyperstimulation. Tachysystole occurred in both groups, and administration of these agents was halted immediately until uterine contractions became inadequate and tocolysis with magnesium sulfate was unnecessary. This suggests that administering misoprostol in small, frequent doses with continuous adjustment according to response is also a better way to avoid uterine hyperstimulation and is analogous to the conventional titrated use of oxytocin.

Our result was in agreement with astudy by **Bricker et al**., who found that fewer cesareans and less failure to achieve vaginal birth within 24 hours in misoprostol group, although not statistically significant.

Our result was not in agreement with the study of **Crane et al.**, who found a significant difference between the misoprostol and the oxytocin group. This may be explained by the higher percentage of nullipara in their study in the misoprostole group (67.3%) and their use of oral dose of misoprostol.

There was no significant difference between the misoprostol, oxytocin and control group in the mode of delivery as 19 women (95%) delivered vaginally in the misoprostol group, 20 women (100%) delivered vaginally in the oxytocin group, and (80%) delivered vaginally in control group. The incidence of cesarean section in the misoprostol group was 5% (one case), and in the oxytocin group was 0%, compared with 20% (four cases) in the control group. These finding were in agreement with those of previous studies, for example;

Nagi et al., study showed that 5% in the oral misoprostol group and 7.5% in the oxytocin group.

Mozurkewich study showed that 20.1% in the oral misoprostol group and 19.9% in the oxytocin group. **Butt et al.,** showed 14.5% in the oral misoprostol group and 13.2in the oxytocin group.

There were no differences between the three groups in the occurrence of hypertonus, and hyperstimulation (5% of women in the misoprostol group, and no occurrence of hyperstimulation in the other two groups. This result was in agreement with that of **Crane et al.,** who found that no differences between the misoprostol and oxytocin groups in the occurrence of hypertonus (6 vs.4.1%respectively).

In addition, Mozurke wich found that there was nosignificant difference toward the occurrence of hypertonus in the misoprostol group compared with the oxytocin group (10.7 vs 8.8%respectively).

No cases of chorioamnionitis were detected in the three study groups. The studies of (Nagi et al., Shetty et al., and cheung et al.) found that there was no significant difference between misoprostol and oxytocin groups in the occurrence of chorioamnionitis.

Our study also found that no significant difference between the three groups in the occurrence of specific drug gastrointestinal side effects such as diarrhea, nausea and vomiting as two patients (10%) developed nausea and vomiting with no occurrence of diarrhea in the three groups. These results were similar to the results of Al-Hussaini et al., who found no significant difference in the occurrence of specific drug side effects, for example, nausea, vomiting, and diarrhea between the two study groups.

Conclusion

In conclusion, titrated oral misoprostol solution was observed to be similar to intravenous oxytocin infusion in labor induction and may be an alternative to the traditional oxytocin. In addition, misoprostol offers several advantages over oxytocin such as longer shelf life, stability at room temperature, and easy administration.

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