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Oral Misoprostol versus Dinoprostone Vaginal Tablets for Labor Induction

Doğum İndüksiyonunu Sağlayan Oral Misoprostol İle Vajinal Dinoprostonun Karşılaştırılması

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ABSTRACT

Purpose: Induction of labour is common in obstetric practice. We conducted this study to find the appropriate and safe drug for labour induction and to compare the safety and efficacy of oral misoprostol and vaginal dinoprostone for labour induction.

Material and Methods: In a provisional, prospective and cross-sectional study, one hundred and fifty five singleton cephalic presentation full term pregnancies with medical or obstetric indication for labour induction were allocated in two groups. First group received oral 50 micrograms for nulliparas and low parity group (1-4), and 25micrograms for grand multiparas (≥ 5) misoprostol orally every 6 hours to a maximum of four doses daily. In the second group vaginal tablets of dinoprostone 3mg then 1.5mg for nulliparas and 1.5mg for low parity and grand multiparas groups were inserted in the posterior fornix, every 8 hours. Primary outcome measures were: induction success, induction-delivery interval and number of used doses. Secondary outcome measures included: maternal side effects, caesarean section rate, mode of delivery and neonatal outcome. Data was collected from patient case notes and analyzed using software SPSS (version 13.0) and p-value < 0.05 was used as statistical significance of differences.

Results: In our study there were no significant differences in baseline parameters in the two groups nor in the indications for labor induction except misoprostol was used in premature rupture of membrane. Induction of labor succeeded in 123 (79.35%) women without other interventions from other methods (80.26% misoprostol group versus 78.5% dinoprostone p=0.492). It was observed that there were no significant differences between the two groups in final outcomes nor in obstetrical complications. There was no significance in differences between misoprostol and dinoprostone groups in induction-delivery interval (15.2 ± 14.5 hours versus 16.4 ± 11.3 hours p=0.6 resp.).

Conclusion: This study demonstrated that oral misoprostol is as effective as vaginal dinoprostone tablets for induction of labor and can be a good alternative for this purpose.

Key Words: Misoprostol, dinoprostone, ınduction of labour, ınduction delivery interval, cervical ripening

ÖZET

Amaç: Doğum indüksiyonu yaygın bir obstetrik uygulamasıdır. Bu çalışma, doğum indüksiyonu için uygun ve güvenli ilacı bulmak ve doğum indüksiyonunda oral misoprostol ve vajinal dinoprostonun güvenlik ve etkinliği bakımından karşılaştırılması için yapılmıştır.

Materyal ve Metod: Provizyonel, prospektif ve kesitsel olan bu çalışmada, doğum indüksiyonu için tıbbi veya obstetrik endikasyonlu baş prezentasyonu ile karaktrize 155 tekil gebe iki gruba ayrılmıştır. İlk grupa nullipar ve düşük doğum sayısı (1-4) olanlar için oral olarak 50 mikrogram, grand multiparite (≥5) için 25 mikrogram misoprostol günde en fazla 4 doz olacak şekilde her 6 saatte bir oral olarak verilmiştir. İkinci grupta dinoproston 3mg vajinal tabletleri nulliparlara 1,5mg, düşük doğum sayısı olanlara ve Grand multipariteye sahip olanlara 1,5 mg olarak her 8 saatte bir posterior

fornikse yerleştirilmiştir. Birincil sonlanım ölçütleri: indüksiyon başarısı, indüksiyon-verilme sıklığı ve kullanılan dozun sayısı. İkincil sonlanım ölçütleri: maternal yan etkiler, sezeryan oranı, ilacın verilme biçimi ve neonatal sonlanım. Bilgiler hasta vaka notlarından toplanmıştır ve SPSS (version13.0) yazılımı kullanılarak analiz edilmiştir. Farklılıkların istatistiksel anlamı için p<0.05 olarak belirlenmiştir.

Bulgular: Çalışmamızda her iki çalışma grubunda; ana parametrelerde ve doğum indüksiyonunun endikasyonlarında, misoprostolün prematüre membran ruptürü için kullanıldığı durum hariç, anlamlı bir farklılık saptanmamıştır. Doğum indüksiyonu diğer müdahale metodlarının uygulanmadığı kadınların 123'ünde başarılı olmuştur (%79,3)(%80,26 misoprostol grup ve %78.5 dinoprostone p=0,492 karşılaştırıldığında). Çalışma sonucunda iki grup arasında nihayi sonuç ve obstetrik komplikasyonlar bakımından farklılık bulunmamıştır. İndüksiyon verilme-doğum arasındaki sure bakımından misoprostol ve dinoproston grupları arasında anlamlı fark bulunamamıştır (15.2 ± 14.5 saat ve 16.4 ± 11.3 saat p=0,6 resp. karşılaştırıldığında).

Sonuç: Bu çalışma doğum indüksiyonunda oral misprostolün vajinal dinoproston kadar etkili olduğunu ve bu amaç için iyi bir alternatif olabileceğini göstermektedir.

Anahtar kelimeler: Misprostol, dinoproston, doğum indüksiyonu, indüksiyon verilme aralığı, servikal olgunlaşma

INTRODUCTION

Induction of labor "IOL" is common in obstetric practice[1]. According to the most current studies, the rate varies from 9.5 to 33.7 percent of all pregnancies annually[2]. Although caution is mandatory when indicating elective labour induction because the increased risk of maternal and perinatal adverse outcomes is not outweighed by clear benefits[3], there are a number of complications of pregnancy that confer significant ongoing risk to the mother or fetus (e.g., preeclampsia; preterm premature rupture of the membranes (PPROM); intrauterine growth restriction (IUGR); and post term pregnancy (pregnancies that progress to and beyond 42 0/7 weeks, or 294 days, gestational age)). For these conditions, induction of labor is often the principal medical intervention utilized to decrease both maternal and neonatal morbidity and mortality[4].

Prostaglandin analogues, dinoprostone (PGE2) and misoprostol (PGE1), are widely used in IOL practice[5], for ripening the cervix and stimulating uterine contractions in order to achieve vaginal delivery[6]. Although dinoprostone has been approved from long time for cervical ripening in women at or near term[7,8], misoprostol was not yet approved for such use by the FDA, although it has the advantages of lower cost, no need for refrigeration and probably higher efficacy.

Because of the harsh circumstances of occupation and siege and difficult economic conditions; we conducted this study to compare the efficacy and safety of these two drugs in order to find the appropriate mean and more economic relevant for labor induction in our settings.

MATERİALS and METHODS

Study design

This study was approved ethically from Helsinki committee and scientifically from Palestinian ministry of health.

Because of difficulties to make randomized clinical trials in our settings; especially to pregnant women we provided a provisional, descriptive, prospective and cross-sectional study. The study took place at Al Helal Al Emirati Maternity Hospital (HEMH) in Rafah, Gaza strip "Palestine" between 1st June and 31st July 2010.

Inclusion and exclusion criteria

We recorded all deliveries in the hospital; but in our study we included all women with a life, cephalic, singleton pregnancy at ≥37weeks' gestation needed induction of labor "IOL" for obstetrical or gynecological reasons. We excluded women with any contraindication to vaginal birth, previous uterine surgery (including caesarean section).

Patient allocation

According to parity, patients were allocated into three groups, para 0 as nulliparas "NP", para

1-4 as multiparas "MP" and para ≥ 5 as grand multiparas "GMP".

Treatment schedules

Misoprostol- Misoprostol 200 mcg tablet (Cytotic, pfizer pharmaceutical) was used in two forms. Oral misoprostol; one fourth of 200 mcg tablet (50 mcg) was used for NP and MP groups and 25 ml of misoprostol solution (concentration 1 mcg/ml, prepared by dissolving one 200 mcg tablet in 200 ml of tap water) for GMP group. Oral doses were repeated 6 hourly up to 4 doses when required.

Dinoprostone- Dinoprostone 3mg vaginal tablets (Prostin E2, Pharmacia & Upjohn) was used in two regimens. Nulliparas group was given one tablet vaginally then half tablet every 8 hours and MP and GMP half tablet every 8 hours.

Data collection and outcome measures

Data was collected from patient's case notes, Labour Ward birth register and neonatal intensive care unit "NICU" admission register and were reviewed in order to monitor maternal and neonatal outcomes. Our primary maternal outcomes were successful induction (Normal vaginal delivery "NVD" without interventions from other prostaglandins or mechanical inducers), induction-delivery interval and number of used doses. Secondary outcomes included: maternal complications, mode of delivery and neonatal outcome (Apgar score, admission to "NICU" and birth weight).

Data analysis

Data was analyzed by statistical package for social sciences (SPSS) program (version 13.0) for different study variables. Some results were represented as means and standard deviations and t-test was applied to evaluate the statistical significance for continuous variables. Chi-square test and Mann-Whitney U-test were used also for discrete variables. $P < 0.05$ was considered statistically significant of differences. Qualitative variables were expressed as percentages.

RESULTS

The baseline data of the study population included maternal age, parity and gestational age. In our study period a total of 1071 pregnant women delivered in HEMH, 893 (83.4%) were with normal vaginal delivery (NVD). From all cases we reported 155 (17.36%) cases needed IOL for different obstetrical or gynecological reasons, 76 (49.03%) were induced with misoprostol while 79 (50.97%) of them were induced with dinoprostone *(table 1)*. There were no significant differences in baseline parameters.

Table 1. Baseline data.

		Misoprostol group	Dinoprostone group	P
N		76	79	
Mean age "years"		25.07 ± 5.66	27.86 ± 6.56	0.34*
Mean gestational age "days"		279.43 ± 11.41	285.57 ± 15.5	0.81*
Mean Parity		2.1 ± 1.97	2.73 ± 2.64	0.053*
	NP	23 (30.26%)	26 (32.91%)	
	MP	41 (53.95%)	30 (37.97%)	
	GMP	12 (15.79%)	23 (29.12%)	

NP Nulliparas *** P >0.05**

MP Multiparas

GMP Grand multiparas

Indications for induction were approximately similar *(Table 2).* Ninety one 91 (58.71%) from all induced women were with postdatism, 38 of them were induced with misoprostol while the rest were induced with dinoprostone. Twenty six 26 (16.77%) were induced for pregnancy induced hypertension

(PIH) and pre-eclampsia, twenty 20 (12.9%) for oligohydramnios and decreased fetal movement, 10 (6.45%) with premature rupture of membrane (PROM) and the rest 8(5.16%) were with different obstetrical and gynecological reasons.

Table 2. Indications for IOL.

Indications	Misoprostol group (n=76)	Dinoprostone group (n=79)
Postdatism	38 (50%)	53 (67.1%)
Pregnancy induced hypertension and Pre-eclampsia	14 (18.42%)	12 (15.19%)
Oligohydramnios and decreased fetal movement	9 (11.84%)	11 (13.9%)
Premature rupture of membrane (PROM)	10 (13.16%)	-
Others	5 (6.58%)	3 (3.81%)

Induction of labor succeeded in 123 (79.35%) women without other interventions. Caesarian section was done in 14 (9.03%), 14 (9.03%) were shifted to other prostaglandins, two (1.29%) needed balloon intervention and the rest two cases were induced with the same prostaglandin after a break. There was no significant difference in induction outcomes *(Table 3)*. Thirty four (27.64%) of succeeded IOL needed oxytocin augmentation, 34 (27.64%) also needed episiotomy and 5 (4%) needed vacuum extraction (VE). Also it was observed that there was no significant difference between two groups in obstetric characteristics.

Table 3. Obstetric characteristics.

		Misoprostol group	Dinoprostone group	P
Success IOL		61 (80.26%)	62 (78.5%)	0.492*
Failed induction		15 (19.74%)	17 (21.5%)	0.492*
	CS	6 (7.89%)	8 (10.1%)	0.369*
	Other prostaglandins	7 (9.21%)	7 (8.9%)	0.289*
	Balloon intervention	1 (1.32%)	1 (1.27%)	0.14*
	Repeated induction	1 (1.32%)	1 (1.27%)	0.6*
Augmentation with oxytocin		16 (26.23%)	18 (29.03%)	0.13*
Episiotomy		17 (27.89%)	17 (27.42%)	0.58*
VE		3 (4.92%)	2 (3.2%)	0.48*

IOL Induction of labor *** P >0.05**
CS Caesarian section
VE Vacuum extraction

Forty four (35.77%) successful cases ended up with variable obstetrical and non-obstetrical complications. Twenty seven (61.36%) from all complications were mild vaginal bleeding while 16 (36.36%) experienced post partum hemorrhage due to vaginal tear and one case from misoprostol group returned to hospital after 11 days with puerperal fever. It was observed that the raise of complications was not associated with the kind of drug *(Table 4).* There were no observed side effects of the used drugs (misoprostol & dinoprostone). Apgar score was good for almost all neonates (8.7±0.48) except one of them who was admitted to NICU. It was observed also, there were no significant variabilities between the newborns of the two groups.

Table 4. Complications and newborn outcomes

		Misoprostol group (n=61)	Dinoprostone group (n=62)	P
N cases with complications		23 (37.7%)	21 (33.9%)	0.43*
	Mild vaginal bleeding	16 (26.23%)	11 (17.7%)	0.2*
	Post partum hemorrhage	6 (9.84%)	10 (16.2%)	0.2*
	Puerperal fever	1 (1.64%)	0	0.37*
Newborn complications				
none		61 (100%)	61 (98.4%)	0.63*
5 min Apgar score		8.76 ± 0.43	8.65 ± 0.52	0.28*
Weight (kg)		3.32 ± 0.6	3.31 ± 0.4	0.96*

M group: Misoprostol group ***P> 0.05**

D group: Dinoprostone group

The induction-delivery interval ranged from 3.67 to 75.33 hours in all cases. This time ranged from 4.50 to 75.33 hours in misoprostol group while it ranged from 3.67 to 64 hours in dinoprostone group. It was noticed that induction-delivery, active phase-delivery and induction-active phase intervals were slightly shorter in misoprostol group *(table 5)* but these differences were insignificant. Approximately similar number of doses were required for both two groups to achieve NVD. Sixty 60 (48.78%) from all delivered within the first twelve hours with average time (8.03 ± 2.4) hours, 45 (36.59%) delivered within the second twelve hours with average time (17.4 ± 3.9) hours while 18 (14.63%) take more than 24 hours to deliver with average time (38.4 ± 15.6) hours. It was noticed that most of misoprostol group (57.4%) delivered within the first twelve hours while only 40.3% from dinoprostone group delivered within the same time *(table 5)* but there was no significance difference in average induction–delivery interval for the two groups.

Table 5. Results

	Misoprostol group (n=61	Dinoprostone group (n=62)	P
Induction-active phase interval (hours)	12.8 ± 10.1	13.7 ±10.8	0.8
Active phase-delivery interval (hours)	2.4 ± 1.7	2.7 ± 2.1	0.5
Induction-delivery interval (hours)	15.2 ± 14.5	16.4 ± 11.3	0.6
Number of doses	2.2 ± 1.3	1.8 ± 0.9	0.07
Total labour time			
0-12 hours	35 (57.4%)	25 (40.3%)	0.029*
average	7.96 ± 2.4	8.1 ± 2.5	0.85
12-24 hours	17 (27.9%)	28 (45.2%)	0.015*
average	16.9 ± 3.67	17.55 ± 3.98	0.69
more than 24 hours	9 (14.7%)	9 (14.5%)	0.517
average	41 ± 20.34	36.6 ± 14.6	0.63

***P< 0.05**

DISCUSSION

Nowadays and even before, induction of labor is more widely used[9,10] especially with prostaglandin analogs. Many studies have addressed this topic from different aspects in order to find the most effective treatment with less side effects as efficiently as economic. However, in our settings there were a clear absence of such studies, therefore we conducted this study; despite repeated in other places to elucidate the potential to change our practices in the field obstetrics and gynecology. Despite misoprostol was not registered for induction of labor although valid information supporting its use has been generated[11]. It is known that, low-dose oral misoprostol leads to longer induction to delivery intervals, but oral route was associated with fewer contractile and fetal heart rate abnormalities[12,13]. In the other side misoprostol is evenly distributed throughout the tablet containing 200mcg and was therefore divided as described in our method[14].

In our study we didn't find significant differences between oral 50mcg misoprostol and 3mg vaginal dinoprostone in respect to the number of vaginal deliveries, similar to that in other studies[15,16,17,18]. Although it was used in less doses and in lower frequency from other studies[19], oral misoprostol in our study proved to be therapeutically equivalent to dinoprostone with no differences in obstetrical complications. In other side we used oral misoprostol every 6 hours in dose of 50mcg which gave us similar results to other studies used it every 4 hours[18].

Many studies demonstrated the feasibility of comparisons between different methods of labour induction. These comparisons were not limited only to the prostaglandins, but were overtaken to mechanical induction with foley catheter. It was found also the lack of importance of the difference in results between these comparisons between mechanical and chemical inductions[20,21,22]. In our study it was noticed also the advantage of misoprostol used for IOL in premature rupture of membranes women. These findings consistent with other studies on this purpose[23]. No instances of maternal death, ruptured uterus, or serious morbidity occurred in our reported study which demonstrated the safety and efficacy of used two drugs.

In this small population study we demonstrated very little difference regarding primary outcomes, therefore a very large sample size would be required in order to obtain possible significant. Because a reliable power calculation was not performed, it is possible that the study was underpowered to detect a true difference in outcomes.

Last, misoprostol has the advantages to be less expensive, more available, more heat stable and can be self administered by patient without medical interventions.

INTERPRETATIONS

This study demonstrated that oral misoprostol is as effective as vaginal dinoprostone tablets for induction of labor and can be a good alternative for this purpose, taking into account the low economic balance of cost, which tends to misoprostol. A similar protocol is recommended for future studies to allow meta-analysis of large numbers to assess rare events such as fetal death or rupture of the uterus and induction with dead fetus.

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