COMPARISON OF ORAL (20 µG 2 HOURLY) VERSUS VAGINAL (25 µG 6 HOURLY) MISOPROSTOL FOR INDUCTION OF LABOUR IN TERM PREGNANCIES

Tahmina Yousaf, Zakia Asher*, Saira Afghan, Komail Malik****

Federal General Hospital Islamabad Pakistan, *Shifa International Hospital Islamabad Pakistan, **Pakistan Institute of Medical Sciences Islamabad Pakistan

ABSTRACT

Objective: To compare the outcome of oral misoprostol (20µg 2 hourly) with vaginal misoprostol (25µg 6hourly) for induction of labour in term pregnancies, in terms of frequency of vaginal delivery and cesarean section.
Study Design: Randomized clinical trial.
Place and Duration of Study: Department of Gynecology and Obstetrics, Unit II, Maternal and Child Health Centre, Pakistan Institute of Medical Sciences, Islamabad from, Jan to Dec 2015.
Subjects: All pregnant women at term (>37 weeks gestation) with obstetric and medical indication for induction of labour and having Bishop Score ≤6 were included in this study. Parity ≥4, previous history of obstetric and gynecological surgery and suspected cephalopelvic disproportion were excluded.
Material and Methods: The study was conducted after approval from the ethical committee of the hospital. The subjects fulfilling inclusion criteria were enrolled after informed consent. The women randomized to group A received 20 ug oral misoprostol 2 hourly orally up to a maximum of 12 doses and the women randomized to group B received 25 micro-grammisoprostol vaginally and was repeated at 6 hours interval upto a maximum of 4 doses. Randomization was done using lottery method. Data was entered on predesigned proforma and was analyzed using SPSS version 10.
Results: Ninety five women were randomly assigned to group A or B. In oral misoprostol group, 91 (95.8%) had vaginal delivery and 4 (4.2%) women needed C-section compared to 379 (83.2%) vaginal delivery and 16 (16.8%) women need C section in vaginal misoprostol group (*p*-value0.004).
Conclusion: It is concluded that women randomized to oral misoprostol had better obstetrics outcome as compared to vaginal misoprostol.

Keywords: Induction of Labour, Misoprostol, Oral and vaginal route.

INTRODUCTION

Induction of labour is defined as the process of artificially stimulating the uterus to initiate the process of labour. Over the past several decades, the incidence of labour induction has continued to rise. In developed countries, the proportion of infants delivered at term following induction of labour, is as high as one in four deliveries[1]. Induction is widely carried out all over the world, in cases where continuation of pregnancy is considered hazardous to both the mother or to the fetus or both[2]. Labour induction is considered as successful when it results in vaginal delivery. However when induction is performed on a patient with an unfavorable cervix, it is often difficult and can result in cesarean delivery[3].

There is wide variety of techniques available for induction of labour, however prostaglandins remain the single most effective means of achieving cervical ripening and labour induction. When combined with amniotomy, it provides good clinical effectiveness and patient satisfaction[4]. Prostaglandin E2 is registered for labour induction in many countries, however it is expensive for routine use in developing countries. It is sensitive to temperature changes so has to be kept under refrigeration. Misoprostol (a prostaglandin E1 analogue) has several potential advantages with few systemic side effects. Advantages include its stability at room temperature, it is relatively inexpensive and it can be given via several routes (oral vaginal,

Correspondence: Dr Tahmina Yousaf, Associate Gynecologist, Federal General Hospital, NIH Islamabad Pakistan
Email: tahmina.farrukh@yahoo.com
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sublingual, buccal). These properties make it an ideal agent for induction of labour, particularly in settings where the use of prostaglandin E2 is not possible owing to lack of availability, facilities for storage, or financial constraints[5]. Although misoprostol is not registered for such use, it has been widely used for obstetric indications such as induction of abortion and of labor. In 2011, World Health Organization (WHO) issued recommendation for induction of labour, which compared the use of low dose oral and vaginal misoprostol for induction of labour. However, owing to concerns about the risk of uterine hyper stimulation with vaginal misoprostol, more recent trials have focused on lower doses of vaginal misoprostol and the oral route for misoprostol administration. In a study conducted in China, low dose oral was compared with low dose vaginal misoprostol for labor induction at term and it concluded a cesarean rate of 4% in oral route and 17% in vaginal route[6]. A number of studies had been performed to compare oral versus vaginal misoprostol for induction of labour but with a higher dose regimen. Few studies are available in previous literature in which low dose (25µg) misoprostol has been used for comparison. These studies have compared 25µg vaginal with 100µg oral misoprostol, but no significant difference has been observed regarding mode of delivery[7]. Similarly another study compared 50µg vaginal with 50µg oral misoprostol without any significant difference in the mode of deliveries[8]. It was therefore suggested that dose can be reduced to avoid the side effects associated with higher doses of misoprostol, without affecting the mode of delivery.

The rationale of this study is to utilize lower dose protocol of misoprostol (25 ug) for induction of labour in term pregnancies and compare the outcome of oral route with vaginal route.

MATERIAL AND METHODS

This randomized clinical trial study was conducted at the department of Gynaecology and Obstetrics, Unit II, Maternal and Child Health Centre, Pakistan Institute of Medical Sciences, Islamabad, form one year from, January 2015 to December 2015.

Total 190 females were selected for this study. Sample size calculated by using WHO sample size calculator taking level of significance 5%; power of test 90%; anticipated population proportion is equal to (P1) 4%[10], anticipated population proportion (P2) is equal to 17%[10]; sample size 95 in each group.

Group A was oral, group B was vaginal, technique used was non-probability convenience sampling.

The inclusion criteria of this study was all term pregnant women (upto parity 4) with obstetric and medical Indication of induction for labour and bishop score ≤6.

Parity ≥4, previous history of obstetric and gynaecological surgery e.g: C-section, myomectomy. Women with genital tract anomalies and suspected cephalopelvic disproportion were exlusion of this study.

Mode of delivery was the main outcome, measured in term of frequency of vaginal delivery and cesarean section.

Data were collected on a pre-designed proforma. Permission from the hospital ethical committee was sought. Patients admitted for induction of labour were recruited after informed consent. Lottery method was used to randomize and allocate the patients to oral or vaginal group. The women randomized to group A received 20 microgramoral misoprostol 2 hourly orally up to a maximum of 12 doses. The women randomized to group B receive 25 microgram-misoprostol vaginally and was repeated at 6 hours interval up to a maximum of 4 doses. Oral misoprostol is currently available in the form of 200µg tablets. The recommended dose of oral misoprostol for induction of labour is 20µg, 2-hourly. It was suggested that rather than breaking the 200µg tablet into eight pieces, the tablet should be dissolved into 200 ml of water and 20 ml of that solution be administered as a

single dose. The primary outcome measure was mode of delivery, (vaginal, instrumental or C-section) and number of doses required for initiation of labour. Secondary outcome was uterine hyperstimulation. Data were entered and analyzed using the SPSS version 10. Descriptive statistics were calculated for both qualitative and quantitative variables. For quantitative variables (age, parity, gestational age and no. of doses) mean ± S.D was calculated and for qualitative variable (mode of delivery) frequency and percentage was calculated. Qualitative variables like mode of delivery were compared by using chi square test. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 190 patients were enrolled for this study. The mean age of participants was 26.93 ± 4.09 years. Mean gravidity of was 1.02 ± 1.19 and 63.7% of women were primigavida and 36.3% were multigravida. Mean gestational age by dates was 38.91 ± 1.02 weeks (table-I). Commonest indication for induction of labour was post dates pregnancy accounting for 87 (45.8%) cases (table-III). Of 190 participants, 113 (59.5%) needed single dose of misoprostol and 77 (40.5%) needed multiple doses (table-IV). Overall, 170 (89.5%) women had spontaneous vaginal delivery and 20 (10.5%) women needed cesarean section (table-II). Stratified analysis of mode of delivery in each study arm by number of doses is summarized in table-IV. No case of uterine hyperstimulation was seen during the study.

Table-I: Comparison of demographic characteristics of two study arms (n=190).

		Treatment		Mean ± SD	*p*-value
		Oral Misoprostol	Vaginal Misoprostol		
Age Group.	≤25years	40 (21.05%)	50 (26.3)	26.93 ± 4.09	0.15
	>25years	55 (28.9%)	45 (23.6%)		
Gravidity.	Primigravida	60 (31.57%)	61 (32.1%)	1.02 ± 1.19	0.89
	Multigravida	35 (18.4%)	34 (17.8%)		
Gestational age.	≤38 weeks	45 (23.6%)	47 (24.7%)	38.91 ± 1.02	0.78
	>38weeks	50 (26.3%)	48 (25.2%)		

Table-II: Mode of delivery (n=190).

		Oral Misoprostol	Vaginal Misoprostol	*p*-value
Mode of delivery.	Vaginal Delivery	91 (47.8%)	79 (41.5%)	0.0045*
	Cesarean Section.	4 (2.1%)	16 (8.4%)	

Table-III: Reasons for induction of labour (n=190).

	Treatment		*p*-value
	Oral Misoprostol	Vaginal Misoprostol	
Post date	42 (22.1%)	45 (23.6%)	0.96
PROM	24 (12.6)	25 (13.1%)	
Poor Bishop	15 (7.8%)	13 (6.8%)	
Oligohydramnios	8 (4.2%)	8 (4.2%)	
NRCTG	6 (3.1%)	4 (2.1%)	

Table-IV: Stratification of mode of delivery in study arms by number of doses (n=190).

Number of doses		Treatment		*p*-value
	Mode of delivery	Oral misoprostol	Vaginal Misoprostol	
Single dose.	Vaginal Delivery	52 (27.3%)	47 (24.7%)	0.07
	Cesarean section.	2 (1.05%)	12 (6.3%)	
Multiple doses.	Vaginal Delivery	39 (20.5%)	32 (16.8%)	0.277
	Cesarean section.	2 (1.05%)	4 (2.1%)	

DISCUSSION

Misoprostol is, a cost effective treatment, being increasingly used for induction of labour since past few years. There have been different published reports of misoprostol use through

different routes (oral, vaginal and rectal) and in varying doses (25 µg to 200 µg). Higher incidence of tachysystole is reported with higher doses[9].

In the present study baseline characteristics such as age, gravidity, gestational age and indication for induction of labour were distributed equally across the treatment arms. This is the impact of randomization which distributes known and unknown confounders across treatment groups.

In this study, oral dosage regimens of 20µg at 2 hourly intervals for maximum of 12 doses and vaginal dose was 25µg 6 hourly up to maximum of 4 doses. Jindal *et al* used same dose of misoprostolvia oral and vaginal route and found that vaginal route was more effective for inducing labour successfully as compared to oral route. Their findings were contrary to results of our study where oral route was found to be more effective[10]. Higher doses of misoprostol were used in a study by Blanchard, Clark *et al*[10,11].

In this study the percentage ofprimigravida women in oral group was 31.5% and in vaginal group 32.1% (*p*-0.50). Literature has reported higher percentage of primiparous women in the treatment arms which was consistent with our resuts[12-14].

Cesarean section rate in group A was 2.1% as compared to 8.4% (*p*-0.004) in group B. Darney *et al* reported (4% and 17%) and Kambhampati *et al* reported (6% and 14%) in both groups[15,16]. In another study by Ratnakhatri *et al* the rates of operative delivery in both groups were 14% and 30% which were higher in comparison to our study[17]. In contrast, other studies reported that no difference in the rate of cesarean delivery in oral vs. vaginal misoprostol. The proportion of cesarean delivery in oral group was 41% and vaginal group was 42% (*p*-0.63)[18-21]. In a study by Sultana *et al* need for cesarean section in oral misoprostol was 30% as compared to 34% in vaginal misoprostol (*p*-0.78)[21].

Commonest indication for induction of labour in the present study was postdates pregnancy (22.1% and 23.6%) in both groups, followed by prelabour rupture of membranes. Jindal *et al* and Osmundson *et al* reported hypertensive disorders as the most common indication whereas oligohydramnios, intrauterine growth restriction and medical disorders in pregnancy are the indications reported in previous studies, for inducing labour at term[10,22].

Misoprostol effectively induces labour, with the vaginal route of administration and has a faster action than with the oral route in equivalent doses. However frequent occurrence of hyperstimulation and the higher intervention rate in the vaginal group mean that the preferred route might be oral. More trials are needed to find the right oral dosage that combines efficacy with safety.

Misoprostol is especially relevant for Pakistan where economic resources are scarce and high temperatures prevail. This drug ischeap as compared to other prostaglandins licensed for pregnancy termination, induction of labour and treatment and prevention of post-partum hemorrhage. It is heat stable so is easily stored at room temperatures and it had few systemic side effects. Although formulated for oral usage, but rapidly absorbable via sublingual, vaginal and per rectal route.

CONCLUSION

It is concluded that women randomized to oral misoprostol had better obstetrics outcome as compared to vaginal misoprostol.

Contribution

Although our contribution to the existing literature is small, but it is significant addition to studies comparing lower dose regimen and provides comparison of oral and vaginal routes in terms of mode of delivery.

LIMITATIONS OF STUDY

This study was performed on limited number of patients. To reach the consensus about the lowest effective dose of oral and vaginal misoprostol, we need further trials on larger scale. However, any increase in dose, while improving clinical efficacy must be balanced

against a potential increase in side effects and adverse complications for the women and her infant.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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