Original Article

Comparing the effect of oral and vaginal isosorbide dinitrate in pre-induction cervical ripening in term pregnancy: A controlled clinical trial

Ladan Haghighi, Somayeh Moukhah[1], Azita Goshtasbi[2]

Department of Obstetrics and Gynecology, School of Medicine, Tehran University of Medical Sciences, [1]Department of Midwifery and Reproductive Health, School of Medicine, The University of Tarbiat Modares, [2]Specialist, Family Health Research Group, Health metrics Research center, Iranian Institute for Health Sciences Research, ACECR, Tehran, Iran

Abstract

Background: Cervical ripening for labor induction is one of the most important issues in midwifery. Isosorbide dinitrate (ISDN) is one of the most important choices that have been proposed for cervical ripening, but still there are controversies regarding its prescription. The present study aimed to evaluate the effects of vaginal and oral ISDN compared to the control group for pre-induction cervical ripening.

Materials and Methods: In this non-blinded clinical trial, 149 nulliparous women with term or prolonged pregnancy were randomly selected and divided into three groups by block randomization. The intervention group included vaginal (50 subjects, 40 mg) and oral (49 subjects, 20 mg) ISDN groups. The third group was the control group (50 subjects) which did not receive any medication. The amount of ripening was given by Bishop score evaluated before taking medication and 24 h after taking it.

Results: After 24 h, Bishop score in vaginal ISDN group significantly increased compared to the oral ISDN and control groups ($P < 0.001$ for both). Although the increase in Bishop score was lower in the oral ISDN group than in the vaginal group, it had a statistically significant increase in comparison to the control group ($P = 0.001$). All the three groups were matched regarding pregnancy termination and cesarean causes, and there was no statistically significant difference among the three groups ($P > 0.05$).

Conclusion: Prescribing vaginal ISDN for cervical ripening was effective, and it can be used with confidence.

Key Words: Bishop score, isosorbide dinitrate, oral, term pregnancy, vaginal

Address for correspondence:
Mrs. Somayeh Moukhah, Department of Midwifery and Reproductive Health, School of Medical Sciences, The University of Tarbiat Modares, Tehran, Iran.
E-mail: so.moukhah@gmail.com

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INTRODUCTION

During delivery, the cervix should be soft and permeable and must be easily dilated. Changes in the cervix during pre-induction cervical ripening are among the factors utilized for evaluation of cervix when performing induction.[1,2]

Many pregnant women have indications for induction, but their cervical condition is inappropriate. Decrease

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in appropriateness of the cervix or Bishop score leads to reduced rate of success of induction. Besides, induction failure leads to lack of progress in labor, increased risk of chorioamnionitis, and increased likelihood of cesarean delivery. There are considerable studies conducted on various methods of cervical ripening prior to stimulating uterine contractions.[2,3] A Bishop score of 4 or lower indicates inappropriate cervix, and might be inclusions for indication of pre-induction cervical ripening.[4]

Cervical ripening is a prerequisite for natural vaginal delivery to occur without complications. It is an inflammatory process with many mediators involved and causes remodeling of the cervix tissue components; this process can be stimulated by pharmacological factors.[5] Many studies have been carried out for cervical ripening using different methods.[4-7]

Cervical ripening (effacement and softening) with prostaglandins reduces the time from admission to delivery, resulting in decreased healthcare cost. Generally, there are two methods for cervical ripening: Pharmacological (including prostaglandin analogs) and non-pharmacological or mechanical (including transcervical catheter, hygroscopic cervical dilator, and denudation of fetal membranes).[3,4,7-9]

The use of prostaglandins in different forms such as suppositories, tablets, and gel gives different results;[9] therefore, still their use is not considered to be a safe and secure method. Mechanical methods such as using Foley catheters and laminaria have been studied for many years, and their efficacy was compared with each other or with pharmacological methods in numerous clinical trials.[10]

Recently, nitric oxide (NO) releasing drugs, which cause endothelium-dependent relaxation and are considered as important biological mediators in the human body, have been focused. NO is a free radical gas that acts as a relaxant for vascular smooth muscle, gastric smooth muscle, and myometrium. In midwifery, NO releasing drugs are used for treatment of preterm labor, acute uterine relaxation for easy removal of the fetus, manual removal of placenta, and improvement of fetal blood flow.[11-14]

Another proven role of these factors is induction of the physiological process of cervical ripening. Vaginal application of NO releasing drugs is effective on pre-induction cervical ripening process of the labor. It directly and also through stimulation of prostaglandin and cyclooxygenase-2 (COX2), release of cytokines, and inhabitation of thromboxane-A2 (TXA2) facilitates cervical ripening without causing complications such as fetal distress.[12] On the other hand, studies on human beings have also reported the effect of NO on cervical ripening during the third trimester and its fewer side effects compared to those of prostaglandins.[15]

Previous studies illustrated that in comparison to prostaglandins, NO products inhibit uterine activities more and increase the uterine blood flow.[9] However, there are still many unanswered questions concerning the prescription and its dosage. Collingham *et al*. used 40 mg of isosorbide mononitrate at 16-h intervals for three preadmission dosages. Due to the slow systemic absorption through vagina, this interval seemed sufficient.[16] Wolfer and Facchinetti used 60 mg of isosorbide mononitrate at a 24-h interval for two preadmission dosages. After 24 h, the cervix began to soften and reached its peak within 48 h.[15] In all these studies, isosorbide mononitrate was administered orally, and it seems that improper absorption of the sufficient amount by vagina and cervix might address the effectiveness of this combination.

Given the fact that isosorbide dinitrate (ISDN) can be an appropriate alternative for cervical ripening compared to prostaglandin analogs, researchers are trying to find the best way of its prescription (vaginal or oral). So far, this comparison has not been made in any study. This study was conducted with an aim to evaluate the effectiveness of oral and vaginal ISDN on pre-induction cervical ripening.

MATERIALS AND METHODS

This was a non-blinded controlled clinical trial registered in the Iranian Registry of Clinical Trial (201108157334N1) and approved by the Ethics Committee of Tehran University of Medical Sciences (License Number: 2014).

Pregnant women referring to the midwifery ward of Shahid Akbar Abadi Hospital (Tehran, Iran) in 2012 were selected by simple random sampling method. This randomized controlled trial was done using parallel technique. Block randomization was used to select the participants according to the inclusion and exclusion criteria. All women who were willing to participate and gave written informed consent were enrolled after consultation.

Inclusion criteria included being nulliparous, gestational age of over 40 weeks and 4 days, Bishop score of less than five, singleton pregnancy, cephalic presentation, not having contraindications for ISDN, and not having previous history of cesarean section or any uterine scar or any underlying disease. They were

required not to have reactive nonstress test (NST) and have normal biophysical profile (BPP) ultrasound.

Exclusion criteria included vaginal bleeding, intolerance to ISDN, labor pain, oligohydramnios, intrauterine growth restriction (IUGR), and non-reassurance fetal heart rare (FHR).

The women were randomly allocated to one of three groups as follows: 50 pregnant women in vaginal ISDN group with ISDN (Tolid Darou Pharmaceutical Co.,Tehran, Iran) given at a dosage of 40 mg for two times every 4 h, 49 pregnant women in oral ISDN group with ISDN (Tolid Darou Pharmaceutical Co.) given at dosage of 20 mg for two times every 4 h, and the control group in which no medication was prescribed for pre-induction cervical ripening. When the medication was administered, they were monitored for 4 h in the emergency ward and then discharged; all the patients were required to refer back to the hospital 24 h later for Bishop score evaluation.

Induction was started with administration of 10 units of syntocinon in 1000 cc Ringer's lactate serum at a rate of 2.5 mU/min every 20 min and was continued to 2 times of the dosage, up to 60 drops/min. Then, the delivery interval up to the beginning of induction was measured. In addition, in case the patient had headache after ISDN administration, acetaminophen was prescribed. In cases of hypotension (blood pressure less than 90/60 mmHg), 1 L Ringer's serum was prescribed. Therefore, our patients immediately became stable and it seemed that outpatient therapy was not dangerous for them.

If the contractions were not proper, the patient was transferred to the perinatal unit for labor trial and was brought back to the delivery room on the next day. If there were proper contractions after 12 h and no change in the Bishop score, induction was stopped; after the contractions were over, the patient was transferred to the ward and was transferred to the delivery room to continue the labor on the next day.

Statistical analysis

Data were analyzed using SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA). Data were presented as mean, standard deviation (SD), and frequency. One-way analysis of variance (ANOVA) was used to compare quantitative data with normal distribution among the three groups. Tukey's *post-hoc* test was used for comparing statistical significance between two groups. Furthermore, chi-square test was used to compare the qualitative data among the three groups. Statistical significance was set at $P < 0.05$.

RESULTS

One hundred and forty-nine women with term and post-term pregnancy were randomly assigned to one of the three groups as follows, based on the inclusion and exclusion criteria: 50 in vaginal ISDN group, 49 in oral ISDN group, and 50 in the control group [Figure 1]. Women in the control group did not receive any medication.

Table 1 shows the age distribution of the mothers in all the three groups. Total mean age of the mothers was 25.8 ± 4.8 years. Age distribution was similar among the three groups, and no statistically significant difference was observed ($P = 0.175$).

The mean gestational age of the mothers was 41.06 ± 0.3 weeks. Mean gestational age of the mothers in the three groups did not show statistically significant difference ($P = 0.109$). In total, only 37 subjects had a gestational age more than 41 weeks, which had the same distribution among the three groups and did not have a statistically significant difference.

Comparison of the distribution of body mass index (BMI) in the three groups did not show any statistically significant difference ($P = 0.549$).

Table 2 illustrates the Bishop scores of the mothers at the beginning of the study, which did not have any statistically significant difference ($P = 0.860$). Compared to the onset of the intervention, Bishop score had a statistically significant increase in 24 h

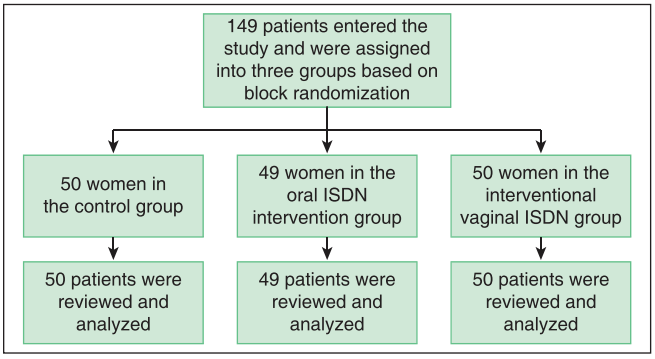

Figure 1: Summary of patients assigned to three groups receiving vaginal ISDN, oral ISDN, or placebo, respectively

Table 1: Frequency distribution of the subjects in terms of age, gestational age, and body mass index (BMI) in the groups

Groups	Age (years) Mean ± SD	Gestational age (weeks) Mean ± SD	BMI (kg/m^2) Mean ± SD
Vaginal ISDN	26.8±4.6	41±0.33	29.8±4.2
Oral ISDN	25.5±5.1	41±0.36	29.4±3.6
Control	25.1±4.7	41.1±0.32	30.5±6.7
P-value	0.175	0.109	0.549

and the highest increase was found in the vaginal ISDN group. According to *post-hoc* analysis, the observed difference between the two ISDN groups and the control group was statistically significant ($P < 0.001$ for both). Although the mean increase of Bishop score in the vaginal ISDN group was more than that of oral ISDN group, the difference was not significant ($P = 0.060$).

In Table 3, the distribution of intervention duration at the beginning of active phase of the labor is shown, which did not have a statistically significant difference ($P < 0.001$). The lowest duration was found in the vaginal ISDN group in which the average duration was a little lower than one-half of the duration of the control group ($P < 0.001$). Moreover, the groups of oral ISDN and control showed significant differences ($P = 0.001$). The difference observed between the oral and vaginal ISDN groups was not statistically significant ($P > 0.050$).

The distribution of the active phase duration until the first stage of delivery is illustrated in Table 3. As indicated, the lowest duration was found in the vaginal ISDN group and the highest in the control group, and the difference was statistically significant ($P < 0.001$). Besides, based on the *post-hoc* analysis, the mean duration of vaginal ISDN was statistically lower than in the control group ($P < 0.001$). The difference between the oral ISDN group and the control group was statistically significant ($P = 0.044$). The difference observed between the oral and vaginal ISDN was not statistically significant ($P = 0.405$).

The duration of the second phase of labor, on average, was approximately 43 min in total. The difference among the three groups was not statistically significant ($P = 0.619$).

Regarding the termination of pregnancy, although cesarean was more in the control group compared to the other two groups, the difference was not statistically significant ($P = 0.573$) [Table 3]. The reason for choosing cesarean was similar in all the three groups and no significant difference was observed among them ($P = 0.810$).

The side effects of using ISDN are illustrated in Table 4. The main side effects included headache, flushing, hypotension, and nausea. In the control group, none of these side effects was reported. Headache was observed more in the vaginal ISDN group compared to the oral ISDN group ($P = 0.005$). The observed difference between the frequency distribution of other side effects of ISDN in both groups was not statistically significant ($P > 0.050$).

Table 2: Comparing the Bishop score at the beginning of the study and 24 h from the onset of the study in the groups

Bishop score chenges	Vaginal ISDN (mean ± SD)	Oral ISDN (mean ± SD)	Control	*P*-value
Bishop score at the onset of the study	1.98±1.3	1.99±1.2	2.1±1.2	0.86*
Bishop score 24 h from the onset of the study	5.14±1.7	4.42±2.1	2.98±1.6	0.001* 0.06†

**P*-value on comparing three groups, †*P*-value on comparing oral and vaginal ISDN groups

DISCUSSION

NO is a common product of arginine metabolism in many tissues. It appears to be an important paracrine vasodilator, and may be involved in cell death and nerve transfers.[12] NO is also released from several vasodilator drug molecules. It is released from important medications such as nitroprusside, nitrates, and nitrites.[13] This substance is a potent vasodilator in all vascular substrates and a powerful relaxant in most smooth muscle cells. Its performance mechanism in this case is activation of guanylyl cyclase and production of cyclic guanosine monophosphate (cGMP) which causes dephosphorylation, and disables the light chains of myosin and causes relaxation of smooth

Table 3: Comparing the prolonged duration since induction to the second phase of delivery, type of delivery, and birth weight in the groups

Variable		Vaginal ISDN	Oral ISDN	Control	*P*-value
Duration from induction to the active phase of delivery (h) (mean±SD)		3.7±2	4.8±2.7	7.1±3.3	0.01
Duration from the active phase to delivery (h) (mean±SD)		2.6±1.6	3±1.3	4.1±1.6	0.01
Duration of the second phase (min) (mean±SD)		40.5±22.3	47.2±27	41.5 ±25.8	0.196
Pregnancy termination					
Frequency (%)	Cesarean	26 (52)	25 (51)	30 (60)	0.735
	Natural vaginal	24 (48)	24 (49)	20 (40)	
Reason for cesarean					
Frequency (%)	Fetal distress	10 (38.5)	6 (25)	9 (30)	0.108
	Meconium defecation	13 (50)	13 (54.2)	15 (50)	
	Fetopelvic disproportion	3 (11.5)	5 (20.8)	6 (20)	

Table 4: Comparing the side effects in both vaginal and oral ISDN groups

Side effect	Vaginal ISDN Frequency (%)	Oral ISDN Frequency (%)	*P*-value
Headache	10 (20)	6 (12.3)	0.005
Flushing	1 (2)	3 (6.1)	0.128
Nausea	2 (4)	–	0.329
Hypotension	–	2 (4)	0.107

muscle. It also has a physiological role in erectile tissue function.[14]

As mentioned earlier, several studies have tried to show the effect of NO on cervical pre-induction ripening.[15-22] Many of these studies have used isosorbide mononitrate and no study has been conducted with ISDN so far. Findings of previous studies indicated that delivery length from the onset of intervention in the misoprostol group was shorter and the need for induction in this group was lower.[16] Due to difficult access to misoprostol and its high cost in Iran, and dangers of using misoprostol including systolic tachycardia, uterine hyperstimulation, and other risks to the fetus, this medication should always be prescribed in certain circumstances only.

Considering that compared to isosorbide mononitrate, vaginal ISDN has shorter duration of effectiveness (half-life of 50 min compared to 4-5 h) and considerable first-pass metabolism, this medication was prescribed for cervical ripening during labor in this study. Authors of the present study believe that ISDN is a more cost-effective medication and is available without any legal problems, and can be a reasonable alternative for misoprostol (unless it is not available or has contraindications). It is a safe medication that is currently prescribed on an outpatient basis for cervical ripening and can be a good alternative for prostaglandin analogs. However, there are still controversies on the route it should be administered (vaginal or oral).

The present study aimed to review the effectiveness of vaginal and oral ISDN for cervical ripening during delivery. Findings showed that compared to the onset of intervention, the Bishop score had a statistically significant increase during 24 h and the highest increase was obtained in the vaginal ISDN group. According to *post-hoc* analysis, the difference observed between the two ISDN groups and the control group was statistically significant. The distribution of the duration in the onset of intervention up to the active phase of delivery was studied and it was found to have a statistically significant difference. The lowest duration was obtained in vaginal ISDN group and its mean duration was less than one-half of the control group. Furthermore, the oral ISDN and control groups showed a statistically significant difference. The difference between the vaginal and oral ISDN groups was not statistically significant.

In conclusion, the present study showed that both ISDN methods, compared to the control group, had a statistically significant increase in cervical ripening during 24 h (increased Bishop score), and vaginal prescription had significantly better effect than oral use. The results of this study also showed that compared to the oral route or the control group, vaginal ISDN prescription could decrease the length of induction for labor until the active phase and from the active phase to the first stage of the labor; however, it did not affect the duration of second stage of labor.

CONCLUSION

The findings showed that vaginal ISDN can be more effective than the oral type. Although the incidence of headaches was higher in patients using vaginal ISDN compared to the oral group, it was not significant. Vaginal ISDN also improved the Bishop score, while oral administration (due to various reasons such as hepatic metabolism) was not a good candidate for cervical ripening. Furthermore, the vaginal prescription of ISDN resulted in shorter delivery time and fetal expulsion, thus reducing the risk of potential complications.

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