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Efficacy of Oral Isosorbide Mononitrate Sustained-release for Pre-induction Cervical Ripening in Term Pregnant Women in an Outpatient Setting: A randomized controlled trial

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ABSTRACT

Objectives: To compare the efficacy of 60 mg oral, sustained-release, isosorbide mononitrate (ISMN SR) with a control for improve pre-induction cervical ripening of term pregnant women in an outpatient setting.

Materials and Methods: In this randomized controlled, superiority trial, 36 women with uncomplicated singleton pregnancy at ≥ 39 weeks gestation and unfavorable cervix attending the antenatal care clinic at Khon Kaen Hospital were randomly assigned to (a) two oral 60 mg doses of ISMN SR every 24 h (n=18) prior to admission for induction of labor or (b) a control group (n=18). The primary outcome was the proportion of favorable cervix on admission. The secondary outcomes were (a) changes in the Bishop score, (b) time from admission to delivery, and (c) neonatal and maternal outcomes.

Results: Demographic characteristics were similar between the groups. The proportion of favorable cervix at 48 h after oral ISMN SR was significantly greater than the control group (0.61 vs 0.17, p = 0.008, RR = 7.85, 95%CI 1.65-37.40). The mean change in the Bishop score was significantly higher in the ISMN SR group than the control (6.05 vs 2.71, p = 0.022). The time from admission to delivery in the ISMN SR was also less than the control (10 vs 23 h, p = 0.002). However, there was no respective significant difference in the rate of cesarean section, maternal complications, or neonatal outcomes.

Conclusion: Our study provides evidence that pre-induction of cervical ripening with 60 mg of oral ISMN SR among outpatient, term pregnant women is effective and with no observed adverse outcomes.

Keywords: cervical ripening, isosorbide mononitrate SR, term pregnancy, induction of labor, outpatient setting

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การศึกษาประสิทธิภาพของการรับประทานยาไอโซซอร์ไบด์ โมโนไนเตรท เอสอาร์ เพื่อการกระตุ้นปากมดลูกให้พร้อมก่อนการชักนำคลอดในสตรีมีครรภ์ครบกำหนดแบบผู้ป่วยนอก

ชื่ณ เชาว์ตระกูล, ศุภศิริ หะยะกังฉัตร์, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพในการเตรียมความพร้อมของปากมดลูกก่อนการชักนำคลอดในสตรีตั้งครรภ์ที่มีอายุครรภ์ตั้งแต่ 39 สัปดาห์ ที่ได้รับประทานยา ไอโซซอร์ไบด์ โมโนไนเตรท เอสอาร์ (ISMN SR) 60 มก. เหนือกว่ากลุ่มควบคุมในรูปแบบผู้ป่วยนอก*

วัสดุและวิธีการศึกษา: *สตรีตั้งครรภ์อายุครรภ์ตั้งแต่ 39 สัปดาห์ และฝากครรภ์ที่ รพ.ขอนแก่น เข้าร่วมการวิจัยแบบผู้ป่วยนอก จำนวนทั้งหมด 36 คน ได้รับการสุ่มและแบ่งเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ได้รับประทานยา ISMN SR 60 มก. จำนวน 18 คน และกลุ่มควบคุมจำนวน 18 คน จากนั้นนัดติดตามเพื่อวัดสัดส่วนความพร้อมของปากมดลูกและชักนำการคลอดหลังเข้าร่วมการวิจัย 48 ชม.*

ผลการวิจัย: *ลักษณะทางประชากรศาสตร์ไม่แตกต่างกันระหว่างกลุ่ม โดยกลุ่มที่ได้รับประทานยา ISMN SR มีสัดส่วนความพร้อมของปากมดลูกมากกว่ากลุ่มควบคุม ร้อยละ 61 และ ร้อยละ 17 ตามลำดับ ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 0.008, RR = 7.85, 95%CI 1.65-37.40) นอกจากนั้นกลุ่มที่รับประทานยามีค่าเฉลี่ยความพร้อมของปากมดลูกเพิ่มขึ้นและลดระยะเวลาในการเริ่มนอนโรงพยาบาลจนถึงคลอดได้อย่างมีนัยสำคัญทางสถิติ (p = 0.022 และ 0.002 ตามลำดับ) อย่างไรก็ตามอัตราการผ่าตัดคลอด และภาวะแทรกซ้อนต่อมารดาและทารกทั้งสองกลุ่ม ไม่มีความแตกต่างกัน*

สรุป: *สตรีตั้งครรภ์ครบกำหนดที่ได้รับประทานยา ISMN SR 60 มก. มีประสิทธิภาพและความปลอดภัยในการกระตุ้นความพร้อมของปากมดลูกก่อนการชักนำการคลอดในสตรีตั้งครรภ์ครบกำหนดได้ในแบบผู้ป่วยนอก*

คำสำคัญ: *ความพร้อมของปากมดลูก, ไอโซซอร์ไบด์ โมโนไนเตรท เอสอาร์, สตรีตั้งครรภ์ครบกำหนด, การเหนี่ยวนำคลอด, ผู้ป่วยนอก*

Introduction

Post-term pregnancy is defined as a pregnancy with a gestational length of ≥ 294 days[1], which occurs in 17% of all births at Khon Kaen Hospital, and is associated with a respective increased rate of multiple maternal and fetal complications[2]. Elective labor induction plays an important role in reducing the risk of adverse outcomes without increasing the risk of operative delivery. According to The American College of Obstetricians and Gynecologists, elective induction may be considered for logistical or psychosocial reasons but not before 39 0/7 weeks of gestation[3].

To our knowledge, cervical ripening is one of the essential factors predicting success of labor induction. Favorable pre-induction cervix is a predictive factor of successful vaginal delivery[3].Various prostaglandin regimens, especially the PGE1 analogue (misoprostol), are commonly recommended for ripening the cervix[4]. Five percent of women, however, have uterine hyper-stimulation after administration of prostaglandin, causing changes in fetal heart rate[5]. For this reason, cervical ripening is conducted on an in-patient basis so that the fetus can be monitored during the process. Since serious maternal and fetal adverse events caused by prostaglandins have been observed, safer and cost-effective cervical-ripening agents have been sought for decades. The ideal cervical ripening agent would induce adequate cervical ripening (soft and thin) without causing uterine contractions[3]; as the lack of contractions obviates the need for fetal monitoring, and such an agent could be given on an outpatient basis. The advantages of outpatient cervical ripening include patient convenience, reduction of workload on labor and delivery units, and reduced hospitalization costs[6-9]. The 2017 Cochrane[10] report on different methods for the induction of labor in outpatient settings showed that it was feasible but that a trustworthy and effective protocol had not yet been established.

Nitric oxide donors (NODs) are free radical gases with a short half-life that acts as a relaxant for vascular or gastric smooth muscle and myometrium. In advanced term pregnancy, NODs are down-regulated in the myometrium but become up-regulated during the physiological process of cervical ripening[11,12]. Vaginal application of NODs is effective on pre-induction of the cervical ripening process of labor. NODs work directly through the stimulation of prostaglandin F2α and cyclooxygenase-2, releasing cytokines and inhibiting thromboxane-B2, which facilitates cervical ripening without any complications such as fetal distress[13]. A 2016 Cochrane review[14] confirmed that NODs can be a useful tool in the process of induction of labor causing favorable cervix compared to placebo. Thus, NODs are considered a fundamental mediator of cervical ripening in an outpatient setting since it is able to induce cervical ripening without causing uterine contractions or other maternal and fetal adverse effects of clinical importance[14,15].

Various studies have demonstrated that NODs for cervical ripening in an outpatient setting had a higher efficacy on vaginal isosorbide mononitrate (ISMN) than placebo and resulted in safe maternal and fetal outcomes[16-20]. Nevertheless, there were differences in drug form (sustained vs non-sustained release), dosage (2-3 doses), drug components (mono- vs di-nitrate) and time for assessment[16-20]. The drug application in most of the studies, moreover, used the vaginal route, which is more difficult to apply than oral administration. Haghighi, et al.[21] reported a statistically significant increase in the Bishop score for both the oral and vaginal isosorbide dinitrate (ISDN) (limited by first-pass metabolism) compared to the control group. Furthermore, the oral isosorbide mononitrate had a sustained release (ISMN SR), which means it has a longer duration of action than ISMN or ISDN and no first-pass metabolism limitation, for ripening cervix in term pregnancy in outpatient setting are absent. The aim of the current study was to evaluate the efficacy once-daily oral administration of 60 mg ISMN SR for cervical ripening prior to induction of labor in an out-patient term pregnancy setting.

Materials and Methods

This randomized controlled trial was conducted at the antenatal care clinic (ANC) at Khon Kaen Hospital, Thailand, between February and March,

2017. The Khon Kaen Hospital Institutional Review Board for Human Research reviewed and approved the study. All participants gave informed consent before being enrolled in the study.

We included pregnant women 18 years old and over at a gestational age of 39 weeks or more. This was a singleton pregnancy, cephalic presentation, with an unfavorable cervix (Bishop score of ≤ 6)[4]. We excluded pregnant women with a contraindication for vaginal delivery, labor pain, ruptured membranes, uterine scaring, pregnancy-induced hypertension or contraindication for ISMN administration (i.e., hypersensitivity or severe hypotension).

Eligible participants were randomized by computer-generated, block of four, and randomly assigned to two groups. Treatment packs containing 2 x 60 mg tablets of ISMN SR (Solotrate SR; ZydusCadila Healthcare Ltd, India) were prepared and numbered by the pharmacist. After each patient's baseline Bishop score was assessed and recorded by the first obstetric resident or staff, they were allocated-using sequentially numbered, sealed opaque envelopes (prepared by the second author who was not apprised of the Bishop score). Participants in study group were given two doses of 60 mg oral tablets of ISMN SR. The first dose was given at the ANC under direct supervision. The patients were instructed to take the second dose in 24 hours. The control group-with no intervention-was discharged after the antenatal care. All participants were asked to admit to the labor room 48 hours later. They had to return immediately if they felt any decrease in fetal movements, increased labor pains, vaginal bleeding, or sudden leakage of amniotic fluid.

Thirty minutes after drug administration, vital signs and a non-stress test were documented at the ANC before their being discharged. The dosage and the interval between the 2 doses was based on the pharmacokinetics of orally administered ISMN SR[22].

The Bishop score was recorded again on admission by one of the authors who were not a part of the investigation. This was thus a single-blind trial as the authors who assessed the Bishop score were not aware whether the participants were given oral ISMN SR or the control. Labor was induced by a 25-µg misoprostol vaginal suppository (Cytotec; Pfizer Inc, New York), which was inserted into the posterior fornix if the score was < 7 and without good uterine contraction. A repeated dose of misoprostol was administered 4 hours later if cervical ripening was insufficient or poor uterine contraction was observed. In those who had a Bishop score ≥ 7, a low-dose oxytocin infusion or 25-µg of misoprostol vaginal were used to augment labor. Induction failure was defined as the non-occurrence of the active phase of labor despite the 25-µg of misoprostol vaginal stimulation lasting at least 6 doses after induction of labor.

The primary outcome was the proportion of pregnant women who had favorable cervix on admission prior to induction of labor. The secondary outcomes included (a) the mean change in the Bishop score, (b) the time from admission to delivery, and (c) the mode of delivery. Other maternal outcomes, neonatal outcomes, and complications were recorded (presence or absence of tachycardia, hypotension, headache, nausea or vomit and dizziness, Apgar scores at 1 and 5 minutes and admission to the neonatal intensive care unit (NICU), uterine hyperstimulation, meconium-stained liquor, and postpartum hemorrhage).

This study used statistical test as superiority trial. The Chi-square test or Fisher's exact test was used as appropriate to analyze the categorical data (for proportion of favorable cervix, maternal, neonatal outcomes and complications). For continuous data, the Student t-test was used to assess the normal distribution continuous data while the Mann–Whitney U test was used to analyze the non-normal distribution continuous data.

Sample size in the current study was used for categorizing outcomes. This was based on a pilot study.

$$\text{N/ group} = \frac{(Z\alpha\sqrt{2pq} + Z\beta\sqrt{p1q1 + p2q2})^2}{(p1 - p2)^2}$$

p1 = Proportion of pregnant women who favorable cervix of ISMN SR group = 0.53

p2 = Proportion of pregnant women who favorable cervix of control group = 0.13

q1= 1 - p1	q2 = 1 - q2
α = 0.05	Zα = 1.64 (one-tailed test)
β = 0.8	Zβ = 0.84
p = (p1 + p2) / 2	q = 1 - p

We used a formula for testing an alpha of 0.05 and a power of 80%. The sample size in each group was 18 cases. $p < 0.05$ was considered statistically significant. Statistical analyses were performed using STATA 13 software.

Results

Thirty-six eligible women were enrolled into the study and were randomized to receive oral the ISMN SR treatment or the control (18 each) (Fig. 1). There were no significant differences in the maternal demographic and obstetric characteristics (i.e., maternal age, parity, gestational age, and baseline Bishop Score) between the two groups (Table 1).

The proportions of favorable cervix after 48 hours (Table 2) in the oral ISMN SR group (0.61) was significantly greater compared to the controls (0.17, p = 0.008, RR = 7.85, 95%CI 1.65-37.40). With respect to secondary outcomes (Table 2), there was significant increase in the change of the Bishop Score in the ISMN SR group (6.05 ± 2.71) compared to the control after 48 hours (3.72 ± 3.12, $p < 0.05$). The time from admission to delivery in the ISMNSR group was significantly shorter than the control group (10 vs. 23 hours, $p < 0.05$). The percentage of women who required misoprostol for secondary cervical ripening was significantly lower in the intervention group. The mode of delivery was similar between groups. The indication for cesarean delivery in both groups was failed induction.

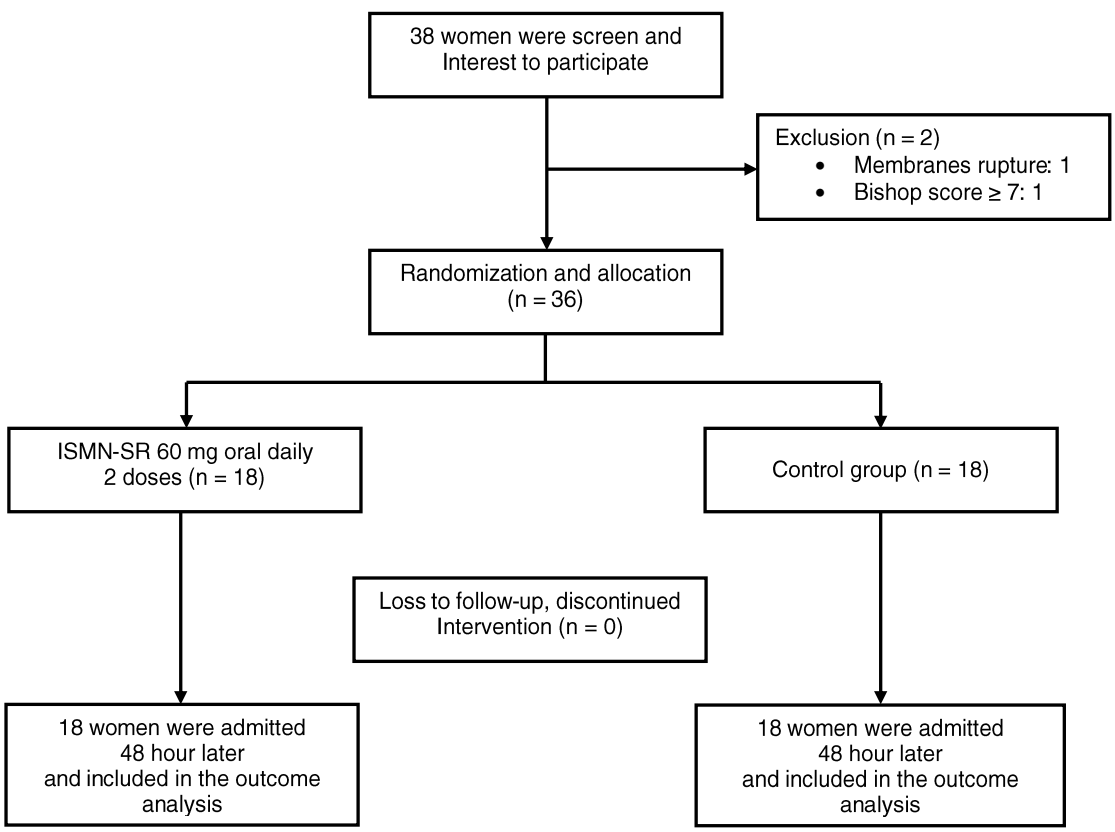

Fig. 1. Flow chart of the study participants.

Table 1. Demographic characteristics.

Characteristics	ISMN SR (n = 18)	Control (n = 18)
Age (years), mean (SD)	26.2 (3.9)	25.0 (5.2)
Parity		
Nulliparous, no. (%)	9 (50.0)	10 (55.6)
Multiparous, no. (%)	9 (50.0)	8 (44.4)
Gestationalage (days), mean (SD)	278 (4)	277 (3)
Baseline Bishop score		
0-1, no. (%)	15 (83.3)	16 (88.9)
2-3, no. (%)	3 (16.7)	2 (11.1)
4-6, no. (%)	0	0
BMI (kg/cm^2), mean (SD)	21.1 (1.9)	20.4 (2.0)

ISMN SR: isosorbide mononitrate sustained release, BMI: body mass index

Table 2. Primary and secondary outcomes.

Duration of delivery	ISMN SR (n = 18)	Control (n = 18)	p value
Primary outcome			
Favorable cervix, no. (%)	11 (61.1)	3 (16.7)	0.008
Secondary outcomes			
Change in Bishop score, mean (SD)	6.1 (2.7)	3.7 (3.1)	0.022
Time admission to delivery (hours), median (IQR)	10 (8,15)	23 (16,29)	0.002
Vaginal Delivery achieved in 24 hour, no. (%)	16 (88.9)	9 (50.0)	0.014
Routes of delivery			1.000
Vaginal delivery, no. (%)	17 (94.4)	17 (94.4)	
Cesarean section, no. (%)	1 (5.6)	1 (5.6)	
Use of misoprostol, no. (%)	7 (38.9)	15 (83.3)	0.008
Use of oxytocin, no. (%)	12 (66.7)	7 (38.9)	0.091

ISMN SR: isosorbide mononitrate sustained release

Table 3 shows no significant difference in birth weight and no cases of fetal distress or Apgar scores < 7 at 1 and 5 minutes, meconium at the time of ruptured membrane, or neonatal ICU admission between groups. There were no serious side effects of ISMN SR and none of the participants denied taking the second dose. The most common side effects experienced in the ISMN SR group were headache, which was relieved by oral analgesics. One woman (5.6%) in the ISMN SR group and 2 in the control group had uterine atony (11.1%), which did not develop into a postpartum hemorrhage. There were no cases of palpitation, uterine hyperstimulation, or changes in vital signs from the baseline that required treatment in either group.

Table 3. Maternal complications and neonatal outcomes.

Outcomes	ISMN SR (n = 18)	Control (n = 18)	p value
Maternal complications			
Uterine hyper-stimulation	0	0	1.000
Uterine atony, no. (%)	1 (5.6)	2 (11.1)	0.500
Headache, no. (%)	2 (11.1)	1 (5.6)	0.500
Nausea/ Dizziness, no. (%)	1 (6.7)	0	0.500
Palpitation, no. (%)	0	0	1.000
Neonatal outcomes			1.000
Neonatal birth weight (g), mean (SD)	3,145 (285)	3,173 (320)	0.695
Fetal non-reassuring, no. (%)	0	0	1.000
Meconium stained AF, no. (%)	0	1 (5.6)	0.500
Birth asphyxia (Apgar ≤ 7)			
At 1 min, no. (%)	0	1 (5.6)	0.500
At 5 min, no. (%)	0	0	1.000
Admission to NICU, no. (%)	0	0	1.000

ISMN SR: isosorbide mononitrate sustained release, AF: Amniotic fluid, NICU: neonatal intensive care unit

Discussion

In the present study, the superior efficacy of oral ISMN SR over the control was demonstrated by the cervix was favorable and the Bishop score had changed. This was consistent with Cochrane review 2016(14) as well as other studies on the use of vaginal ISMN SR administration for in-patients[23,24] and other out-patient vaginal NODs with a control group or placebo[16-18]. The reason for the high efficacy of nitric oxide in cervical ripening—apart from stimulation of prostaglandin F2α and cyclooxygenase-2, releasing of cytokines, and inhibiting of thromboxane-A2—is that it could facilitate an increasing level of physiologic cervical nitric oxide metabolites[13]. In contrast with Schmitz et al[19], and Bullarbo et al[20], studies, they reported that the change in the Bishop score was not significantly different. These could be explained by the dosage, drug form, and duration of action which were inadequate. About the route of drug administration: the first report, Haghighi et al., regarding the oral route of ISDN, similar results to our study, gave a significantly higher efficacy as defined by the mean change in the Bishop score over the control group[21]. Moreover, oral ISMN SR, suitable than oral ISDN, does not undergo first-pass metabolism.

The mean time from admission to delivery was also significantly shorter in the study group which was consistent with several previous studies[16,18,20,23,24]. Notwithstanding, Bollapragada et al[17], and Schmitz et al[19], found no significant reduction in the study group which might be explained by the use of low-dose ISMN and that most of their participants were beyond term which lowers nitric oxide metabolites in the cervical fluid[25].

The cesarean delivery rate was similar between groups, and in most recent outpatient studies comparing other NODs to placebo or control[16-20, 24].

The most common adverse effect in the study group was mild headache, which was found in other studies both outpatients[16-20] and inpatients[23, 24], and there were no major adverse effects in either the maternal or fetal hemodynamic. Oral ISMN SR

treatment in the present study induced neither uterine hyperstimulation nor abnormal fetal heart rate; as was observed in all of previous studies[21].

In the present study, most of the participants reported satisfaction with the oral route of administration and as an outpatient treatment. This is because of the advantage of not being hospitalized for cervical ripening and the simply route of administration which outweighed the minor adverse effects of the treatment as previously described[6, 8]. The oral ISMN SR prescription apparently results in a significant improvement in the proportion of favorable cervix for pre-induction and to a decrease in the usage of misoprostol, as well as a decrease in the length of induction for labor until delivery which are associated with a decrease in the risk of maternal and fetal adverse outcomes (from post-term pregnancy and side effect of other cervical ripening agent such as misoprostol)[6, 8]. The most important advantage was the convenience of drug administration.

Strengths of the study

The current study reduced bias by designing a randomized controlled trial and blinding the outcome to assessors. Our primary outcome was a statistically significant result from 30 participants; a number based on a pilot study with superior trial, and the known high efficacy of ISMN SR for cervical remodeling. There were no dropouts in the current study, suggesting a non-stressful and convenient process.

Conclusion

Sixty milligrams of oral ISMN SR administered at home is safe and effective for cervical ripening prior to induction of labor in term pregnant women without any evidence of maternal or fetal adverse outcomes.

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Potential conflicts of interest

The authors declare no conflict of interest.

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