Outpatient Vaginal Administration of Isosorbide Mononitrate for Preinduction Cervical Ripening

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ABSTRACT

Objective: The aim of the study was to determine whether isosorbide mononitrate (ISMN) 60 mg administered vaginally is effective for preinduction cervical ripening on an outpatient basis. **Material and methods:** The study was carried out at Karnataka Institute of Medical Sciences, Hubli, Karnataka from November 2007 to October 2008. Hundred women with singleton pregnancies with Bishop score ≤6 were randomized to receive either ISMN slow-release (ISMN-SR) 60 mg or vitamin C vaginally on an outpatient basis. Bishop score, proportions establishing spontaneous labor were assessed after 48 hours. Requirement of additional cervical ripening agent, need for oxytocin, admission-delivery interval, neonatal outcome (Apgar score 5 minutes, neonatal intensive care unit [NICU] admission and meconium-stained liquor) and side effects were compared. **Results:** In ISMN-SR group, there was a marked increase in the proportion of women establishing spontaneous labor (36% vs. 12%) and being favorable for induction of labor (40% vs. 9.09%). There was a significantly higher Bishop score (6.76 ± 2.65 vs. 4.6 ± 2.17) and decrease in proportion of subjects requiring further ripening (38% vs. 80%). Admission-delivery interval was shorter in ISMN group ($p < 0.001$). There were no significant differences in mode of delivery and fetal distress. Headache was seen in 22% of women in the ISMN group ($p < 0.01$). **Conclusion:** ISMN administered vaginally is effective for preinduction cervical ripening.

Keywords: Outpatient cervical ripening, isosorbide mononitrate, nitric oxide

Before the onset of labor, the cervix usually undergoes a process called 'ripening', in which it softens, dilates and effaces. These changes result in substantially decreased cervical resistance to labor pains. Sometimes, it is necessary to bring on labor artificially because of safety concerns for the mother or baby. Labor induction, when performed in a woman with unripe cervix often results in prolonged and difficult labor. Failed induction, secondary to ineffective labor or excessive uterine activity causing fetal distress are the main problems resulting in increased risk of cesarean delivery.

Nitric oxide (NO) is produced through NO synthetase (NOS) which is expressed in three isoforms: Neuronal, inducible and endothelial NOS,[1] all of which are present in the various cells of the uterine cervix.[2-4] The expression of NOS isoforms and the release of NO in the cervix have been shown to increase with advancing gestational age and during cervical ripening. Since, it does not cause uterine contractions, it may be suitable for outpatient use as against prostaglandins.

An ideal cervical ripening agent would induce ripening without causing contractions, since the lack of uterine contractions obviates fetal monitoring; such an agent could be used on an outpatient basis. There is increasing interest in carrying out cervical ripening on an outpatient basis, advantages of which are - patient convenience and reduced hospitalization costs. There is increasing interest in outpatient cervical ripening which is driven at least in part by financial costs associated with an inpatient stay in the labor ward. Additionally, there is a wish to 'deinstitutionalize' the process of labor, and, where appropriate, to offer women the opportunity to remain as an outpatient for a longer period of time.

The present study was conducted to determine the efficacy of NO donor: Isosorbide mononitrate (ISMN), as a preinduction cervical ripening agent on an outpatient basis.

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MATERIAL AND METHODS

This study was carried out in Karnataka Institute of Medical Sciences, Hubli during the period from November 2007 to October 2008. It included 100 patients with various indications for induction of labor with unripe cervix.

Study design: Randomized stratified (nulliparous/multiparous), placebo-controlled study. Active placebo treatment was allocated in a 1:1 ratio.

Each of the women selected had been subjected to detailed history, general and abdominal examination. Vaginal examination was done to examine the bony pelvis and to detect cervical score. Inducibility was predicted using the Bishop pelvic scoring system. Ultrasound examination was done to assess fetal viability, lie, presentation, position, fetal weight, fetal number, amniotic fluid volume, placental location and fetal well-being.

Indications for induction of labor were according to hospital protocols. Common indications for induction were to be postdated pregnancies, pregnancy-induced hypertension, intrauterine growth restriction, Rh-isoimmunization, fetus with major congenital anomaly, intrauterine death of fetus, etc.

Pregnant women were eligible for enrollment if they were: Between 37 and 43 week's gestation, singleton pregnancy with the fetus in cephalic presentation, unfavorable cervix, (defined as a Bishop score ≤6), had intact membranes and willing to participate in the study. Exclusion criteria were: Cephalopelvic disproportion (CPD), previous uterine scar, nonvertex presentation, multifetal pregnancy, significant vaginal bleeding, chorioamnionitis, severe pre-eclampsia, uncontrolled diabetes mellitus, contraindication to receive prostaglandins or NO (history of hypersensitivity, heart disease, glaucoma or asthma), prelabor rupture of membranes, established fetal distress, fetal compromise of sufficient degree that daily fetal monitoring is scheduled.

Eligible patients were taken for study. Procedure having been explained and having obtained their written consent for participation, subjects were randomly divided into two groups. The first group (A) consisted of 50 cases that used 60 mg ISMN tablet introduced into posterior vaginal fornix. The second group (B) consisted of 50 cases used as a placebo vitamin C tablet applied into posterior vaginal fornix. Subjects were examined after 48 hours or earlier if they came with any complaints. Cervix was defined as ripe if Bishop score was >6. After assessment of Bishop score, subjects received inpatient cervical ripening if Bishop score was ≤6 and oxytocin drip if Bishop score was >6. Cervical ripening was done with misoprostol 25 μg placed in posterior vaginal fornix every 6 hours till Bishop score was >6. After that cervical score and depending on the uterine contraction frequency and duration, augmentation with oxytocin was done.

If the cervical score was >6, augmentation of labor was done by oxytocin drip. When regular uterine contractions with a favorable cervix and a well-fitted vertex, amniotomy was performed. Intrapartum monitoring was continued. Failed labor induction was defined as the inability to achieve a cervical dilation of 4 cm and 90% effacement, or at least 5 cm (regardless of effacement) after a minimum of 12-18 hours of membrane rupture and oxytocin administration (with a goal of 250 MU or 5 contractions/10 minutes). Favorable cervix was defined as Bishop score of >6. Cesarean section was done for obstetric indications and documented.

Mode of delivery and neonatal outcome were recorded with respect to meconium staining, Apgar score at 1 minute and 5 minutes and admission to neonatal intensive care unit (NICU). Indications for operative deliveries were documented.

The analytic statistics was performed using the unpaired student test. To compare two rates or percentages, Chi-square test was used. Fisher's test was if numbers in the contingency table were very small (<5).

RESULTS

The clinical characteristics for women in both groups were comparable as regards to clinical criteria namely: Maternal age, parity, gestational age and initial Bishop score with no significant difference between both groups ($p > 0.05$) as shown in Table 1. Indications for induction of labor were presented in Table 2.

There were 34% unscheduled admissions in cases and 16% in controls ($p < 0.001$). Significant number of women in ISMN-treated group went into spontaneous labor <48 hours in cases (13 [26%] vs. 5 [10%]) (Table 3). Cases had improved Bishop score (6.76 ± 2.65 vs. 4.6 ± 2.18, $p < 0.001$), change in Bishop score (4.36 ± 2.83 vs. 2 ± 2.24, $p < 0.001$) as well as favorable Bishop score at 48-hour/next visit (31 vs. 10, $p < 0.001$).

Table 1. Clinical Characteristics of Women in Study Group

Clinical characteristics	ISMN group (n = 50)	Placebo group (n = 50)	P value	Significance
Maternal age (years)				
Range	18-29	18-29	>0.05	Not significant
Mean ± SD	23.12 ± 2.82	23.08 ± 2.78	>0.05	Not significant
Gestational age (days)				
Range	273-299	270-303	>0.05	Not significant
Mean ± SD	286.56 ± 5.89	286.28 ± 8.59	>0.05	Not significant
Bishop score				
Range	1-4	1-5	>0.05	Not significant
Mean ± SD	2.369 ± 0.72	2.62 ± 0.9	>0.05	Not significant

ISMN = Isosorbide mononitrate; n = Number of subjects.

Table 2. Indications for Induction of Labor

	Case (n = 50)	Control (n = 50)	Total
Postdated pregnancy	33 (66%)	25 (50%)	68 (68%)
Pre-eclampsia	12 (24%)	22 (44%)	34 (34%)
Oligohydramnios	5 (10%)	3 (6%)	8 (8%)
Others	—	—	—

The number of doses of additional cervical ripening was higher with controls (38% vs. 80%, $p < 0.05$). Inpatient induction/admission in labor to delivery was shorter in cases than controls (9.21 ± 4.55 hours vs. 12.9 ± 4.65 hours, $p < 0.001$).

There were no differences in duration of first, second and third stages of labor. Also, no differences were observed between both groups regarding the mode of delivery, for indications for operative delivery as well as fetal outcomes in both groups as found through Apgar score, meconium-stained liquor or admissions to NICU. Table 4 demonstrates maternal and fetal side effects and their incidence among both groups. Headache was more common in ISMN group (22% vs. 4%, $p < 0.05$).

DISCUSSION

The need to ripe the cervix prior to induction of labor has become a reality in our lives as induction especially with unfavorable cervix in a full-term pregnancy is still a problem to the obstetricians. NO donors were tried for the first time before surgical evacuation of the first trimester pregnancy' in the form of vaginal tablet by Thomson et al[5] and intracervically by Arteaga-Troncoso et al.[6]

The results from the current study show that ISMN is an efficient cervical ripening agent compared to placebo; especially on an outpatient basis. In ISMN group, there was increase in the proportion of women establishing spontaneous labor and having Bishop score favorable for induction of labor. In present study, in ISMN group there was a significantly higher Bishop score at 48-hour (6.76 ± 2.65 vs. 4.6 ± 2.17, $p < 0.001$), a higher change in score (4.36 ± 2.83 vs. 2 ± 2.24, $p < 0.001$) and decrease in proportion of subjects requiring further ripening (38% vs. 80%, $p < 0.001$) (Table 3).

In those who needed inpatient cervical ripening, doses in ISMN-treated group were less than in placebo-treated. Similar response was seen by Rameez et al[7] where proportion establishing spontaneous labor was (28% vs. 7.5%), score being favorable for induction of labor was (40% vs. 9%), an increase in Bishop score (3.8 vs. 1.3) and need for additional cervical ripening was seen in 32% versus 79% in placebo group. Admission to delivery interval was shorter in ISMN group in the present study (9.21 ± 4.65 hours vs. 12.91 ± 4.55 hours, $p < 0.001$).

No significant differences in cesarean delivery rates including any differences in fetal outcomes and admissions to intensive care unit were noted in the present study. Headache was the main side effect seen in 22% of women in the ISMN group but was not so severe to need analgesia. However, in the present study, women who had headache did not feel it to be significant.

Table 3. Comparison Between Study Groups

	Case (n = 50)	Control (n = 50)	P value	Significance
Unscheduled admissions	17 (34%)	8 (16%)	<0.001	Significant
Unscheduled admissions for cause other than labor	4 (8%)	3 (6%)	>0.05	Not significant
Established labor (<48 hours)	13 (26%)	5 (10%)	<0.05	Significant
Established labor (≥48%)	5 (10%)	1 (2%)	>0.05	Not significant
Bishop score at 48-hour/next visit				
Range	3-12	2-12	<0.001	Significant
Mean ± SD	6.76 ± 2.65	4.6 ± 2.18		
Change in Bishop score at 48-hour/next visit				
Range	0-10	0-10	<0.001	Significant
Mean ± SD	4.36 ± 2.83	2 ± 2.24		
Favorable score (>6)	31 (62%)	10 (20%)	<0.001	Significant
Unfavorable score (≤6)	19 (38%)	40 (80%)	<0.001	Significant
Bishop score favorable for induction with oxytocin	13 (40.6%)	4 (9.09%)	<0.001	Significant
Women who needed inpatient cervical ripening	19 (38%)	40 (80%)	<0.001	Significant
Requirement of oxytocin	47 (94%)	47 (94%)	>0.05	Not significant
Duration from inpatient induction/admission in labor to delivery				
Range	1.66-20.91 hours	1-23 hours	<0.001	Significant
Mean ± SD	9.21 ± 4.55 hours	12.9 ± 4.65 hours		
Duration of first stage				
Mean ± SD	6.193 ± 2.6 hours	5.7 ± 2.3 hours	>0.05	Not significant
Duration of second stage				
Mean ± SD	41.3 ± 19.9 minutes	40.42 ± 20.3 minutes	>0.05	Not significant
Duration of third stage				
Mean ± SD	6.58 ± 3.98 minutes	5.88 ± 3 minutes	>0.05	Not significant
Normal vaginal delivery	40 (80%)	42 (84%)	>0.05	Not significant
Operative vaginal delivery	3 (6%)	2 (4%)	>0.05	Not significant
Cesarean section	7 (14%)	6 (12%)	>0.05	Not significant
Apgar score 1 minute				
Range	4-9	4-9		
Mean ± SD	7.88 ± 0.93	7.38 ± 1.08	>0.05	Not significant
Apgar score 5 minutes				
Range	7-10	6-10		
Mean ± SD	9.62 ± 0.69	9.34 ± 0.96	>0.05	Not significant
Thick meconium	2 (4%)	4 (8%)	>0.05	Not significant
Thin meconium	11 (22%)	12 (24%)	>0.05	Not significant
Admissions to NICU	1 (2%)	4 (8%)	>0.05	Not significant

Table 4. Complications Seen in Both Groups

	Case	Control	P value	Interpretation
Nausea and vomiting	2 (4%)	3 (6%)	>0.05	Not significant
Headache	11 (22%)	2 (4%)	<0.05	Significant
Palpitation	—	—	—	—
Hyperstimulation	—	—	—	—
Tachysystole	—	—	—	—
Fetal tachycardia	0	2 (4%)	>0.05	—
Postpartum hemorrhage	4 (8%)	5 (10%)	>0.05	—

CONCLUSION

To summarize, it was found from the study that ISMN was more effective than placebo with respect to number of women going into spontaneous labor, improvement in cervical score, favorability for induction of labor, admission to delivery interval and reduced the number of doses of inpatient cervical ripening agent without increasing cesarean delivery rate and affecting neonatal outcomes.

However, following are the drawbacks of the study: 1) ISMN tablets intended for oral administration were administered vaginally. NO donors in vaginal paste or gel form may allow better drug absorption. 2) Study population is less. The definitive clinical efficacy needs to be evaluated in larger series of patients.

Use of NO donor, ISMN may have the major advantage that uterine contractions are not stimulated and may allow cervical ripening before induction of labor to be performed as an outpatient procedure. The use of NO donors for the induction of cervical ripening at term may prove to be a major therapeutic advance.

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