Original Article

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Effect of Vaginal Administration of Nitric Oxide Donor Isosorbide Mononitrate on Cervical Ripening Before Induction in Term Pregnancy: A Randomized Controlled Study

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Abstract

Introduction: Nitric oxide donors have been shown to cause cervical ripening. The aim of this study was to investigate whether sustained-release isosorbide mononitrate (ISMN-SR) 60 mg administered vaginally is effective for preinduction cervical ripening in term pregnancy and any effect on mother and fetus.

Materials and Methods: A single-blinded study was conducted in Raja Mirasudar Hospital, Thanjavur for a period of 12-month. This study was conducted in 200 patients with uncomplicated singleton pregnancies at term. These patients were randomly allocated to receive either ISMN-SR 60 mg (n = 100) or vitamin C 100 mg (n = 100) vaginally. Modified Bishop's Score was evaluated after 24 h in each group.

Results: At the commencement of the study, there were no differences between mean ages, Bishop score of the two groups. In the ISMN-SR group, there was a significantly higher increase in the mean modified Bishop score (2.466 vs. 0.561) $P < 0.05$ after 24 h. Percentage of those requiring additional ripening agent found to be lower in the study group (56.7%) compared to control group (91.7%). Cesarean section rates were similar in both groups.

Conclusion: ISMN-SR administered vaginally in effective for pre-induction cervical ripening.

Key words: Cervical ripening, Labor, Nitric oxide, Term pregnancy

INTRODUCTION

Most exciting events in women's life are labor. Many steps are involved normally in a normal course of labor. Labor usually follows a normal pattern and result in delivering a healthy child to the mother and to the world. This study is mainly focused on the effects of nitric oxide (NO) donor isosorbide mononitrate (ISMN) for cervical ripening in term pregnancy. Induction of labor is necessary in situation, where it could be hazardous to wait for the spontaneous onset of labor. In the case of ripened cervix, the most common methods of labor induction are oxytocin infusion and/or amniotomy. In unripened cervix, it is wise to use local medical or other mechanical methods to achieve ripening. The most common medical agents used for ripening of cervix are prostaglandin (PG) administered intracervically or vaginally. Thus, PG kept via these routes are associated with side effects like hyperstimulation. Hyperstimulation is registered in 5% of women treated with PG, moreover, treatment is not always effective and it has to be repeated. Hence, many cases of failed induction have been reported with PGE_2. Therefore, it is necessary to find an alternative drug that is the more effective and it should not be associated with hyperstimulation. One such drug is NO donors, ISMN.

NO, a free radical synthesized endogenously in human uterine cervix.[1] Studies were performed by Ledingham

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et al., 2000; Vaisanen-Tommiska *et al*., 2003 shown that it has been up regulated at term pregnancy. Hence, NO was believed to play a major role as ripening agent (Chwalisz, 1997; 1998).[2,3] Many studies on vaginally administered NO donor have shown ripening effects of this drug (Thomson *et al*., 1997,).[4,5] Current study aims to give role of NO donor, ISMN on cervical ripening and labor induction.

Drugs commonly used in hospital settings such as PGE_2 and E_1 (PGE_1) were effective for cervical ripening. However, the high incidence rates of myometrial hyperstimulation, uterine tachysystole and fetal distress associated with their use.

ISMN, an NO donor had been shown to induce ripening of cervix NO found to be the final mediator of cervical ripening. NO donor inhibit uterine contractions and promote uterine blood flow. It acts by altering cervical collagen tissue.

NO play a major role in regulating many factors in the inflammatory process of cervical ripening. There are three major isoforms of NO synthases (NOS). All these three major isoforms of NOS are present in human uterine cervix (Bao *et al*., 2001, Tschugguel *et al*., 1999).[2] Moreover inducible NOS have been found in epithelial cells and stromal spindle cells (Tschugguel *et al*. 1999)[2] and it has also been demonstrated by immunostainin g in the uterine cervix at term (Ekerhovd *et al*., 2000). Many studies have shown that inducible enzymes have been upregulated in human uterine cervix during delivery.[2] Metabolites of oxides of nitrogen in the cervical fluid are increased at term compared to preterm. Inducible NOS isoform can be induced by cytokines, tumor necrosis factor α, interferon λ or endotoxins in a calcium-independent manner. NO may exert its effect through stimulation of endogenous PG synthesis through cyclooxygenase stimulation[3] or through stimulation of at least one matrix metalloproteinase (MMP), MMP-1 .[6]

During late pregnancy, there is an alteration in glycosaminoglycan composition of the cervix, which plays an important role in ripening process. Amount of hyaluronic acid that is present in the cervix is increased at term. Together these changes bring an alteration in the binding affinity to collagen thus altering the tissue hydration and cervical extensibility (Rechberger *et al*., 1996).

NO suppresses the synthesis of proteoglycan (Hauselmann *et al*., 1998). NO promote apoptosis that has been demonstrated in smooth muscle cells (Romero *et al*., 1990) and fibroblasts (Leppert, 1998) during cervical ripening. Several lines of evidence from studies of other tissue suggest that this process is stimulated by NO (Nicotera *et al*., 1997).[7] Finally, cervix is constituted by only 10-15% of smooth muscle cells, the role of which has been studied to some extent only. Relaxing effects of cervical smooth muscle following administration of NO donors have been demonstrated *in vitro* in cervical tissue specimens from term women.

Taken together, NO found to be the final mediator of cervical ripening. The present study was performed to evaluate the safety and effectiveness of ISMN treatment for cervical ripening.

MATERIALS AND METHODS

A randomized prospective placebo-controlled study was conducted in Raja Mirasudar Hospital, Thanjavur during the period of August 2014-August 2105. Institutional Ethical Committee approval was obtained.

The participants all had a singleton pregnancy, with gestational age >40 weeks, uncomplicated pregnancy and intact membranes.

Exclusion criteria were antepartum hemorrhage, previous uterine incision, fetal malpresentation, ruptured membranes, preeclampsia, intrauterine growth restriction, oligohydramnios, heart disease, diabetes, patient with H/O headache, palpitation, and hypotension.

Informed consent was obtained from the women. Patients were randomly allocated to one of the two study groups. Induction is necessary, since the progression of pregnancy after 40 weeks, increases the risk of adverse outcomes such as meconium passage, chorioamnionitis, macrosomia, intrauterine death, and need for caesarean delivery.

Baseline Bishop's Score was recorded. The participants were given either ISMN 60 mg, 2 tablets administered 12 h apart into posterior fornix of the vagina or vitamin C 100 mg 2 tablets as placebo.

If Bishop score 6 or higher, labor was induced by oxytocin. In participants, whose Bishop score <6 after second dose, 0.5 mg PGE_2 gel instilled intracervically. Treatment with PGE_2 gel repeated after 6 h, only once, if cervical did not occur and was followed by oxytocin infusion.

The second dose of ISMN repeated only after evaluation of blood pressure, pulse rate, fetal heart rate, and verification of symptoms such as a headache.

Primary outcome variable was Bishop Score of baseline and 12 h after the second dose, duration of labor, whether delivered vaginally or by caesarean section. Other maternal outcome variables were presence or absence of tachycardia, hypotension, headache, and palpitation.

Fetal outcome variables were Apgar score at 1 and 5 min and whether neonatal intensive care unit admission necessary or not. Secondary outcome variable was operative delivery rates and complications such as uterine hyperstimulation, meconium stained amniotic fluid, tachysystole, and post-partum hemorrhage.

The data, from our study, were collected compiled and statistically analyzed using SPSS statistics, software version 20. A statistical test used for analysis were *t*-test and Chi-square test. $P < 0.05$ was taken as significant.

RESULTS

A total of 200 women were randomized.

- 100 to the study group
- 100 to the control group.

Comparisons of Bishop score, PGE_2 oxytocin usage, labor duration between study and control group. All the results are depicted in tabular form. (Tables 1-6).

DISCUSSION

In obstetrics and gynecology, NO donor has been used for the treatment of preterm labor. NO donor has been shown to induce cervical ripening without causing uterine contraction by rearrangements of cervical collagen tissue and ground substance. In contrast to PG, they also inhibit uterine contraction and promote uterine blood flow.

ISMN is a slow releasing NO donor. Levels of NO metabolites in the cervix are known to be increased at term.

A significant improvement in Bishop score was noted in study group after second dose of ISMN. Similar results were reported in earlier studies by Rameez *et al.*, 2007,[8] Hana *et al.*, 2010, Bullarbo *et al.*, 2007,[9] Agarwal *et al.*, 2012,[10] Helal *et al.*, 2004.

The need for additional ripening agent PGE_2 was found to be lesser in the study group (56.7% vs. 91.67%). This was in agreement with study by Agarwal *et al.*, 2012, Bollapragada *et al.*, 2009 and Bullarbo *et al.*, 2007.[9]

The requirement for oxytocin was found to be lesser in the study group compared to control group (56.7% vs. 71.7%). However, the differences were not statistically significant. On contrary study by Eddama *et al.*, 2009,[11] Habib *et al.*, 2008 show oxytocin requirement found to be lesser in ISMN group and was statistically significant.

Duration of labor was found to be significantly lesser in study compared with that of the control group. This was

Table 1: Demographic characteristics of the study participants

Characteristics	Study group (*n*=100)	Control group (*n*=100)	*P* value
Age (years)	23.78±1.757	23.67±1.820	>0.05
Gestational age (week)	3.62±1.075	3.68±1.172	>0.05
Parity (%)			
Primigravida	53.5	55	>0.05
II Gravida	30	26.7	>0.05
III Gravida	16.7	18.3	>0.05

Table 2: Demographic characteristics of the study and control groups were comparable

Variable	Study group	Control group	*P* value
Baseline Bishop score	1.80±0.879	1.82±0.39	>0.05
Post intervention Bishop score	4.87±2.466	2.08±0.561	<0.05
PGE_2 used (%)	56.7	91.7	<0.05
PGE_2 not used (%)	43.3	8.3	<0.05
Oxytocin (%)			
Used	56.7	71.7	>0.05
Not used	43.3	28.3	>0.05

PGE_2: Prostaglandin E_2

Table 3: Comparison of mode of delivery between study and control group

Variable	*n*=100 (%)		*P* value
	Study group	Control group	
Vaginal delivery	65	53.3	>0.05
Outlet forceps	10	15	>0.05
Vacuum delivery	3.3	0	>0.05
LSCS	21.7	31.7	>0.05

LSCS: Lower segment Cesarian section

Table 4: Adverse maternal side effects

Effect	*n*=60 (%)		*P* value
	Study group	Control group	
Palpitation	16.7	0	<0.05
Headache	65	1.7	<0.05

Table 5: Comparison of labor complication

Variable	Study group (%)	Control group (%)	*P* value
Hyper stimulation	0	5	>0.05
PPH	1.7	3.3	>0.05

PPH: Postpartum hemorrhage

Table 6: Fetal variables

Meconium			
With PGE_2	13.3%	15%	>0.05
Without PGE_2	1.7%	5%	
Total	15%	20%	
Non-reactive CTG			
With PGE_2	3.3%	11.7%	>0.05
Without PGE_2	-	-	
Total	3.3%	11.7%	

PGE_2: Prostaglandin E_2

in agreement with study, Agarwal *et al*., 2012, Helal *et al*., 2004, Habib *et al*., 2008.

The common side effects were palpitation and headache. In the present study, percentage of study group and control group reporting palpitation found to be 16.7% and 0% ($P < 0.05$).

Agarwal *et al*., 2012[10] found that in his study percentage of those experiencing palpitation in study group as 18% and none in control group. This result was in agreement with the present study.

Habib *et al*., 2008[12] in his study reported that those experiencing palpitation in ISMN group found to be 13.73% and none in control group. $P = 0.02$ is statistically significant. This result was in agreement with this study. In the present study, no cases of tachysystole and hyperstimulation have been found in ISMN group.

This study confirmed that vaginally administered ISMN neither induced tachysystole nor hyperstimulation.

No abnormal fetal heart tracings were noted in women after ISMN treatment.

Use of ISMN by vaginal route helps in improving Bishop score and reduces the duration of labor. It has no effect on the hemodynamic state of the mother. In constrict to the other cervical ripening agents, NO donor administered vaginally had the advantage of the absence of uterine contraction. Hence, it removed the main reasons that women were monitored during the induction of cervical ripening.

NO donors suitable agents for preinduction cervical ripening. The absence of contraction had obviated the need for fetal monitoring.

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CONCLUSION

The use of ISMN by the vaginal route as ripening agent before induction of labor at term helps in improving Bishop score and reduces the duration of labor. It has no effect on the hemodynamic state of the mother and fetus. In contrast to the other cervical ripening agents, NO donor, administered vaginally, has the advantage of absence of uterine contractions. Hence, it removes the main reason that women are monitored during the induction of cervical ripening. Hence, NO donors are suitable agents for pre-induction cervical ripening at term. The absence of contraction has obviated the need for fetal monitoring such agent could be given on as outpatient basis.

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