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Nitric oxide donor isosorbide mononitrate for pre-induction cervical ripening at 41 weeks' gestation: A randomized controlled trial

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Abstract

Objective: Nitric oxide donors have been shown to cause cervical ripening. The aim of this study was to determine whether sustained release isosorbide mononitrate (ISMN-SR) 60 mg administered vaginally is effective for pre induction cervical ripening at 41 weeks' gestation.

Methods: A double-blind randomised controlled trial was carried out at the University Obstetric Unit, Galle, Sri Lanka for a period of 9 months, commencing 1st August 2003. One hundred and fifty-six consecutive women with uncomplicated singleton pregnancies at 41 weeks' gestation with a modified Bishop Score <5 were allocated by stratified (primip/multip) block randomization to receive either ISMN-SR 60 mg ($n = 78$) or vitamin C 100 mg ($n = 78$) vaginally. Modified Bishop Score at 41 weeks + 2 days' gestation and the proportions establishing spontaneous labor or becoming favorable for induction of labor (IOL) by 41 weeks + 2 days' gestation were evaluated in each group.

Results: At the commencement of the study there were no differences between the mean age, parity or modified Bishop Score of the two groups. In the ISMN-SR group, there was a marked increase in the proportion establishing spontaneous labor (28% *vs* 7.5%, $P < 0.01$) and being favorable for IOL (40% vs 9% $P < 0.001$), 2 days after therapy. In the ISMN-SR group, there was a significantly higher increase in the mean modified Bishop Score (3.8, 95% CI 2.3–5.3 *vs* 1.3, 95% CI 0.3–2.2, $P < 0.01$) and a marked decrease in the proportion of subjects requiring further ripening of the cervix with a Foley catheter. (32% *vs* 79%, $P < 0.001$). The cesarean section rates were similar in both groups.

Conclusion: Sustained release ISMN administered vaginally is effective for preinduction cervical ripening.

Key words: cervical ripening, induction of labor, isosorbide mononitrate.

Introduction

Adequate cervical ripening is a prerequisite for uncomplicated vaginal delivery It is the degree of the changes of cervical ripening that have been incorporated into the Bishop's score[1] and its modified versions,[2] which are used to assess the favorability of the cervix for induction of labor. An ideal ripening agent should make the cervix soft, compliant and partially dilated without stimulating uterine contractions and have no clinically significant side-effects in the mother or her baby. The process of cervical ripening is the initial part of an ongoing process that continues in to the active phase of labor. If any therapeutic agent causes adequate cervical ripening, labor could spontaneously commence.

Induction of labor (IOL) in the presence of an unripe cervix is associated with failed induction, failure to progress in labor, and an increased risk of chorioamnionitis and cesarean section (CS). Achieving vaginal

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delivery for a woman who does not have a clear indication for a CS is a challenge because a large number of these women will not have a cervix favorable for induction. Several methods have been described to achieve pre-induction cervical ripening. Of these, the methods recommended are sweeping of membranes,[3] intra cervical foley catheter,[4–7] intra cervical and vaginal prostaglandin (PGE_2),[4,5,8,9] vaginal and oral misoprostol[6,7,9] and oral mifepristone.[10,11]

Nitric oxide (NO), a free radical gas with a short half life, is thought to be a fundamental mediator of cervical ripening.[12] The NO donor isosorbide mononitrate (ISMN) has been shown to be effective in inducing cervical ripening before surgical termination of pregnancy in the first and second trimesters.[13,14] Therefore the role of NO donors as preinduction cervical ripening agents in pregnancies at term is being studied.[15–18] The maternal and fetal hemodynamic changes that occur after vaginal administration of ISMN for preinduction cervical ripening at term have not been found to be clinically significant.[18–20]

ISMN is normally used in a dose ranging from 20 to 120 mg daily in divided doses or 60–120 mg once daily in a sustained release form (ISMN-SR) in the prophylactic management of angina pectoris.[21] When given orally, ISMN achieves peak levels in serum in 30 min and has a half life of approx. 5 h. The common side-effects of ISMN; namely, headache, sinus tachycardia and hypotension, are less severe than the side-effects associated with PGE_2.[13] Vaginal PGE_2 which is the commonest cervical ripening agent used, not only has significant gastrointestinal side-effects but also has a serious side-effect of uterine hypertonus, which can lead to acute fetal hypoxia[22] and even uterine rupture.[23] Misoprostol is not available in Sri Lanka. In the Teaching Hospital at Galle, PGE_2 is in short supply on account of its relatively high cost (US $ 9/= for 3 mg) and the available stocks are inadequate to meet the requirements of the relatively large number of patients who need ripening of the cervix and induction of labor. ISMN-SR is inexpensive (US$ 0.06 for 60 mg) and freely available. Therefore it was decided to carry out a trial in order to determine whether ISMN-SR 60 mg administrated vaginally was effective as a pre induction cervical ripening agent.

Method

The trial Nitric oxide donor for cervical ripening was conducted between August 2003 and April 2004 at the University Obstetric Unit, Teaching Hospital, Galle, Sri Lanka. Ethical approval was obtained from the Ethical Committee, Faculty of Medicine, Galle.

It was thought that at least 25% of the women at 41 weeks' gestation will either establish spontaneous labor or become favorable for IOL within the next 48 h, according to the audits carried out in the unit. To detect a 25% increase in this percentage in the ISMN-SR group with a power of 80% (type II error of 20%) and a confidence level of 95% (α error of 5%), using the standard formula,[24] the sample size was calculated to be 78 women in each group.

Therefore, 156 consecutive women with uncomplicated singleton pregnancies and cephalic presentations of the fetus at 41 weeks' gestation, where the dates had been confirmed by an early ultrasound scan, and having an unfavorable cervix with a modified Bishop Score[2] of less than five, were recruited for the study. Subjects with any medical or obstetric problems and any contra-indications for the use of ISMN-SR were excluded.

Informed written consent was obtained from all the women recruited. None declined to participate. The subjects were allocated to two groups by stratified (primigravida and multigravida) block randomization. Sequentially numbered, sealed, opaque envelopes were packed with a tablet of either ISMN-SR 60 mg (study group) from Micro Laboratories (Bangalore, India) or a vitamin C 100 mg (control group) by the second author. The subjects were initially assessed by the first author at 41 weeks' gestation and their modified Bishop Scores were noted. This was followed by the insertion of the contents of the appropriate envelope allocated for each subject by the on call Senior House Officer. The contents of the envelopes were placed in the posterior fornix of the vagina. Thereafter, in all the subjects the maternal pulse and blood pressure were monitored hourly for 4 hours and then every 2 hours for another 6 hours. In all the subjects, cardiotocography was carried out at baseline and at 4 hours and 8 hours after the insertion of the ISMN-SR or vitamin C tablets, to assess fetal well-being The first author, who was blinded to the treatment given to the subjects, reassessed the cervix after 48 h unless they had either established spontaneous labor or undergone CS by then. At this reassessment the modified Bishop Score was noted again. If the cervix was favorable (modified Bishop Score was equal to or more than seven) they were induced on the same day. Otherwise an intracervical extra amniotic Foley catheter was inserted to further ripen the cervix. Thereafter, they were reassessed in another 24 h and if the cervix had

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become favorable, IOL was carried out, and if it was still not favorable, CS was carried out according to the clinical guidelines adopted in the unit.

Baseline data recorded included age, parity and the modified Bishop Score at 41 weeks. The main outcome measures were, at 41 weeks + 2 days the modified Bishop Score, proportion establishing spontaneous labor or becoming favorable for IOL or requiring Foley catheter insertion to further ripen the cervix in each group, and at 41 weeks + 3 days the proportion becoming favorable for IOL in each group. The other outcome measures included induction–delivery intervals and the CS rates in each group. Statistical analyses were carried out using the statistical package Epi Info 2002. As the data were normally distributed the Student's *t*-test and the chi-squared test was used to compare means and proportions, respectively, with $P < 0.05$ considered to be statistically significant.

Results

There were no significant differences in mean age, the proportion of primigravida or the mean modified Bishop Score between the subjects in the study group and the controls on recruitment at 41 weeks' gestation (Table 1).

Compared to the controls, in the study group there was a marked increase in the proportion establishing spontaneous labor (7.5% *vs* 28%, $P < 0.01$) and being favorable for IOL (9% *vs* 40% $P < 0.001$), 2 days after the ISMN-SR. There was a significantly higher increase in the mean modified Bishop Score in the study group compared to the controls at this time. (3.8, 95% CI 2.3–5.3 *vs* 1.3 95% CI 0.3–2.2, $P < 0.01$) The number of subjects who underwent CS for fetal distress after spontaneous onset of labor or IOL at 41 weeks + 2 days were similar in the two groups (one in each) (Table 2).

The proportion of subjects requiring further ripening of the cervix with a Foley catheter was markedly lower in the study group compared to the controls. (32% *vs* 79%, $P < 0.001$) However after insertion of Foley catheter, the number of subjects still having an unfavorable cervix and therefore requiring a CS were similar in the two groups (5 *vs* 6). After IOL at 41 weeks + 3 days, the number of subjects requiring a CS for failure to progress or fetal distress were similar in the two groups (five in each) (Table 3).

None of the subjects had a pulse rate of more than 95 beats per minute or a blood pressure of less than 90/60 mmHg after the intervention. Forty-seven (60%) of the subjects in the study group complained of headaches but only a 20 (26%) requested paracetamol, and this relieved their headaches. The subjects did not have any other complaints. There were no cardiotocographic abnormalities after the intervention.

Table 1 The basic characteristics of the study population ($n = 156$)

	ISMN-SR 60 mg ($n = 78$)	Vitamin C 100 mg ($n = 78$)
Mean age	26.9 year, SD 4.9	26.3 year, SD 4.8
Primigravida	43 (55%)	44 (56%)
Mean Bishop Score at 41 weeks	3.02 SD 0.95	2.89 SD 1.01

ISMN-SR, iso sorbide mononitrate-sustained release; SD, standard deviation.

Table 2 Results at 41 weeks + 2 days ($n = 156$)

	ISMN-SR 60 mg ($n = 78$)	Vitamin C 100 mg ($n = 78$)	*P*
Spontaneous labor (SL)	22 (28%)	9 (11.5%)	<0.01
CS for fetal distress after SL	3	2	*NS
Mean modified Bishop Score	6.8, SD 2.42	4.6, SD 2.04	<0.01
Change in mean modified Bishop Score	3.8, 95% CI = 2.3–5.3	1.3, 95% CI = 0.3–2.2	<0.01
Favorable for IOL	31 (40%)	7 (9%)	<0.001
Mean induction delivery interval after IOL (min)	410, SD 141	405, SD 130	*NS
CS for fetal distress after IOL	1	1	*NS

95% CI, 95% Confidence interval; CS, Caesarean section; IOL, Induction of labor; ISMN-SR, iso sorbide mononitrate-sustained release; SD, standard deviation; *NS, not significant.

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Table 3 Results at 41 weeks + 3 days ($n = 156$)

	ISMN-SR 60 mg ($n = 78$)	Vitamin C 100 mg ($n = 78$)	*P*
Requirement of Foley catheter	25 (32%)	62 (79%)	<0.001
Favorable for IOL	20 (80% of subjects with Foley catheter)	56 (90% of subjects with Foley catheter)	0.28 (*NS)
Mean induction delivery interval after IOL (min)	334, SD 129	339, SD 164	*NS
CS for fetal distress after IOL	1	–	*NS
CS for lack of progress after IOL	4	5	*NS
CS because cervix unfavorable for IOL	5	6	*NS

CS, cesarean section; ISMN-SR, iso sorbide mononitrate-sustained release IOL, induction of labor; SD, Standard deviation; *NS, not significant.

Discussion

There was a highly significant and greater increase in the proportion of subjects becoming favorable for IOL or establishing spontaneous labor after 48 h of vaginal ISMN-SR, compared to the placebo. It has been suggested that although further changes in the cervix may not be apparent after approximately 6 hours of nitric oxide donor therapy, uterine contractions may commence 16–19 h later and up to 1 in 5 women may establish spontaneous labor within 24 h.[15,16]

Although a large number of women in the ISMN-SR group complained of headaches, they had satisfactory relief with paracetamol. There were no complaints of additional palpitations and giddiness as in other studies.[15–18] No clinically significant hemodynamic changes were detected in the current study. Although significant tachycardia and hypotension have also been noted with vaginal ISMN therapy, they have been found to be of no clinical significance.[17–19] Prenatal assessment of the fetus, as well as assessment of the new born have not shown any adverse effects of vaginal ISMN treatment.[16,18,20]

There were no differences in the CS rates either at 48 h or at 72 h after the intervention between the ISMN-SR and the control groups. There were also no significant differences detected in the induction delivery intervals between the two groups either at 48 h or at 72 h after the intervention. However, a study that compared the use of vaginal glyceryl trinitrate (another NO donor) and PGE_2 for preinduction cervical ripening at term found that the subjects in the PGE_2 group established spontaneous labor earlier and if induced had shorter induction delivery intervals.[16]

The ISMN-SR 60 mg tablet used in the current study is likely to have not only achieved peak serum levels late but also to have a more sustained action. Therefore, all the subjects were monitored for 10 h but no clinically significant adverse effects were noted. It has been shown that although oral administration of ISMN results in peak serum levels occurring within 2 hours, vaginal ISMN results in peak serum levels being achieved much later; 6 hours or more after administration.[19] This could be due to the drug being first transmitted to the cervix and body of the uterus; the first uterine pass mechanism.[25]

In our unit, a frequently adopted method to ripen a cervix that was unfavorable for induction was the use of a foley catheter,[4–7] because it is freely available and cheaper than vaginal PGE_2 and misoprostol is not available in Sri Lanka. Furthermore, at the time of the current study, the clinical guideline adopted in the unit was to aim at IOL and delivery of all uncomplicated pregnancies by 41 weeks + 3 days. Therefore after the intervention of 41 weeks, all the subjects were reviewed at 48 h rather than 24 h. The fact that in the ISMN-SR group, 28% of subjects established spontaneous labor and another 40% of subjects were favorable for IOL by the end of 48 h, justifies this approach.

Conclusion

Sixty mg of the nitric oxide donor ISMN-SR appears to be effective and safe when used vaginally as a pre induction cervical ripening agent in pregnancies at 41 weeks' gestation. The only significant side-effect is maternal headache, which easily responds to simple analgesics. Further research is necessary to confirm the ideal formulation, dose and frequency of administration, its efficacy in comparison to PGE_2 and misoprostol, and its safety to both mother and baby. NO donors such as ISMN-SR may well become a safe, cheap and effective option for preinduction cervical ripening at 41 weeks' gestation in situations where PGE_2 and misoprostol are not available.

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