The efficacy of two different doses of vaginal isosorbide mononitrate in pre induction cervical ripening: a double blind randomised controlled trial

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(Index words: cervical ripening, induction of labour, isosorbide mono nitrate)

Abstract

Objective Nitric oxide donors have been shown to cause cervical ripening. The aim of this study was to evaluate the effects on the mother and the fetus when isosorbide mononitrate (ISMN) 40 mg or the sustained release ISMN (ISMN – SR) 60 mg was administered vaginally for pre-induction cervical ripening.

Methods A double blind randomised controlled trial. Consecutive women (n=156) with uncomplicated singleton pregnancies between 40 weeks +5 days and 41 weeks' gestation with modified Bishop Scores (MBS) <5 were allocated by stratified (primp / multip) block randomisation to receive ISMN 40 mg, ISMN – SR 60 mg or the placebo vitamin C 100 mg vaginally.

Results At the commencement of the study the parity and mean age, MBS, pulse rate (PR), systolic and diastolic blood pressure (SBP and DBP), umbilical artery resistance index (RI) and pulsatility index (PI) were similar among the three treatment groups. There was significant increase (p<0.001) of mean MBS by 1.3 (95% CI 0.8, 1.7) in primips and by 1.7 (95% CI 1.3, 2.0) in multips at 6 hours and by 2.4 (95% CI 1.9, 2.7) in primips and by 2.3 (95% CI 2.0, 2.6) in multips at 48 hours. Greater proportions of primips (42% with ISMN – SR 60 mg and 31% with ISMN 40 mg, p<0.05) were favourable for induction of labour (IOL) after 48 hours in comparison with the controls (7.6%). Greater proportions of multips (46% with ISMN – SR 60 mg and 40% with ISMN 40 mg, p<0.05) were favourable for IOL after 48 hours in comparison with the controls (16%). A mean increase of PR by 6.7-10.2 bpm (95% CI 5.0 - 12.5, p<0.001) in both ISMN groups at 180 minutes persisted up to 360 minutes. A mean reduction of SBP by 7.3 – 10 mmHg (95% CI = 8.0-11.5, p<0.001) in both ISMN groups at 180 minutes persisted up to 360 mins. No significant change was seen in DBP, RI or PI. Frequency of maternal side effects (mainly headache) were higher in ISMN groups.

Conclusions When compared with the placebo Vitamin C 100 mg, vaginal ISMN 40 mg and ISMN – SR 60 mg lead to significantly greater cervical ripening after 6 hours and 48 hours respectively. Therefore vaginal ISMN leads to more women becoming favourable for IOL. Vaginal ISMN does not affect placental blood flow but causes headaches and clinically insignificant maternal haemodynamic changes.

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Introduction

In Sri Lanka, induction of labour (IOL) is commonly carried out if spontaneous labour is not established at 41 weeks' gestation. However, at 41 weeks' gestation, the cervix is unfavourable for IOL in a large number of women. IOL in the presence of an unfavourable cervix is associated with failed induction, failure to progress in labour, and an increased risk of chorioamnionitis and caesarean section (CS).

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 methods commonly used to achieve pre induction cervical ripening at term are sweeping of membranes, intra cervical catheters including Foley catheter intra cervical and vaginal prostaglandins (PGE2), and vaginal and oral misoprostol [1-7]. Although prostaglandins are frequently used, they are associated with several adverse effects such as gastrointestinal symptoms and hyperpyrexia, as well as a high incidence of uterine hyper stimulation, acute fetal distress and rarely even uterine rupture [4- 8].

Nitric oxide (NO), a free radical gas with a short half life, is considered to be a fundamental mediator of cervical ripening [9, 10]. Cervical ripening is thought to be brought about by the interaction of NO and several other inflammatory cytokines which are produced in the cervix [11, 12]. NO donors cause the release of NO *in vivo*. In the prophylactic management of angina pectoris, the NO donor isosorbide mononitrate (ISMN) is usually used in a dose ranging from 20-120 mg in divided doses or 40-120 mg once daily as a sustained release form [13]. The

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contraindications for the use of ISMN include a history of hypersensitivity or idiosyncratic response to nitrates, presence of marked anaemia, severe hypotension and hypovolaemia [13]. When given orally, the onset of action of ISMN 40 mg is about 45 minutes, peak levels are achieved within 2 hours and it has a duration of action of about 6 to 7 hours. ISMN – SR 60 mg has a longer duration of action of about 12 hours [14, 15]. Vaginal administration of ISMN has been shown to result in lower plasma levels with peak levels being achieved only after 6 hours or more [14]. However, vaginal ISMN is thought to have its effects on the cervix much earlier due to the direct transport of the ISMN from the vagina to the cervix [14, 16, 17].

Although the mechanism of action in the process of cervical ripening is unclear, vaginally administered NO donors have been shown to be effective for preinduction cervical ripening at term [7, 18]. The maternal and fetal haemodynamic changes occurring after vaginal administration of ISMN for pre-induction cervical ripening at term, have not been found to be clinically significant [4, 17, 19].

The common side effects of ISMN viz headache, sinus tachycardia and hypotension are less severe than the side effects associated with PGE_2. In Sri Lanka PGE_2 is not freely available in the government health sector and misoprostol is not registered for use as a pre-induction cervical ripening agent. Furthermore, vaginal PGE_2 is more expensive (US$ 8) compared to ISMN tablets (US$ 0.1).

In a previous study we have shown that ISMN – SR 60 mg was a safe, cheap and effective option for preinduction cervical ripening at 41 weeks' gestation in situations where PGE_2 and misoprostol are not available [18]. The only side effect was maternal headache, which easily responded to simple analgesics.

However, ISMN is a preparation designed for oral therapy. It is possible that an ISMN specially formulated for vaginal use may have even better results. The use of vaginal ISMN for cervical ripening has the added advantage that, unlike prostaglandins, it does not stimulate uterine contractions. Therefore it can be safely used in grand multiparous women as well as women with uterine scars and even in an outpatient setting. Although prostaglandins are more effective than ISMN, outpatient use of prostaglandins carries a high risk and is not recommended. Recent studies have demonstrated that ISMN could be safely self administered by women on an outpatient basis [20, 21]. The women who participated in these studies had greater maternal satisfaction and were very positive about the opportunity to undertake cervical ripening at home. Although these studies were conducted in the UK, the results are of great relevance to non industrialised countries with poor resources and limited availability of prostaglandins like Sri Lanka. The use of outpatient ISMN for cervical ripening could result in a shorter hospital stay and decreased costs to the health services.

The optimal dose of vaginal ISMN for pre-induction cervical ripening has not been established. The objectives of our current study were:

a) to compare the effects of vaginally administered ISMN 40 mg , ISMN – SR 60 mg, and the placebo Vitamin C 100 mg in ripening the cervix and making it favourable for IOL,

b) to compare the effects of these three interventions on the cardiovascular system of the mother and the fetus,

c) to compare the systemic side effects of these three interventions on the mother,

d) to compare the outcome in the women who had IOL following the three interventions.

Methods

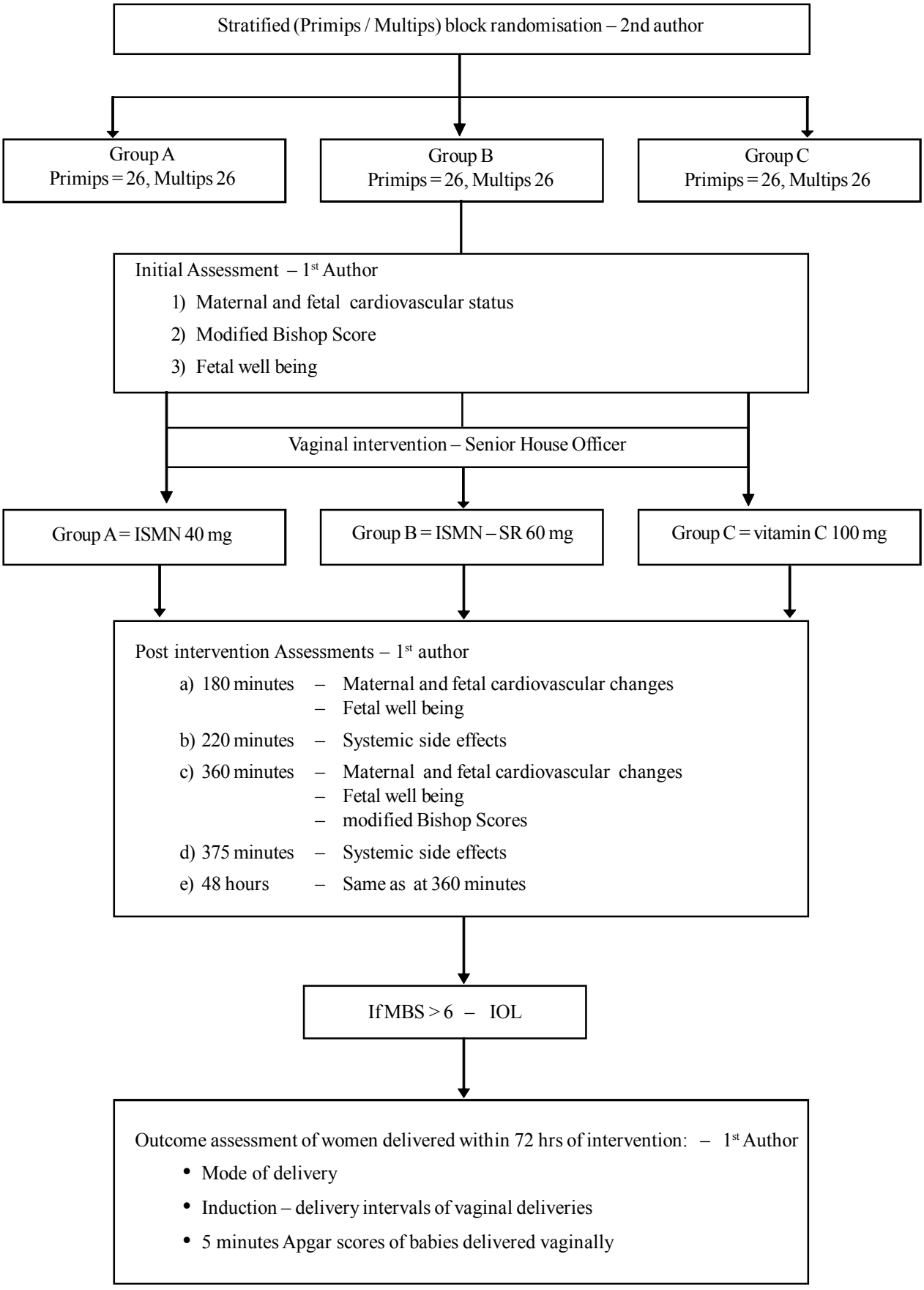
This double blind randomised controlled trial was conducted between March 2006 and April 2007 at the University Obstetric Unit, Teaching Hospital Mahamodara, Galle, Sri Lanka. Approval was obtained from the Ethical Review Committee, Faculty of Medicine, Galle and the trial was registered in the Sri Lanka Clinical Trials Registry.

According to studies previously carried out in the unit, it was estimated that approximately 20% of women between 40 weeks + 5 days and 41 weeks' gestation will either establish spontaneous labour or become favourable for IOL within the next 48 hours. In order to detect an increase of this percentage by a further 25% after treatment with ISMN, with a power of 80% (Type II error of 20%) and a confidence level of 95% (Type I error of 5%) the total sample size was calculated to be 156.

Therefore 156 consecutive women with uncomplicated singleton pregnancies with cephalic presentations, and between 40 weeks + 5 days and 41 weeks' gestation, where the dates had been confirmed by an early ultrasound scan, and having a cervix unfavourable for IOL with a modified Bishop Score (MBS) <5 were recruited for the study [22]. Women with any medical or obstetric problems and any contraindications for the use of ISMN were excluded.

Informed written consent was obtained from all the women who were recruited. None declined to participate. The women were randomly allocated to three groups using stratified (primigravidae and multigravidae) block randomisation. Sequentially numbered sealed opaque envelopes were prepared with either a ISMN – SR 60 mg tablet or two ISMN 20 mg tablets (both from Micro Laboratories, Bangalore India) or a vitamin C 100 mg tablet (placebo) by the second author and kept in a secure place in the obstetrics ward. Maternal pulse rate (PR) systolic and diastolic blood pressure (SBP and DBP) a 10 minute cardiotocogram (CTG), umbilical artery resistance index (RI), pulsatility index (PI), and the modified Bishop Scores were recorded initially by the first investigator. If the CTG

Double blind randomised controlled trial. n = 156, uncomplicated, singleton pregnancies between 40 weeks + 5 days and 41 weeks gestation, modified Bishop Score <5



was non reactive it was followed by the fetal acoustic stimulation test (FAST). If the FAST was negative (no fetal movement felt by mother and CTG persisted as non reactive) in any woman, she was excluded from the study and managed according to the clinical guidelines adopted in the unit. The pulseoximeter (N -595 Nellcor), Ireland, the digital blood pressure monitor (Omron Corporation, Japan, corometric cardiotocograph (172 Wipro GE Medical Systems USA), corometric model 146 fetal acoustic stimulator and the logiq 3 pro console ultrasound scanner (Wipro GE Medical Systems USA), were used to monitor the PR, BP and to carry out the CTG, FAST and the umbilical artery RI and PI respectively.

After initial assessment by the first author, the women were handed over to a senior house officer (SHO). The SHO selected in sequence the appropriately numbered, sealed, opaque envelope and its contents were inserted into the posterior fornix of the vagina of each woman.

All the women recruited for the study were given refreshments, four hours after the therapy. All subsequent assessments were carried out by the first author who initially assessed the women and he was blind to the therapy given to the women. The PR, BP, CTG and umbilical artery RI, PI were recorded at 180 minutes and 360 minutes after the intervention. If the CTG persisted to be non reactive even after FAST in any woman, she was removed from the study and an emergency CS arranged.

At 210 minutes and at 360 minutes, all the women were asked to complete a questionnaire regarding the presence of headache, hot flushes, palpitations, dizziness, abdominal pain, pelvic pain and nausea. If any of these symptoms were present, the mothers were requested to describe the intensity of the symptoms based on a visual analogue scale. For statistical assessment of the intensity of these symptoms, each scale was graded from 0 (no symptoms) to 10 (symptoms of maximal intensity). The first author carried out a reassessment of the MBS at 375 minutes after the intervention.

If any woman delivered (vaginally or by CS) within 48 hours after administration of therapy the babies' 5 minute Apgar scores were recorded. All the other remaining women had a repeat assessment 48 hours after the initial therapy. If the CTG was non reactive and the FAST was negative, CS was carried out.

In the women who had cervices which were grossly unfavourable for IOL 48 hours after the initial therapy, cervical ripening was carried out with an intra-cervical Foley catheter according to the clinical guidelines adopted in the unit. The women who had favourable cervices (modified Bishop Scores >6) had IOL with amniotomy and intravenous oxytocin infusion and their induction delivery interval, mode of delivery and babies' 5 min Apgar scores were recorded if they successfully delivered vaginally.

The outcome measures of the study were PR and BP at 180, 360 minutes and after 48 hours, RI and PI at 180 and 360 minutes and after 48 hours, modified Bishop Scores at 375 minutes, CTG and FAST results, the side effects, the proportion establishing spontaneous labour or becoming favourable for IOL or needing CS within 48 hours of the therapy, and in the women who underwent IOL, mode of delivery, induction delivery interval and the 5 minutes Apgar scores of babies delivered vaginally within 72 hours of the initial therapy.

Analysis of variance was used to compare the means of the continuous variables if the data were normally distributed and the Bonferroni post hoc test if the overall F value showed significant differences between the groups ($p< 0.05$). The Chi Square Test and Fisher's Exact Limits were used to compare the proportions of the dichotomous variables. The statistical package SPSS 14th edition was used.

Results

By the end of the study period (one year), 156 women had been recruited for the study. Two of the multigravid women were excluded from the analysis because they had pre-labour rupture of membranes within two hours of drug administration. Therefore in this study, 51 women received ISMN 40 mg, 52 women received ISMN – SR 60 mg and 51 women received the placebo vitamin C 100 mg vaginally. At the commencement of the study there were no significant differences in parity and mean age, MBS, PR, SBP and DBP, RI and PI among the three treatment groups (Table 1).

There was a significant increase ($p< 0.001$) of mean MBS by 1.3 (95% CI 0.8, 1.7) in primips and by 1.7 (95% CI 1.3, 2.0) in multips after 6 hours in the ISMN 40 mg treatment group and no significant increase thereafter. There was a significant increase ($p< 0.001$) of mean MBS by 2.4 (95% CI 1.9, 2.7) in primips and by 2.3 (95 % CI 2.0, 2.6) in multips after 48 hours in the ISMN SR – 60 mg treatment group. In the vitamin C treatment group there were no significant changes in the mean MBS even after 48 hours. There were no significant differences in the changes in the MBS between primips and multips (Table 2).

There were no significant changes in maternal DBP and the umbilical artery RI PI in any of the treatment groups. The maternal PR increased by a mean of 6.7 – 10.2 bpm (95% CI 5.0 – 12.5, $p< 0.001$) and the maternal SPB decreased by a mean of 7.3 – 10 mmHg (95% CI 5.5 – 11.7, $p< 0.001$) by 180 minutes and persisted up to 360 minutes after vaginal ISMN therapy with no similar changes observed with the placebo vitamin C (Table 3). However, these changes were not of any clinical significance. The side effects reported are given in Table 4. The intensity of headache was mild and it responded to paracetamol. At 48 hours the maternal PR and SBP had returned to the baseline levels prior to therapy (Table 3).

Table 1. **The basic characteristics of subjects (n = 154)**

	*ISMN 40 mg n = 51**	*ISMN – SR 60 mg n = 52*	*Vitamin C n = 51**
Number of primips	26	26	26
Mean age of primips – years (95% CI)	24.5 (23.2, 25.8)	25 (23.6, 26.4)	24.5 (22.9, 26.1)
Mean age of multips – years (95% CI)	29.0 (27.2, 30.8)	29.1 (27.4, 30.8)	28.6 (26.9, 30.3)
Mean MBS (95% CI)	3.45 (3.3 - 3.7)	3.50 (3 .3 - 3.7)	3.40 (3.2 - 3.7)
Mean pulse rate – bpm (95% CI)	83.1 (80.9 - 85.3)	83.2 (81.6 - 84.9)	82.7 (81.4 - 83.9)
Mean SBP – mmHg (95% CI)	117.0 (114 - 120)	118.0 (116 - 119)	118.0 (115 - 120)
Mean DBP – mmHg (95% CI)	72.0 (69.3 - 74.6)	71.6 (69.8 - 73.4)	71.8 (69.7 - 73.9)
Mean PI (95% CI)	0.84 (0.83 - 0.90)	0.87 (0.84 - 0.89)	0.86 (0.82 - 0.90)
Mean RI (95% CI)	0.57 (0.53 - 0.58)	0.56 (0.54 - 0.58)	0.57 (0.54 - 0.59)

*One participant from each of these groups was excluded from the study due to pre-labour rupture of membranes.

ISMN – SR ISO-sorbide mononitrate slow releasing form

PI pulsatility index

SBP systolic blood pressure MBS modified Bishop Score DB diastolic blood pressure

RI resistance Index 95% CI 95% confidence Interval

Table 2. **Mean changes in modified Bishop Score (n = 154)**

Primips	*ISMN 40 mg (n = 26)*	*ISMN – SR 60 mg (n = 26)*	*Vitamin C (n = 26)*
Mean change in MBS at 360 minutes (95% CI)	**1.3** (0.8, 1.7) $p<0.001$	**0.3** (-0.1, 0.5)	**0.2** (0.03, 0.35)
Mean change in MBS at 48 hours (95% CI)	**1.6** (1.2, 1.9)	**2.4** (1.9, 2.7) $p<0.001$	**0.5** (-0.08, 0.97)
Multips	(n=25)*	(n=26)	(n=25)*
Mean change in MBS at 360 minutes (95 % CI)	**1.7** (1.3, 2.0) $p<0.001$	**0.2** (0.07, 0.4)	**0.2** (-0.03, 0.4)
Mean change in MBS at 48 hours (95% CI)	**1.9** (1.4, 2.3)	**2.3** (2.0, 2.6) $p<0.001$	**0.9** (0.4, 1.31)

*One participant from each of these groups was excluded from the study due to pre-labour rupture of membranes.

ISMN – SR iso-sorbide mononitrate slow release form MBS modified Bishop Score 95% CI 95% confidence interval

Table 3. **Haemodynamic changes at 180 mins, 360 mins and 48 hours (n = 154)**

	*ISMN 40 mg (n=51)**	*ISMN - SR 60 mg (n=52)*	*Vitamin C (n=51)**	*p value*
Mean increase in PR (bpm)				
At 180 minutes (95% CI)	**10.2** (7.9 - 12.5)	**6.7** (5.0 - 8.4)	**0.45** (-2.3 - 1.4)	<0.001
At 360 minutes (95% CI)	**8.9** (6.6 - 11.3)	**7.8** (6.0 - 9.6)	**0.45** (-2.2 - 1.3)	<0.001
At 48 hours (95% CI)	**0.08** (-1.6 -1.7)	**0.12** (-1.9 - 1.7)	**0.75** (-1.2 - 2.7)	NS
Mean reduction in SBP (mmHg)				
At 180 minutes (95% CI)	**9.8** (8.2 - 11.7)	**10** (8.6 - 11.4)	**0.5** (1.3 - 2.3)	<0.001
At 360 minutes (95% CI)	**7.3** (4.7 - 9.8)	**7.8** (5.5 - 9.2)	**0.6** (-2.4 - 1.2)	<0.001
At 48 hours (95% CI)	**1.9** (-6.66 - 4.3)	**1.2** (-1.4 - 3.8)	**2.9** (3.7 - 5.5)	NS
Mean reduction in DBP (mmHg)				
At 180 minutes (95% CI)	**2.2** (0.45 - 3.9)	**1.3** (0.4 - 2.8)	**0.25** (-1.4 - 1.9)	NS
At 360 minutes (95% CI)	**1.5** (- 0.4 - 3.3)	**0.5** (-1.4 - 2.4)	**-0.25** (-1.9 - 1.4)	NS
At 48 hours (95% CI)	**-2.2** (- 2.6 - 2.1)	**-2.1** (-4.3 - 0.2)	**-4.1** (-6.3 -1.9)	NS
Mean change in RI				
At 180 minutes (95% CI)	**-0.015** (- 0.04 - 0.01)	**0.0021** (0.016 - 0.02)	**0.0045** (.022 - 0.014)	NS
At 360 minutes (95% CI)	**0.01** (- 0.04 - 0.15)	**0.02** (-0.02 -0.016)	**0.01** (- 0.02 - 0.02)	NS
At 48 hours (95% CI)	**0.07** (- 0.03 - .023)	**0.01** (-0.02 -0.02)	**0.04** (- 0.03 - 0.02)	NS
Mean change in PI				
At 180 minutes (95% CI)	**0.01** (-0.06 - 0.04)	**0.005** (-0.02 - 0.03)	**0.008** (-0.04 - 0.03)	NS
At 360 minutes (95% CI)	**0.01** (-0.03 - 0.05)	**0.005** (-0.03 - 0.02)	**0.01** (- 0.05 - 0.025)	NS
At 48 hours (95% CI)	**0.06** (-0.05 - 0.06)	**0.02** (-0.06 - 0.02)	**0.01** (-0.07 - 0.04)	NS

*One participant from each of these groups was excluded from the study due to pre-labour rupture of membranes.

ISMN – SR iso-sorbide mononitrate slow releasing form
SBP systolic blood pressure
bpm beats per minute
95% CI 95% confidence interval
NS not significant
PI pulsatility index
DBP diastolic blood pressure
RI resistance index
MBS modified Bishop Score

Table 4. **Number of women with side effects in the six hour period after the intervention (n=154)**

	Side effects ISMN				Intensity of side effects ISMN			
	*ISMN 40mg n=51**	*-SR 60 mg n=52*	*Vitamin C n=51**	*P value*	*ISMN 40mg n=51**	*-SR 60 mg n=52*	*Vitamin C n=51**	*P value*
Headache								
210 minutes	26	19	1	<0.01	3.2	2.38	1.1	<0.01
360 minutes	18	10	1		2.08	1.4	1.02	
Nausea / vomiting								
210 minutes	6	4	0	<0.01	1.45	1.25	1.1	<0.01
360 minutes	3	0	0.00		1.1	1	1	
Pelvic pain								
210 minutes	5	1	3	NS	1.35	1.1	1.1	NS
360 minutes	4	2	0		1.22	1.2	1.02	
Abdominal pain								
210 minutes	7	2	1	NS	1.24	1.06	1.02	NS
360 minutes	4	2	2		1.18	1.1	1.08	
Dizziness								
210 minutes	6	2	1	NS	1.27	1.1	1	NS
360 minutes	5	1	0		1.2	1.02	1	
Palpitations								
210 minutes	1	0	0	NS	1.06	1	1	NS
360 minutes	3	1	0		1.14	1.02	1	
Hot flushes								
210 minutes	2	1	2	NS	1.08	1.02	1.02	NS
360 minutes	0	0	1		1	1	1	

*One participant from each of these groups was excluded from the study due to pre-labour rupture of membranes.

ISMN – SR	Iso-sorbide mononitrate slow release form
MBS	modified Bishop Score
95% CI	95% confidence interval
mins	minutes
NS	not significant

Greater proportions of primips (42 % with ISMN – SR 60 mg and 31% with ISMN 40 mg, $p< 0.05$) were favourable for IOL after 48 hours in comparison with the controls (7.6%). Greater proportions of multips (46 % with ISMN – SR 60 mg and 40% with ISMN 40 mg, $p< 0.05$) were favourable for IOL after 48 hours in comparison with the controls (16%). Within the first 48 hours of the intervention there were no significant differences in the proportions establishing spontaneous labour or requiring emergency CS among the three groups and between primips and multips. Furthermore there were no significant differences between primips and multips in the proportions becoming favourable for IOL after ISMN therapy (Tables 5 and 6).

In the women who underwent IOL, there was no significant difference in emergency CS rates due to fetal distress or failed IOL, or in the mean induction-delivery intervals and mean 5 minutes Apgar scores of babies delivered vaginally within 72 hours of the interventions among the three groups and between primips and multips (Table 7).

Table 5. **Outcomes 48 hours after the intervention in the primips (n= 78)**

	ISMN 40 mg (n = 26)	*ISMN – SR 60 mg (n = 26)*	*Vitamin C (n = 26)*
Spontaneous onset of labour within 48 hours	7 (27%)	6 (23%)	8 (31%)
Emergency caesarean section within 48 hours	0	0	1 (3.8%)
Not delivered at 48 hours	19 (73%)	20 (77%)	17 (65%)
Favourable for IOL after 48 hours	8 (31 %) $p < 0.05$	11 (42%) $p < 0.05$	2 (7.6%)
Not favourable for IOL after 48 hours	11 (42 %) $p < 0.05$	9 (35 %) $p < 0.05$	15 (58 %)

ISMN iso-sorbide mononitrate
ISMN – SR iso-sorbide mononitrate slow release form
IOL induction of labour

Table 6. **Outcomes 48 hours after the intervention in the multips (n= 76)**

	*ISMN 40 mg (n = 25)**	*ISMN – SR 60 mg (n = 26)*	*Vitamin C (n = 25)**
Spontaneous onset of labour within 48 hours	9 (36%)	6 (23%)	9 (36%)
Emergency caesarean section within 48 hours	1 (4%)	1 (3.8%)	0
Not delivered at 48 hours	15 (60%)	19 (73%)	16 (64%)
Favourable for IOL after 48 hours	10 (40 %) $p < 0.05$	12 (46%) $p < 0.05$	4 (16%)
Not favourable for IOL after 48 hours	5 (20 %) $p < 0.05$	7 (27 %) $p < 0.05$	12 (48 %)

*One participant from each of these groups was excluded from the study due to pre-labour rupture of membranes

ISMN– iso-sorbide mononitrate
ISMN – SR iso-sorbide mononitrate slow release form
IOL induction of labour

Table 7. **Outcome in the women who underwent induction of labour (n = 47)**

	*ISMN 40 mg (n =18)**	*ISMN – SR 60 mg (n = 23)*	*Vitamin C (n =6)**
Mean I /D interval in primips undergoing IOL after 48 hours – minutes (95% CI)	n = 8 317.5 (276 - 358)	n = 11 329.7 (282 - 377) *p*- NS	n = 2 342.1 (282 - 402)
Mean I /D interval in multips undergoing IOL after 48 hours – minutes (95% CI)	n = 10 277 (203.5 - 351.2)	n = 12 308 (260 - 356) *p*- NS	n = 4 302 (263 - 340.5)
Intrapartum emergency CS for failed IOL or fetal distress in primips	n = 2	n = 3	n = 1
Intrapartum emergency CS for failed IOL or fetal distress in multips	n = 0	n = 1	n = 1
Mean 5 min Apgar score of babies delivered within 72 hours of the intervention (95% CI)	n= 51 9.2 (9.04, 9.36)	n = 52 9.9 (9.82 , 9.98)	n = 51 9.4 (9.24 , 9.56)

I/ D Interval	induction delivery Interval
IOL	induction of labour
CS	caesarean section
95% CI	95% confidence interval
NS	not significant

Discussion

This trial provides further evidence that in comparison with vitamin C a placebo, vaginal administration of the NO donor ISMN results in greater ripening of the cervix in post dated pregnancies. Due to practical problems, the effects of the vaginal ISMN could be evaluated only up to 6 hours after the intervention on the first day. Therefore any effects occurring after 6 hours and up to 48 hours (the time of the next evaluation) would not have been detected in the current study. For example if a reduction of DBP occurred after 6 hours, especially in the group of women administered ISMN – SR 60 mg, it would have been missed.

A study carried out in Norway demonstrated a mild but significant ($p< 0.01$) increase in maternal. PR and a mild but significant decrease of both SBP ($p< 0.001$) and DBP ($p< 0.0001$), 180 minutes after vaginal ISMN 40 mg. However, none of the women in that study required medical treatment [19]. In the current study, although a mild increase of maternal PR ($p< 0.001$) was noted in both ISMN 40 mg and ISMN – SR 60 mg groups, there was no significant reporting of palpitations by these women. Although a mild headache was reported by 51% of women in the ISMN 40 mg group and 37% of women in the ISMN – SR 60 mg group, paracetamol was adequate to relieve their discomfort and no other clinically significant adverse effects were reported in the current study. As seen in the Norwegian study in the current study too there was no evidence of any adverse effects on the fetus detected by CTG and umbilical artery Doppler RI and PI [19].

Although ISMN 40 mg led to significant ripening of the cervix in 6 hours, the greater degree of cervical ripening after 48 hours and the larger proportion of women becoming favourable for IOL after 48 hours, suggests that therapy with 60 mg of the sustained release form ISMN – SR is a better agent for pre-induction ripening of cervix. There were no significant differences in the change in MBS after ISMN therapy between primips and multips and the proportion of primips and multips becoming favourable for IOL after 48 hours of ISMN therapy. Similarly in the women whose cervices were favourable for IOL at 48 hours and therefore underwent IOL, there was no significant difference in the mean induction – delivery intervals between primips and multips.

The optimum dose, formulation and frequency of administration, and the value of repeated doses of vaginal ISMN, needs to be established. The feasibility and the acceptability of outpatient self medication with vaginal ISMN too needs further study.

Conclusions

When compared with the placebo vitamin C 100 mg, vaginal ISMN 40 mg and ISMN – SR 60 mg lead to significantly greater cervical ripening after 6 hours and 48 hours respectively. Therefore vaginal ISMN leads to more women becoming favourable for IOL. Vaginal ISMN does not affect placental blood flow but causes headaches and clinically insignificant maternal haemodynamic changes.

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