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Pre-Induction Cervical Ripening Using a Transcervical Foley Catheter Combined with ISMN Vaginal Tablets for Vaginal Birth after Previous Caesarean Section (VBAC)—A Comparative Study

D. Liyanapatabandi[1*], J. Karunasinghe[1], M. H. Ziard[1], R. Prathapan[1], S. I. Wickramasinghe[2]

[1]Colombo South Teaching Hospital, Kalubowila, Sri Lanka
[2]Queensland, Australia
Email: *dinusha495@hotmail.com

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Abstract

Objective: To compare the effectiveness, safety and client acceptability of concurrent application of transcervical Foley catheter with vaginal ISMN-sustained release (SR) 60 mg tablet versus transcervical Foley catheter alone for pre-induction cervical ripening in women who are undergoing Vaginal birth after C-section (VBAC). **Method:** A prospective single blind randomized control study was carried out including 110 pregnant women who had unfavorable cervix (MBS less than 6) at 40 weeks and 3 days of gestation. The two groups received either the trans-cervical foley catheter with a vaginal ISMN 60 mg sustained release (SR) tablet on 40 weeks and 3 days (Treatment arm 1, n = 57), or trans-cervical Foley alone on 40 weeks and 3 days (Treatment arm 2, n = 53). **Results**: At 40 weeks + 3 days gestation, the mean age, mean parity and the mean modified Bishop Score (MBS) were comparable among the two treatment groups. Majority (n = 98, 89.1%) remained without spontaneously establishing labour at 24 hours of intervention. The difference in mean MBS at 40 weeks + 4 days (24-hours following the intervention) in the two groups was statistically not significant (P > 0.05). The group who received concurrent ISMN vaginal tablets achieved a higher number of successful VBACs (n = 33, 62.3%) over the group who received the Foley catheter only method (n = 29, 50.9%), however, not statistically significant (P > 0.05). **Conclusions:** The concurrent use of vaginal ISMN tablets (60 mg SR) with a transcervical Foley catheter failed to show higher effectiveness compared to a transcervical Foley catheter alone as an induction method.

Keywords

Isosorbide Mononitrate (MeSH), Vaginal Birth After a Cesarean (MeSH), Induced Labor (MeSH)

1. Introduction

There is a gradual rising trend in the Caesarean Section (CS) rate in Sri Lanka [1]. The rising rate of primary caesarean section has led to an increased number of pregnant women with past Caesarean section registering to antenatal care.

A planned vaginal birth after a Caesarean delivery (VBAC) is an accepted method of delivery in the absence of other contraindications. The success rate of VBAC is dependent on various modifiable and non-modifiable factors [2]. Among these, higher Bishop scores on admission have been shown to increase the likelihood of successful VBAC [2]. Therefore, cervical priming and making the cervix favourable for induction incur a significant impact on the success rate of the VBACs.

Application of vaginal prostaglandin, vaginal nitric oxide donors (such as Isosorbide Mononitrate (ISMN)) and trans-cervical Foley catheter insertion have shown to be effective methods of induction of labour [3] [4]. However, with compared to unscarred uteri, pregnancies with previous lower segment Caesarean section carry an increased risk of uterine rupture and associated mortality and morbidity. This risk is even higher when using vaginal prostaglandins as a method of pre induction cervical ripening [2] [3] [5]. Compared with prostaglandins, the trans-cervical Foley catheter is associated with a lower risk of uterine hyperstimulation with fetal heart rate changes [6].

In Sri Lanka, Foley catheter has been often used as a pre induction cervical ripening method in VBACs. The evidence has shown that Foley catheter insertion is an effective method of pre induction cervical ripening in VBAC [3]. Further it has been recommended as a safe method of labour induction for women with scarred uterus, since it is less likely to be associated with hyperstimulation of the uterus [4] [6] [7].

Several researchers have shown vaginal insertion of ISMN to be a proven and effective method in a pre-induction cervical ripening [4] [8] [9]. Vaginal insertion of ISMN 60 mg sustained release (SR) tablets has shown to be an effective method in pre induction cervical ripening in primiparous and multiparous women in Sri Lanka. However, the effect of ISMN on VBACs has not been evaluated in the Sri Lankan context [4]. The pharmacological properties of nitric oxide donors (NO) which is to inhibit rather than stimulate uterine contractions appear to be the ideal cervical ripening agent for use in scarred uteri [8].

However, some research shows that trans-cervical Foley catheter insertion alone or vaginal ISMN insertion alone is not as effective as vaginal insertion of

prostaglandin in terms of successful vaginal delivery rates in VBACs [8] [10]. The effectiveness, safety and acceptability of the above two methods in isolation have been tested and compared in women with scared uteri [11].

Further synergistic effect of combining vaginal ISMN and trans-cervical Foley catheter insertion as a method of pre induction cervical ripening in unscarred uteri has been shown to be a safer method in terms of less fetal distress, absent uterine hyperstimulation and good neonatal outcome compared to vaginal prostaglandins [12]. A modified Bishop's score (MBS) of 5 or less is considered as unfavorable for induction and a score of 6 or more is considered favorable [13]. An MBS of ≥6 is associated with successful VBAC (odds ratio [OR] 2.07, 95% CI 1.28 - 3.35, $P < 0.001$) [14].

Due to paucity of the published data, recommendations on concurrent use of vaginal ISMN with transcervical Foley catheter in pre-induction cervical ripening in VBAC remains as an area requiring further research.

2. Study Aims

2.1. General Objective

To assess the effectiveness of concurrent application of vaginal Isosorbide mononitrate (ISMN) 60 mg sustained release (SR) vaginal tablet combined with trans-cervical Foley catheter insertion for the pre induction ripening of the uterine cervix in pregnant women at 40 weeks and 3 days of gestation awaiting vaginal birth after caesarean (VBAC) compared to trans-cervical foley catheter alone method.

2.2. Specific Objectives

1) To assess effectiveness of combined effect of concurrent application of trans-cervical Foley catheter with vaginal ISMN 60 mg (SR) versus trans-cervical Foley catheter alone as a method of pre induction cervical ripening used in VBAC in the stipulated study group (by assessing the MBS).

2) Compare the number of women who established the labour within 24 hours after the intervention in each group.

3) To assess the change in MBS at 24 hours after the intervention in both study groups.

4) To assess the intervention to delivery time in both study groups.

5) To assess the outcome (mode of delivery) of each induction method used.

6) To assess and compare the adverse effects to the mother and to the fetus/neonate in both groups of pre induction cervical ripening methods.

7) To assess the maternal acceptability in both groups of the induction methods.

3. Methodology

3.1. Design

A prospective randomized single blind comparative study.

3.2. Setting

Ward 18 (Obstetric Ward), Colombo South Teaching Hospital, Kalubowila, Sri Lanka. The principal investigator (PI) is a postgraduate trainee in Obstetrics and Gynaecology at this hospital, and the supervisor is a Consultant Obstetrician and Gynaecologist at the same hospital.

3.3. Methods

Participant selection pregnant women with uncomplicated pregnancies other than previous one lower segment Caesarean section and who are suitable and counseled to offer VBAC admitted to ward 18 of Colombo South Teaching Hospital for confinement at 40 weeks and 0 days of period of gestation (POG). The POG was confirmed by the first trimester ultrasound scan using the Crown Rump Length (CRL) [15] in addition to the POG calculated by the date of the last regular menstrual period.

Treatment group 1: Transcervical Insertion of 16Fr (French units) Foley catheter inflated with 40 cc of sterile water at a POG of 40 weeks and 3 Days with simultaneous Insertion of ISMN-SR 60 mg vaginally Inpatient.

Treatment group 2: Transcervical Insertion of 16 Fr (French units) Foley catheter inflated with 40 cc of sterile water at a POG of 40 weeks and 3 Days– Inpatient.

3.3.1. Investigational Product (IP)

1) Transcervical 16 *Fr* (*French units*) Foley catheter (IP-1)

Standard 2 way natural latex siliconized sterile single use 16 Fr Foley catheter (Manufactured by Uro Technology SDN. BHD, Lot 2491, Batu 39 1/2, Pontian Besar, 82000 Pontian, Jahor, Malaysia) kept for 24 hours after insertion or the time of spontaneous expulsion from the cervix till the whichever event comes first. Foley catheter inserted using aseptic technique above the internal cervical os and inflated with 40 ml of sterile water. The catheter was taped to the inner thigh).

2) ISMN 60 mg sustained release tablets (IP-2)

Isosorbide-5-mononitrate (Non-proprietary name) sustained release tablets 60 mg, containing diluted Isosorbide mononitrate BP equivalent to Isosorbide mononitrate 60 mg (Manufactured by Cadila Healthcare Limited, Kundaim Industrial Estate, Plot 203-213, Kundaim, Goa-403 115, India). This applied once only during the study to the posterior fornix of the vagina of the subjects, soon after the insertion of the transcervical Foley catheter (IP-1) under aseptic condition.

3.3.2. Non Investigational Products

Standard products of sterile water, sterile cotton gauze, povidone iodine, paracetamol 500 mg tablets, 0.9% saline infusion, oral rehydration solution, cefuroxime 750 mg vials, metronidazole 500 mg vials etc. available in the institution of the place of conduction of the study were used.

3.3.3. Description of Intervention and Administration

Pregnant women who are suitable for VBAC, routinely have been counseled at 36 weeks of POG in order to determine the mode of delivery as a unit policy. At this point, eligible pregnant women got detailed information (written and verbal) about elective Caesarean section and VBAC. The group of women who had given consent for VBAC were followed up till the due date (40 weeks) as out-patients and advised to admit on the due date to the ward for confinement according to the unit protocol.

The group who had chosen VBAC as their mode of delivery was approached by a trained research assistant (RA) provided with information about the study. This group was briefed in their first language by the RA or an interpreter and enrolled them into the study at POG of 40 weeks and 0 days after obtaining informed written consent. They were informed that they are free to withdraw from the study before commencement *i.e.* in 3 days, or during the study.

These mothers who were having a reactive cardiotocography (CTG) were assessed by the PI at 40 weeks and 3 days of gestation if they haven't delivered. Those with unfavorable cervix (modified Bishop's score of 5 or less) were selected to the study and their modified Bishop's score documented.

The subjects were allocated to two groups by simple randomization. Sequentially numbered and sealed opaque envelopes packed with the appropriate treatment regimen prepared by the senior registrar of the unit who was not a member of the research team. Each mother randomized to the treatment group 1 and 2 had the intervention administered by the senior registrar of the unit according to the predetermined randomized allocation sequence. Transcervical Foley catheter inserted under the aseptic conditions and inflated with 40 cc of sterile water. The ISMN tablet in the envelope is inserted to the posterior vaginal fornix for the subjects in the treatment group 1.

Throughout the study period maternal and fetal well being was monitored by the consultant obstetrician and senior registrar of the ward in order to detect any adverse effects. The mothers were monitored by periodical (hourly for four hours, two hourly for eight hours and four hourly for twelve hours) assessment of blood pressure, heart rate, pain, vaginal bleeding, watery vaginal discharge etc. Fetal well being was assessed by monitoring of fetal heart rate assessment (hourly) and cardiotocography (CTG) at 4-hourly and 1-hourly intervals after the intervention. (Participants were freely allowed to withdraw from the study if they wished to do so at any time.)

In a case of serious adverse effect (abnormal CTG, fresh vaginal bleeding, severe headache, etc) that subject was withdrawn from the study and necessary immediate obstetric and medical management was carried out. All such adverse effects were recorded.

If the subjects had established the first stage of labour before 24 hours of the intervention, they were assessed by the PI who was blinded to the treatment regimen and their modified Bishop's score (MBS) and time elapsed following the intervention were documented. Their mode of delivery, induction to delivery

interval, neonatal Apgar score at 5 minutes was recorded.

If the Foley catheter was expelled before 24 hours of the intervention, but not established in labour till 24 hours after the intervention, kept inward for assessment at 24 hours of the intervention.

At 40 weeks and 4 days (24 hours after insertion of the Foley catheter) all the mothers who had not commenced spontaneous labour and had not delivered, were reassessed by the principal investigator, and MBS were documented. If the cervix was favorable (MBS of 6 or more), they underwent amniotomy (without oxytocin infusion) on the same day. If the MBS was less than 6, Caesarean section was carried out according to the unit policy. Throughout the labour, continuous electronic fetal monitoring was carried out and labour managed according to the unit policy of VBAC. After the delivery, neonatal Apgar score at 5 minutes was recorded and noted if admitted to a special baby care unit.

3.3.4. Primary Endpoint

Women with established first stage of labour within 24 hours after the intervention or Change in MBS at 24 hours of the intervention if not yet established in first stage of labour at 24 hours after the intervention.

(Established first stage of labour was defined as pregnant women with regular painful uterine contractions and progressive cervical dilatation from 4 cm [3].)

3.3.5. Secondary Endpoints

1) Delivery

2) Adverse effects (Maternal):

Headache, allergic reactions, Systolic blood pressure (SBP) < 90 mmHg or diastolic blood pressure (BP) < 60 mmHg, pulse rate (PR) > 100 min, uterine hyperstimulation (Defined as a contraction frequency of more than five in 10 minutes or contractions exceeding 2 minutes in duration and accompanied by an abnormal fetal heart rate pattern [7]), uterine tachysystole (Defined as a contraction frequency of more than five in 10 minutes or contractions exceeding 2 minutes in duration [7]), nausea, vomiting, diarrhea, fever(axillary temperature more than 38˚C), palpitations, fresh vaginal bleeding, uterine rupture (defined as separation of the entire thickness of the uterine wall, with extrusion of fetal parts and intra-amniotic contents into the peritoneal cavity [16].

3) Fetal and Neonatal outcome and morbidity:

Abnormal CTG [3], Apgar score at 5 minute, admission to the neonatal intensive care unit and its reason.

3.4. Data Collection

Data was recorded on a special data collection form developed by the PI.

Demographic and clinical history data recorded at the recruitment by the PI by interviewing and reviewing the antenatal record. Primary outcomes were recorded by the PI, at the time of establishing the first stage of labour within 24 hours or at 24 hours after the intervention in whichever occurred first.

Secondary outcome data were recorded from the clinical notes of respective patients and by interviewing the mothers in the postnatal ward following 24 hours of delivery of the fetus and on the day of discharge from the hospital. These data were documented by the PI.

Adverse events, serious adverse events were monitored by the consultant Obstetrician (supervisor) and the senior registrar of the unit. Adverse events documented in the patients clinical notes were extracted to the data sheet by the PI.

Neonatal outcome was assessed by the consultant neonatologist and data gathered from the relevant clinical notes by the PI at the discharge of the neonate.

Data stored by a research assistant (RA) in a password protected computer based data storage programme. The hard copies will be kept in a locked storage for 5 years. The electronic archives will be deleted and the hard copies will be shredded after this period. No personal identification data were collected and only the principal investigator will have access to demographic data.

Withdrawals and Attritions

All the mothers included in the study had freedom to withdraw from the study at any point after the randomization.

Those mothers who withdrew from the study after the intervention (irrespective of time from the intervention) were followed up using a similar protocol (according to unit policy) as per the mothers who continued in the study.

3.5. Sample Size and Sampling Techniques

3.5.1. Sample Size

The numbers of patients, n_1 and n_2, required in groups 1 and 2 to detect a difference Δ in means with significance level α and power $1-\beta$ assuming variances σ_1^2 and σ_2^2 in populations 1 and 2 are:

$$n_1 = \left(\sigma_1^2 + \sigma_2^2/k\right)\left(z_1 - \alpha/2 + z_\beta\right)^2 \Big/ \Delta^2$$

$$n_1 = \left(k\sigma_1^2 + \sigma_2^2\right)\left(z_1 - \alpha/2 + z_\beta\right)^2 \Big/ \Delta^2$$

where $k = n_2/n_1$ = ratio of 2 sample sizes.

The Primary outcome is the change in Modified Bishop's score at 24 hours.

If the expected range of change in the Modified Bishop's score is 0.06 SD [9].

Assuming $\Delta = 0.5$, $\sigma_1 = 1.01$ [9], $\sigma_2 = 0.95$ $\alpha = 0.05$, 80% power, the sample size per group was 55.

3.5.2. Sampling Techniques

Selection of the participants for the study was conducted at a period of gestation of 40 weeks and 0 days. This was done on clinic days, consecutively from Monday to Friday excluding the weekends over a period of eight months.

Simple randomization techniques were chosen with a 1:1 ratio into both groups.

Inclusion and Exclusion criteria

Figure 1 shows how inclusion and exclusion criteria were applied in selecting participants.

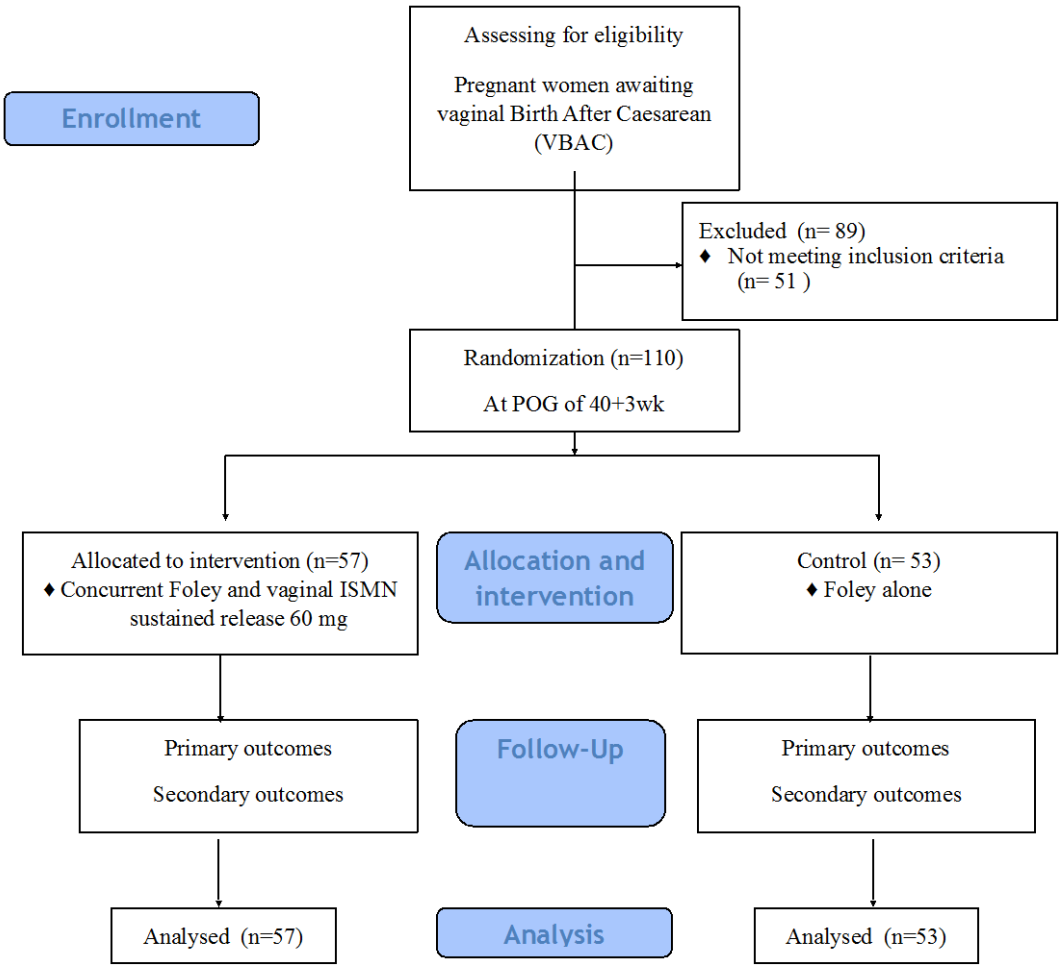

Figure 1. Selection of participants, flow chart.

3.5.3. Inclusion Criteria

Pregnant women with history of past (one-only) caesarean section and currently uncomplicated singleton pregnancy with cephalic presentation at 40 weeks and 0 days of period of gestation.

3.5.4. Exclusion Criteria

At time of recruitment Contraindications for VBAC

- Women with a prior history of two or more uncomplicated low transverse caesarean sections.
- Women with previous uterine rupture.
- Women with a prior history of one classical caesarean section or women with a prior inverted "T" or "J" incision or women with a previous uterine incision other than an uncomplicated low transverse caesarean section incision.
- Other absolute contraindications to vaginal birth that apply irrespective of the presence or absence of a scar [2].
- Malpresentations.
- Multiple pregnancies.

At time of recruitment and at the time of intervention, contraindications

for pre-induction transcervical Foley insertion

- Pregnancies associated with spontaneous rupture of membranes (Preterm or term).
- Maternal pyrexia (axillary temperature > 38˚C).
- Suspected Chorioamnionitis.
- Low-lying placenta.
- Allergic to Latex used in Foley catheter.

At the time of recruitment, other exclusion conditions

- Pregnancies with uncertain dates not confirmed by early scan (first trimester scan).
- Pregnancies associated with Intrauterine growth restriction (defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile sonographically according to the Hadlock's formula) [17] [18].
- Pregnancies complicated with diabetes in pregnancy, fetus with large for gestational-age (Estimated fetal weight (EFW) > 90th centile, or EFW > 4000 g sonographically according to the Hadlock's formula) [18].
- Pregnancies complicated with hypertension in pregnancy, preeclampsia, eclampsia.
- Medical conditions complicating pregnancies.

At the time of recruitment contraindications for ISMN

- Patients who have shown hypersensitivity reactions to other nitrates or nitrites.

3.6. Outcome Measures

3.6.1. Primary Outcomes

1) Number of women with established first stage of labour within 24 hours after the intervention.

(Established first stage of labour defined as pregnant women with regular painful uterine contractions and progressive cervical dilatation from 4 cm [3].)

2) Change in MBS at 24 hours of the intervention if not in established first stage of labour at 24 hours after the intervention.

3.6.2. Primary Outcome(s) Time of Assessment(s)

1) Number of women with established first stage of labour after the intervention assessed from intervention till 24 hours of intervention.

3.6.3. Secondary Outcome(s)

1) Intervention to delivery interval (minutes) of subjects who have delivered vaginally.

2) Mode of delivery.

3) Adverse effects (Maternal).

4) Fetal and Neonatal outcome and morbidity.

5) Maternal satisfaction about the induction method being used.

3.6.4. Secondary Outcome(s) Time of Assessment(s)

1) From the time of intervention to the time of vaginal delivery by minutes.

2) At the time of delivery.

3) From intervention to discharge from the obstetric unit.

4) From the delivery of the neonate at 5 minutes Apgar score and admission to the neonatal intensive care unit will be assessed till the discharge of the neonate.

5) At the discharge of the subject from the obstetric unit.

3.7. Statistical Analysis

Data were analyzed through the IBM® SPSS® Statistics version 23 software. For descriptive statistics, differences in outcome between groups would be analyzed for continuous variables with independent samples T-test, and for categorical variables with Chi-square test. Significant level was tested at 0.05.

3.8. Ethical Considerations

Clinical safety: All the participants of this study (both groups) received the standard, accepted treatment (pre-induction transcervical Foley catheter induction) for women who had chosen VBAC as their mode of delivery in a similar time. Both groups received the similar treatment (Induction of labour or Caesarean section according to the cervical favorability) following the intervention, irrespective of the induction method used.

The ethical clearance for the proposal was obtained from the Ethical Review Committee of Faculty of Medicine, University of Colombo, Sri Lanka.

Suspected Unexpected Serious Adverse Reaction (SUSAR)/Serious Adverse Event (SAE) were reported to the ethics review committee of Faculty of Medicine, University of Colombo, Sri Lanka as soon as possible.

3.8.1. Safety Monitoring

A data and safety monitoring board (DSMB) was appointed, comprising three members.

3.8.2. Definitions of Adverse Events (AE)

An adverse event (AE): any unfavorable and unintended symptom or sign (including a pathological CTG), which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen.

Serious adverse event (SAE): any untoward medical occurrence to the pregnant woman or to the fetus that results in death, is life threatening, requires prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or a congenital anomaly.

Suspected, Unexpected, Serious Adverse Reactions (SUSAR): unexpected serious adverse events in patients, but not consistent with current information.

All the adverse events were dealt according to the standard protocols and clinical practices of the unit.

3.8.3. Follow-Up

All the subjects were followed up for 72 hours from the time of delivery in the

event of a caesarean section and 24 hours from the time of delivery in the event of a vaginal delivery.

4. Results

The study was carried out from 01st June 2015 to 31st April 2016. One hundred and ten women were recruited to the study according to the eligibility criteria and were randomly selected into two treatment groups.

Socio-demographic data—Treatment group 1 (Trans-cervical Foley and vaginal ISMN 60 mg SR tablet) consisted of 57 (51.8%) women and treatment group 2 (Trans-cervical Foley alone) consisted of 53 (48.2%) women. None of the women were withdrawn from the study before the intervention.

Both groups were comparable in the characteristics such as age, parity, inter-delivery interval, and mean modified Bishop's Score (MBS) at the time of intervention (POG of 40 weeks and 3 days) refer to Table 1.

Majority of the participants (n = 85, 77.3%) were below the age of 30 years, 92 (83.6%) participants included, had one living child and 18 (16.4%) women had two living children. Twelve (10.9%) of them had a previous vaginal birth. However, the majority (n = 9) of them had been randomized to the treatment group 2 and it was not a statistically significant proportion (Fisher's exact test P > 0.05). Among the indications for the previous Caesarean section (CS), abnormal cardiotocography (CTG)/fetal distress (n = 38, 34.5%), labour dystocia (n = 27, 24.5%) and malpresentation (n = 16, 14.5%) were the main contributors. Inter-delivery interval between the last pregnancy and current had a range of 22 to 49 months (mean 33.45, SD 5.80).

Out of 110 participants, 88 (80%) had a "normal booking body mass index" (BMI 18.5 - 25.0). Sixteen (14.5%) were overweight (BMI 25.0 - 30.0) and 6 (5.5%) were obese class 1 (BMI 30.0 - 35.0) at the time of booking at the antenatal clinic in the first trimester.

The MBS at the time of the intervention had a range of 3 to 5 (mean MBS of 4.12, SD 0.59) within the whole study group.

Nine (8.2%) women had spontaneous onset of labour; (6 (66.7%) belonged to treatment group 1) and three (2.7%) women underwent emergency CS due to

Table 1. Characteristics of subjects at POG 40 weeks at 3 days (n = 110).

Variable	Treatment grp. 1 Foley + ISMN (n = 57)	Treatment grp. 2 Foley alone (n = 53)	Significance
Mean Age (years)	29.2 (SD = 2.99)	28.5 (SD = 2.47)	P > 0.05
Mean Parity	1.16 (SD = 0.36)	1.17 (SD = 0.37)	P > 0.05
Mean inter delivery interval (Months)	34.49 (SD = 6.56)	32.34 (SD = 4.66)	P > 0.05
Mean MBS at 40 weeks + 3 days	4.09 (SD = 0.57)	4.15 (SD = 0.60)	P > 0.05

MBS = Modified Bishops Score, Data are mean ± standard deviation.

maternal pyrexia within 24 hours. All who had spontaneous onset of labour achieved a vaginal delivery. Out of the 110 participants, 98 (89.1%) remained without going to spontaneous labour at 24-hours after the intervention (POG at 40 weeks and 4 days) (Table 2).

In general, MBS at 24 hours following the intervention had a range of 5 to 7 (mean 6.29, SD 0.77). The mean MBS at 24 hours following the intervention between the two treatment groups were not statistically significant ($p > 0.05$). Similarly mean change in MBS for 24 hours didn't have a statistically significant difference between the two groups (Table 3).

The proportion of women with an unripe cervix (defined as MBS of < 6) after 24 hours of the intervention was not significantly different in the two treatment groups (20.8% versus 18%; $X^2 = 0.126$, df = 1, p = p > 0.05) (Table 4). The 19 (17.27%) women with unfavorable cervix underwent CS on the same day according to the unit policy.

Of the 79 women with favorable cervix, 76 (96.2%) proceeded to the labour induction by amniotomy and 3 (3.8%) had spontaneous onset of labour without amniotomy. Out of this 53 achieved a vaginal delivery (67.1%). Twenty six women (32.9%) underwent emergency CS. Treatment group 1 had a slightly higher number of caesarean deliveries (n = 15) than vaginal deliveries (n = 23) compared to the treatment group 2 which had 11 Caesarean deliveries and 30 vaginal deliveries. However, the mode of delivery and proportion of women who

Table 2. Outcomes assessment from time of intervention up to 24 hours.

Characteristic	Treatment group 1	2	Significance
	Foley + ISMN	Foley alone	
Established 1st stage of labour within 24 hours (%)	6 (10.53 %)	3 (5.67%)	*
CS within 24 hours before the established labour (%)	3 (5.26%)	0 (0%)	*
Not established 1st stage of labour at 24 hours (%)	48 (84.21%)	50 (94.34%)	-

MBS = Modified Bishop's Score, CS = Caesarean Section. *Numbers are not adequate to do a meaningful analysis.

Table 3. Outcome assessment at 24 hours from the intervention.

Characteristic	Treatment grp. 1		2		Significance
	Foley + ISMN		Foley alone		
	Mean	SD	Mean	SD	
MBS at 40 weeks + 4 days	6.19	0.76	6.38	0.78	P > 0.05
Change in MBS at 40 weeks + 4 days	2.21	0.65	2.24	0.65	P > 0.05

Table 4. Outcomes of cervical favorability at 24 hours of intervention and mode of delivery of the all participants.

Characteristic	Treatment grp. 1 Foley + ISMN		Treatment grp. 2 Foley alone		Significance
	n	%	n	%	
Favorability (at 24 hours)					
Favorable cervix	38	79.2	41	82.0	$X^2 = 0.126$
Unfavorable cervix	10	20.8	9	18.0	df = 1, $p \geq 0.05$
MOD					
Vaginal deliveries (Including AVD)	29	50.9	33	62.3	$X^2 = 4.274$,
CS	28	49.1	20	37.7	df = 1, $p \geq 0.05$

MOD = Mode of delivery, CS = Caesarean Section, AVD = Assisted Vaginal Deliveries, X^2 = Chi square value, df = degree of freedom.

achieved a vaginal delivery didn't reach a statistically significant difference between the two treatment groups (Odds ratio 0.562, CI = 0.218 - 10.452).

The mean time duration from the intervention to vaginal delivery in the treatment group 1 had 1839.83 minutes (SD = 257.684). This time was 1852.88 minutes (SD = 217.83) in the treatment group 2. This total intervention-to-delivery time did not differ between groups (P > 0.05) (Table 5).

Cumulative data on mode of delivery, 48 (43.6%) out of 110 women had undergone a CS whereas 62 (56.4%) women achieved a vaginal delivery (Table 4). This too didn't show a significant difference between the two treatment groups.

Among the indications for the CS, failed induction (n = 19, 39.6%), significant meconium stained liquor (n = 13, 27.1%) were main reasons (Table 6).

Secondary safety outcomes are shown in Table 7 and Table 8. The proportion of patients who experienced side effects was low in treatment group 2. Maternal headache was predominantly found in the treatment group 1 (n = 13, 22.8%). Nausea/vomiting was experienced in almost all participants of treatment group 1 (n = 12, 2.1%) There was a statistically significant association of maternal headache and nausea/vomiting in the treatment group 1. Uterine hyperstimulation, antenatal CTG abnormalities and uterine rupture were not reported in either of the treatment groups. Importantly there were no serious adverse events reported during the study.

Fetal and neonatal safeties were assessed by 5-minute Apgar score and number of special care baby unit (SCBU) admissions following the delivery. All the babies delivered (n = 110) had a 5-minute Apgar score of 8 or more. Out of 110 neonates, 16 (14.5%) were admitted to the SCBU. Nine (15.8%) of treatment group 1 and 7 (13.2%) neonates from treatment group 2. The difference of admission to SCBU in the two groups was not statistically significant (P > 0.05) (Table 8).

Maternal discomfort was assessed by a visual analogue scale of 1 to 10. The

Table 5. Comparison of time taken from the intervention to vaginal delivery in two treatment arms.

Characteristic	Treatment grp. 1 Foley + ISMN		Treatment grp. 2 Foley alone		Significance
	Mean	SD	Mean	SD	
Intervention to vaginal delivery interval (minutes)	1839.83	257.68	1852.88	217.83	t = −0.216, df = 60, P > 0.05

t = t value, df = degree of freedom.

Table 6. Indications for CS carried out in the study population (n = 48).

Indication	Treatment grp 1 Foley + ISMN	Treatment grp 2 Foley alone	n (%)
Significant meconium stained liquor	9	4	13 (27.1)
Maternal pyrexia	3	0	3 (6.3)
Failed induction	10	9	19 (39.6)
Lack of progression	3	3	6 (12.5)
Pathological CTG	3	4	7 (14.6)

CS = Caesarean Section, CTG = Cardiotocograph.

Table 7. Comparison of adverse effects between two treatment arms-Maternal.

Characteristic	Treatment grp. Foley + ISMN		Foley alone		Significance
	n	%	n	%	
Headache					
Presence	13	22.8	3	5.7	P < 0.05*
Absence	44	77.2	50	94.3	
Nausea/Vomiting					
Presence	12	21.1	0	0	P < 0.05**
Absence	45	78.9	53	100	
Palpitations					
Presence	3	100	0	0	***
Absence	54	50.5	53	49.5	
Maternal pyrexia					
Presence	3	100	0	0	***
Absence	0	0	0	0	

*Chi-square test, **Fisher's exact test, ***Two cells have expected count less than 5.

Table 8. Comparison of adverse effects between two treatment groups, Neonatal.

Adverse Effects	Treatment grp.				Significance
	Foley + ISMN		Foley alone		
	n	%	n	%	
Admission to SCBU					
Admitted	9	15.8	7	13.2	P > 0.05
Not admitted	48	84.2	46	86.8	
5 minutes Apgar score					
More than 8	57	51.8	53	48.2	**
Less than 8	0	0	0	0	

SCBU = Special Care Baby Unit, ** Two cells have expected count less than 5.

reported range was 5 to 8 with a mean of 5.90 (SD = 0.766). The mean visual analogue scores recorded for maternal discomfort was slightly higher (5.98, SD = 0.88) in treatment group 1. However this difference did not reach a significant level. Slightly higher percentage of mothers (n = 38, 71.7%) were satisfied within the treatment group 2 although this wasn't a statistically significant difference (Table 9).

5. Discussion

This was a single-centre randomised comparative study of concurrent insertion of transcervical Foley catheter and ISMN vaginal tablets versus insertion of transcervical Foley catheter alone. The study focused on exploring the efficacy and safety of the combined method (treatment group 1) against the catheter-alone method (treatment group 2) of pre-induction cervical ripening in women awaiting VBAC.

Among the various confounding factors affecting the likelihood of a successful VBAC, having a previous vaginal birth (particularly successful VBAC), maternal obesity (BMI > 30), previous labour dystocia being the indication for the past CS, and admission MBS were considered to have a significant impact [2]. In the study, most of the above parameters were comparable without any significant difference in both treatment groups and minimised the confounding effect of the above factors to the results.

5.1. Efficacy

The time taken to (vaginal) delivery and vaginal delivery achieved in 24 hours can be used as a benchmark to measure the efficacy of a chosen induction method.

This study didn't show significant results on one of our primary outcome measures, the number of women with established labour within 24 hours after the intervention. Only 9 out of 110 subjects (8.18%) had established labour within 24 hours in both groups. Chi square or Fisher's exact test couldn't be performed

Table 9. Maternal feedback on pre-induction cervical ripening method used (n = 110).

Variable	Treatment grp. 1 Foley + ISMN (n = 57)	Treatment grp. 2 Foley alone (n = 53)	Significance
Maternal discomfort			
Mean visual analogue score	5.98 (SD ± 0.87)	5.81 (SD ± 0.622)	P > 0.05*
Maternal satisfaction n (%)			
Satisfied	38 (66.7)	38 (71.7)	P > 0.05**
Not satisfied	19 (33.3)	15 (28.3)	

*t-test, **Chi-square test.

for the values obtained due to lack of valid figures for the 2 × 2 table. Similarly, the proportion of women who underwent CS before 24 hours of the intervention was 3 out of 110 (2.73%). This has led to failure in doing a meaningful statistical analysis for that outcome data.

Mean MBS at 24 hours following the intervention—The findings for this parameter did not support either method as superior, in terms of greater MBS at the time of assessment (P > 0.05). This finding is in contrast to a previous study [9] which found that at term, when ISMN compared with a placebo, showed significant difference in mean MBS in the ISMN group. However, this parameter had been measured at 48 hours following the intervention (In contrast to that study, our study checked the mean MBS after 24 hours of the intervention).

There is a lack of published data on the effect of mean MBS by combining two methods using Foley and ISMN concurrently. One clinical trial has assessed the Concurrent Foley and ISMN versus vaginal misoprostol, however it hasn't assessed the effect on mean MBS following the intervention [12]. Therefore further studies with large sample sizes are needed to explore the synergistic effect of concurrent use of Foley and ISMN on MBS. The mean change of MBS for the period of 24 hours also didn't show a statistically significant difference between two treatment groups in our study (P > 0.05).

Neither treatment group 1 nor treatment group 2 was superior for changes in the MBS measurement, in terms of cervical favorability. Thirty eight out of 57 (66.67%) and 41 out of 53 (77.35%) were favorable for the labour induction at 24 hours in treatment group 1 and 2 respectively. However, this outcome measure wasn't statistically significant, and it is consistent with a recent local trial [9]. If a third group to the study which did not involve any pre-induction cervical ripening method (do nothing), we could have analyzed this outcome more precisely. The concurrent method (treatment group 1) failing to elicit a significant demonstrable cervical ripening efficacy over the treatment group 2 is perhaps surprising.

Twenty eight subjects (49.1%) in treatment group 1 ended up with CS while 20 subjects (37.7%) underwent CS in treatment group 2. Though this difference too is not statistically significant—the increased number of CS deliveries observed in the study may be due to other confounding factors affecting the suc-

cess rate of the VBAC. Overall, 48 (43.6%) participants underwent CS. Among the indications for CS were, failed induction, leading cause (n = 19, 39.6%). Both treatment groups showed comparable proportions of failed inductions. Labour dystocia contributed to 6 (12.5%) CS.

Intervention to delivery interval was similar in both treatment groups resulting in a non-significant difference. In contrast to our finding, a recent study [19] revealed that length of the labour is reduced significantly when using combined induction methods compared to single induction methods. The differences could possibly be explained by the subsequent augmentation done by the oxytocin infusion which we have not used.

Considering all the effectiveness factors (cervical favorability/effect on MBS and mode of delivery), we couldn't elicit any added advantage/effectiveness of our combined (concurrent use of Foley and ISMN) method over the current practice of Foley catheter-alone method at least per the dose, formulations and frequency used and for the patient population in whom it was tested.

5.2. Safety

During the study period no incidents were reported on serious adverse effects (SAE) such as uterine rupture, death in utero, neonatal deaths, neonatal brain injuries etc. The adverse events (AE) experienced were mainly known and expected adverse events. None of the subjects had to be excluded from the study due to intolerable side effects. Therefore, our study further reinforced the available evidence on the clinical safety of use of two treatment groups in pre induction cervical ripening in VBAC.

Similarly, a comparable opinion on the acceptability of the methods used, mothers of both treatment groups showed acceptance, without significant preference towards one method. However, women who achieved vaginal delivery this time (successful VBAC) had a very statistically significant satisfaction towards the method they had undertaken for the pre-induction cervical ripening (Fisher's exact test, $P < 0.001$). Therefore, birth outcomes may have influenced patient view on the satisfaction since the satisfaction survey was conducted during the postpartum period.

The safety data analysis gives an inference of acceptable safety in terms of adverse effects on maternal or fetal wellbeing, in both methods.

5.3. Strengths and Limitations

The strengths of the study were its prospective design, randomisation and being conducted in a limited research domain.

Although the study was powered to detect differences of the mean MBS after 24 hours of the intervention, the study might have lacked the power to detect potentially important differences for other outcomes (spontaneous labour within 24 hours, mode of delivery) between the two groups. A larger sample would have given the opportunity to study the adverse events in detail and provide the op-

portunity for a subgroup analysis of the proportion of women who established labour within 24 hours after the interventions.

6. Conclusions

The findings of this study refute our alternative hypothesis, which assumed that there was significant effectiveness on cervical ripening by vaginal administration of ISMN 60 mg sustained release tablets concurrently with transcervical Foley catheter compared to transcervical Foley catheter alone in pre-induction cervical ripening in pregnant women who are awaiting VBAC.

Concurrent use of vaginal ISMN 60 mg (SR) with transcervical Foley catheter method failed to show any higher effectiveness compared to transcervical Foley catheter alone method, in terms of making the cervix more favorable and reducing the intervention to delivery time. However both methods were comparable in its efficacy (outcomes) at the expense of more adverse effects in the concurrent use of vaginal ISMN with Foley catheter method.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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