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SYNERGISTIC EFFECT OF ISOSORBIDE MONO NITRATE AND MISOPROSTOL FOR PRE-OPERATIVE CERVICAL RIPENING IN FIRST TRIMESTER MISSED MISSCARIAGES: A RANDOMISED CONTROLLED TRIAL.

Amatunnafe Naseha Department of Obstetrics & Gynaecology, ESIC Medical College, Sanathnagar, Hyderabad.

Mohammed Ismail Khan* Department of Obstetrics & Gynaecology, ESIC Medical College, Sanathnagar, Hyderabad. *Corresponding Author

Asna Yasmeen Department of Pharmacology, Mesco College of Pharmacy, Mustaidpura, Hyderabad.

ABSTRACT

Background: Cervical ripening is indispensible for an uneventful surgical evacuation of uterine cavity. Misoprostol is a well established cervical ripening agent with documented adverse effects. Isosorbide mononitrate (ISMN), a nitric oxide donor has emerged as a potential cervical ripening agent with lesser adverse effects.

Methods: A prospective randomized controlled trial was conducted on 120 patients with 60 patients in group – A and 60 in group – B. 400µg misoprostol alone and 400 µg misoprostol + 40mg ISMN were placed per vaginally at zero hour in group A and B respectively. The dose was repeated every three hours after a cervical assessment up to a maximum of 4 doses. Cervical ripening was evaluated using Hegar's dilators. The number of dilator which could be easily negotiated and time required to easily negotiate a No.10 or larger dilator was assessed. Intraoperative blood loss was assessed. Adverse effects were noted using a symptom questionnaire.

Results: ISMN appears to significantly reduce the time required for cervical ripening in group B (6.29±1.8 hrs) compared to 8.63±1.62 hrs in group A. Significantly higher ripening was seen after 1st and 2nd dose in patients who were administered combination. 5% and 16% additional patients showed attainment of requisite cervical priming in group B compared to group A after 1st and 2nd dose respectively. Abdominal pain, diarrhea, fever and vomiting appeared to be less associated with the use of combination therapy. Dizziness and headaches appeared to be significantly more with combination therapy. 60% patients reported adverse effects with combination therapy compared to 55% with misoprostol, when used alone.

Conclusion: Combination of misoprostol and ISMN appear to be synergistic in cervical priming with improvement in the quality of cervical ripening, time required for ripening, procedural time, number of dosages required, less variance and more uniformity with lesser adverse effects and a better ptient acceptance profile.

KEYWORDS : Misoprostol, Isosorbide mono nitrate, cervical ripening, first trimester, surgical evacuation

INTRODUCTION:

Missed miscarriage represents a type of pregnancy loss that mandates surgical evacuation (SE) of the retained products of conception (RPOC) from the uterine cavity. SE-RPOC requires specific instruments to be passed into the uterine cavity through the cervix in order to evacuate the cavity. For this it is required that the cervix of the uterus be favourable to negotiate the instrument/s through it. These changes are collectively referred to as ripening, and essentially include softening of the cervix and opening of the cervical os. Cervical ripening is hence considered as an essential pre-requisite for successful termination of pregnancy and SE-RPOC [1]. Several complications associated with SE-RPOC like uterine perforation and cervical laceration can be minimized by ensuring cervical ripening [2]. This will ensure that the procedure is completed with ease with a better grip on the instrument/s used and controlled manipulation of the instrument within the uterine cavity. As SE-RPOC largely remains a blind procedure, it depends on the obstetrician's skill, perception and appreciation of various tissue consistencies and uterine boundaries. Ensuring proper cervical ripening will ensure easy negotiation which will facilitate the process.

Prostaglandins are well accepted pharmacological agents which cause cervical ripening. These prostaglandin analogues cause both cervical ripening and myometrial contractions. The use of hygroscopic mechanical dilators like laminaria which was more common in the past has decreased over years, as prostaglandin analogues exhibited more effective ripening of the uterine cervix [3]. Misoprostol, a prostaglandin E1 analogue is licensed in the UK for cervical ripening in missed miscarriages [4]. The NICE guidelines permit per vaginal and oral route of administration of misoprostol as per the patients comfort and wish. Though misoprostol appears as an ideal cervical ripening agent, it is not devoid of adverse effects. These include, but are not limited to nausea, vomiting, diarrhea, abdominal cramps, vaginal bleed, chills and fever [5].

Nitric oxide (NO) synthetase has been recognized in cervix and NO has been demonstrated as a final mediator of cervical ripening [6]. Several studies have assessed the role of NO in cervical dilatation in animals and humans [7, 8] and have proved it's cervical ripening potential. Isosorbide mononitrate which is a NO donor is an effective and safe agent for cervical ripening [9, 10]. Vaginal administration of NO donors is not associated with occurrence of any serious adverse effects which may warrant drug withdrawal [11]. ISMN predominantly produces dizziness, headache and palpitation as its side effects among others. These undesirable symptoms appear to be extended pharmacological side effects rather than adverse effects of the drug.

We have initially demonstrated that misoprostol causes faster cervical ripening with more adverse effects compared to ISMN which when used as a sole agent causes slower ripening of cervix but with higher patient acceptance [12]. An ideal cervical ripening agent should produce sufficient cervical ripening within an acceptable time period with minimal adverse effects. Since both the drugs fulfill these criteria partially, we hypothesized that using them in combination will afford the promptness and efficacy of misoprostol with the acceptance of ISMN. This will also create a synergism wherein the total dosage requirement of both the drugs will reduce hence a combination would offer better therapeutic eventualities.

The study was conducted to evaluate the synergism of ISMN when used along with misoprostol in first trimester missed miscarriages as a premedication for surgical evacuation. The primary outcomes included the time required to achieve the desired cervical ripening in first trimester SE-RPOC for missed abortions. The rate of cervical ripening was measured in term of the number of Hegar's dilator (HD) which could be easily negotiated through the cervix at specific

time intervals. Intra operative blood loss and time required to evacuate the uterus was also assessed. Associated adverse effects were observed and compared.

PATIENTS AND METHODS

The study was conducted at the Department of Obstetrics and Gynaecology, ESIC Medical College Hospital, Sanathnagar, Hyderabad, which is a tertiary care teaching hospital with referrals from more than 35 ESIC hospitals and dispensaries. The study was designed as a double blinded, randomized controlled trial and was conducted over a period of one year from April 2016 to March 2017. The study was taken up after approval from the Institutional Ethics Committee and 120 patients were recruited after obtaining written informed consent.

Patients with confirmed ultrasound diagnosis of missed miscarriage (intrauterine gestation sac with no signs of viability) in the first trimester of pregnancy were recruited. These patients were admitted and worked up for surgical evacuation (SE) of retained products of conception (RPOC). Clinical history was obtained and gestational age was calculated by menstrual dates. SE-RPOC was done by removal of RPOC by ovum forceps followed by a gentle curettage using the blunt end of a uterine curette. Both these instruments which had to be negotiated through the cervix were standardised by using instruments provided by the same manufacturer. The width of the ovum forceps at its tip in its largest dimension measured 8.343 mm and the largest dimension of the blunt curette measured 7.783 mm. These measurements were made using standard vernier calipers.

The recruited patients were randomized into Group A and Group B, by using a table of random numbers which were then placed in serially arranged sealed envelopes. A transvaginal scan with a confirmed diagnosis of a non viable gestation with menstrual dates suggestive of gestational age less than 12 weeks were admitted and consecutively worked up. After appropriate investigations and reservation of one unit of cross matched packed cells, the patients were taken up for cervical ripening. One investigator placed the specific medications per vaginally and the other investigator assessed parameters for primary outcomes who was unaware of the drug used.

Two tablets of misoprostol 200 µg (T. Tector 200mcg ©Zee Laboratories Limited) were placed per vaginally in the posterior vaginal fornix at an interval of 3 hours up to a maximum of 4 doses in patients randomized to Group – A and two tablets of Misoprostol 200 µg and two tablets of Isosorbide mononitrate 20 mg (T.Ismo 20mg © Nicholas Piramal India Ltd.) were placed vaginally in the posterior fornix at an interval of 3 hours up to a maximum of 4 doses in patients randomized to Group – B. Both groups were given the tablets after moistening with 4 – 5 drops of saline before placing them per vaginally.

The time of placing the first dose was considered as zero hour and consequently the blinded investigator assessed cervical changes every 3 hours up to a maximum of 12 hours. Standard Hegar's dilators (HD), procured from the same manufacturer were used to assess cervical dilatation. The HD which could be negotiated easily without any resistance was noted at every assessment. The time required to easily negotiate HD-10 or greater through the cervix was also recorded. Those patients in whom the cervical priming was sufficient to negotiate HD-10 or greater were taken up for SE-RPOC. The size of HD-10 used in the study, measured by vernier was found to be 8.411 mm. No further assessments were performed after cervical dilatation allowed a HD-10 to easily pass through, the number was standardized to HD-10 as its diameter corresponds closely to the diameter of curette and ovum forceps which need to be negotiated through the cervix for SE -RPOC.

The SE-RPOC was performed by both the investigators with the intra procedural outcomes measured by a nurse who was blinded. Time taken to complete the procedure in minutes was measured from the start of SE-RPOC to signs of complete evacuation. Blood and RPOC were collected in a kidney tray and the RPOC were filtered through multiple layers of gauze and the amount of blood was measured in milliliters. Adverse effects were noted when complained by the patient and specifically all the patients were given a questionnaire about the occurrence of adverse effects and these were noted by the blinded investigator or the blinded nurse.

All mothers with rhesus negative blood type were administered 300 µg of Anti Rh Immunoglobulin (Inj. Plasma Rh_0 300 µg in 2 ml vial ©PlasmaGen Biosciences Pvt. Ltd). Appropriate antibiotic cover was given in accordance with hospital protocols and patients were discharged in stable condition after ensuring complete evacuation by ultrasound.

Data was collected and statistically analysed using Chi Square Test for qualitative data and unpaired t test for quantitative data. Chi square test was performed using online software at www.socscistatistics.com and unpaired t test was performed by using online software at www.graphpad.com.

Inclusion Criteria:

1. Age >18 years and <40 years
2. First Trimester gestation
3. Confirmed non-viable pregnancy (TVS)
4. Confirmed intra uterine gestation
5. Haemodynamic stability at recruitment
6. Normal coagulation profile
7. Normal blood counts, urine analysis, liver and renal functions

Exclusion Criteria:

1. Haemorrhagic disorders
2. Known allergy to the drugs
3. Cardiovascular and / or respiratory morbidity
4. Blood pressure less than 90 systolic and / or 60 diastolic at presentation
5. Patients on Aspirin and / or Heparin
6. Contraindications to the use of ISM – severe anaemia, head injury, severe anaemia, malabsorption syndromes and methaemoglobinaemia
7. Contraindications to the use of Misoprostol – seizure disorders, sickle cell anaemia and glaucoma

Research involving Human Participants

1. All procedures performed on the patient were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1975 Helsinki declaration and its latest amendment in 2000 and other comparable ethical standards.
2. All treatment protocols followed are in accordance with the latest accepted Evidence Based Medicine Norms of the RCOG.
3. Foetal sex was neither detected nor informed in accordance with the PNDT Act 1994.
4. All surgical evacuations were governed by the MTP Act 1971 and its amendments.

RESULTS:

The baseline characteristics of study and control group are compared in Table-1. None of the differences, demographic, parity and past obstetric history are statistically significant, hence the groups are comparable.

Table 1 - Demographic - Obstetric Characteristic

S.No.	Characteristic	Group A Misoprostol 400 µg	Group B Misoprostol 400 µg + ISMN 40mg	P
1.	Age (M ± SD)	24.4±2.37	24.9±2.43	0.25
2.	Gravidity (M ± SD)	2.13±0.94	2.09±1.06	0.82
3.	Gestational Age (weeks) (M ± SD)	6.2±1.29	6.8±2.03	0.42

4.	Parity			
	Primi	18(30)	11(18.3)	0.3
	Para 1 – Para 3	33(55)	37(61.67)	
	Grand Multi	9(15)	12(20)	
5.	Previous abortions n (%)	13 (21.7)	16 (26.67)	0.52

Third hourly cervical assessment findings are tabulated in Table-2, At first assessment at 3rd hour after placing the drug vaginally group A allowed a mean dilator of 3.4±0.19 to negotiate easily compared to group B which allowed a mean dilator number 3.9±0.53 to pass through it without resistance and this showed a P value of <0.001. Similarly at second assessment, group B allowed a larger HD to negotiate whereas group A allowed a smaller HD to pass through it with mean HD size of 6.1±0.83 and 5.2±0.76 respectively (P <0.001). At 9th and 12th hour assessment too, group B allowed a larger dilator to negotiate compared to group A, 9.2±0.97 vs. 9.2±0.97 (P <0.03) and 13.1±2.03 vs. 11.9±1.89 (0.25) respectively.

ΔAB(N%) represents the difference (Δ) in the number (N) of patients in group A and B (NA, NB) expressed as percentage (%) who have shown the desired cervical changes after each assessment. 5 % decrease is seen in NB at second assessment implicating that 5% additional patients in group B showed favorable cervical changes compared to group A after the first dose itself. Requisite response was seen in 13.4% additional patients in group B compared to group A after the second dose and an additional 1.7% showed requisite response after third dose in group B compared to group A.

Average time taken for negotiating a HD – 10, was higher in group A with a mean of 8.63 ± 1.62 hrs whereas patients in group B took lesser time with a mean of 6.29 ± 1.8 hrs. This was statistically highly significant with a P value of <0.001.

Table 2: Assessment of cervical ripening

S.No.	Outcome	Group A	Group B	P	ΔAB (N%)
A.	HD (number) passed with ease				
1.	3rd hour (M ± SD) (NA = 60, NB = 60)	3.4±0.19	3.9±0.53	< 0.001	Nil
2.	6th hour (M ± SD) (NA = 42, NB = 39)	5.2±0.76	6.1±0.83	< 0.001	5% (NB<NA)
3.	9th hour (M ± SD) (NA = 24, NB = 16)	8.2±1.56	9.2±0.97	0.03	13.4% (NB<NA)
4.	12th hour (M ± SD) (NA = 8, NB = 7)	11.9±1.89	13.1±2.03	0.25	1.7% (NB<NA)
B.	Time taken to easily negotiate ≥ No.10 HD				
1.	Time taken in hours (M ± SD)	8.63±1.62	6.29±1.8	< 0.001	-

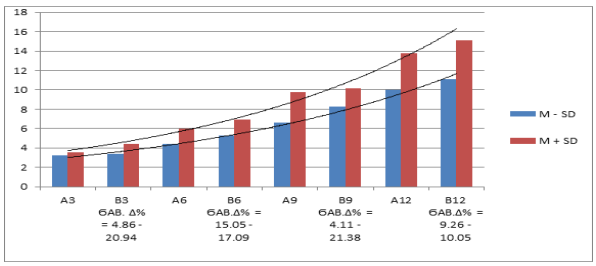
Table 3 tries to deduce the consistency of cervical changes when the cervix was differentially treated in group A and group B. Variance (б) represents the sum total of differences of observations obtained from the mean value. A greater variance would implicate greater scattering of values from mean. бx.Δ% represents the percentage (%) difference (Δ) in variance (б) between M-SD and M+SD at a particular assessment in a particular group (бx.Δ% as бA.Δ% or бB.Δ%) whereas Σ бx.Δ% represents the total differences obtained at all assessments in a particular group. Variance was seen to increase rapidly with the order of assessment in group A compared to group B, which showed rather small changes in variance with the order of assessment. бA.Δ% was also seen to vary widely compared to бB.Δ%. The total percentage variance was also more in group A compared to group B (110.2% vs. 106.45%).

Figure 1 also aims to deduce consistency in the performance of both interventions by comparing the percentage difference (Δ%) between the lower end of means of variance (-SD) to the upper end of means of variance (+SD) with the arithmetic mean (M) at each assessment in both groups simultaneously. The same is represented by exponential curves on the graph. The range of percentage variation at 1st assessment varied from 4.86% to 20.94%, at consecutive assessments at 6th, 9th and 12th hour the differences were found to vary as 15.05% to 17.09%, 4.11% to 21.38% and 9.26% to 10.05% respectively.

Table 3: Consistency in cervical ripening

S.No.	Group A		б	бA.Δ %	Group B		б	бB.Δ %
	M – SD	M + SD			M – SD	M + SD		
1st Assessment	3.21	3.59	0.03	11.17	3.37	4.43	0.28	27.17
2nd Assessment	4.44	5.96	0.58	29.23	5.27	6.93	0.68	27.21
3rd Assessment	6.64	9.76	2.43	38.04	8.23	10.17	0.94	21.08
4th Assessment	10.01	13.79	3.57	31.76	11.07	15.13	4.12	30.99
Total percentage variance	110.2				106.45			

Figure 1: Consistency in cervical ripening



A higher proportion of patients showed better cervical priming at every assessment in group B compared to group A. At 1st assessment 35% in group B showed desired changes whereas 30% showed similar changes in group A. 58.97% had completed cervical priming after second dose in group B compared to 42.85% in group A. After fourth dose the differential behavior in group B vs. group A was 85.71% vs. 75%. At third assessment alone a higher proportion was noted to have better cervical priming in group A compared to group B (66.67% vs. 56.25%). None of the differences were statistically significant.

Table 4: Proportion of patients with desirable cervical ripening at every assessment

S.No.	Dosing pattern	Chracteristic	NA (%)	NB (%)	P
1.	1st dose n (%) (NA = 60, NB = 60)	> 10 HD	30	35	0.55
		<10 HD	70	65	
2.	2nd dose n (%) (NA = 42, NB = 39)	>10 HD	42.85	58.97	0.14
		<10 HD	57.14	41.02	
3.	3rd dose n (%) (NA = 24, NB = 16)	>10 HD	66.67	56.25	0.5
		<10 HD	33.33	43.75	
4.	4th dose n (%) (NA = 8, NB = 7)	>10 HD	75	85.71	0.6
		<10 HD	25	14.28	

Intra-operative characteristics were assessed with a higher blood loss being noted in group B compared to blood loss in group A, 72.3 ± 33.8ml vs. 63.4 ± 27.68ml respectively. This difference did not appear statistically significant with a P value of 0.10. Time taken was lesser in group B with a mean time of 6.13±2.38 minutes compared to 7.28±2.15 minutes in group A. This was highly statistically significant with a P value of 0.006. This is tabulated in table 5

Table 5: Intra operative Characteristics

S.No	Characteristic	Group A (M ± SD)	Group B (M ± SD)	P
1.	Blood Loss	63.4±27.68	72.3±33.8	0.10
2.	Time taken	7.28±2.15	6.13±2.38	0.006

Adverse effects like abdominal pain, diarrhoea, fever and vomiting were lesser in group B but of these, the differences were statistically significant for fever with a P value of 0.04. Dizziness, headache, nausea and palpitations were noted to occur more in group B compared to group A. Dizziness and headache were statistically more in group B with a P value of 0.0001 and 0.01 respectively. Though palpitations and nausea occurred more in group B this was not statistically significant with a P value of 0.56 and 0.79 respectively.

Total symptom free patients in group B were 40% compared to 45% symptom free patients in group A, which shows a better patient acceptance with misoprostol alone compared to combination therapy, but this was statistically insignificant. The same is highlighted in Table 6.

Table 6: Adverse Effects

S.No	Characteristic	Group A	Group B	P
A.	Specific Adverse effects			
1.	Abdominal Pain	24(40)	19(31.67)	0.34
2.	Diarrhoea	12(20)	6(10)	0.12
3.	Dizziness	4(6.67)	21(35)	0.0001
4.	Fever	18(30)	9(15)	0.04
5.	Headache	6(10)	17(28.3)	0.01
6.	Nausea	8(13.33)	9(15)	0.79
7.	Palpitations	6(10)	8(13.33)	0.56
8.	Vomitings	4(6.67)	1(1.67)	0.16
B.	Patient Acceptance			
1.	Adverse Effects	33(55)	36(60)	0.57
2.	No Adverse Effects	27(45)	24(40)	

Discussion:

Missed miscarriage is a rather common obstetric issue which demands immediate attention given the undesirable consequences it potentiates in terms of coagulative disorders. This warrants evacuation of POC to ensure that such morbidities are avoided. Misoprostol or Misoprostol acid or 15-deoxy-16-hydroxy-16-methylprostaglandin E1 is a PG E1 analogue that has established, evidence based role in cervical ripening in first trimester terminations and SE-RPOC. Randomised controlled trials as early as 1997, proved NO donors like ISMN and glyceryl trinitrate to cause effective cervical ripening compared to placebos, when placed vaginally [13].

NO is a naturally occurring substance which mediates several physiological processes including inflammation, immune response, smooth muscle relaxation, vasculae haemostasis and neurotransmission [14]. NO donors like ISMN and GTN increase the concentration of NO locally and systemically when applied locally at mucosal surfaces. NO donors have found a place in obstetrics for a variety of therapeutic applications like foetal growth restriction [15], manual removal of placenta [16], and surgical termination of pregnancy or surgical evacuation [13] and for acute uterine relaxation for foetal extraction [17]. Denison et al have reported that NO leads to enhancement of PG production in cervical tissue when tested in vitro [18]. NO is also a smooth muscle relaxant which explains it's cervical dilatation component during ripening by relaxation.

A randomized controlled trial conducted by us to compare ISMN and misoprostol as therapeutic agents for pre operative cervical ripening revealed ISMN to produce slow cervical priming [12]. We concluded from this study that adverse effects of misoprostol appear to make the process more unpleasant and the adverse effects of ISMN appear to be extended pharmacological effects that can be avoided by proper intravenous and / or oral hydration [12]. As both the agents are a safe choice for cervical priming with differentially appreciable properties, it was thought to use a combination of both drugs to increase speed of priming by misoprotol and lower adverse effects exhibited by ISMN.

Mean HD negotiable through the os was higher in patients administered combination therapy compared to single therapy with misoprostol. Differences appeared statistically significant (<0.001, <0.001 and 0.03) at 3rd, 6th and 9th hour after intervention. This brings us to a conclusion that ISMN when added to misoprostol hastens cervical priming. More patients also exhibited the desired cervical dilatation (HD-10) in group B compared to group A at 1st, 2nd and 3rd assessment. Hence using ISMN as an add on drug reduces the need for additional doses of misoprostol and ISMN due to faster therapeutic end points.

More number of patients showed the desired cervical changes when primed with a combination therapy compared to a lesser number who achieved similar targets when primed with misoprostol alone. 35% showed cervical priming > HD-10 after the first dose in group B whereas 30% showed similar end points when treated with misoprostol. Similarly at 6th hour, after administration of the second dose, 58.97% achieved end points in combined therapy group whereas only 42.85% achieved end points in group A. This again represents towards a higher tendency to start and achieve good cervical dilatation and priming by the combination, compared to a single agent priming. ISMN not just relaxes smooth muscles but also induces the production of prostaglandins in cervical tissue hence potentiating the action of prostaglandin analogues [18]. Salvemini et al and and Sautebin et al have also demonstrated the up-regulation of cyclooxygenase activity upon exposure to NO [19, 20].

Intra-procedural characteristics varied considerably in both groups. Blood loss was more in patients primed with combination but was lesser in those primed with misoprostol alone. But this did not appear statistically significant. This can be ascribed to the smooth muscle relaxation properties of ISMN which negate the uterotonic properties of misoprostol, which are beneficial in reducing blood loss. The time taken to complete the procedure was considerably less in the group primed with combination therapy with stark differences in those who were primed with misoprostol alone, and this appeared statistically significant. This could be due to a reduced need for intra-procedural dilatation as good dilatation was obtained before stating the procedure itself. This can be attributed to the smooth muscle relaxation properties of ISMN which synergise with the ripening properties of misoprostol to cause a better dilatation and relaxation. A study by Marie et al also reported slightly excess intra-procedural blood loss in the combined drug group compared to misoprostol alone, but was insignificant [21].

A study conducted by Shanti et al also compared two similar groups for cervical priming for second trimester miscarriages and reported a shorter induction abortion time with the use of ISMN and mean dosage of misoprostol used was also less when used with ISMN. They also reported a higher chance of complete abortion and lesser chance of retained POC with the use of ISMN [22]. Our results also seem to be in close agreement to the study done by Mousiolis et al who demonstrated a total net clinical benefit when ISMN was used along with misoprostol as a ripening agent [23].

Some adverse effects were reported to decrease with the use of ISMN along with misoprostol. Abdominal pain and diarrhea were less in the combined regime group which can be explained by the smooth muscle relaxant properties of ISMN when used with misoprostol. Fever also appeared to be less in the group B compared to group A. Headache and Dizziness have show an additive effect when ISMN was used. This appeared statistically significant. This again is explainable by smooth muscle relaxation in capacitance vessels which will decrease venous return to heart and hence decreases systemic blood pressures and reduces cerebral blood flow. Altogether the total number of adverse effects were slightly less in group A compared to group B, but this was statistically insignificant. Shanti et al also reported a decrese in the occurrence of adverse effects like fever, diarrhea and abdominal pain with the use of ISMN [22]. Our findings also appear to be in agreement with the findings of Marie et al who reported a statistically significant

reduction in abdominal pain with the use of ISMN with misoprostol [21]. Headache and dizziness were also reported to be significantly higher in the combination group [21].

CONCLUSIONS:

The findings of the study are suggestive of the clinical superiority of combining misoprostol with ISMN for cervical ripening in first trimester missed miscarriages. ISMN acts synergistically with misoprostol and the combination affords greater efficacy in terms of the rapidity of the priming, lower amounts of drug required, lower adverse effects and also affords a greater comfort to the surgeon by reducing the need for intra-procedural dilatation and the ease of manipulating the instrument/s inside the uterine cavity for evacuation. Since the adverse effects of synergistic use of ISMN are either not significant or can be avoided by proper hydration it appears to be a safe option to enhance the efficacy of misoprostol.

DECLARATION:

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Ethical approval: The study was approved by the Institutional Ethics Committee of ESIC Medical College.

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