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Comparative Efficacy and Acceptability Profile of Prostaglandin E1, Nitric Oxide Donors and their combination in Pre-Operative Cervical Priming for Surgical Evacuation of Missed Miscarriages: A Randomised Controlled Trial

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Abstract:
Background: *Cervical ripening is an essential pre requisite for surgical evacuation in missed miscarriages. This requires an agent that can ripen the cervix effectively with minimal adverse effects.*
Patients & Methods: *In this three group randomised controlled trial we have compared group M (misoprostol 400µg), group – I (40mg Isosorbide mono nitrate – ISMN) and group – C (combination of misoprostol 400µg and 40mg ISMN). All patients were administered the drug at zero hour and were assessed for desired dilatation which was taken as easy negotiation of a Hegar dilator – 10 (HD-10). They were assessed every 3 hours and those with ripened cervix were taken for surgical evacuation. Those who didn't meet the end point were again administered the drug/s. Intra-operative blood loss and procedural time were noted. Adverse effects were recorded.*
Results: *Statistically significant difference was noted at each assessment with maximum dilatation in group – C and least in group – I. No of doses were also least in group – C and maximum in group – I. Adverse effects were least in ISMN, followed by combination and were highest in misoprostol.*
Conclusion: *Combination appears to synergistically improve therapeutic benefits and reduce the adverse events.*
Keywords: *Misoprostol, Isosorbide mono nitrate, first trimester, cervical priming, cervix ripening, missed miscarriage.*

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I. 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 that specific instruments are 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 [1]. It is a well established fact that cervical ripening prior to SE has been shown to reduce the associated operative morbidity [2]. Several complications associated with SE-RPOC like uterine perforation and cervical laceration can be minimized by ensuring cervical ripening [3]. Priming ensures 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 [4].

Misoprostol or Misoprostol or Misoprostol acid or 15-deoxy-16-hydroxy-16-methylprostaglandin E1 is a Prostaglandin (PG) E1 analogue that has established, evidence based role in cervical ripening in first trimester terminations and SE-RPOC [5]. PGs act on connective tissue stroma and leads to disintegration and dissolution of collagen [6]. Early animal studies in 1994 showed nitric oxide (NO) as a fundamental mediator of cervical ripening [7]. Later studies in 1997 demonstrated local application of NO donors induced cervical ripening with associated with ultrastructural and functional changes in lab animals [8]. Later in early 21st century the efficacy of NO donors in causing morphological changes in human cervix were documented in non-pregnant women [9]. Soon after, its efficiency in cervical ripening for surgical evacuations was proved [10]. studies as early as 1997

reported the safety profile of NO when used as a pre-medication in SE-RPOC [11]. We have initially reported NO donors to be potential cervical ripening agents in our population [4].

Though misoprostol appears as an ideal cervical ripening agent, it is not devoid of adverse effects [4]. These include, but are not limited to nausea, vomiting, diarrhea, abdominal cramps, vaginal bleed, chills and fever [12]. NO donors on the other hand don't produce any serious adverse effects which may warrant drug withdrawal [12, 4]. ISMN predominantly produces dizziness, headache and palpitation as its side effects among others and these undesirable symptoms appear to be extended pharmacological side effects rather than adverse effects of the drug [1]. Based on our initial results, we hypothesized that a combination of PG E1 and ISMN would potentiate their ripening effects and would reduce the total dosage required for achieving the desired ripening. To this end we planned a three group randomised controlled trial to compare the variability between these groups which can be differentially and preferentially be applied for maximizing therapeutic outcomes in patient interest and surgeon convenience. This study was taken up with a primary intention of testing the hypothesis that a combination potentiates therapeutic outcomes and decreases adverse event occurrence.

II. 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, randomised controlled trial and was conducted over a period of one and a half year from April 2016 to September 2017. The study was taken up after approval from the Institutional Ethics Committee and 180 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.

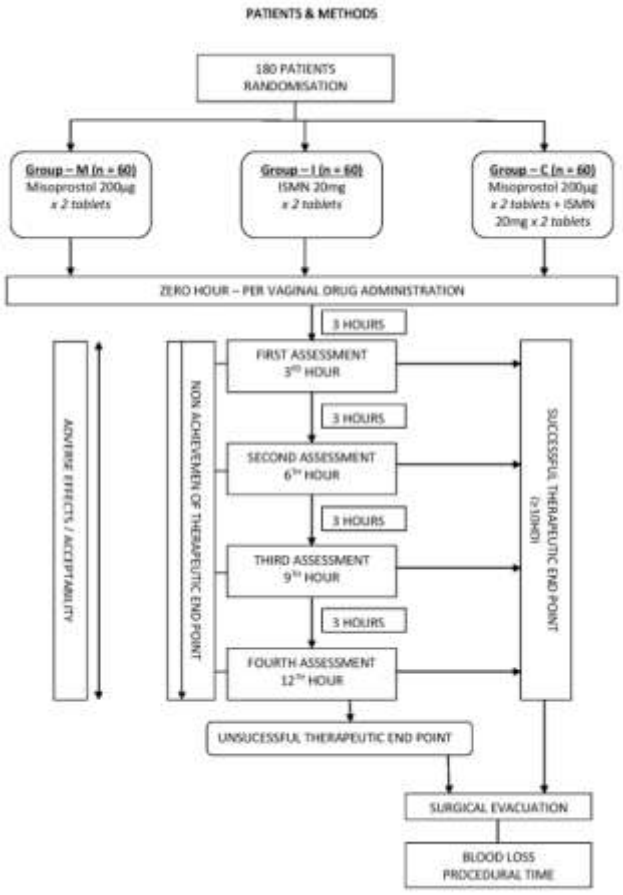
The recruited patients were randomised into Group M, Group I and Group C by using a table of random numbers which were then placed in serially arranged sealed envelopes. A transvaginal scan with a confirmed diagnosis of a non viable gestation, with menstrual dates suggestive of gestational age less than 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. The tablets were always placed vaginally in the posterior fornix after moistening them with 4 – 5 drops of saline. Tablets were placed at an interval of 3 hours up to a maximum of 4 doses. In group M (Misoprostol), 2 tablets of misoprostol 200 µg (T. Tector 200mcg ©Zee Laboratories Limited) were placed vaginally and in group I (ISMN), two tablets of isosorbide mononitrate 20 mg (T.Ismo 20mg © Nicholas Piramal India Ltd.) were placed vaginally. In group – C (combination), 2 tablets of misoprostol 200 µg (T. Tector 200mcg ©Zee Laboratories Limited)and two tablets of isosorbide mononitrate 20 mg (T.Ismo 20mg © Nicholas Piramal India Ltd.) were placed vaginally. Doses were consistently maintained at each administration.

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 HD lesser than the one at which slightest resistance was felt was taken for measurements. A small length of the HD sufficient to just pass through the internal os was noted. 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 (3 standard gauze pieces) 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.

Fig 1: Research Methodology



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 ANOVA for comparing the mean of three groups followed by a post hoc comparison test. Chi Square test was used for proportional data for assessing statistical significance in inter- group variation. Chi square test and ANOVA were performed using online software at www.socscistatistics.com. P_a represents the P value obtained by ANOVA and P_{phc} represents the P value for post hoc comparison test. P χ^2 represents the P value calculated by a chi-square test.

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.

III. Results

Table 1 enlists the demographic and obstetric characteristics in different groups. None of the differences are significant hence the groups are comparable.

Table 1 - Demographic Characteristics

S.No.	Characteristic	Group - M	Group - I	Group - C	P_{phc} (M.I)	P_{phc} (M.C)	P_{phc} (I.C)	P_a
1.	Age (M ± SD)	24.4±2.37	25.1±1.97	24.9±2.43	0.21	0.44	0.87	0.22
2.	Gravidity (M ± SD)	2.13±0.94	2.47±1.17	2.09±1.06	0.18	0.97	0.12	0.1
3.	Gestational Age (weeks) (M ± SD)	6.2±1.29	7.1±1.58	6.8±2.03	0.18	0.97	0.12	0.1
	Obstetric Characteristics				P χ^2 (M.I)	P χ^2 (M.C)	P χ^2 (I.C)	-
4.	Parity n (%)							
	Primi	18(30)	13(21.67)	11(18.3)	0.42	0.3	0.45	-
	Para 1 – Para 3	33(55)	40(66.67)	37(61.67)				
	Grand Multi	9(15)	7(11.67)	12(20)				
5.	Previous abortions n(%)	13 (21.7)	21 (35)	16 (26.67)	0.1	0.52	0.32	-

Cervical findings at every 3rd hourly assessment have been compared. Statistically significant changes have been observed at all assessments. Post hoc comparison tests have also shown significant differences between all groups except at 3rd and 4th assessment between misoprostol and combination therapy group. Highest means are observed with combination therapy group followed by misoprostol and least responses in patients treated with ISMN alone. The same is shown in table 2

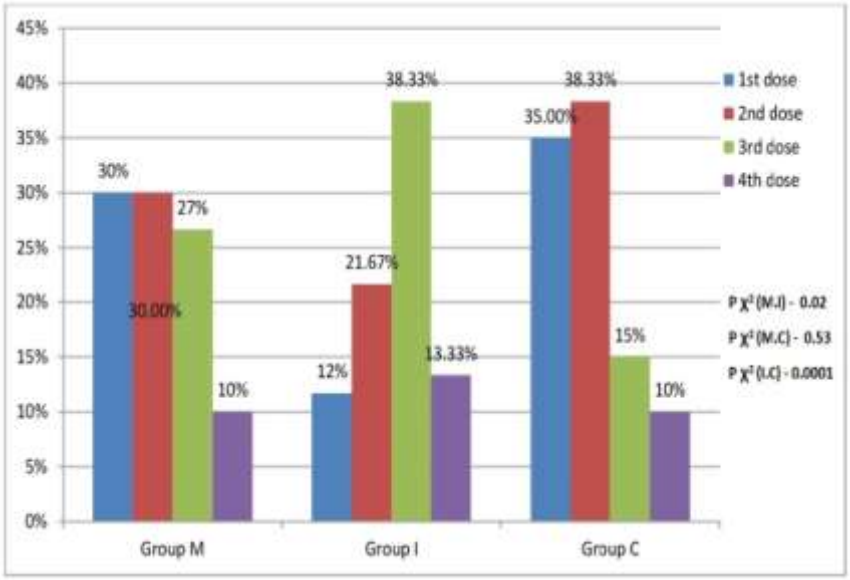
Table 2: Extent of cervical ripening at consecutive assessments

S.No.	Characteristic	Group – M	Group – I	Group - C	P_{phc} (M.I)	P_{phc} (M.C)	P_{phc} (I.C)	P_a
A.	HD (number) passed with ease							
1.	3rd hour (M ± SD) (N_M = 60, N_I = 60, N_C = 60)	3.4±0.19	2.6±0.29	3.9±0.53	< 0.0001	< 0.0001	< 0.0001	<0.0001
2.	6th hour (M ± SD) (N_M = 42, N_I = 53, N_C = 39)	5.2±0.76	4.3±0.65	6.1±0.83	< 0.0001	< 0.0001	< 0.0001	<0.0001
3.	9th hour (M ± SD) (N_M = 24, N_I = 40, N_C = 16)	8.2±1.56	7.3±1.48	9.2±0.97	0.04	**0.08**	<0.0001	<0.0001
4.	12th hour (M ± SD) (N_M = 8, N_I = 17, N_C = 7)	11.9±1.89	9.9±1.48	13.1±2.03	0.02	**0.37**	0.0007	0.0005
B.	Time taken to easily negotiate No.10 HD							
1.	Time taken in hours (M ± SD)	8.63±1.62	10.52±2.25	6.29±1.8	< 0.0001	< 0.0001	< 0.0001	<0.0001

Figure 2 shows the consecutive proportion of patients who showed the desired cervical changes after consecutive dosing. A higher proportion of patients showed desired cervical changes after first and second dose in misoprostol and combination group. Patients in the combined group showed faster cervical changes compared

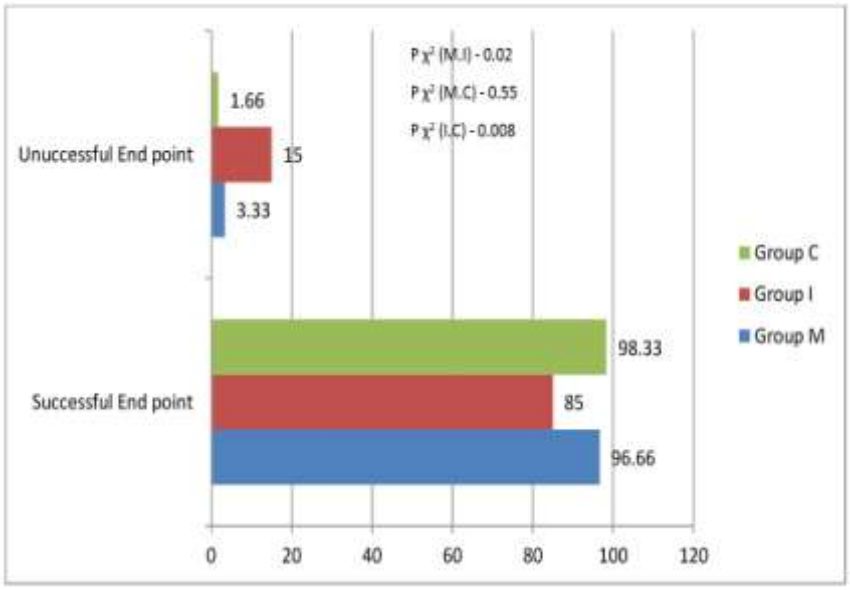
to patients in misoprostol group but this was not statistically significant. Patients treated with ISMN alone showed a much slower ripening which was less than group M and much lesser in group C.

Fig 2: Consecutive Proportional Ripening



After 4 doses also some patients in each group did not achieve the desired therapeutic end points. The PG E1 group showed treatment failure in 3.33%. 15% in ISMN group did not respond to treatment, whereas only 1.66% didn't have cervical ripening in the combined therapy group. Differences between misoprostol and ISMN groups and ISMN and combination groups appeared statistically significant. Difference between 3.33% and 1.66% did not appear significant. The same is graphically represented in figure 3.

Fig 3: Proportional success rates



As figure 2 represents proportional differences all throughout the study, table 3 represents qualitative differences at each assessment after a particular dose. 1st dose showed highest ripening changes in combined group, followed by misoprost group and least with ISMN. The second dose appeared to again cause more ripening in combination therapy group, but its difference with misoprostol treated patients was insignificant and with ISMN treated patients was significant. Statistically significant differences appeared to be less common after the 3rd and 4th dose.

Table 3: Proportional differences after consecutive dosing

S.No.	Dosing pattern	Characteristic	N_M (%)	N_I (%)	N_C (%)	P χ^2 (M.I)	P χ^2 (M.C)	P χ^2 (I.C)
1.	1st dose n (%) (N_M = 60, N_I = 60, N_C = 60)	> 10 HD	30	11.67	35	0.01	**0.55**	0.002
		<10 HD	70	88.33	65			
2.	2nd dose n (%) (N_M = 42, N_I = 53, N_C = 39)	>10 HD	42.85	24.52	58.97	**0.58**	**0.14**	0.0008
		<10 HD	57.14	75.47	41.02			
3.	3rd dose n (%) (N_M = 24, N_I = 40, N_C = 16)	>10 HD	66.67	57.5	56.25	**0.46**	**0.5**	**0.93**
		<10 HD	33.33	42.5	43.75			
4.	4th dose n (%) (N_M = 8, N_I = 17, N_C = 7)	>10 HD	75	47.05	85.71	**0.18**	**0.6**	**0.08**
		<10 HD	25	52.94	14.28			

Intra-operative characteristics have been illustrated in table 4, which has analysed variations in 3 groups. Differences in these groups with respect to blood loss and procedure time varied significantly. ISMN appears to cause higher blood loss when used alone (M vs. I – P 0.0001) or used in combination (M vs. IM – P 0.01). Time taken to complete a procedure appears to decrease when used as a combination (M vs C – 0.02).

Table 4: Intra operative characteristics

S.No	Characteristic	Group M (M ± SD)	Group I (M ± SD)	Group C (M ± SD)	P_{phc} (M.I)	P_{phc} (M.C)	P_{phc} (I.C)	P_a
1.	Blood Loss	63.4±27.68	89.9±41.41	72.3±33.8	0.0001	**0.3417**	0.0168	0.0002
2.	Time taken	7.28±2.15	10.31±2.69	6.13±2.38	<0.0001	0.026	<0.0001	<0.0001

Adverse effects as compared have been tabulated below in table 5. Abdominal pain, diarrhea, fever, and vomiting appear to characterize the misoprostol group but were found to decrease when ISMN was added to therapy. Similarly dizziness and palpitations appear to be associated with ISMN group and decrease upon addition of misoprostol as combination therapy. Headache appears to be synergistically high in combination therapy. Overall patients acceptance appears to be insignificantly variable in different groups.

Table 5: Side Effects

S.No	Characteristic	Group – M n(%)	Group – I n(%)	Group – C n(%)	P χ^2 (M.I)	P χ^2 (M.C)	P χ^2 (I.C)
A	**Specific Adverse effects**						
1.	Abdominal Pain	24(40)	9(15)	19(31.67)	0.002	0.34	0.03
2.	Diarrhoea	12(20)	2(3.33)	6(10)	0.004	0.12	0.14
3.	Dizziness	4(6.67)	23(38.33)	21(35)	0.0003	0.0001	0.7
4.	Fever	18(30)	4(6.66)	9(15)	0.0009	0.04	0.14
5.	Headache	6(10)	14(23.33)	17(28.3)	0.05	0.01	0.53
6.	Nausea	8(13.33)	2(3.33)	9(15)	0.04	0.79	0.02
7.	Palpitations	6(10)	12(20)	8(13.33)	0.12	0.56	0.32
8.	Vomitings	4(6.67)	0	1(1.67)	0.09	0.16	0.004
B	**Acceptance**						
1.	Adverse Effects	33(55)	29(48.33)	36(60)	0.46	0.57	0.19
2.	No Adverse Effects	27(45)	31(51.67)	24(40)			

IV. Discussion

NO is a free radical with a short half life, and is a major paracrine mediator for numerous biological processes like smooth muscle relaxation, immunological defense and inflammation [12]. Cervical ripening is essentially caused and associated with changes in local cytokines, PGs, metalloproteases and an array of bio-regulators that cause inflammation and collagen breakdown [13]. Liggins compared this to an inflammatory response and ascribed this role to NO, citing the amplification and of cytokine cascade as a probable mechanism [14]. These factors also regulate the synthesis and release of NO [15]. These evidence were used to predict that NO is a mediator of cervical ripening.

Our findings in the previous study on the same population concluded that PG E1 causes more ripening compared to ISMN when used alone (4). Thomson et al also described similar findings when they used ISMN at regular and even higher doses [11, 16]. The criteria for an ideal cervical ripening agent is variable in different papers, Norman et al describe that an ideal ripening agent would induce cervical remodeling without causing uterine contractions [17], while Ledingham et al describe an ideal agent as one that is clinically effective with minimal side effects[18]. We describe an ideal ripening agent, in the context of missed miscarriages as the one with a short induction-ripening interval, with minimal blood loss and adverse effects which is easy to administer and provides the surgeon with enough convenience to do a SE procedure.

Significant variations in the extent of cervical ripening have been noted in our study between the groups, with least ripening in ISMN group and maximum in the combination group. Ledingham et al in their three group comparison study described analogous results in terms of cumulative force required to cause cervical dilatation, where least force required in combination group and most force required in ISMN group [18]. Our results have shown that ISMN is a less potent and slow acting ripening agent, but this doesn't imply that ISMN as a single drug therapy is ineffective as a ripening agent. Similar findings have been reported by several studies [11, 12, 15, 16, 18]. This is further backed with the evidence of close inter-relationship between PGs and NO. NO is said to induce PG synthesis and PGs applied locally are said to increase the activity of inducible nitric oxide synthetase (iNOS) in human tissues [19, 20].

Another parameter which has been assessed is the time required and number of doses required to cause cervical ripening in different groups. Less time and lesser dose is used in combination therapy compared to ISMN and misoprostol when used as solitary agents, this difference appeared statistically significant in ISMN vs. combined group but not significant in misoprostol vs. combined group. Proportionally less patients had ripening in the first 6 hours in the ISMN group but this increased dramatically during the 6^{th} to 9^{th} hour. This is in agreement to the findings of Bates et al and Ekerhovd et al who separately described the action of ISMN to start at 3 hours and peak at 6 and 10 hours respectively [21, 22]. The proportion of patients who failed to have cervical dilatation was high in the ISMN group which varied significantly to misoprostol group and combination group. There was almost no difference between misoprostol and combination group on this parameter. Gabriel et al have reported similar findings where the proportion of patients on ISDN was consecutively lesser compared to patients on Misoprostol [23]. A shorter induction – ripening interval does not just represent faster results but also translates to a reduction in the total dosage required to achieve requisite or desired ripening. This will further ensure a reduction of adverse effects of either drug used in combination.

Intra-procedural blood loss appeared to be significantly more in group –I compared to the two other groups. Lesser blood loss in group –M can be explained by the uterotonic property of PG E1 which closes maternal sinuses and reduces bleeding. This effect of ISMN can be counteracted when used in combination as there is no statistically significant difference in blood loss in group -M and group –C. Chan et al have described similar results with use of NO donors [24].

Several adverse effects were noted in all the groups, with the least seen in ISMN group followed by combination and highest in misoprostol group. Though none of the differences were significant it appears that addition of ISMN in combination therapy reduces the adverse effect profile of misoprostol. Adverse effects of certain relevant studies have been discussed in table 6.

Table 6: Adverse Effect Occurence

S.No	Outcomes	Marie et al [18]			Chan et al [24]		Gabriel et al [23]		Uzma et al [25]	
		A	B	C	A	B	A	B	A	B
A.	Characteristics									
1.	Number	21	22	22	100	100	30	30	50	50
2.	Drug	Miso	ISMN	A + B	Miso	SNP	Miso	ISDN	Miso	ISMN
3.	Dose	400µg	40mg	A + B	400µg	10mg	400µg	80mg	400 µg	80mg
4.	Formulation	Tab	Tab	Tabs	Gel	Gel	Gel	Gel	Tab	Tab
5.	Route	P/v	P/v	P/v	P/v	P/v	I/c	I/c	P/v	P/v
6.	Dosage	Stat	Stat	Stat	Stat	Stat	R-3hrs	R-3hrs	R-3hrs	R-3hrs
B.	Adverse Effects									
1.	No Adv effects	52	64	50	-	-	-	-	-	-
2a.	Abdominal Pain	43	5	32	48	20	13.3	3.3	12	2
2b.	Pelvic pain	-	-	-	-	-	60	3.3	-	-
2c.	Backache	-	-	-	-	-	13.3	13.3	10	10
3.	Diarrhoea	0	0	0	-	-	-	-	-	-
4.	Dizziness	0	0	5	-	-	-	-	0	4
5.	Fever	-	-		5	4	-	-	-	-
6.	Headache	0	32	36	5	12	16.7	60	12	60
7.	Nausea	10	0	0	13	24	17.2	0	16	0
8.	Palpitations	0	0	5	4	20	-	-	8	0
9.	Vaginal bleed	10	0	-	14	6	-	-	-	-

10.	Vomitings	-	-	0	3	6	10	0	-	-

A – Misoprostol group | B – NO Donor group | C - Combination
Miso – Misoprostol | ISDN – Isosorbide dinitrate
Tab – Tablet | P/v – Per vaginal | I/c – intra cervical | R – Repeat every

V. Conclusion

ISMN is an established ripening agent with longer induction – ripening interval and more blood loss but lesser adverse effects. Misoprostol on the other hand is a faster ripening agent with lesser blood loss but more adverse effects. Their combination appears to be synergistic as far as their therapeutic action is concerned but adverse effects appear to decrease on addition of ISMN in the ripening regime.

Declarations

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee of ESIC Medical College.

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