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The effect of vaginal administration of isosorbide mononitrate on cervical ripening and induction of labour in term and post term pregnancy

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Abstract

Background: The NOS (Nitric oxide synthase) or the NO system has a regulatory role in the myometrium and cervix during pregnancy and parturition. NOS activity is found to be higher before the onset of labour and decreases during labour thereby having a role in the onset of uterine contractions. Nitric oxide (NO) plays an important role in cervical ripening. The aim of this study was to know a better knowledge about the effect of vaginal administration of Isosorbide mono-nitrate on cervical ripening and Induction of labor in term and post term pregnancy.

Materials and Methods: This prospective Observational study is conducted in women with singleton live pregnancy (between 37 to 42 weeks of gestation) and an unfavorable cervix(modified Bishop score of 0-6), requiring induction of labour with different indications in the Department of Obstetrics and Gynaecology at Rajah Muthiah medical college, Chidambaram for a period of 2 years. They are enrolled after assessing inclusion and exclusion criteria. 40mg of Isosorbide mononitrate inserted in the posterior fornix and second dose repeated after 6 hours. Oxytocin was started after 12hours if needed. If bishop score is not changed after 24 hours of insertion, it is considered as induction failure and patient is taken for caesarean section.

Results: There is no association found in age wise distribution. The mean BISHOP score was found to be similar between good contractions and suboptimal contractions at baseline and 6 hours while at 12 hours, the mean of good contractions group was significantly more than that of the Suboptimal contractions group ($p<0.05$). The mean induction to delivery interval was similar among the participants between good contractions and suboptimal contractions augmentation ($p<0.05$). Both the groups were similar with regard to maternal side effects and foetal outcome with ($p<0.05$).

Conclusion: The administration of Isosorbide mononitrate has no effect on the hemodynamic state of the mother and fetus. The use of ISMN by the vaginal route as ripening agent before induction of labor at term helps in improving bishop score and reduces the duration of labor.

Keywords: IMN- Isosorbide mononitrate, MSL- Meconium Stained Liquor, FI- Failed Induction, CPD- Cephalo Pelvic Disproportion, NPL- Non Progress of Labour

Introduction

Induction of labor is defined as artificial initiation of labor before its spontaneous onset for the purpose of delivery of the fetoplacental unit. Labor induction is one of the most common procedures performed in obstetrics, reaching 10-20% of deliveries worldwide. The increasing rate of labor induction has probably played a role ^[1]. Cervical ripening is the process of softening, shortening and partial dilatation of the cervix which takes place in days or weeks prior to the onset of labor ^[2]. It is important to note that cervical ripening can also be influenced by other factors, such as the woman's parity, gestational age, and overall health status. Nitric oxide is synthesised from L - Arginine by NOS, of which 3 isoforms are identified ^[3]. Isoforms are endothelial NOS (NOS 3), brain or neuronal NOS (NOS 2) and macrophage or inducible NOS (NOS 1). Cervical ripening is associated with increase in the expression of inducible NOS and brain NOS in the cervix. i NOS activity is increased by the resident and migrating inflammatory cells. Nitric oxide (NO) plays an important role in cervical ripening. Increase in NO causes increase in matrix metalloproteinase activity, cellular apoptosis and glycosaminoglycans synthesis in the cervix. Nitric oxide donors when applied to the cervix induce cervical ripening. This study aimed to determine whether Isosorbide mononitrate is an effective agent for ripening of cervix, to compare changes in bishop score, progress of labour, induction to delivery interval, after administration of Isosorbide mononitrate, to compare the efficacy, safety, and acceptability

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of Isosorbide mononitrate for cervical ripening before induction of labor at term and post dated pregnancy, to evaluate the various effects of Isosorbide mononitrate (ISMN) on cervical ripening at term, and post term, to study various maternal and fetal outcome after use of this agent for cervical priming in unfavorable cervix.

Materials and Methods

Study Design: Prospective Observational study.

Study Setting: Department of Obstetrics and Gynecology, Rajah Muthiah Medical College Hospital-Annamalai University.

Study Period: 2 years.

Study Population

75 pregnant women admitted in delivery room for induction of labour who have fulfilled both Inclusion and exclusion criteria.

Inclusion criteria

Women who have completed 37 to 42 weeks of gestation, Primi of 18-35 years of age, Unfavorable cervix with modified Bishop score (0 to 6), Uncomplicated Singleton pregnancy with cephalic presentation, Absent uterine contractions and intact membranes, Normal Doppler indices and normal CTG, Rh-immunization, Fetus with intrauterine growth restriction and intrauterine death.

Exclusion criteria

Multiparity, Multiple pregnancies, Placenta previa, Abruptio placenta, Premature rupture of membranes, Polyhydramnios, Previous LSCS or any other uterine surgery like myomectomy, Major degree of CPD with Established fetal distress, Women with history of epilepsy, Heart disease, Liver disease and Anaemia complicating, Gestational Hypertension complicating Pregnancy, Fetal malpresentations, Non reassuring NST, Any contraindications to Isosorbide mononitrate will be excluded.

Study procedure

Institutional ethics committee approval was obtained before the start of the study. Informed consent was obtained from both the husband and the subjects. This prospective Observational study is conducted in women with singleton live pregnancy (between 37 to 42 weeks of gestation) and an unfavorable cervix (modified Bishop score of 0-6), requiring induction of labour with different indications in the Department of Obstetrics and Gynaecology at Rajah Muthiah medical college, Chidambaram. They are enrolled after assessing inclusion and exclusion criteria. After taking informed consent, detailed history is taken regarding relevant medical, surgical and obstetric conditions. Obstetric examination is performed for height of uterus, presentation, position, fetal heart and liquor. Vaginal examination is performed to rule out cephalo-pelvic disproportion. Bishops score was assessed by 2 independent observers. Gestational age is confirmed by date of last menstrual period and earlier ultrasound scan reports. Recent ultrasound is done for assessing gestational age, liquor content and estimated fetal weight and CST to assess fetal condition. Baseline investigations are taken. Women recruited for induction, are counseled before the procedure. NST was performed before insertion of Isosorbide mononitrate. 40 mg of Isosorbide mononitrate inserted in the posterior fornix and second dose repeated after 6 hours. After insertion, the patients were

monitored for uterine contractions, fetal heart rate. Monitoring of fetal heart was done by intermittent auscultation and uterine action by number of contractions, duration and intensity in ten minutes NST was repeated with interval of 6 hours. Monitoring of Maternal pulse rate, blood pressure for every 30 minutes. Oxytocin was started after 12hours if needed at the dose of 8 drops / min with increments, every 30 minutes. Membranes is ruptured, when the cervix is fully effaced with a cervical dilatation of more than 3 cms. If bishop score is not changed after 24 hours of insertion, it is considered as induction failure and patient is taken for caesarean section if signs of fetal distress appears.

Results

This prospective observational study was conducted among the study population between November 2020 to October 2022 in department of Obstetrics and Gynecology at Rajah Muthiah Medical College, Chidambaram based on the inclusion and exclusion criteria. During the study period, there were 4858 deliveries in our institution of which 2588 were normal vaginal deliveries which constitutes 53% of total deliveries. P Value less than 0.05 was considered statistically significant.

Table 1: Change in mean bishop score among the participants.

Variable	Score	
	Mean	SD
Baseline	3.05	0.80
6 hours	4.95	1.03
12 hours	6.16	0.92

Table 2: Comparison of mean age between good and suboptimal contractions

Variable	Good contractions		Suboptimal contractions		T Value	P Value
	Mean	SD	Mean	SD		
Age (in years)	25.09	4.28	24.23	4.34	1.42	0.158

Table 3: Comparison of mean gestational age between Good and suboptimal contractions

Variable	Good contractions		Suboptimal contractions		T Value	P Value
	Mean	SD	Mean	SD		
Gestational Age (in weeks)	38.84	0.96	38.77	1.08	0.280	0.780

Table 4: Comparison of mean bishop score between good and suboptimal contractions

Variable	Good contractions		Suboptimal contractions		T Value	P Value
	Mean	SD	Mean	SD		
Baseline	3.09	0.83	3	0.77	0.480	0.633
6 hours	5.07	1.02	4.77	1.05	1.211	0.230
12 hours	6.45	0.87	5.77	0.86	2.74	0.008

Table 5: Distribution according to mode of delivery between the groups

Mode of delivery	Good contractions		Suboptimal contractions		Total	
	N	%	N	%	N	%
Labour natural	36	81.8	20	64.5	56	74.7
Forceps	4	9.1	3	9.7	7	9.3
LSCS	4	9.1	8	25.8	12	16

$X^2 - 3.912$

DF - 2

P Value - 0.141

Table 6: Comparison of mean labour to delivery interval between good and suboptimal contractions.

Variable	Good contractions		Suboptimal contractions		T value	P value
	Mean	SD	Mean	SD		
Labour to delivery interval	693.86	149.19	683.39	148.68	0.30	0.765

Table 7: Comparison of mean induction to delivery interval between good and suboptimal contractions.

Variable	Good contractions		Suboptimal contractions		T value	P value
	Mean	SD	Mean	SD		
Induction to delivery interval	1180.11	175.78	1165.00	174.9	0.367	0.714

Table 8: Distribution according to maternal side effects between the groups

Maternal side effects	Good contractions		Suboptimal contractions	
	N	%	N	%
Nil	26	59.1	16	51.6
Headache	7	15.9	7	22.6
Nausea	5	11.4	2	6.5
Palpitation	4	9.1	2	6.5
Hyperstimulation	0	0	2	6.5
Hypotension	2	4.5	0	0
Tachycardia	0	0	2	6.5

X² – 8.33

DF – 6

P value - 0.215

significantly lesser duration for both labour onset to delivery and admission to delivery in the IMN administered group than their control group.

Habib SM *et al.* [9] also reported a similar shorter admission to delivery interval among the IMN administered group in comparison to control group. Yazdizadeh *et al.* [6] reported the induction to delivery interval among the IMN to be 9.9 ± 3.4 hours. The above duration was similar to what was observed in the resent study. Yazdizadeh *et al.* [6] also reported the duration to be significantly lesser than the control group they compared.

In study by Bollapragada SS *et al.* [5] 20% reported a strong head ache and 17% reported nausea. The other complications reported include flushes, faintness, drowsiness, vaginal soreness and indigestion.

In study by Habib SM *et al.* [4], 11.76% reported headache among the IMN administered participants and the occurrence of headache was significantly more in the IMN group than in the control group. Similar result of increased headache among participants administered with IMN by the Y Sharma S *et al.* [9] study. Adellah M *et al.* [7] reported 35% to have headache and 2.75% to have nausea following administration of IMN.

Over all IMN could be effective and safe drug when utilised for induction of labour. Most of the parameters are either comparable to other agents used for labour induction or much effective. One of the area of concern would be increased proportion of headache reported which could be effectively treated using analgesics.

Conclusion

The administration of isosorbide mononitrate has no effect on the hemodynamic state of the mother and fetus. In contrast to the other cervical ripening agents, No donor, administered vaginally, has the advantage of absence of uterine contractions. The absence of contraction has obviated the need for fetal monitoring such agent could be given on as outpatient basis. Hence, it removes the main reason that women are monitored during the induction of cervical ripening and NO donors are suitable agents for pre-induction cervical ripening at term. It also improves bishops score when administered alongside an augmenting agent like oxytocin, thereby reducing duration of labour. The use of ISMN by the vaginal route as ripening agent before induction of labor at term helps in improving bishop score and reduces the duration of labor.

Conflict of Interest

Not available

Financial Support

Not available

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Table 9: Distribution according to faetal outcome between the groups.

Foetal outcome	Good contractions		Suboptimal contractions	
	N	%	N	%
Nil	40	90.9	23	74.2
Foetal distress	1	2.3	5	16.1
Grade II MSL	1	2.3	2	6.5
FI	1	2.3	0	0
CPD	1	2.3	0	0
NPL	0	0	1	3.2

X² – 8.592

DF – 5

P value - 0.126

Discussion

In obstetrics and gynecology, No donor has been used for the treatment of preterm labor. No donor has been shown to induce cervical ripening without causing uterine contraction by rearrangements of cervical collagen tissue and ground substance. ISMN is a slow releasing No donor. Levels of No metabolites in the cervix are known to be increased at term

Bollapragada SS *et al.* [5] reported the mean change in IMN group to be 2.29 which was comparable to the present study. The study also reported in comparison to placebo the change was 0.65 points more. Agarwal K *et al.* [3] also reported a similar change in bishop score following the administration of IMN. The study reported the change in score to be 3.17.

Yazdizadeh *et al.* [6], Abdellah MS *et al.* [7] also reported a similar change in bishop score among those administered with IMN.

The magnitude of change in bishop score was found to be significantly good following the administration of IMN. The rest of the studies had reported the magnitude to be more than that of the control groups.

In study by Abdellah MS *et al.* [7], 84.8% had delivered vaginally following administration of IMN and 15% delivered through Caesarean section. The above proportion was similar to the present study and was comparable to the control group.

Agarwal K *et al.* [3] reported the time from labour onset to delivery interval as 5.67 ± 1.88 hours. The study reported

- ripening in induction of labor Moustafa Abbas Ibrahim, Hussein Mohammed Abdel Dayem, Amr Ahmed Abdelrhman, Doaa Hamed Abo El-Khir * Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt. 2021 Apr;83(1):862-868.
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