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Original Research Article

A comparative study of safety and efficacy of vaginal isosorbide mononitrate (40mg) with dinoprostone gel (0.5mg)

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ABSTRACT

Background: It is essential to intervene pregnancy for safety of mother, fetus or both. Successful labor induction is clearly related to the state of the cervix. Women with an unfavorable cervix who have not experienced cervical ripening phase before labor present the greatest challenge with regard to labor induction. Therefore, it is necessary to use optimal technique for cervical ripening and safe confinement. One of the common methods includes use of PGE2 gel for cervical ripening. The rationale of this study is to compare the safety and efficacy of Iso-sorbide mononitrate as pre-induction cervical ripening with PGE2 gel induction.
Methods: After attaining ethics approval [PSG IHEC], a prospective randomised, case-controlled study was conducted on 182 women undergoing elective induction of labour. They were allocated to either Study or Control group by computer generated random number table method. ISMN was used vaginally prior to labour induction in the study group whereas PGE2 gel induction was used in the control group. Change in bishop score and Induction to delivery interval was assessed in both the groups.
Results: There was a significant reduction in induction to delivery interval in the study group (ISMN) 15.2 hours when compared to 23.2 hours in the control group (PGE2 gel) with p=0.000. Need for augmentation of labour was reduced in the study group significantly with p=0.003. Cost of induction was less when compared to the control group. ISMN had less side effects hence can be used as OP basis.
Conclusions: Vaginal Isosorbide mononitrate when used as a cervical ripening agent significantly reduces induction to delivery interval. Use of Isosorbide mononitrate was associated with very less side effects and it is a cost-effective drug. Thus, ISMN can be used safely and effectively in term patients for pre-induction cervical ripening when compared to PGE2 gel.

Keywords: Cervi prime gel, safety, Induction delivery interval, Induction of labour, Iso-sorbide mononitrate

INTRODUCTION

Induction of labor is indicated when the risks to either the mother or the fetus of continuing the pregnancy outweigh the benefits. The conditions which commonly necessitate induction of labor include preeclampsia, postdatism, prelabor rupture of membranes, maternal medical disorders, fetal growth restriction and intrauterine fetal demise (Hibbard et al). The success of labor induction largely depends on the `favorability' of cervix.[1] Various methods like insertion of extra amniotic self-retaining catheter, hygroscopic cervical dilators and prostaglandins have been tried in an effort to ripen the cervix prior to induction (Hibbard, Vengalil, Owen).

Prostaglandin E2 or dinoprostone administered intracervically, has been shown to improve bishop score and induction to delivery times in comparison to untreated controls (Owen). However, use of prostaglandins is associated with complications like uterine tachysystole and rupture of uterus and fetal cardiac rhythm abnormalities (Keller, Vaisanen).[2] Besides, more caution is advocated when these agents are used in women with a scarred uterus.[3]

Nitric oxide (NO) has been recently postulated to have a regulatory role in the myometrium and cervix during pregnancy and parturition, and an endogenous NO system is documented in the human cervix.[4] The present study was planned to evaluate the effects of NO donor isosorbide mononitrate (ISMN) on cervical ripening at term, to compare its efficacy and safety with that of dinoprostone gel and to evaluate the maternal and fetal outcome after use of these agents for cervical priming.

METHODS

This prospective study was carried out on 182women with singleton live pregnancy (between 37 to 42 weeks of gestation) and an unfavorable cervix (modified Bishop score of 0-6), posted for induction of labour during the period between June 2014 to May 2015, in the Department of Obstetrics and Gynaecology at PSG, Coimbatore. Women with malpresentations, multiple pregnancy and those with history of epilepsy, hypertension or bronchial asthma were excluded from the study.

After a thorough history, general physical and obstetric examination (including assessment of Bishop Score) all women underwent admission NST to assess the fetal condition. Randomization was done, Women of group I were administered 40 mg ISMN vaginally 2 doses 12 hours apart while those of group II received dinoprostone gel (0.5 mg in 3 gm base) intracervically which was repeated after 6 hours, if the bishop score remained below 6. Bishop score was reassessed after 24 and 6 hours in group I and II respectively. EFM was used in labour.

All women were monitored for pulse rate, blood pressure, fetal heart rate, uterine contractions, any adverse effects and maternal and neonatal outcome.

RESULTS

The majority of women (39 in group I and 44 in group II) in the study were in the age group of 20-24 years. A total of 63 (78%) women in group I and 43 (57%) in group II were between 40-42 weeks of gestation, the remaining being at 37 weeks. Indications of induction in the study were postdated fetal growth restriction, decreased fetal movements, oligohydramnios or maternal medical disorders. Table 1 shows the change in bishop score in the study. The change in bishop score after 6 hours of instillation of the ripening agent in both groups was not significant. In group II, 80% (24 out of 30) women with an initial score of 0-3 and 20% (4 out of 20) of those with initial score of 4-5 needed a repeat dose of dinoprostone.

Table 1: Change in Bishop score.

Bishop score	ISMN (group I)	PGE2 gel (group II)	P value
Pre-score	1.84±0.87	2.16±1.1	0.151
Post score	4.1±1.91	3.6±2.1	0.134
P value	0.08	0.144	

In group I- as ISMN was used as a pre-induction cervical ripening agent, induction of labour was done with PGE2 gel after 2 doses of ISMN. In group II- PGE2 gel not only ripens the cervix but also initiates labour, hence maximum of 3 doses PGE2 gel were instilled 6 hrs apart depending upon the bishop score. Further augmentation of labour was done with misoprostol, ARM and oxytocin as indicated. Induction to delivery interval was calculated from time of first PGE2 gel dose to delivery in both the groups. 24 hours of ISMN was excluded from group I as it was used only as a pre-induction ripening agent.

Table 2: Induction to delivery interval.

Interval (hours)	ISMN		PGE2 gel	
	No.	%	No.	%
<12 hours	36	39	10	11.1
12-24 hours	44	47.8	38	42.2
24-36 hours	9	9.7	35	38.8
36-48 hours	3	3.2	7	7.7
>48 hours	-	-	-	-
Mean±SD	15.2±9.08		23.2±9.14	
Inference	The difference between both is statistically significant			

The mean duration of induction to delivery is more with PGE2 gel 23.2 hours and mean duration in ISMN group was 15.2 hrs. In PGE2 gel group 11% had induction delivery interval <12 hrs whereas 39% had less than 12 hours in ISMN group. This was statistically significant. Similarly, duration of labour from 36-48 hrs was 7.7% in PGE2 gel and 3.2% in ISMN group this was not statistically significant. Overall, In ISMN group 86.8% had delivered within 24hrs whereas in PGE2 gel group only 53.3% delivered within 24hrs.

Table 3: Acceleration of labour.

Acceleration	ISMN		PGE2 gel	
	No.	%	No.	%
Nil	30	32.6	14	15.5
Required	62	67.3	76	87.4
Total	92		90	
Inference	Cases which required acceleration were significantly reduced in ISMN group p=0.003			

None of the patients went into labour after administration of ISMN, as it had no action on myometrium. In PGE2 gel group apart from ripening of cervix patients also had onset of uterine contractions even with a single dose. In group I, requirement of drugs such as misoprostol, PGE2 gel and oxytocin for acceleration is less (67%) when compared to group II (87.4%).32.6% of the patients did not require acceleration of labor in the study group when compared to 15.5% of the patients in PGE2 gel group did not require acceleration. Patients with spontaneous rupture of membranes were augmented with oxytocin and others had ARM and oxytocin.

Table 4: Cost of induction.

Cost	ISMN		PGE2 gel	
	No.	%	No.	%
<200	28	30.4	-	0
200-500	57	61.9	22	24.9
>500	7	7.6	68	75.5
Mean±SD	285.3±123.9		463.3±256.8	
Inference	There was a significant reduction in cost of induction when ISMN was used as number of PGE2 gel used was less.			

The mean cost of ISMN used is Rs. 12, each ISMN 20mg tablet cost Rs. 3 each PGE2 gel cost Rs. 375. Average cost of induction in PGE2 gel was Rs. 463, and this was reduced by 50% when ISMN was used prior to induction as number of PGE2 gel used was significantly reduced.

DISCUSSION

NO is a common product of arginine metabolism in many tissues. It appears to be an important paracrine vasodilator and may be involved in cell death and nerve transfer.[5] NO is also released from several vasodilator drug molecules. It is released from important medications such as nitroprusside, nitrates, and nitrites.[6] This substance is a potent vasodilator in all vascular substrates and a powerful relaxant in most smooth muscle cells. Its performance mechanism in this case is activation of guanylyl cyclase and production of cyclic guanosine monophosphate (cGMP) which causes dephosphorylation and disables the light chains of myosin and causes relaxation of smooth muscle. It also has a physiological role in erectile tissue function.[7]

As mentioned earlier, several studies have tried to show the effect of NO on cervical pre-induction ripening.[8,9] Findings of previous studies indicated that delivery length from the onset of intervention in the misoprostol group was shorter and the need for induction in this group was lower.[10,11]

The results were comparable to other studies like Bollapragada et al who concluded that clinical utility of IMN as a pre-induction cervical ripening agent was minimal.[12] Though in their study, IMN had a significant effect on the change in cervical Bishop score (mean difference of 0.65, p=0.013), they could not demonstrate a significant change in their primary outcome measure which was admission to delivery interval (mean difference-1.03 hours, p=0.68).

Bishop score appeared to be an important predictor for induction to delivery interval in the study. Of the women with an initial score of 0-3, only 3.71% (1 patient) from group I and 16.67% (5 patients) from group I delivered vaginally within 12 hours. While 66.67% (18 patients) of women with an initial bishop score of 0-3 delivered between 12-24 hours in group I, only 40% (12 women) did so in group II. Of the women with bishop score of 4-5, 34.78% (8 women) women of group I and 40% (8 women) of group II delivered in the first 12 hours and another 47.83% (11 women) and 30% (6 patients) woman delivered between 12-24 hours in group I and II, respectively. The mean induction to delivery interval was 15.2±9.08 in group I and 23.2±9.14 hours in group II (p=0.00). Oxytocin was required in (38 of group I and 33 of group II) women in the study.

The mean difference in cervical scores at 24 hours was 0.01 with a p = 0.983 and there was no significant change in drug insertion to delivery time. Osmanet al also concluded in their study that isosorbide mononitrate was less effective as a cervical ripening agent, though they used prostaglandins (PGE2) as the comparator. In contrast, Agarwal et al attested to the effectiveness of IMN as cervical ripening agent by showing a significant change in Bishop scores after 2 doses of 40 mg IMN (3.17±2.02; $p < 0.001$) and a reduction in admission to delivery interval ($p < 0.001$).[13,14]

There was no case of hyper stimulation in the IMN group in the study done by Habib et al, but a higher incidence of tachysystole (1.96%) was observed in the IMN group.[15] Most of the other studies have reported headache as the most common side effect of IMN, although it was treatable with simple analgesics like paracetamol. Maternal hemodynamics, like blood pressure or pulse rate was also not affected. In a study conducted by Ekerhovd et al, significant changes were recorded in maternal hemodynamics which however did not prove to be of any clinical importance (at 180mins, change in maternal PR, $p < 0.01$, SBP, $p < 0.001$, DBP, $p < 0.0001$).[16]

Fetal distress formed the indication of CS for 8 (out of 36) patients of group II and 7 (out of 27) patients of group I ($p<0.05$). 4 patients of group I and 6 of group II underwent abdominal delivery for failed induction. Bollapragada et al did not report any differences in the number of women going into labour within the first 24 hrs (9% in IMN; 4% in placebo, p = 0.09).[12] However, in the study conducted by Bullarbo et al more women went into labour within 24 hours in the IMN group than in the placebo group.[16]

Most of the studies such as those conducted by Agarwal et al and Habib et al have shown lower incidence of

caesarean deliveries in IMN group albeit statistically insignificant.[14,15] Though the number of caesarean deliveries were more in IMN group than placebo in present study, it was not statistically significant. Most of these were done for fetal distress following PGE2 and failed induction of labour after 2 doses of PGE2 and maximal doses of oxytocin infusion.

Headache was the most common adverse effect observed in group I 31 women (33%). 9 women of group II had uterine hyperstimulation, in comparison to none from group I. Two women of group I had atonic postpartum hemorrhage (PPH). One woman of group I had cervical tears. NICU admissions and APGAR scores were not significantly different in both the groups. There was a significant reduction in cost of induction when ISMN was used as number of PGE2 gel used was less.

CONCLUSION

Induction of labour is a challenge to all obstetricians. Various drugs were used for labour induction, among which PGE2 gel was most widely accepted. ISMN has been studied as a pre-induction cervical ripening agent in recent times.

Advantage in this group was that cervix became soft and responded well to induction with other drugs. Side effect was only headache which subsided with analgesics. There was no evident change in bishop score following ISMN induction. Whereas induction to delivery interval in this group was significantly reduced. There was no case of hyper stimulation recorded in any of the studies as it does not cause myometrial contractions.

It is a cost-effective method of cervical ripening does not require monitoring during the period of ISMN induction. Hence patients do not require admission. It can be safely used at home.

Hereby authors conclude that ISMN is an effective drug when used as a pre-induction cervical ripening agent.

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REFERENCES

1. Tschugguel W, Schneeberger C, Lass H, Stonek F, Zaghlula MB, Czerwenka K, et al. Human cervical ripening is associated with an increase in cervical inducible nitric oxide synthase expression. Biol Reprod. 1999;60(6):1367-72.
2. Keirse MJ, de Koning Gans HJ. Randomized comparison of the effects of endocervical and vaginal prostaglandin E2 gel in women with various degrees of cervical ripeness. Am J Obstet Gynecol. 1995;173(6):1859-64.
3. Ledingham MA, Thomson AJ, Young A, Macara LM, Greer IA, Norman JE. Changes in the expression of nitric oxide synthase in the human uterine cervix during pregnancy and parturition. Mol Human Reprod. 2000;6(11):1041-8.
4. Chwalisz K, Shao-Qing S, Garfield RE, Beier HM. Cervical ripening in guinea-pigs after a local application of nitric oxide. Human Reprod (Oxford, England). 1997;12(10):2093-101.
5. Väisänen-Tommiska M, Nuutila M, Aittomäki K, Hiilesmaa V, Ylikorkala O. Nitric oxide metabolites in cervical fluid during pregnancy: further evidence for the role of cervical nitric oxide in cervical ripening. Am J Obstet Gynecol. 2003;188(3):779-85.
6. Chanrachakul B, Herabutya Y, Punyavachira P. Potential efficacy of nitric oxide for cervical ripening in pregnancy at term. Int J Gynecol Obstet. 2000;71(3):217-9.
7. Yazdizadeh H, Abedi P, Najar S, Angali KA. The impact of isosorbide mononitrate on cervical ripening and labor induction in primiparous women with term pregnancy: A double-blind, randomized, controlled trial. Iranian J Nursing Midwifery Res. 2013;18(3):246-50.
8. Kelly AJ, Munson C, Minden L. Nitric oxide donors for cervical ripening and induction of labour. Cochrane Database Systematic Reviews. 2011(6).
9. Krishnamurthy R, Pallavee P, Ghose S. Evaluation of Isosorbide Mononitrate for Preinduction of Cervical Ripening: A Randomized Placebo-Controlled Trial. J Fam Reprod Health. 2015;9(2):75-81.
10. Radulovic N, Norström A, Ekerhovd E. Outpatient cervical ripening before first-trimester surgical abortion: a comparison between misoprostol and isosorbide mononitrate. Acta Obstetricia et Gynecologica Scandinavica. 2007;86(3):344-8.
11. Sharma Y, Kumar S, Mittal S, Misra R, Dadhwal V. Evaluation of glyceryl trinitrate, misoprostol, and prostaglandin E2 gel for preinduction cervical ripening in term pregnancy. J Obstet Gynaecol Res. 2005;31(3):210-5.
12. Bollapragada SS, MacKenzie F, Norrie JD, Eddama O, Petrou S, Reid M, et al. Randomised placebo-controlled trial of outpatient (at home) cervical ripening with isosorbide mononitrate (IMN) prior to induction of labour–clinical trial with analyses of efficacy and acceptability. The IMOP Study. BJOG: Int J Obstet Gynaecol. 2009;116(9):1185-95.
13. Osman I, MacKenzie F, Norrie J, Murray HM, Greer IA, Norman JE. The "PRIM" study: a randomized comparison of prostaglandin E2 gel with the nitric oxide donor isosorbide mononitrate for cervical ripening before the induction of labor at term. Am J Obstet Gynecol. 2006;194(4):1012-21.
14. Agarwal K, Batra A, Batra A, Dabral A, Aggarwal A. Evaluation of isosorbide mononitrate for cervical ripening prior to induction of labor for postdated pregnancy in an outpatient setting. Int J Gynecol Obstet. 2012;118(3):205-9.

15. Habib SM, Emam SS, Saber AS. Outpatient cervical ripening with nitric oxide donor isosorbide mononitrate prior to induction of labor. Int J Gynecol Obstet. 2008;101(1):57-61.
16. Bullarbo M, Orrskog ME, Andersch B, Granström L, Norström A, Ekerhovd E, et al. Outpatient vaginal administration of the nitric oxide donor isosorbide mononitrate for cervical ripening and labor induction postterm: a randomized controlled study. Am J Obstet Gynecol. 2007;196(1):50e1-5.

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