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RESEARCH ARTICLE

Isosorbide mononitrate followed by misoprostol compared with misoprostol alone for induction of labour at term: a randomized controlled trial

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ABSTRACT

Background: The rate of induction of labour is on rise globally due to various indications. The use of well established methods for induction of labour like prostaglandins is associated with various maternal and fetal adverse effects. **Objective:** Present study was designed to investigate the efficacy and safety of Nitric Oxide (NO) donor, Isosorbide mononitrate (ISMN) for cervical ripening and labour induction. To see the effect of sequential use of ISMN followed by misoprostol compared to misoprostol alone on induction of labour at term. **Methods**: This prospective randomized controlled trial was conducted from May 2012 to April 2013. Total 100 women, who fulfilled the inclusion criteria were admitted for labor induction during the study period. Study group received 60 mg sustained release tablet of Isosorbide mononitrate (ISMN) and control group received placebo, per vaginally, for cervical ripening. Bishop score was reassessed after 16 hours and participants in each group received 25mcg of misoprostol tablet per vaginally at 4 hrs interval for maximum of 4 doses till 3 contraction in 10 min or if cervix was dilated 3cm or more. Progress of labor was monitored using partograph. **Results:** There was significant difference between ISMN group and control group with respect to mean Bishop score (5.5±0.54 verses 4.16±0.76, p value <0.001). Vaginal delivery were more in ISMN group (66% vs 32%), so caesarean section were less in ISMN group (34% vs 68%, p=0.46). Lesser doses of misoprostol was required in ISMN group and reduced requirement of oxytocin to achieve vaginal delivery in ISMN group as compared to control group (9.1% vs 81.25%, p=0.001). Induction to vaginal delivery interval less than 12 hrs was seen on 54% cases in study group whereas none patient delivered in this interval in control group which was statistically significant (p=0.0002). Major side effect of ISMN was headache which responded to analgesia. **Conclusion**: ISMN is an ideal agent for effective cervical ripening, which induces ripening of cervix without causing uterine contraction. It significantly improves mean Bishop score, reduces the number of misoprostol doses required to achieve vaginal delivery and less induction failure.

Keywords: Isosorbide mononitrate (ISMN), NO donors (Nitric oxide donors).

Induction of labor is on rise and is a common phenomenon in modern obstetrics. Although prospective studies for evaluation of the benefits of elective induction are limited, primiparous women undergoing induction of labour with unfavourable cervices should be counseled about two fold increased risk of caesarean delivery[1-3]. Various pharmacological as well as non-pharmacological methods are available for cervical ripening. When Bishop score is favorable, oxytocin also may be used [4] as it has been widely used since 1950s for cervical ripening and induction of labour.[5]

Prostaglandins, particularly dinoprostone (PGE2) has been used as pre-induction cervical ripening however, it is expensive, unstable at room temperature and requires refrigeration for storage.[6] The only drawback appears to be an increase rate of uterine stimulation and accompanying

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fetal heart rate (FHR) changes.

Misoprostol is an interesting alternative, with good efficacy, low cost and temperature stability.[7]A meta-analysis based on Cochrane database review concluded that vaginal administration of misoprostol is effective for induction of labour.[8] Despite the widespread use and low dose recommendation for labour induction, prostaglandins are associated with various adverse effects which have always led to a search for an ideal ripening agent to induce cervical ripening without stimulating uterine contractions and other harmful effects on fetus. In this context, nitric oxide (NO) donors may prove to be an important milestone as an agent for pre induction cervical ripening. NO donors can induce cervical ripening without stimulating myometrial contractility. Isosorbide mononitrate (ISMN), a NO donor, induces cyclo-oxygenase-2 which leads to the production of endogenous prostaglandins in human cervix and causes ultra structural rearrangement in the cervix similar to spontaneous onset of labour.[9]

The recognition of nitric oxide donors as a better cervical ripening agent without significant adverse effect has opened new avenues of investigation for use of NO donors for induction of labor at term with an unripe cervix. In view of this, present study was undertaken to see the usefulness of ISMN for pre-induction cervical ripening followed by misoprostol 25 mcg every 4hrs for maximum of 4 doses. Primary objective was to investigate the efficacy and safety of NO donor, Isosorbide mononitrate (ISMN) for cervical ripening and labour induction. Secondary objective was to see whether sequential use of misoprostol with prior ripening of cervix reduces the induction to delivery interval, decreases the number of misoprostol doses and further reduces the side effects associated with other more potent uterotonics.

Materials and method

This prospective randomized controlled trial was conducted in the department of Obstetric and Gynecology at ESIPGIMSR & ESIC Hospital & ODC (EZ), Joka, Kolkata between May 2012 to April 2013. Before initiation, study was approved by ethical committee of the university. Women were explained about induction of labour and study protocol and informed written consent was taken. Total 100 women, who fulfilled the inclusion criteria, were admitted for labor induction.

Inclusion criteria includes singleton live pregnancy at term in cephalic presentation, absence of active labor, presence of obstetric or medical indication for labor induction viz postdated, bishop score less than 6.

Whereas exclusion criteria includes multipara (3 or more), known hypersensitivity to the use of prostaglandins, previous caesarean section, or any other types of uterine surgery like myomectomy, fetal macrosomia or growth restriction, malpresentation, FHR abnormalities, maternal medical disorders, cephalopelvic disproportion, Bishop score more than or equal to 6, multiple pregnancy.

Detailed history and examination of patients were taken. At admission cardiotocography was done to ensure normal fetal heart activity. Pelvic examination was done to assess Bishop score and to rule out cephalo-pelvic disproportion. Total 100 women gave consent to participate in the study and were randomized under two groups.

Randomization: Simple randomization method was used. Patients were allocated to two groups (Study group and Control group) by computer generated random number. The participants were enrolled and assigned to ISMN group and placebo group in accordance with list of code. This was a single blinded trial as participants were not aware about the allocation of group and intervention given. Study group received 60 mg sustained release tablet of isosorbide mononitrate (ISMN) and control group received placebo, per vaginally, for cervical ripening.

Bishop score was reassessed after 16 hours and participants in each group received 25 mcg of misoprostol tablet per vaginally at 4 hrs interval for maximum of 4 doses till 3 contraction in 10 min or if cervix was dilated 3cm or more. Progress of labor was monitored using partograph. Various findings are noted viz. improvement of mean Bishop score, mode of delivery, indication for caesarean section, need for misoprostol and oxytocin, induction to delivery interval, maternal and fetal condition during labor.

Statistical analysis: Nominal data were expressed as percentage and comparison between two groups were done by Chi square test with Yates correction and Fisher's extract test. The "p" value < 0.05 was considered statistically significant.

Results

Baseline demographic characteristics of both groups were comparable. Mean age for study group was 22.2±3.8yrs and for control group was 21.9±2.8yrs which was comparable in both groups. A total number of 50 cases were enrolled in each group. Out of 50 cases 39 (78%) in study group and 84% (42/50) cases in control group were primigravida and rest was second gravida (table 1). Mean Bishop score in both the groups were comparable before administration of drug, but changes in mean Bishop score was statistically significant after administration of drug (p value < 0.001).

Mean Bishop score after administration of drug in study group was 5.5±0.54 and control group was 4.16 ± 0.76 (table 2).

Table 1: Baseline characteristics

Characteristics		Study group (n=50)	Control group (n=50)
Age in years	≤ 20	18(36%)	16(32%)
	21-25yrs	21(42%)	29(58%)
	26-30yrs	9(18%)	5(10%)
	31-35yrs	2(4%)	0(0%)
Mean ± SD (Years)		22.2±2.8	21.9±2.8
Gravida	Primi	39(78%)	42(84%)
	G2	11(22%)	8(16%)

SD: Standard deviation

Out of 50 patients 33 (66%) patients had vaginal delivery in study group. Seventeen out of fifty (34%) patients had caesarean section in study group which was less as compared to control group 68% (34/50), but the difference in both the group was not statistically significant. Most common indication for caesarean section in both groups was meconium stained liquor followed by induction failure (table 3).

Table 2: Effect of drug ISMN (Isosorbide mononitrate) on mean Bishop score

Sl. No	Mean Bishop score	Study group	Control group	P value
1	Before drug	3.86±0.59	3.9±0.5	0.28(NS)
2	After drug	5.5±0.84	4.16±0.76	<0.0001

NS: Statistically non significant

Table 3: Delivery outcomes

Outcomes		Study group (n=50)	Control group (n=50)	P value
Mode of delivery	LSCS	17(34%)	34(68%)	0.4626 (NS)
	Vaginal Delivery	33(66%)	16(32%)	
Indications of caesarean section	Meconium stained liquor	11(64.7%)	19(55.88%)	0.67 (NS)
	Pathological CTG	2(11.76%)	3(8.82%)	
	Induction failure	4(23.5%)	12(35.29%)	

LSCS – Lower segment caesarian section, CTG – Cardiotocography, NS – Non significant

Table 4: Obstetrics outcome

Obstetrics outcomes		Study group (n=33)	Control group (n=16)	P value
Number of misoprostol doses required for vaginal delivery	0	4(12.12%)	0	0.2534(NS)
	1	6(18.18%)	0	
	2	20(60.6%)	1(6.25%)	
	3	3(9%)	13(81.25%)	
	4	0	2(12.5%)	
Need of oxytocin to achieve vaginal delivery	Yes	3(9.1%)	13(81.25%)	0.001(statistical significant)
	No	30(90.9%)	3(18.75%)	
Time interval between induction to vaginal delivery	<12hrs	18(54.54%)	0	0.0002(statistica-lly significant)
	≥12hrs	15(45.46%)	16(100%)	

NS: Statistically non significant

Out of vaginal delivery most of patients 60.6% (20/33) delivered with two doses of misoprostol as compared to control group where 76.48% (13/16) required 3 doses to achieve active labour and vaginal delivery. Oxytocin was not required in majority of cases (90.9%) in study group whereas 81.25% cases in control group required oxytocin to achieve vaginal delivery. The induction to delivery interval was between 6-12 hrs in 17 (51.5%) in study group while in control group, no case could deliver in this interval. Most of cases 93.75% in control group had induction to delivery interval between 12-18 hrs as compared to 15 (45.4%) cases in control group which was statistically significant (table 4).

Table 5: Maternal and neonatal outcomes

Categories		Study group (n=50)	Control group (n=50)	P value
Adverse effects of mother	Headache	26(52%)	0	
	Palpitation	0	0	
	Hypotension	0	0	
Birth weight (Kg)	2-2.5	7(14%)	15(30%)	0.11(NS)
	2.51-3	30(60%)	28(56%)	
	3.01-3.5	12(24%)	7(14%)	
	3.51-4	1(2%)	0	
Apgar score (5 minutes)	<7	0	3(6%)	0.2 (NS)
	7 to 8	2(4%)	3(6%)	
	9	48(96%)	44(88%)	
NICU admission (Days)	0	33(66%)	16(32%)	0.2(NS)
	1	13(26%)	7(14%)	
	2	4(8%)	23(46%)	
	3	0	3(6%)	

NS - Non significant, NICU – Neonatal intensive care unit

Most common maternal adverse effect was headache observed in 26 (52%) cases in study group. No adverse effect was observed in control group. Majority of babies had birth weight between 2.51-3 kg in both groups and were comparable. Forty eight (96%) babies in study group and 44 (88%) babies in control group had Apgar score of 9. NICU care was not required in 33 (66%) babies in study group and 16 (32%) babies in control group. The findings were not statistically significant (table 5).

Discussion

Prostaglandins like PGE1 and E2 are most widely accepted methods for cervical ripening but the major problems associated with their use is the induction of uterine contraction leading to uterine hyperstimulation, meconium stained liquor and FHR abnormality due to stimulatory effect on the myometrium.[10] The discovery of the presence of NO generating system in the cervix and their pivotal role in the ripening of cervix may prove to be a major turning point for cervical ripening prior to labour induction. The major advantage of using NO donors as a cervical ripening agent lies in the fact that they induce cervical ripening without stimulating myometrial contractility.

Recently the efficacy and safety of NO donors ISMN for outpatient pre-induction cervical ripening has been

investigated and results of these studies indicated that this agent shows some promise as an effective cervical ripening agents.[11, 12]

In our study, we compared ISMN with placebo for cervical ripening prior to induction of labour with misoprostol in each group. The two groups were comparable in demographic parameters such as age and parity. We found statistically significant change in mean Bishop's score after 16 hrs in ISMN group as compared to placebo. These results are consistent with study conducted by other authors [13-16]. Solimun [17] noted statistically significant improvement in mean Bishop score in combination therapy of ISMN with misoprostol as compared to ISMN or misoprostol alone. Their result have substantiated that combined use of these drugs may be synergistic and more effective in cervical ripening. However Bullarbo et al [18] failed to demonstrate any significant change in mean Bishop score after ISMN administration as compared to placebo, though number of women going into labour after 24 hrs of drug administration was significantly more in ISMN group (p value 0.01). This discrepancy in the finding could be due to higher baseline Bishop score in ISMN group before drug administration as compared to placebo group.

In current study, the number of vaginal deliveries was more than twice in the study group as compared to control group, thus reducing the caesarean section to half in study group. But the results were not statistically significant. However no statistical significant difference noted in rates of vaginal deliveries and caesarean section rate between ISMN or misoprostol group in study conducted by other authors [13, 19]. All these trial have used ISMN alone or in combination with misoprostol but not sequentially as we did in our study. The most common indication for caesarean section in both groups in our study was meconium stained liquor which may be due to the use of misoprostol in both groups. Similarly Collingham et al [20] reveal that ISMN is not associated with meconium staining of liquor.

In the present study, induction failure was more common in control group as compared to study group. Chanrachakul et al[19] noticed less induction failure in misoprostol alone group as compared to ISMN alone group and results were statistically significant. Induction failure was not statistically different in misoprostol plus ISMN group (27.2%) as compared to misoprostol plus placebo group (23.5%) in trial conducted by Abdellah et al [13]. This contrast in finding may be due to smaller sample size in our study (100 as compared to 290) and also sequential use of misoprostol after 16 hrs of either ISMN or placebo as compared to concurrent use of the drugs in their trial.

In our study, number of misoprostol doses required to achieve vaginal delivery was less in study group as compared to control group whereas, oxytocin was required in 81.25% cases in the control group as compared to only 9.09% cases in the study group. While Soliman[17] observed that the mean durations of the first and the second stage of labor were significantly shorter in the misoprostol and the combination therapy groups compared with the IMN group (p - 0.048 and 0.02, respectively). Oxytocin was needed in 61 women (93.8%) in the IMN group compared with 14 women (21.5%) in the misoprostol and 17 women (25.8%) in the combination therapy groups ($p < 0.0001$). However Soliman[17] compared the ISMN, with misoprostol and combination of two drugs in contrast to our study where we use sequential use of ISMN and misoprostol and misoprostol group.

In the present study, induction to delivery interval was shorter for most of the cases (54.5%) in the study group, who delivered vaginally within 12 hrs while all cases in control group delivered vaginally beyond 12 hrs. Similar results were found in trial conducted by Hamideh et al[16]. However Chanrachakul et al [19] noticed significantly longer induction to delivery interval in ISMN alone group as compared to misoprostol alone group. This discrepancy in the findings may be due to comparing ISMN alone with misoprostol alone in their trial in contrast to our study where ISMN with misoprostol was compared with misoprostol alone. This shows that combination of misoprostol with ISMN has synergistic effect on cervical ripening as compared to ISMN alone.

In our study mild headache was noted in ISMN group, which responded to simple analgesic while other adverse effects like palpitation, dizziness and hypotension were not reported by patients in either group. These results were similar to the findings in other trials.[15, 20] Both the groups were comparable in neonatal birth weight in our study. In present study, 5 minute neonatal APGAR scores were comparable in both the groups. In our study, there was no statistical difference in neonatal NICU admissions in the two groups (p-value - 0.2). These findings are consistent with other trials. [13, 19, 20]

Conclusions

Nitric oxide (NO) donor, Isosorbide mononitrate is safe, well tolerated and effective cervical ripening agent, which induces ripening of cervix without causing uterine contraction. In present study, use of NO donors prior to labour induction has lead to significant improvement in mean bishop score and also reduced the number of misoprostol doses required to achieve vaginal delivery in study group. However, larger studies may be required.

Conflict of interest: None. **Disclaimer:** Nil.

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