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Intravaginal Isosorbide Mononitrate and Misoprostol Versus Misoprostol Alone For Induction Of Labour

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Abstract:
Background*: Induction implies stimulation of uterine contractions before the onset of labour with or without ruptured membranes , a process that generally employs prostaglandins to soften and open the cervix. Cervical ripening is necessary for cervical dilatation and commonly used to enhance the rate of successful labour induction. Prostaglandins are used commonly for ripening but it causes uterine contractions which cause hyperstimulation of the uterus leading to fetal distress. So, the search continues for an ideal ripening agent that cause cervical ripening without stimulating uterine contractions and reducing the risk of tachysystole.. Isosorbide mononitrate causes increase in cyclo-oxygenase-2 which induces endogenous prostaglandin production in the cervix and also leads to cervical ultrastructural rearrangement that is similar to spontaneous onset of labour. We aim to study vaginal isosorbide mononitrate with misoprostol compared to misoprostol alone to assess safety and efficacy of isosorbide mononitrate in pre-induction cervical ripening.*
Materials and Methods*: In this Open labelled randomized controlled trial 80 patients requiring induction of labour with an unfavourable cervix (Bishop score ≤ 6) were included. They were randomly divided into two groups by using computer generated random number tables..In group I, 20mg of isosorbide mononitrate and 25mcg misoprostol was given intravaginally in the posterior fornix 4 hours apart upto maximum 8 doses or till Bishop>6. In group II induction was done with misoprostol alone 25mcg was given 4 hourly maximum upto 200mcg or Bishop>6 which ever is earlier. Augmentation was done in both the groups either by artificial rupture of membranes or Oxytocin drip. Labour was monitored by WHO PARTOGRAPH. Primary outcomes (cervical ripening, change in the Bishop score, induction to delivery time interval, no of vaginal deliveries)and secondary outcomes (neonatal APGAR SCORE at 1 and 5 min , rate of admission to NICU and maternal side effects like headache , hypotension, PPH and gastrointestinal symptoms) was compared in both the groups.*
Results*: In both the groupsprimigravida subjects were more in number (45% in group I and 42.5% in group II).Most common indication for induction at term was post dated pregnancy. Both groups were found to be comparable in terms of pre induction Bishop score. The mean Bishop score at 12 h was significantly higher in the group I (7.1 ± 1.9) than the group II (4.8 ± 2.3) ;p value <0.001. The caesarean rate was less in group I but the result was not statistically significant (p=0.11). Most common indication for caesarean section was acute fetal distress in both the groups (82.35% in group I and 65% in group II). Neonatal outcome was comparable in terms of APGAR score and admission in NNU/NICU .There were minimal side effects in both the groups with no maternal and fetal compromise.*
Conclusion:*Induction of labour with Isosorbide Mononitrate and Misoprostol versus Misoprostol alone has better outcome in terms of change in the Bishop score, reduced induction to delivery time interval and more number of vaginal deliveries with reduced caesarean delivery rates and minimal side effects and no fetal compromise*
Key Word*: Cervical ripening, Isosorbide mononitrate, Prostaglandins, Bishop score*

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I. Introduction

Induction implies stimulation of uterine contractions before the onset of labour with or without ruptured membranes. When the cervix is closed and uneffaced labour induction will always commence with cervical ripening; a process that generally employs prostaglandins to soften and open the cervix.[1] Cervical ripening usually begins prior to the onset of labour and is necessary for cervical dilatation and subsequent passage of the fetus.[2] Cervical ripening is commonly used to enhance the rate of successful labour induction. Induction of labour with an unripe cervix is the main cause of induction failure.[3] There are various

pharmacological drugs used for cervical ripening and induction like PGE1 and PGE2. Prostaglandins cause uterine contractions which cause hyperstimulation of the uterus leading to fetal distress. So, the search continues for an ideal ripening agent that cause cervical ripening without stimulating uterine contractions and reducing the risk of tachysystole which may reduce the incidence of meconium stained liquor and fetal heart rate abnormalities.

During the recent years, Nitric oxide donors (NODs), like isosorbide mononitrate (IMN), has been studied as an agent for pre induction cervical ripening with less adverse effects. In addition, NODs have a relative relaxant effect on the uterine myometrium. Thus, these are not expected to cause uterine hyperstimulation in contrast to prostaglandins. Isosorbide mononitrate causes increase in cyclo-oxygenase-2 which induces endogenous prostaglandin production in the cervix and also leads to cervical ultrastructural rearrangement that is similar to spontaneous onset of labour.[4] Isosorbide mononitrate is an **FDA** approved **CATEGORY C** drug; IT IS COST EFFECTIVE and easily available in the market.

Thus, we aim to study vaginal isosorbide mononitrate with misoprostol compared to misoprostol alone after randomization to assess safety and efficacy of isosorbide mononitrate in pre-induction cervical ripening and to assess whether there is any reduction in the required number of doses of misoprostol when used in cervix that is primed with isosorbide mononitrate which may reduce the dose related adverse effects of misoprostol.

II. Material And Methods

This open labelled randomized control trial was carried out on patients of Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh from june 2017 to june 2018. A total 80 pregnant females were included in this study.(10)

Study Design: open labelled randomized control trial

Study Location: This was a tertiary care teaching hospital based study done in Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh, India.

Study Duration: June 2017 to June 2018

Sample size: 80 patients.

Sample size calculation: 80 pregnant women as per the formula[5]

N = 16 SIGMA2/ d2 + 1 ± 20% contigency in each group.

Subjects & selection method: The study population was drawn from Ante natal Clinic (ANC Clinic) who presented to Department of Obstetrics and Gynaecology in Queen Mary Hospital, Lucknow, Uttar Pradesh from june 2017 to june 2018. Patients were divided into two groups (each group had 40 patients) using computer generated random number tables.

Group I received 20mg of isosorbide mononitrate and 25mcg misoprostol intravaginally in the posterior fornix 4 hours apart upto maximum 8 doses or till Bishop>6.

Group II received misoprostol alone 25mcg was given intravaginally in the posterior fornix 4 hourly maximum upto 200mcg or Bishop>6 whichever is earlier.

Inclusion criteria:

1. Singleton pregnancy at term in cephalic presentation.
2. Intact membranes
3. Obstetrical indication for labour induction.
4. Bishop score <6.

Exclusion criteria:

1. Parity (≥ 4)
2. Bishop score >6.
3. Rupture of membranes ;chorioamnionitis.
4. Previous caesarean section, or any other type of uterine surgery like myomectomy).
5. Malpresentation.
6. Multiple pregnancy.
7. Maternal medical disorder.
8. Contracted pelvis.

Procedure methodology

80 women requiring indicated induction of labour with an unfavourable cervix (Bishop score ≤ 6) were included in the study. Cases were selected from antenatal clinic (ANC OPD) and patients admitted in the hospital. They were randomly divided into two groups by using computer generated random number tables. Written and informed consent was obtained, they were enrolled in the study. This study was approved by the ethics committee of Faculty of medicine King George Medical University.

At admission cardiotocography was performed to ensure that the fetal heart activity was normal. After taking consent from patients ,detailed history and examination of the patient was recorded in the working proforma

In group I, which included 40 women, 20mg of isosorbide mononitrate and 25mcg misoprostol was given intravaginally in the posterior fornix 4 hours apart upto maximum 8 doses or till Bishop>6. Vital signs were monitored every 30 minutes to 1hr. Women were also monitored for symptoms such as headache, palpitations, nausea , dizziness, fainting, and gastrointestinal symptoms.According to the protocol , FHR and uterine activity were monitored continuously and recorded every 15 minutes in first stage and every 5 minuted in 2nd stage of labour.

In group II which included another 40 women induction was done with misoprostol alone 25mcg was given 4 hourly maximum upto 200mcg or Bishop>6 which ever is earlier.

Augmentation was done in both the groups either by artificial rupture of membranes or Oxytocin drip (2.5 U or 5U in 500ml of Ringer's lactate solution)was started and it was titrated according to the frequency and intensity of contractions. An oxytocin infusion was started at 2Mu/min and increases in increments of 1-2 mU/min at 15-30 min intervals as needed to achieve an adequate contraction pattern.

Labour was monitored by WHO PARTOGRAPH. Caesarean delivery was performed for obstetrical indications, including failed induction, dystocia, and persistant non reassuring FHR pattern after resuscitation. In both groups primary and secondary outcome was recorded as the proforma designed for the study.

Primary outcomes were cervical ripening, change in the Bishop score, induction to delivery time interval, no of vaginal deliveries. Secondary outcomes were measured in terms of neonatal APGAR SCORE at 1 and 5 min , rate of admission to NICU and maternal side effects like headache , hypotension, PPH and gastrointestinal symptoms.

Statistical analysis

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD Student's *t*-test was used to ascertain the significance of differences between mean values of two continuous variables and confirmed by nonparametric Mann-Whitney test. In addition, paired *t*-test was used to determine means in the case of two samples that are. The level $P < 0.05$ was considered as the cutoff value or significance.

III. Result

A total of 40 patients in each group were included in the study. Most of the patients were unbooked in my study with 77.5% and 62.5% respectively in both the groups(p value 0.14 NS). Among all the patients Majority of the subjects were 21- 25 years of age group(62.5% in group I and 50% in group II) followed by 26-30 years(15% in group I and 16% in group II)(p value 0.143 NS). Most of the subjects in both the groups were primiparous (45% in group I and 42.5% in group II) followed by para 2(25% in group I and 32.5% in group II)(p value 0.780 NS). Maximum number of subjects were of period of gestation >37-≤38 wks (50% in group I and 55% in grou II)(p value 0.634 NS). Mean gestational age in grp I and grp II was 37.50±2.48 weeks 37.87±2.00 weeks. (p value0.91 NS). General condition of all the subjects : Satisfactory (100.00%) Pulse rate ; Systolic BP; Diastolic BP; and Respiratory ratewere within normal limits and comparable in both the groups. All were Afebrile (100.00%). Presentation of all the subjects was Cephalic (100.00%) Liquor was Adequate in all the subjects (100.00%) Fetal heart sound was 130-140 beats/min in all the subjects (100.00%) on auscultation with stethoscope**.** Maximum number of subjects in the study were induced in view of post dated pregnancy in both the groups (30% in group I and 25% in group II) which was significant (p=0.009) followed by fetal growth restriction (20% in group I and 15% in group II) followed by cholestasis. The initial Bishop score was similar among the study groups. No significant improvement was noted in the Bishop score at 8 h in both groups was of 4.1 ± 1.2 and 3.8 ± 1.3 *respectively* (P value= 0.287). **The mean Bishop score at 12 h was significantly higher in the combination therapy group I(7.1 ± 1.9) than the group II (4.8 ± 2.3) ;p value <0.001.(table 1)**

Time to delivery from induction was not significant among grpI and grp II(17.95±9.16 vs 22.30±24.39 p value 0.294NS). **The induction-delivery intervals, time from start of medication to onset of Active labour was significantly shorter in group I (11.1±4.8 hr vs 14.6±2.4 hr in group II p< 0.001).**The time from start of ARM and/or oxytocin to the 2nd stage of labour was significant (group I (6.1±1.5 hr vs 7.9±1 hr in group II p value < 0.001). The time from start of medication to complete vaginal delivery was shorter in group I (17.95±9.16 vs 22.30±24.39); p value=0.294. **(table 2)**

Maximum number of subjects in group I responded after 3 doses (55%) which was statistically significant while in group II maximum number of patients responded after dose 4(40 %) **(table 3).**

Mode of delivery was comparable in both the groups (grp I 45% Lscs and 55% vaginal / grp II 62.5% Lscs and 37.5% vaginal p value NS). This non significant p value was maintained when comparison was done

among primiparous to multiparous. The most common indications for caesarean section in both groups was acute fetal distress (77.7%) . The number of failed inductions were almost equal in both groups. Comparable side effects were present in both the groups **(table 4).**

Fetal outcome was four newborn (10.8%) in group 2 had an Apgar scores ≤7 compared with one newborns (2.5%) in group 1 (p value=0.139); though the NNU/NICU admission were none in Group I ;2newborn in group 2 were shifted to NNU;and none to NICU. Neonatal Outcome of Study Population in terms of Birth weight was comparable in both groups (grp I 2.72±0.31 (n=40) Grp II 2.70±0.44 (n=40) p valvu 0.792 NS**(table 5)**

IV. Discussion

Induction of labour in women with unripe cervix is frequently prolonged and very often unsuccessful , resulting in caesarean delivery. Studies have established that prelabour cervical status highly correlates with the induciblity of labour. In this study the two groups were comparable in their demographic profile, preinduction Bishop score and indication for induction of labour. The time from start of medication to complete vaginal delivery was non significant between group I (17.95±9.16 vs grp II22.30±24.39); p value=0.294 which was against the study done by E**lsokary et al. 2015** [6]who demonstrated significant reduction with IMN and time of 19.56 hrs (p value <0.001) and also in discordance with **Ahmed T. Soliman et al. 2013** [7] who demonstrated a time of14.8±6.2 hrs (p value <0.001) .The difference inthe results could be due to the dose of IMN used in the present study(20 mg) when compared to other two studies (40 mg). A less dose was considered in view of synergestic action of misoprostrol when used with IMN in grp I patients.

In present study there was significant reduction in the number of repeat doses required for cervical ripening(Bishop>6) between grp I and grp II (3 doses vs 4 doses p value 0.02 Significant) signifying that addition of IMN can decrease the net dose of PG's when used in combination. In thisstudy ,not much improvement was seen in the Bishop score after 8 hrs. However, significant change in the Bishop score was observed in my study after 12 hrs of start of induction (7.1±1.9) in study groupI comparing to group II 4.8±2.3 which was statistically significant ***p <0.001.*** which is in concordance with study done by Ahmed T Soliman[7]he mean Bishop score at 6 h was significantly higher in the combination therapy (7.1 ± 1.9) and the misoprostol (6.8 ± 2.3) groups compared with the IMN group (6.1 ± 2.1, $P = 0.02$)

The need of oxytoxin for induction was less in Grp II as compared to Grp I (37.5% vs 15%) and the most common method to augement labour was combined ARM and oxytocin in both the groups which was comparable (50%vs 57.5% p value 0.5 NS).this was in accordance with study done by Ramya Krishnamurthy [8] as she also noted that the need for oxytocin was less in IMN group when compared to placebo group but not in harmony with study done by Abdul Razaq[9] regarding oxytocin need there is significant decrease in use of oxytocin for initiation or augmentation of labour .

In both the groups there was no statistically significant difference between both the groups as regard to birth weight, Apgar score, and need for NNU/NICU admissions. The result were comparable with other studies Elsokary et al. 2015 [6], Ahmed T. Soliman et al. 2013[7]and Elmahdy et al. 2016[10]

In the present study , not many patients complained of headache as compared to the previous studies where headache was the major side effect as shown in a study done by Elsokary et al. 2015 [6]where incidence of headache was 46.7% in IMN group [41] Abdellah et al. 1997 [5] found no significant difference between the two groups in the incidence of uterine hypersystole or tacysystole , which was similar to the present study.

V. Conclusion

The present study suggests that both intravaginal misoprostol and combination of isosorbide mononitrate and misoprostol are safe and effective modes of labour induction. Isosorbide mononitrate and misoprostol is more effective than misoprostol alone in terms of post induction Bishop Score, shorter induction to active phase interval and no of repeat doses.

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Table 1 Pre induction bishop score and post induction scores at 8 and 12 hours.

	GROUP I (ISM+Misoprostol) (n=40)	GROUP II (Misoprostol) (n=40)	p value
Pre induction Bishop score	3.1±1.1	3.4±1.0	't'=1.342 p= 0.184(NS)
	GROUP I	GROUP 2	p value
After 8 hrs(2 doses)	4.1±1.2	3.8±1.3	't'= 1.072 p=0.287(NS)
After 12 hrs(3 doses)	7.1±1.9	4.8±2.3	't'= 4.876 ***p <0.001***

Table 2.Induction to delivery time interval. Time to onset of active labour after induction and from augementation to onset of 2nd stage of labour was significantly less in Grp I as compared to Grp II.

	GROUP I Mean±SD(Hr)	GROUP II Mean±SD(Hr)	P value
TIME FROM START OF MEDICATION TO ONSET OF ACTIVE LABOUR	11.1±4.8	14.6±2.4	't'= 4.125 **p< 0.001**
TIME FROM ARM/ OR OXYTOCIN TO ONSET OF 2ND STAGE OF LABOUR (h)	6.1±1.5	7.9±1.5	't' =5.367 **p< 0.001**
TOTAL TIME FROM START OF MEDICATION TO DELIVERY (h)	17.95±9.16	22.30±24.39	't'= 1.056 p=0.294

Table 3. Comparison of Number of doses required in Grp I and II showed that significant patients in Grp I were induced at 3rd dose as compared to 4th dose in GrP II.

No. of doses required	GROUP I (n=40)	GROUP II (n=40)	p value
2 doses	12(30%)	11(27.5%)	0.6
3 doses	22(55%)	8(30%)	**0.02** p< 0.001
4 doses	4(10%)	16(40%)	0.10
≥5 doses	2(5%)	5(12.5%)	0.4

Table 4.Comparison of side effects between both the groups.

SIDE EFFECTS	GROUP I (n=40)	GROUP II (n=40)	't'	p value
Headache	2	0	2.051	0.152
Nausea and vomting	2	3	0.213	0.644
Palpitations	1	0	1.013	0.314
Tachysystole	0	3	3.117	0.077
PPH	1	0	1.013	0.314

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Table 5. Fetal outcome and neonatal outcome between the groups

	Group I (n=40)		Group II (n=37)		Total (n=77)	
	No.	%	No.	%	No.	%
<7	1	2.50	4	10.81	5	6.49
≥7	39	97.50	33	89.19	72	93.51
	χ^2=2.186(df=1); p=0.139					

	Group I (n=40)	Group II (n=40)	Total (n=80)
Birth Weight (Kg)	2.72±0.31 (n=40)	2.70±0.44 (n=40)	2.71±0.38 (n=40)
	t=0.264; p=0.792 (NS)		