Original Article

Use of Nitric Oxide Donor Isosorbide Mononitrate for Cervical Ripening at 41 Weeks' gestation: a Double Blind, Randomized, Controlled Trial.

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Abstract:

Background: The ideal agent for cervical ripening would induce adequate cervical ripening with minimal adverse effects to the mother and the fetus, the most favorable method for cervical ripening is not fully agreed till now, however, vaginal administration of isosorbide mononitrate (IMN) is considered a low-risk method of labor induction for post term. Our study was designed to assess the effect of IMN on cervical ripening and labor induction among 41week's pregnant women. **Materials and Methods:** This study will be conducted on 100 pregnant women recruited from the outpatient clinic at El Shatby Maternity University-Hospital, all cases pregnant at 41 weeks gestational age, uncomplicated singleton pregnancy, cephalic presentation, intact membranes and not in labor. Cases divided into 2 groups in first group 40 mg isosorbide mononitrate (IMN) tablet applied vaginally in posterior fornix, and in second group placebo applied vaginally in posterior fornix. Follow up the cervical status after 24 hours of administration, the patient were asked about new symptoms especially headache, palpitation, dizziness or abdominal pain and the mode of delivery was be assessed. **Aim of the Work:** The aim of this study is to assess the efficacy of the nitric oxide donor isosorbide mononitrate on cervical ripening at 41 weeks' gestation. **Results:** There was a significant difference between the IMN group and the controls with respect to the Bishop score (4. 40 vs. 3. 68, *P* = 0. 031) table (1), but there was no significant differences in the mode of delivery between the two groups table (2) The major side effect of IMN was headache, about 70% of cases complain from headache, which responded to a mild analgesia. **Conclusions:** Vaginal administration of IMN reduces the cervical resistance and induces cervical ripening without inducing uterine hyperstimulation or abnormal fetal heart rate. So IMN can be used in outpatient clinic for cervical ripening with no need for admission or close fetal monitoring.

Keywords: Cervical ripening, Nitric oxide donor.

Introduction:

Post term pregnancy refers to any baby born after 42 weeks gestation or 294 days past the first day of the mother's last menstrual period. [1] Post term may be in itself be high risk The placenta, which supplies the fetus with nutrients and oxygen from the mother start aging and will eventually fail,[2] The etiology of post-term pregnancy is not unknown; however miscalculation of last menstrual period (LMP) may be common cause of post term.[3] The use of ultrasound in early pregnancy for precise dating significantly reduces the number of post-term pregnancies compared to dating based on the LMP. [4]

Post-mature baby are larger than average size baby, so increase the incidence of cephalopelvic disproportion, shoulder dystocia, operative vaginal delivery[5], postpartum hemorrhage and caesarean sections rate[6]. Meconium aspiration.[7] fetal macrosomia increase incidence of birth injury, [8] neonatal encephalopathy and[9] Sudden infant death syndrome. [10]

Once fetus is diagnosed post-mature, the mother should be offered additional monitoring as this can provide valuable clues that the fetus's health is being maintained. Compared with waiting indefinitely or waiting at least one week for labor to occur spontaneously, labor induction after 41 weeks of gestation is associated with fewer perinatal deaths.[11]

Physiological cervical ripening is an active biochemical process; it has been described as an inflammatory process.[12] The Bishop Score is a common measure used to assess the cervical repining[13]. Non pharmacologic approaches to cervical ripening included herbal compounds, castor oil, hot baths, enemas, sexual intercourse, and breast stimulation till now have not proven efficacy for cervical ripening or induction of labor.[14] Surgical methods for cervical repining (stripping of the Membranes, amniotomy, balloon catheter insertion in cervix), have been recommended for cervical ripening, however risks of this techniques including infection, bleeding, accidental rupture of the membranes, and patient discomfort. [15, 16]

Pharmacological cervical ripening, Prostaglandins E2 (Misoprostol) are the current method used for cervical ripening and labor induction. [17] But risks associated with it, s use include uterine hyperstimulation, nausea, vomiting, diarrhea, fever and accompanying FHR changes. [18] Uterine rupture in women with previous cesarean section limiting its use to women who have a uterine scar.[19] There is insufficient information to support the use of mifepristone and relaxin for cervical ripening.[20] Oxytocin is the preferred pharmacologic agent for inducing labor when the cervix is favorable or ripe.[21]

Nitric oxide (NO) is a small, highly reactive, free radical gas with a half-life time of a few seconds, [22] expressed in three isoforms, all of these isoforms are present in the various cells of the uterine cervix.[23] Cervical nitric oxide production is very low in post term pregnancy. Thus, it has been suggested that reduced cervical nitric oxide release may contribute to prolonged pregnancy.[24] In cervical ripening immunological mediators play a crucial role in this process. NO is involved in the acute inflammatory response and amplifies the cytokine cascade stimulated during this response,[25] via interactions either with prostaglandin biosynthesis or with lytic enzymes. It stimulates cyclooxygenase to increase the production of pro-inflammatory prostaglandins.[26] Its action accomplished by effects on connective tissue and smooth muscle cells.[27] Isosorbide mononitrate (IMN) is a drug used principally in the treatment of angina pectoris. Vaginal administration IMN reduces the cervical resistance without inducing uterine hyperstimulation,or abnormal fetal heart rate.[28]

Participants:

Participants in this study consisted of 100 post term pregnant women at 41 weeks gestational age; the participants were selected according to the inclusion/ exclusion. Inclusion criteria were: women gestational age of 41weeks, not in labor, cephalic presentation, singleton fetus, having a normal non-stress test and biophysical test. Exclusion criteria: pregnancy associated diseases as preeclampsia, placenta previa or unexplained vaginal bleeding during pregnancy, cardiac, pulmonary, renal or hepatic disease, history of severe persistent headache, polyhydramnios, placenta previa, probability of placenta abruption, or any contraindication for induction of labor were excluded.

Intervention:

At the first visit each woman will be subjected to: complete history taking, routine investigations: complete blood picture, fasting blood sugar and complete urine analysis, general examination, obstetric examination (vaginal examination to assess the pelvis, Bishop score and the presenting part), obstetric ultrasonography, biophysical profile and doppler to assess fetal condition.

Cases divided into 2 groups, first group received 40 mg IMN tablet applied vaginally in posterior fornix, second group received placebo applied vaginally at the same site. Women were permitted to go home and instructed to come to the hospital immediately if they had any sign of dangerous symptoms (leakage of amniotic fluid, vaginal bleeding or reduction in fetal movements), otherwise they were asked to come back to the hospital after 24. The women were examined vaginally by the same physician to assess the cervical status, fetal monitoring and follow up the case till delivery.

Results:

There was a significant difference between the IMN group and the controls with respect to the Bishop score (4. 40 vs. 3. 68, P = 0. 031) table (I), but there was no significant differences in the mode of delivery between the two groups table (II) The major side effect of IMN was headache, about 70% of cases complain from headache, which responded to a mild analgesia.

Table (I): Comparison between the two studied groups regarding the Bishope base score before and after 24 hours of administration

	Study group	**Control group**
Bishope base score before administration		
Min. – Max.	0. 0 – 6. 0	0. 0 – 6. 0
Mean ± SD.	3. 72 ± 1. 29	3. 60 ± 1. 54
Median	4. 0	3. 0
p	0. 471	
Bishope score after administration		
Min. – Max.	0. 0 – 7. 0	0. 0 – 7. 0
Mean ± SD.	4. 40 ± 1. 81	3. 68 ± 1. 73
Median	5. 0	3. 0
p	0. 031*	

Table (II): Comparison between the two studied groups regarding the mode of delivery.

	Study group		**Control group**	
	No.	**%**	**No.**	**%**
Mode of delivery				
Normal vaginal delivery	32	64. 0	26	52. 0
C. S.	18	36. 0	24	48. 0
p	0. 224			

Discussion:

Our study demonstrated that outpatient use of IMN has a significant effect in cervical repining and Bishop Score after 24 hours of administration in posterior cervix. In our study 30 women (60%) in the IMN group in contrast to 10 women (20%) in the placebo group had positive cervical repining after 24 hours (p=0. 001*). These results are consistent with previous studies were done by Erling Ekerhovd study in 2003.[28], Maria Bullarbo, [29] and Rameez study in 2007, which concluded that outpatient cervical ripening followed by labor induction with isosorbide mononitrate seems to be an effective, safe and well tolerated procedure. [30]Another study done by Eddama et al, demonstrated

that the proportion of women with an unripe cervix after 24 h of outpatient treatment was significantly lower in the IMN group as compared with the placebo group (64% vs. 77%, *P* = 0. 02). [31]In our study there was a significant difference between the IMN group and the controls with respect to the Bishop score (4. 40 vs. 3. 68, *P* = 0. 031*), which was consistent with Hamideh Yazdizadeh et al, study in which There was a significant difference between the IMN group and the control group with respect to the Bishop score (4. 92 vs. 4. 03, *P* = 0. 0. 01). [32] In another study done by Kavita Agarwal et al, the Bishop score was significantly improved 24 hours after initiation of the outpatient IMN treatment (*P*<0. 001) and the needs for further cervical ripening and oxytocin infusion were less in the study than in the control group (*P*<0. 001 and *P*=0. 008). [33]

In our study there was no significant differences in the mode of delivery between the two groups, In our study 32 women treated with isosorbide mononitrate went into normal labor compared to 26 women in the placebo group (p>0. 05), there was no significant differences as regard to normal labor. In Mohamed Furukan study reported that there was marked increase in the proportion establishing spontaneous labor (28% *vs* 7. 5%, *P* < 0. 01) and cervix being favorable for oxytocin infusion (40% vs 9% *P* < 0. 001) 2 days after therapy, in the same study the cesarean section rates were similar in both groups. [34]

In our study there was no significant differences in cesarean delivery rate (36. 0%vs 48%, p>0. 05), neonatal outcomes and apgar score between the two groups, which was consistent with Sherif M. Habib et al, study. [35]

The most common side effect in women treated with (IMN) was headache, experienced by 35 women (70%) compared to 4 women (8%) in placebo group ((p< 0. 05) the intensity of headache was be from mild to moderate headache. However in Maria Bullarbo study reported more higher incidence (88%) of women treated with isosorbide mononitrite was complain from headache compared to (4%)in placebo group. [29]

Conclusions:

Vaginal administration of IMN reduces the cervical resistance and induces cervical ripening without indu cing uterine hyperstimulation or abnormal fetal heart rate. So IMN can be used in outpatient clinic for cervical ripening with no need for admission or close fetal monitoring.

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