Nitric oxide donor isosorbide mononitrate for cervical ripening at term

"Randomized Double Blind, Controlled Study"

Thesis

Submitted for partial fulfillment of Master Degree in

Obstetrics & Gynaecology

By

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بسم الله الرحمن الرحيم

" الْحَمْدُ لِلّهِ الَّذِي هَدَانَا لِهَـــذَا وَمَا
كُنَّا لِنَهْتَدِيَ لَوْلا أَنْ هَدَانَا اللّهُ "

صدق الله العظيم

سورة الأعراف – آية 43

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Hossam Younis
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INTRODUCTION

Induction of labour is defined as an intervention designed to artificially initiate uterine contractions leading to progressive dilatation and effacement of the cervix and birth of the baby. This includes both women with intact membranes and women with spontaneous rupture of the membranes but who are not in labour. The term is usually restricted to pregnancies at gestations greater than the legal definition of fetal viability (24 weeks in the UK). Induction of labour is indicated only when it is agreed that the mother or fetus will benefit from a higher probability of a healthy outcome than if birth is delayed. ***(RCOG Guidelines 2001)***

The process of induction of labour should only be considered when vaginal delivery is felt to be the appropriate route of delivery. ***(SOGC 1996)***.

Physicians are often pressured to "do something" after a women's due date has arrived, and it is often difficult not to intervene. Elective induction is not without consequences, such as increased cesarean delivery rates in nulliparous women and the potential for increased health care cost ***(Kaufman et al., 2002)***.

Cervical ripening, clinically diagnosed by softening, effacement, and dilatation of the uterine cervix, is commonly stimulated pharmacologically by the use of vaginally administered prostaglandins before induction of labour. However, prostaglandins may cause adverse maternal and fetal effects, mainly because of their stimulatory action on uterine contractions ***(Ekerhoved et al., 2003)***. It has been estimated

that about 5% of women have uterine hypertonus after administration of prostaglandins for the induction of cervical ripening ***(Keirse, 1995)***. Uterine hypertonus often results in abdominal pain and anxiety, but it may also cause circulatory complications that could be fatal to the unborn child. An ideal agent for cervical priming would induce adequate cervical ripening without adverse maternal and fetal effects (***Calder, 1998)***.

A few studies have investigated alternatives to induction of labor and management of the non ripe cervix at term. One such alternative is outpatient cervical ripening with prostaglandine E_2 has been shown to be effective in improving Bishop scores and decreasing the length of gestation ***(Magann et al., 1998)***. ***Stitely et al., 2000*** found one to two applications of intravaginal prostaglandin E_1 (misoprostol) at 41 weeks gestation decreased the length of gestation. ***Incerpi et al., 2001*** used a similar protocol and found 1 to 2 serial applications of intravaginal misoprostol were effective in reducing the need for induction in women with gestational diabetes at 38.5 weeks.

McKenna et al., 2004 reported that outpatient cervical ripening with a single 25-µg intravaginal dose of misoprostol in women with unfavorable cervices at term is potentially an excellent alternative to induction of labour, especially when there are marginal indications for induction and was effective in improving the Bishop score and decreasing the mean interval to delivery

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Nitric oxide is a free radical with a short half-life. It exists in the body for at most 6–10 seconds before it reacts

with oxygen and water to form nitrates and nitrites. Nitric oxide diffuses across cell membranes rapidly and is only synthesized on demand. It is a major chemical messenger in the human body, mainly in the central nervous system. Its first discovered function was as an endothelium-derived relaxing factor and a primary regulator of blood pressure.The nitric oxide– generating system is present in the cervix and is upregulated towards term as well as during labor in animal studies ***(Li et al., 2003)***.

During the last few years it has become clear that intravaginal administration of nitric oxide donors, such as isosorbide mononitrate and glyceryl trinitrate, induces cervical ripening in first trimester of pregnant women before surgical termination of pregnancy. In addition, pretreatment with the nitric oxide donor isosorbide mononitrate has proved to be associated with fewer side effects than the prostaglandin analog. On the basis of these studies, it has been suggested that nitric oxide donors may produce cervical ripening for the induction of labor, without causing serious adverse effects ***(Ekerhoved et al., 2003)***.

AIM OF THE WORK

Estimation of the efficacy of vaginal nitric oxide donor isosorbide mononitrate (IMN) at 38 weeks or more gestation as a cervical ripening agent for unfavorable cervix .

PATIENTS AND METHODS

The study will include 60 pregnant women recruited from Obstetric outpatient clinic of Ain Shams University Maternity Hospital.

A Detailed history will be taken from women with gestational age of at least 38 weeks, clinical examination and investigation by ultra-sound and non stress test will be done for them all to determine who will be included and excluded from the study.

Criteria for enrollment will include:

(1) Gestational age of at least 38 weeks (determined by the date of the last menstrual period [LMP] preceded by regular menstrual cycles and confirmatory ultrasound <20 weeks).

(2) Singleton pregnancy.

(3) Cephalic presentation.

(4) An unfavorable cervix (Bishop Score <5).

(5) Amniotic fluid index >5.

(6) Reactive Non stress test.

(7) Intact membranes.

(8) Absence of contraindication to vaginal delivery.

(9) No contraindication to use of nitric oxide donor

isosorbide mononitrate.

(10) Ability to comprehend the nature of the study.

Women with the following criteria will be excluded from the study:

1. Maternal age< 18 years.
2. Estimated fetal weight >4000 gm or under 2000 gm.
3. Placenta previa, vasa previa or other unexplained vaginal bleeding.
4. Hypersensitivity to prostaglandins or nitric oxide donor isosorbide mononitrate.
5. Prior uterine surgery or previous caesarian section.
6. Evidence of intra amniotic fluid infection.
7. Severe asthma or cardiovascular disease, renal or hepatic dysfunction.
8. Evidence of pre-eclampsia.
9. Parity >5.
10. Presence of contraindication to vaginal delivery.
11. Major cephalopelvic disproportion or fetal malpresentation.
12. History of cesarean delivery or major uterine surgery.
13. Fetal distress.
14. Ruptured fetal membranes.

Women who will be included in the study will be divided randomly into 2 groups:

Group I: Will include 30 prgnant women and they will receive 40mg nitric oxide donor isosorbide mononitrate which will be inserted in the posterior fornix.

Group II: Will include 30 prgnant women and they will receive placebo which will be inserted in the posterior fornix.

After insertion of the tablet each woman will be observed for one hour for fetal heart rate and uterine contractions.

At that point, the woman will be discharged with instruction to return after 24 hours to reassess Bishop score and if it is less than 7, Non stress test will be done and if it is reactive another dose of nitric oxide donor isosorbide mononitrate or placebo will be inserted in the posterior fornix according to which group the woman belongs to. The woman will be observed for one hour for fetal heart rate and uterine contractions and will be discharged home with instructions to return to the hospital if spontaneous labor failed to occur at 41weeks of gestation or if she experienced diminished fetal kick counts or contractions occurring one every 5 minuts .

The two groups will be compared for :

- Bishop score on the day of addmession to the hospital.
- Interval to onset of spontaneous labor.
- Incidence of oxytocin use .
- Induction- delivery time .
- Incidence and indication of caesarean section .
- Abnormal CTG findings .
- Uterine hyper stimulation.
- Neonatal out-come

RESULTS

The collected data will be organized, tabulated and analyzed using appropriate statistical tests.

DISCUSSION

Discussion of the obtained findings and analyzed data will be done based on current related literature.

CONCLUSION AND RECOMMENDATIONS

Will be derived from the discussed items.

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