

# **NITROGLYCERINE SKIN PATCH VS PLACEBO PATCH FOR ENHANCING CERVICAL RIPENING IN LABOR INDUCTION: A RANDOMIZED CONTROLLED TRIAL**

Protocol of a Thesis

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*by*

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## **Introduction:**

Nitrous oxide donors are widely used in clinical practice for many medical conditions. Nitrous oxide (NO) is known to have a secondary messenger role in signal transduction process for many cellular functions. NO signal transduction pathway is mediated by another secondary messenger, cGMP, through activation of guanyl cyclase which in turn participate in a cellular process. For instance, NO is produced by the endothelial cell layer of blood vessels causing relaxation of the blood vessel smooth muscles and causes vasodilation (endothelial derived relaxing factor, EDRF) (**Ignarro, 1990**). The same mechanism may cause relaxation of other smooth muscles in the body. In the obstetrics and gynecology field it is approved for tocolysis in cases of risk of preterm labor (**Green-top guidelines, 2011**).

NO is expected to have a role in the remodeling process that occur in the cervix prior to onset of labor. During the cervical ripening process, chemical and physical changes to the *collagen* composition of the cervix are required to make the cervix more soft and distensible for effacement and dilation during normal delivery (**Liu et al., 2014**). There is an increasing evidence that there is a rise in the activity of inducible NO synthase (iNOS)

in the cervix before the onset of labor which may have a role in the ripening process ( **Tschugguel et al., 1999**).

Many studies have been held out to establish the efficacy of the NO donors in promoting cervical ripening and labor induction. Many patients who need termination of pregnancy may benefit its use as a safe and affordable method. Nevertheless, there is so much debate regarding their ability to have such effect. Some studies concluded that NO donors guarantee a safe method for outpatient induction of labor (**Bullarbo et al., 2007**). Other studies disagreed that they have any considerable action at all. They concluded that NO donors do not appear to be a useful tool in the process of induction of labor (**Collingham et al., 2010** ).

There is an increasing rate of deliveries by caesarean section in Egypt lately (**DHS, 2014**). One of the major causes that makes the obstetrician favors delivery by caesarean section is fear of failure or complications of induction of labor. Many preparations used in induction of labor have been associated with fetal and maternal compromise. While in developed countries, labor induction is widely

practiced; for example it accounts for 20% of pregnancies in the UK. Therefore, the search of a safer and reliable method of induction is still ongoing (**NHS Maternity statistics, 2015**).

A *Cochrane* systemic review in 2011 considered 19 trial studies to compare the efficacy of NO donors in labor induction with other agents. It concluded that NO donors do not appear to be more useful than other agents. It suggested that more studies are required to examine how NO donors may work alongside established induction of labor protocols, especially those based in outpatient settings (**Kelly et al., 2011**).

## **Aim and Objectives:**

*Aim:* This study aims to establish the efficacy of nitroglycerine skin patch as a NO donor in addition to dinoprostone for induction of labor.

*Objectives:* The primary outcome of the study is to compare the changes occurring to the cervix through the progression in the Bishop's score between NO donor (nitroglycerine patch) vs placebo; in combination with a well-established method of induction (Dinoprostone).

*The secondary objective* of the study is to observe and report possible fetal and maternal side effects that may be associated. This will establish the safety and tolerability of NO donors.

## **Research Question:**

Does the usage of Nitroglycerine skin patch enhance cervical ripening and facilitate induction of labor by Dinoprostone?

## **Research Hypothesis :**

*Null hypothesis:* Nitroglycerine skin patch does not cause advantage for ripening of the cervix nor facilitate the process of labor induction.

*Alternative hypothesis :* Nitroglycerine skin patch has favorable effect in enhancing cervical ripening and the outcome of induction of labor.

## **Methodology:**

This study will be a double-blinded randomized controlled trial and will be conducted in Ain Shams University Maternity Hospital. It will include 100 pregnant women at term who will be indicated for induction of labor.

### **Sample Size Justification:**

The study was calculated using STATA® version 11 program, setting the type-1 error at 0.5 and the power ( $1-\beta$ ) at 0.8. Sample size is correlated to former studies in induction of labor (**Collingham et al., 2010**). Calculation according to these values produced a minimal sample size of 45 cases in each group.

*Alpha error*= 0.05 (two sides)      *Power of study*= 0.8

Based on favorable outcome of cervix ( $p_1 = 41\%$ ,  $p_2 = 81\%$ ) with ratio of intervention group to control group 1:1.

### **Inclusion criteria are:**

- (1) Singleton living full-term fetus.
- (2) Cephalic presentation,
- (3) Bishop score less than 5,
- (4) Assuring fetal monitoring,
- (5) The mother does not have PROM,

**The exclusion criteria are;**

- (1) Expected fetal anomaly (eg. by ultrasound),
- (2) Abnormal presentation,
- (3) Multiple pregnancy,
- (4) Non assuring fetal CTG,
- (5) Fetus more than 90<sup>th</sup> percentile of expected weight,
- (6) Previous maternal obstructed labor or previous cesarean section,
- (7) Maternal obstetric or medical complication,
- (8) Structural anomaly of the uterus

Any woman with other general or obstetric risk will be excluded. The women that fulfill these criteria will be admitted to the hospital for induction of labor.

**Assessment:**

The women who fulfill the inclusion criteria will undergo a thorough assessment and evaluation as follow:

- 1- History: personal, medical and detailed obstetric history. Previous history of obstetric or medical complication with pregnancy and expectance of recurrence should be considered.

2- General examination: for vital signs and cardiopulmonary diseases.

General signs of other complications (eg. anemia with pregnancy) should be taken in consideration.

3- Obstetric examination: fundal level and pelvic grip for assessment of fetal size and lie. Vaginal exam will be done to assess the presentation and scoring the cervix according to Bishop's score:

(Table):Bishop score for cervical assessment(**Williams Obstetrics, 23<sup>rd</sup> ed**)

Score	Cervical Dilation	Cervical Effacement	Station of Baby	Cervical Position	Cervical Consistency
0	closed	0-30%	-3	posterior	firm
1	1-2cm	40-50%	-2	mid-line	moderately firm
2	3-4cm	60-70%	-1,0	anterior	soft (ripe)
3	5+ cm	80+%	+1, +2		

Add 1 point to overall score for pre-eclampsia and for each prior vaginal delivery.

Subtract 1 point off overall score do postdate pregnancy, no prior births, premature or prolonged rupture of membranes (water breaking).

A score of 5 or less is said to be "unfavorable." Unfavorable scoring shows mother is a candidate for cervical ripening prior to induction. A score of 6 or higher would indicate that the cervix is ripe and induction would have a higher probability of being successful. A score of 9 or higher indicates a very high probability of induction being successful.

### **Method:**

After approval of Ethics Committee of Scientific Research, the women under the study will be informed about the study plan and possible



benefits and adverse effects. After having an informed consent, they will be *randomized* into two groups receive either nitroglycerine skin patch (Nitroderm TTS® 5mg, Novartis) or a placebo patch.

**Group A:** will receive nitroglycerine skin patch at time of admission plus induction with dinoprostone 3mg (Dinoglandin® 3gm, Rotabiogen) / 8 hours vaginal tablet into the posterior fornix of the vagina.

**Group B:** will receive placebo patch at time of admission plus induction with dinoprostone 3mg (Dinoglandin® 3gm, Rotabiogen)/ 8 hours into the posterior vaginal fornix.

**Allocation and Concealment:**

Both nitroglycerine and placebo patches will be randomized according to a sequence of random numbers generated by computer. They will be enclosed in opaque, sealed, easy opening envelopes. Each envelope contains either a nitroglycerine skin patch or a placebo patch. Opening the envelope at the moment the mother enters the labor ward for induction of labor. The intervention and control groups and the investigator will be blinded about which patch the women will be assigned to.

### **Randomization and Administration:**

Both placebo and Nitroderm TTS® patches will be identical in appearance. They are randomly numbered and delivered to the residents in the admission ward. The resident obstetrician is asked to deliver the patch to the mother to apply it on the upper chest.

At the same time, dinoprostone (as Dinoglandin E2® Rotabiogen 3mg vaginal tablet) will be administered into the posterior fornix of the vagina after soaking it with gel. Another dose will be given after 8 hours according to Ain Shams University Hospital protocol for labor induction. Neither the mother nor the obstetrician would know which patch is given.

### **Evaluation of the effect:**

Assessment of the cervix will be done at the second dose and after 12 and 24 hours through the changes and progression of the Bishop's score. A *blank table of Bishop's score* will be delivered to the examiner who will be asked to fill the table according to the cervical state. The table will be filled twice for every patient. Data will be collected at the end of the study for final assessment of the results.

### **Management and Monitoring:**

If the case managed to initiate labor, reevaluation of the mother and the fetus will be carried out. And the mother will be monitored according to routine management via the partogram.

If there is a progression in the Bishop's with no onset of labor, induction will be initiated by amniotomy. Provided that the liquor is clear, oxytocin intravenous drip will be initiated. If the liquor is meconium stained, thorough fetal monitoring will take place. Persistent abnormal fetal CTG or deeply stained liquor will be referred to theater for cesarean section.

The fetus will be monitored by the cardiotocography. The mother will be evaluated by the vital signs and other signs of headache, palpitation, dizziness, GI upset ....etc.

### **Data presentation and Statistical Methods:**

Data will be collected, tabulated, then analyzed using PC using Statistical package for Social Science (**SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001**).

Normally distributed numerical data will be presented as mean and SD, and skewed data as median and interquartile range. Qualitative data will be presented as number and percentage.

Comparison between the means will be done by paired t test for independent samples. Skewed data will be compared using the Mann-Whitney test. Categorical data will be compared using the chi-squared test for qualitative data comparison.

**A p-value <0.05 will be considered statistically significant.**

### **Both groups will be compared regarding:**

- Time from the start of labor induction to vaginal delivery
- Time from start of drug administration to the earliest uterine contraction
- Progression of Bishop's score
- Duration of the first, second and third stages of labor
- Whether they eventually need to have a cesarean section or not.
- Incidence of maternal complications, namely; headache, nausea, postpartum hemorrhage,
- Neonatal outcome through Apgar score at 1 and 5 minutes after delivery.

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