Intravaginal isosorbide mononitrate in addition to misoprostol versus misoprostol only for induction of labor: a randomized controlled trial

Thesis

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By

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List of abbreviations

- ACOG: American college of Obstetricians and Gynecologists.
- IM: Isosorbide Mononitrate.
- M: Misoprostol.
- RCOG: Royal college of Obstetrician & Gynecology.
- NO: Nitric oxide.
- BHIVA: British HIV Association.
- NICE: The National Institute for Health and Care Excellence.
- FIGO: The international federation of Obstetrics and Gynecology.
- NICU: Neonatal intensive care unit.
- GA: Gestational age.
- IOL: Induction of labor.
- NHS: National Health service.
- Hrs: Hours.
- SD: Standard deviation
- No: Number
- FFN: Fetal Fibronectin
- Wks: Weeks
- CTG: Cardiotocography

PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF MASTER DEGREE IN OBSTETRICS & GYNAECOLOGY

Title of the Protocol:
Intravaginal isosorbide mononitrate in addition to misoprostol versus misoprostol only for induction of labor: a randomized controlled trial.

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What is already known on this subject? AND What does this study add?
In modern Obstetrics, induction of labor (IOL) is one of the most common decisions to be taken in different situations, so trials and studies seeking for the novel way for IOL that brings both maternal satisfaction while maintaining the least feto-maternal adverse effects possible are of a great value. Nitric oxide (NO) donors are pharmacologically active substances that release NO in vivo or in vitro. NO has a variety of functions such as the release of prostanoids (Including Prostaglandins), vasodilation, inhibition of platelet aggregation, effect on angiogenesis, and production of oxygen free radicals. During previous studies comparing isosorbide mononitrate (ISM) to misprostol in cervical ripening, there were no tachysystole or uterine hyperstimulation in the ISM group while in misoprostol group it was 17% and 11% respectively, maternal satisfaction was higher in IMN group, cervical ripening is satisfactory with IMN, though misoprostol is singly more

effective than IMN but IMN with oxytocin results in more vaginal delivery, fetal and maternal side effects are less in IMN group. Other studies have shown lower cesarean section rate associated with isosorbide mononitrate compared to dinoprostone at term.

NO donors such as isosorbide mononitrate could be of a great use for cervical ripening because of their effect on release of prostaglandins and vasodilation while having no effect on uterine activity; since they are relatively safe and has low number of non-vital adverse effect if used with caution, they could be added to misoprostol to shorten to time needed for cervical ripening thus accelerating the whole process of induction of labor.

1.INTRODUCTION/ REVIEW

The first reports of the use of the natural prostaglandins (PG) in the field of obstetrics and gynecology appeared in 1968, initially for the induction of term labour in patients with fetal death and subsequently for patients with a live fetus **(Craft et al., 1977).**

Nowadays, prostaglandins such as misoprostol have contributed widely in modern obstetrics and have been reviewed in literature while comparing it to different methods of induction of labor (IOL). Prostaglandins such as misoprostol have been under review for efficacy and safety while combining them with other cervical ripening agents. Such combination includes misoprostol and mechanical dilatation for IOL **(Kehl et al., 2011)**, combination of misoprostol and oxytocin versus oxytocin alone for IOL **(Balci et al., 2010).**

Despite the fact that other agents have been proposed to be useful in inducing labor and cervical softening, like oxytocin, corticosteroids, estrogen, relaxin, and nitric oxide donors **(Kavanagh et al., 2006), (Kelly et al., 2001**) ; the standardized cervical priming and induction of labor is predominantly achieved by means of prostaglandins administration such as misoprostol, misoprostol has been widely available PG and has been given a prestigious value in literature and various guidelines **(FIGO, 2017), (NICE guidelines, 2008).**

There has been an increasing interest in the use of nitric oxide (NO) donors such as isosorbide mononitrate while comparing it with other cervical ripening agents such as misoprostol for cervical ripening and labor induction **(Chanrachakul et al., 2002).**

NO donors have been shown to stimulate prostaglandin production in the human cervix after topical administration **(Ekerhovd et al., 2003),** although the effect of NO donors may not be efficable as prostaglandins, they are still safe to use compared to misoprostol **(Guha et al., 2015)**. They do affect maternal and fetal hemodynamics when applied vaginally, but without clinical significance **(Nicoll et al., 2001).**

Since we strongly support the hypothesis enforcing that combining NO donors such as isosorbide mononitrate which known to be a safe, cheap agent, to a potent PG E1 analogue such as misoprostol, we will accelerate cervical ripening thus decreasing length and cost of IOL process without increasing feto-maternal adverse effects. A previous study was done by **Abdellah et al., 2010** showed shortening in the Induction of labor process when isosorbide mononitrate was added to misoprostol for cervical ripening **(Abdellah et al., 2010).**

A recent study comparing vaginal misoprostol vs Foley's catheter combined with vaginal IMN for induction of labor in term and post-term pregnancies concluded that ; vaginal misoprostol is more effective but less safe than Foley's catheter combined with vaginal IMN for induction of labor in term and post-term pregnancies, this support the promising safety of NO donors in Induction of labor **(EL-Khayat et al., 2016).**

A recent review of 23 studies including total of 4777 women concluded that NO donors can be a useful tool in the process of induction of labour causing the cervix to be more favourable in comparison to placebo. However, additional data are needed to assess the true impact of NO donors on all important labour process and delivery outcomes. **(Ghosh et al., 2016)**

2.AIM / OBJECTIVES

- Evaluation of safety & efficacy of nitric oxide donors such as intravaginal isosorbide mononitrate in addition to misoprostol Versus misoprostol only for the whole process of induction of labor.

- Research hypothesis: In pregnant women undergoing induction of labor, the use of nitric oxide donor with misoprostol is similar to misoprostol alone as regard induction delivery interval.

- Research question: In pregnant women undergoing induction of labor does the use of nitric oxide donor with misoprostol similar to misoprostol alone as regard induction-delivery interval.

3.METHODOLOGY:
Patients and Methods/ Subjects and Methods/ Material and Methods

- **Type of Study:** Randomized controlled clinical trial.

- **Study Setting:** This study will be conducted at Ain Shams University's Emergency department of the Maternal Hospital.

- **Study Period:** From January 2018 to June 2018 (6 months)

- **Randomization:** Will be done using computer generated randomization sheet using MedCalc© version 13. (Appendix 1)

- **Allocation and concealment:** Fifty opaque envelop will be numbered serially and, in each envelope, the corresponding letter which denotes the allocated group will be put according to randomization table. Then all envelopes will be closed and put in one box. When the first patient arrives, the first envelope will be opened and the patient will be allocated according to the letter inside.

- **Study Population:** Fifty pregnant women.

-Inclusion Criteria:

- Primigravida.
- From 20 to 30 years old.

- Singleton term (between 40 to 42 weeks of gestation).
- Good general condition with straightforward enthusiasm for the trial.

-Exclusion Criteria:

- IUGR.
- Rupture of membranes.
- Favorable cervix (Bishop score: '8' or more)
- Cephalopelvic disproportion,fetal malpresentation.
- Antepartum hemorrhage, any abnormal placentation such as placenta previa, morbidly adherent placenta.
- Uterine fibroid.
- Previous uterine major surgery such as: myomectomy.
- Any medical disorder such as: gestational diabetes, diabetes mellitus, hypertension, preeclampsia, coagulation disorders, renal and hepatic dysfunction.

- **Sampling Method:** Convenience sampling.

- **Sample Size:** Fifty women.

- **Sample Justification:** Using data from previous study by Abdellah et al. 2010, which compared isosorbide mononitrate and misoprostol versus misprostol only. Misoprostol only group induction to delivery interval was 23 hours while in the isosorbide mononitrate and misorprostol group it was 19.6 hours. We will use sample size of 25 women in each of the two groups to achieve 91% power to detect statistical difference of atleast 3.4 hours. With estimated group standard deviations of 4.0 and 2.6 and with a significance level (alpha) of 0.05 using Mann-Whitney test; the sample size of 50 women as stated before is satisfactory to detect difference between initial dose to delivery.

- **Ethical Considerations:** An informed consent will be taken from all participants, it will be in Arabic language and confirmed by date & time. No harm will be inflicted & no benefit will be deprived in this study.

- **Study Procedures:**
  - Fifty Primigravida women will be recruited according to inclusion and exclusion criteria.
  - History taking.
  - Physical examination.
  - Ultrasound: for placental localization excluding abnormal localization, exclude Fetal IUGR, oligohydraminos, polyhydraminos, fibroids.
  - Laboratory investigations: CBC (complete blood count), Coagulation Profile, Liver function test, Kidney function test, ABO Rhesus D (RhD).
  - Counseling of the patient about isosorbide mononitrate and misoprostol.
  - Recruited patients will fill a written consent.
  - Two types of envelopes will be available, one with misoprostol & placebo, other will contain misoprostol & isosorbide mononitrate which will be given by vaginal route.
  - Patient will choose an envelope from the previous 2 types.
  - 2 groups will be formed; group 1 will take both misoprostol & isosorbide mononitrate, group 2 will take Misoprostol only. Group 1 will take intial dose of 40mg isosorbide mononitrate (Mono-Mak) in the posterior vaginal fornix which will not be repeated; followed by intravaginal 25mcg of misoprostol (Vagiprost), misoprostol will be repeated every 6 hours for maximum of 5 doses (i.e. 125mcg), (FIGO recommendation for misoprostol regimen 2017 & WHO recommendations for induction of labour 2011). Misoprostol will be stopped when labour is established defined by 3 contractions every 10 minuites, each contraction of 30 seconds duration, with amplitude of 40 mmHg or if 6 hours passed after the last misoprostol dose and labour is not established as defined before with unfavorable cervix defined by bishop score of 6 or less, cesarean delivery will be performed. Group 2 will take only misoprostol with same scheme for misoprostol as before in group 1.
  - Induction of labor process will take place, during which:

    -Maternal blood pressure & pulse will be assessed every 30 minutes for the first 2 hours then hourly after that; temperature will be assessed every 4 hours.

-Fetal auscultation will be carried out every 15 minutes in 1st stage of labor, every 5 minutes in 2nd stage of labor after uterine contraction for at least 1 minuite.

-CTG will be performed every 2 hours or if there are concerns during fetal ausculatation. Continuous CTG maybe continued upon maternal request or if there are high risk factors such as contractions that last longer than 60 seconds(hypertonus) or more than 5 contractions in 10 minutes(tachysystole), Oxytocin use.

- **Study Interventions:** Cesarean Delivery will be performed in the following circumstances:

  -if Induction of labor failure is established defined by unfavorable cervix after 6 hours from the last dose of 5 doses of Misoprostol each is 25 mcg (maximum dose of 125mcg)

  -If management of protraction & arrest disorders failed.

  -If CTG monitoring was classified as pathological and conservative management failed; or if CTG monitoring warned the need for urgent intervention.

- **Statistical Analysis:** Descriptive statistics for measured variables will be expressed as range mean and standard deviation (for metric data); range, median and interquartile range (for discrete data); and number and proportion (for categorical data). Demographic data and primary and secondary outcomes of all women will be compared using t-test (for quantitative parametric measures), Mann-Whitney's U-test (for quantitative non-parametric measures) and chi squared and Fisher's Exact tests (for categorical measures). Pearson's correlation coefficient (for metric variables) and Spearman's correlation coefficient (for rank variables) will be used to estimate association between variables.

- **Statistical Package:** Data will be collected, edited and entered into suitable software for data entry & analysis such as 'SPSS version 20'.

Appendix 1: Shown here the number of envelopes corresponding to number of patients who will be enrolled in this study and the contents within each one of the envelopes. Noting that 'I' stands for Isosorbide mononitrate, while 'M' stands for Misoprostol.

1	I &M	10	M	19	M	28	I &M	37	M	46	I & M
2	M	11	M	20	I &M	29	M	38	I &M	47	M
3	I &M	12	I &M	21	I &M	30	I &M	39	M	48	I &M
4	I &M	13	M	22	M	31	M	40	I &M	49	M
5	I &M	14	I &M	23	I &M	32	I &M	41	M	50	M
6	M	15	I &M	24	I &M	33	M	42	M	----	--------
7	I &M	16	I &M	25	M	34	I &M	43	M	----	--------
8	I &M	17	M	26	I &M	35	M	44	M	----	--------
9	M	18	I &M	27	M	36	M	45	I &M	----	--------