Propranolol and Oxytocin versus Oxytocin Alone for Induction of Labor: A Randomized Controlled Trial

Thesis

Submitted for partial fulfillment of Master degree
in ***Obstetrics and Gynecology***

By

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2019

Acknowledgments

First and foremost, I feel always indebted to **Allah**, *the* **Most Beneficent** *and* **Merciful** *who gave me the strength to accomplish this work,*

My deepest gratitude to my supervisor, **Prof. Magdy Mohamed Mahmoud Abd El-Gawad,** *Professor of Obstetrics and Gynecology, Faculty of Medicine - Ain-Shams University,, for his valuable guidance and expert supervision, in addition to his great deal of support and encouragement. I really have the honor to complete this work under his supervision.*

I would like to express my great thanks to **Dr. Reda Mokhtar Kamal,** *Lecturer in Obstetrics and Gynecology, Faculty of Medicine - Ain-Shams University, for his meticulous supervision, and his patience in reviewing and correcting this work.*

Special thanks to my **Patients** *who accepted to help me in this study.*

Abd El-Rahman Mahmoud

Thata * Sohag

March, 2019

List of Contents

List of Abbreviations

Abbr.		Full-term
ACTH	**:**	Adreno Corticotropin Hormone
CAPs	**:**	Contraction Associated Proteins
CNS	**:**	Central Nervous System
CRH	**:**	Corticotrpin Releasing Hormone
CS	**:**	Cesarean Section
CTRH –BP	**:**	CorticoTropin Releasing Hormone –Binding Protine
D5W	**:**	5% Dextrose in Water
DHEAS	**:**	DeHydroepiandrosterone sulfate
FHR	**:**	Fetal Heart Rate
FFN	**:**	Fetal Fibronectin
GBS	**:**	Group B Streptococcus
IL-1	**:**	Interleukin -1
IOL	**:**	Induction Of Labor
ISA	**:**	Intrinsic Sympathomimetics Activity
MIs	**:**	Myocardial Infarction
MMPs	**:**	Matrix Metaloproteases
NICU	**:**	Neonatal Intensive Care Unit
NO	**:**	Nitric Oxide
PG	**:**	Prostaglandin
PGF2alpha	**:**	Prostaglandin F2 alpha
PROM	**:**	Premature Rupture Of Membrane
PTH-RP	**:**	Parathyroid Hormone Related Peptide
RPP	**:**	Rate Pressure Product
TIMMPs	**:**	Tissue Inhibitors Matrix Metaloproteases
TNFalpha	**:**	Tumor Necrosis Facor alpha
TOL	**:**	Trial of Labor
VD	**:**	Vaginal Delivery

List of Tables

List of Figures

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INTRODUCTION

Labor is defined as the state of being in uterine contractions of adequate frequency, duration, and strength to cause effacement and dilataion of the cervix ***(ACOG, 2003)***. Induction of labor is defined as stimulation of uterine contractions before they occur spontaneously ***(Martin et al., 2006)***.

Prolonged labor can lead to maternal and neonatal complications, and these adverse labor outcomes increase in prolonged pregnancy in comparison with term gestational age ***(Cheng et al., 2009)***.The rates of cesarean section are increasing during the last decade in an international setting ***(Roberts et al., 2015)***. Previous studies suggested that induction of labor might be associated with increased rates of CS. High maternal and gestational age at delivery affect these rates both in nulliparous and multiparous women. Similarly, the presence of low Bishop score and a neonatal birth weight >3.5 kg increase the possibility of failure of induction ***(Ramasamy and Thunga, 2011)***. The contribution of trial of labor (TOL) on the cesarean section rates has become a matter of debate during the last decade. Recent meta-analyses, however, suggest it doesn't influence these rates ***(Wood and Cooper, 2014)***.

Oxytocin is the best known and most widely used agent to induce and augment uterine contractions ***(Hinshaw et al., 2008)***; but the Institute for Safe Medication has termed oxytocin as a *high-alert medication* due to the risk of high dose or wrong prescription. This institute

recommended many programs to minimize the maternal and neonatal risks of oxytocin administration ***(Palomaki et al., 2006)***.

Other agents are currently used for induction and augmentation of labor as prostaglandins are the most widely spread. Intravaginal misoprostol (PGE_1) seems to be more efficient and less expensive than dinoprostone (PGE_2) which is applied intracervically or intravaginally, although evidence in this field are contradictive ***(Jha et al., 2015)***. However, dinoprostone appears to be safer because it is accompanied by lower incidence of uterine hyperstimulation and tachysystole ***(Liu et al., 2014)***.

Taking into mind the potential side effects of misoprostol and the expensive value of dinoprostone, it would be prudent to investigate the efficacy of other agents in the field. In the last 20 years, scarce evidence have been reported regarding propranolol's efficacy and mode of action during the latent and active phases of labor. Propranolol is a sympatholytic non-selective beta-blocker. Twenty five years ago, ***Peiker et al.*** suggested that it causes contractions of uterine muscle stripes in pregnant rats and eventually to induction of labor. Since then, various molecular pathways which involve the adrenergic system have been implicated in the regulation of uterine contractility ***(Rouget et al., 2005)***.

Despite these evidence, however, the interest in propranolol use as a means to induce and/or enhance contractions is very limited.

Direkvand-Moghadam et al. studied the Comparison Effect of Oral Propranolol and Oxytocin Versus Oxytocin Only on Induction of Labour in Nulliparous Women and found that The mean duration for obtaining good contractions was significantly shorter in the Propranolol group than in the placebo group, on both the first and second day of induction ($p<.05$). The mean duration of latent phase was shorter in the first in Propranolol group ($p<.05$). In Propranolol plus Oxytocine group, frequency of cesarean deliveries significantly decreased than in the placebo plus Oxytocin group (21% versus 39.7%). No significant differences in neonate outcome, such as Apgar scores of minutes 1 and 5 and need of admissions to NICU, were found between the groups ($p>.05$) ***(Direkvand-Moghadam et al., 2013).***

Pergialiotis et al., were studied Propranolol and oxytocin versus oxytocin alone for induction and augmentation of labor and found that propranolol administration during the latent phase effectively reduces the cesarean section rates (OR 0.49, 95 % CI 0.27, 0.89). However, this beneficial effect is not observed during the active phase of labor. The 5 min neonatal Apgar scores are not influenced by its administration (MD -0.07, 95 % CI -0.017, 0.02). Respectively, the neonatal admissions to a NICU are similar to those of neonates exposed only to oxytocin (OR 0.96, 95 % CI 0.36, 2.53 ***(Pergialiotis et al., 2016).***

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AIM OF THE WORk

The aim of this study is to evaluate the efficacy of propranolol supplementary agent to oxytocin in women undergoing induction of labor to decrease cesarean section rate.

Research hypothesis :

In pregnant women undergoing induction of labor propranolol supplementary agent to oxytocin may decrease the rate of cesarean section.

Research question:

In pregnant women undergoing induction of labor does propranolol supplementary agent to oxytocin decrease the rate of cesarean section?

Outcome measures :

***1-Primary outcome*:**

Evaluation and measurement the efficacy of propranolol supplementary agent to oxytocin in women undergoing induction of labor to decrease cesarean section rate.

***2-Secondary outcome*:**

Evaluation and measurement the efficacy of propranolol supplementary agent to oxytocin in women undergoing induction of labor on

- Duration of latent phase.
- Duration of active phase .
- Duration of second stage.
- Mode of delivery.
- Neonatal condition after labor as APGAR scores and NICU admission.

SUBJECTS AND METHODS

Study design: Randomized controlled clinical trial.

Settings: Ain Shams Maternity University Hospital in the period between May 2017 and May 2018.

Population: The study will include 160 women planned for induction of labor.

Sample size justification: Sample size will calculated using MedCalc ® version 12.3.0, setting the power (β) at 0.02 and the significance level (α) at 0.05. Data from previous reports ***(Pergialiotis et al., 2016)*** indicated that propranolol administration during the latent phase effectively reduces the cesarean section rates with OR 0.49 (95% CI: 0.27-0.89). Calculation according to these values produced a minimal sample size of 152 women to yield statistically significant results. Assuming a drop-out rate of 5%, a total sample size will approximately be 160 women, to be randomized into 2 groups.

RESEARCH METHODOLOGY

- After approval of the ethical committee, all participants in the study will give a written, informed consent, after explaining the details of the study to them (appendix 1).

Inclusion Criteria:

- Age between 20 years and 35 years.
- Gestational age 38 - 41 weeks (according to a reliable last menstrual period and ultrasound evaluation at first trimester).

- Singleton viable pregnancy.
- Cephalic vertex presentation.
- Intact membranes..
- Bishop score > 5.
- Reassuring fetal well-being status.
- Maternal BMI btween (18-30kg/m2).
- Primigravida,or Previous one or previous two vaginal delivery.

Exclusion Critera:

- Age more than 35 years or less than 20 years.
- Multiple pregnancy.
- Multigravida more than two vaginal delivery.
- Non-cephalic presentation.
- Presence of uterine contractions.
- History of uterine surgery eg. Cesarean section, myomectomy.
- Polyhydramnios.
- Pre-labor rupture of membranes.
- Non-reassuring fetal well-being status
- Contraindications to β-adrenergic agents, such as systolic blood pressure less than 100 mmHg or pulse rate less than 60/min and more than 120/min
- History of any known cardiac disease
- Mother's pulmonary or metabolic disorders
- Fetal distress
- Intrauterine fetal death.
- Estimated weight of the fetus more than 4 kg by ultrasound of cephalic presentation.
- Maternal obesity BMI >30kg/m2.
- Underwight patient BMI<18kg/m2.

Randomization:

Patients fulfilling the inclusion criteria will be randomized to two groups.

Study Group:

This group will include 80 women undergoing induction of labor. In this group, patients will receive a tablet containing 20 mg propranolol orally two hours before beginning induction, in addition to intravenous oxytocin. The tablet will be repeated after 8 hours if no sufficient uterine contractions have been reached.

Control Group:

This group will include 80 women undergoing induction of labor. In this group, patients will receive a placebo tablet orally before beginning induction, in addition to intravenous oxytocin. The tablet will be repeated after 8 hours if no sufficient uterine contractions have been reached.

Random allocation sequence generation

A computer generated list via MedCalc ® Software, version 13.2.2 will be used, assigning each participant number to either study groups (appendix 2).

Allocation Concealment

Assignment will be done by sequentially numbered, otherwise identical, sealed envelopes (SNOSE), each containing a 2-inch by 2-inch paper with a written code designating the assigned group. These papers will be placed in a folded sheet of aluminum foil fitted inside the envelope. Effort will be taken to assure absence of any detectable differences in size or weight between intervention and control envelopes. Envelopes will be