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CHRISTIAN MEDICAL COLLEGE AND HOSPITAL

LUDHIANA

**THESIS PERFORMA FOR M.D. OBSTETRICS AND GYNAECOLOGY**

**BABA FARID UNIVERSITY OF HEALTH SCIENCES**

**FARIDKOT, PUNJAB**

**A Randomized control study of titrated and   
static oral misoprostol solution for induction of labor at term**

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ABSTRACT

**Background:** Incidence of induction of labor continues to increase worldwide. Misoprostol, a synthetic prostaglandin E1 analog, can be administered orally, sublingually, buccally, intravaginally, or rectally and is used as an effective agent for both cervical ripening and labor induction. The World Health Organization recommends a fixed oral misoprostol dose of 25 mg every 2 h for labor induction. However, more research is required to optimize the use of oral misoprostol solution for induction of labor.

**Aim and Objectives**: To evaluate effectiveness and safety of titrated oral misoprostol solution (OMS) in comparison with 2-hourly static-dose oral misoprostol solution for induction of labor in term pregnant women.

**Materials and Methods:** A comparison of induction of labor (IOL) using a titrated oral regime with static 2 hourly regime will be studied in 270 randomly assigned pregnant women with clinical indication for labor induction and poor modified Bishop’s score. Two groups will be compared with respect to maternal outcomes including indication of labor induction, mode and outcome of delivery, maternal morbidity, and neonatal outcomes for evaluating the efficacy and safety of each regimen.

**Statistics:** Data will be entered in the Microsoft excel and analysed by SPSS version 21. Frequency, proportions, mean, mode, standard deviation will be calculated. ‘t’- test, ANOVA and Chi square test will be the tests of significance. ‘p’ value <0.05 will be considered significant.

**Keywords:** induction of labor, oral misoprostol solution, titrated oral misoprostol solution

INTRODUCTION

Induction of labor is a commonly practiced obstetric intervention to artificially initiate the process of labor when the benefits to either mother or fetus outweigh those of pregnancy continuation.1 In recent years, the rate of induction has shown a gradual increase and the incidence for labor induction dramatically varies 8–44%.2-4 Adopting safe and effective methods of labor induction at appropriate gestation age can greatly decrease complications and morbidity of pregnancy and fetus. Therefore, looking for induction methods with safety, efficacy, feasibility, low cost, and patient preferences is a constant pursuit for all obstetric providers.

Each obstetrical department has its own protocol for administration of different methods for labor induction and augmentation. Various methods of induction of labor include administration of oxytocin, prostaglandin analogues, smooth muscle stimulants such as herbs or castor oil, mechanical methods such as digital stretching of the cervix and sweeping of the membranes, hygroscopic cervical dilators like laminaria tents, extra-amniotic balloon catheters and artificial rupture of membranes. The ideal inducing agent should be able to bring about cervical changes and initiate uterine contractions with minimal risk to mother and fetus.

Oxytocin has been used over decades for induction and augmentation of labor. Presently prostaglandins, such as dinoprostone and misoprostol, are used as most potent and acceptable methods for cervical ripening and labor induction. Oral misoprostol has been shown to be more effective than intracervical prostaglandins in achieving vaginal birth within 24 hours.5,7 A reduced risk of caesarean births was observed without any increase in the risks of adverse maternal and perinatal outcomes with oral misoprostol as compared to vaginal prostaglandins.6 Oral misoprostol has been shown to be as effective as vaginal misoprostol7 and has the advantage of being more acceptable to women and can be self-administered. In 2012, the International Federation of Gynecology and Obstetrics (FIGO) recommended an oral dose of 25 μg misoprostol solution every 2 hours to induce labor, citing the 2011 World Health Organization (WHO) recommendations for labor induction5. The WHO strongly recommended this regimen, rating the quality of evidence as moderate6.The data included was from the 2006 Cochrane review by Alfirevek.7

Absorption by the oral route is more rapid and predictable with peak concentrations being achieved in 34min.8 Its terminal half-life is 20–40 min8 following oral administration, followed by a rapid decline to low levels during the period of 120 min, thereafter with a more gradual decline, and no drug accumulation phenomenon.12 Thus the administration of oral misoprostol in titrated doses may provide a steady drug serum level with better efficacy and improved clinical induction outcome as compared with 2-hourly dosing.

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equivalent (Dilapan), into the cervical canal; (2) the introduction

of a catheter (Foley, Atad or other ty pe), through th e cervix into

the extra-amniotic space, either with or without traction; (3) use

of a catheter to inject ﬂuids, usually saline water, in the extra-

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Aim and Objectives

To evaluate effectiveness and safety of titrated oral misoprostol solution (OMS) in comparison with static-dose oral misoprostol solution for induction of labor at term.

MATERIALS AND METHODS

STUDY DESIGN

This comparative study will be conducted in the Department of Obstetrics and Gynaecology, Christian medical college and hospital, Ludhiana for a period of one year beginning from 1st December, 2017 to 30th November, 2018. The study group will consist of all antenatal women admitted in labor room at term for induction of labor.

Informed consent will be taken for all the selected patients. Women will be subjected to detailed history taking, a complete physical examination including a per vaginum examination (to calculate modified bishop’s score1 and to rule out cephalopelvic disproportion), investigations and a CTG/NST. Gestational age will be established by the first date of the last menstrual period and confirmed by 1st trimester ultrasound. Presentation will be confirmed by palpation and third trimester ultrasound. Indication of induction of labor will be noted.

INCLUSION CRITERIA

1. Singleton live pregnancy;
2. ≥37 weeks gestation;
3. Cephalic presentation;
4. Reassuring fetal heart rate;
5. Modified Bishop’s score1 ≤6;

EXCLUSION CRITERIA

1. Hypersensitivity to misoprostol;
2. Uterine scar due to previous caesarean section or other uterine surgery;
3. Grand multipara;
4. Multiple gestations;
5. High risk pregnanacies
   * preeeclampsia with severe features
   * significant maternal cardiac, renal, liver disease
6. Any contraindication to induction and vaginal delivery e.g. cephalopelvic disproportion, malpresentation, fetal compromise and ante partum hemorrhage.
7. Intrauterine fetal demise

SAMPLE SIZE

The sample size by using the Clinical data is 132 for each group i.e. required sample size for the study is 264completed cases. The formula used is; sample size= (r+1) (p\*)(1-p\*)(Z1-α/2+Z1-β)2/r\*(p1-p2)2 Where,

Z1-α/2=1.96, is standard normal deviate at type 1 error α =0.05,

Z1-β=0.84is standard normal deviate at 80% power,

r is ratio of cases, in case of equal number it is 1,

p\* =Average proportion exposed

= (proportion of exposed cases in group 1 + proportion of exposed cases in group 2)/ 2

p1 is proportion in case 1 and p2 is proportion in case 2,

p1-p2 = Effect size or difference in proportion expected based on previous study11

Women will be randomized (1:1) into the treatment groups using computer generated numbers.

A) Titrated-dose OMS group

B) Static dose OMS group

Allocation concealment will be carried out by using opaque envelopes that will be distributed by the obstetrics nurse.

METHODS OF PREPARATION OF ORAL MISOPROSTOL SOLUTUION

Based on the WHO labor induction recommendation9, and for the purpose of achieving precise oral misoprostol dosage, one misoprostol tablet (200 mcg) will be pulverized and dissolved into 200 ml water. Preparing a misoprostol solution allows precise dosing as compared to cutting the tablets which is difficult and imprecise. Thus 1ml of solution will contain 1mcg of misoprostol. This misoprostol solution can be preserved at room temperature and will remain active for 24 hours.

METHOD OF ADMINISTRATION

1. TITRATED OMS GROUP

All the women enrolled into the titrated group will be given oral misoprostol solution according to the regimen described by Wang X et al, 2016 which is as follows.10

1. STATIC OMS GROUP

In the static-dose group, the recommended FIGO regimen will be used.Oral misoprostol solution 25 mcg (25 ml) will be administered every 2 hours for a maximum of 12 doses or until the onset of regular uterine activity.

Once labor has started, vital signs will be closely monitored every 2 hours; fetal heart rate (FHR) and uterine activity every 15mins during first stage of labor. Per vaginum examinations will be done 4-hourly or as indicated.

Procedure will be CEASED at any time when one of the following criteria is reached:

1) Regular uterine contractions every 3–5 min and lasting 60 s or more;

2) Dilatation of cervix reached 2.0 cm;

3) Uterine hyperstimulation/tachysystole/hypertonus13, 14;

4) Non-reassuring fetal heart rate13,14.

If contractions subsequently become inadequate, artificial rupture of membranes will be done and/or oxytocin will be started ≥2 hours after the last misoprostol dose according to the discretion of the attending consultant.

OUTCOME

The primary outcome will be the induction to delivery time. The secondary outcome measures will pertain to safety (maternal and fetal complications).

OBSERVATIONS

* Change in modified Bishop’s score
* Mode and outcome of delivery

1. Induction to delivery time: less than 12 h, 12–24 h and 24–48 h;
2. Induction to onset of labor
3. Incidence of vaginal/operative delivery/cesarean section;
4. Bishop’s score at amniotomy
5. Total oral misoprostol dosage;
6. Indication for operative delivery and cesarean section;
7. Need for augmentation with Oxytocin(duration and dose);
8. Pertus precipitatus (defined as the total time of labor stage less than 3 hours)

* Maternal morbidity

1. Blood loss and transfusions
2. Incidence of Tachysystole, Hyperstimulation, Uterine hypertonus, Uterine rupture.
3. Maternal infection during labor or within 1 week postpartum e.g. endo(myo)metritis or urinary tract infection proven positive vaginal/urine culture;
4. Other medications used during labor such as tocolytics

* Neonatal parameters:

1. Birth weight;
2. Incidence of meconium-stained liquor;
3. Apgar scores at 1,5 min;
4. NICU stay, duration and reason.

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PATIENT INFORMATION SHEET

You are invited to take part in a study titled: “A Randomized control study of titrated and static oral misoprostol solution for induction of labor in term pregnant women”. This study is being conducted in the Department of Obstetrics and Gynaecology, Christian Medical College, Ludhiana.

You will be examined by the doctor and relevant investigations will be sent. You are being induced as per obstetrical indication. There are various methods of induction of labor. In this study, induction of labor will be done with Oral Misoprostol Solution by two different methods. You will be randomnly assigned to either of the two groups - A) Titrated OMS B) Static OMS. The process of Labor progression and various outcomes will be noted. The complications associated with all labor induction methods including the one used in this study consist of cesarean delivery, chorioamnionitis, uterine tachysystole and post partum haemorrhage from uterine atony. Careful monitoring will be done during the whole procedure and all measures will be taken to ensure safety.

You are free to decline your consent to participate in the study at any time. After understanding all the aspects of the study, you may sign as consent to participate in the study. Your identity will be concealed in an appropriate manner.

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vki fdlh Òh le; bl v/;;u esa Òkx ysus ds fy, nh xÃ viuh lgefr ls bUdkj djus ds fy, Lora= gSa A v/;;u ds lÒh igyw tkuus ds ckn bl v/;;u esa Òkx ysus ds fy, lgefr ij gLrkÕj dj ldrh gSaa A vki dh igpku mfpr jhfr ls xqIr jÂh tk;sxh A

****









INFORMED CONSENT

* I,-----------------------------------, , do hereby voluntarily give my consent to be included in this study, titled “A Randomized control study of titrated and static oral misoprostol solution for induction of labor in term pregnant women” being conducted at Christian Medical College and Hospital, Ludhiana by Dr. Barbie Sharma, Department of Obstetrics and Gynaecology.
* I have been explained the implications of this study, procedure involved in a language I understand. I also understand that the study is for the purpose of medical research and I am willing to extend my full co-operation towards the same. I also know that I can withdraw from this study without providing any reasons and that will not affect my routine treatment in Christian Medical college, Ludhiana.

Signature/thumb impression of the patient Signature of investigator

Name of the patient: Name of the investigator:

Date: Date:

lwfpr lgefr QkeZ

eSa----------------------------bl v/;;u esa Òkx ysus dh LoSbPNk ls lgefr nsrh gw¡ ftldk ÓhÔZd gS]^^ xÒZ dh iwÆZ vofÌ okyh xÒZorh efgykv¨a esa çlo d¨ çsfjr djus ds fy, fu;fer varjky **ij** vuqekfur **rÉk** fuf’pr ek=k esa e©fÂd :i ls fn, tkus okys fel¨ç¨LV¨y feJÆ dk csrjrhc fu;af=r v/;;u A\*\* t¨ fØLph;u esMhdy dkyst yqfÌ;kuk esa Mk- ckchZ ÓekZ }kjk tPpk cPpk foÒkx esa fd;k tk jgk gS A

eq>s bl v/;;u ds ykxwdjÆ v©j çfØ;k ds ckjs esa foLr`r :i esa esjh le> vkus okyh ÒkÔk esa crk fn;k x;k gSA eSa tkurh gw¡ fd ;g v/;;u fpfdRldh; mís’; ds fy, gS blds fy, eSa viuk iwjk lg;¨x nsuk pkgrh gw¡ A eSa ;g Òh tkurh gw¡a fd v/;;u ds n©jku fdlh Òh le; fcuk d¨Ã dkjÆ crk;s eSa bl v/;;u ls vyx g¨ ldrh gww¡ blls fØLph;u esMhdy dkyst yqfÌ;kuk esa esjk fu;fer bykt çÒkfor ugha g¨xk A

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çfrÒkxh ds gLrkÕj@vaxwBs dk fuÓku v/;;udÙkZ ds gLrkÕj

çfrÒkxh dk uke v/;;udÙkZ dk uke

frfÉ% frfÉ%







 

 

  

 

ANNEXURE- A

Name: Unit number:

Age: Education:

Married for: Case no:

Parity: Group no:

LMP: Date of admission:

EDD:

Period of gestation:

Number of antenatal visits in CMC:

Antenatal complications:

Past obstetric history:

Past medical history:

Family history:

Indication of induction of labour:

General examination:

1. Height= 2) Weight= 3) BMI=

Abdominal examination:

P/V:

Modified Bishop’s score:

Investigations:

CBC-

USG FWB-

INTRAPARTUM

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| DATE | TIME | MISOPROSTOL DOSE | P/V | Modified Bishop’s score | Complications | Management |
| TIME OF INDUCTION |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| TOTAL number of doses= |  |  |  |  |  |  |

Oxytocin required: Yes/No

If Yes, maximum amount of oxytocin dose required:

Rupture of membranes: Spontaneous/ Artificial

Modified Bishop’s score on rupture of membranes:

Mode of delivery:

Indication for operative delivery and cesarean section:

|  |  |  |
| --- | --- | --- |
| Duration of Labour | Hours | Minutes |
| Length of first stage of labour |  |  |
| Length of second stage of labour |  |  |
| Length of third stage of labour |  |  |
| Total duration of labour |  |  |

Duration of rupture of membranes:

Meconium staining of liquor: Yes/No

If Yes, Grade:

Induction to onset of labour interval:

Induction to delivery time: (i) less than 12 h, (ii) 12–24 h and (iii) 24–48 delivery;

Epidural/Analgesics used:

Other drugs used:

Blood loss:

Blood transfusions if any: ante natal/ intrapartum/post partum

MATERNAL MORBIDITY

History of fever:

Foul smelling liquor:

UTI:

Uterine rupture:

Neonatal outcomes

Birth weight:

Apgar scores at 1 min: 5min:

Incidence of meconium-stained liquor:

NICU stay:

Duration

Reason: