COMPARATIVE STUDY BETWEEN SUBLINGUAL MISOPROSTOL VAGINAL MISOPROSTOL FOR ELECTIVE INDUCTION OF LABO IN PRIMIGRAVIDAS WITH UNFAVOURABLE CERVIX

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ABSTRACT

Misoprostol (cytotecR) is a prostaglandin El analog originally intended For prevention Of Gastric Ulcers caused by non-steroidel anti –informmatory drugs.misoprostol is not Registered for use during pregnancy ,but in most countries physicians may use licenced Medications outside the recommendationdation given in the license with appropriate informed Patient consent .misoprostol has anumber of advantages for clinhcal use .it has a long Shelf life, is easy to administerand ,unlike other prostaglandins used in obstetrics ,it is Significantly cheaper and does not require refrigeration. Misoprostol is manufactured in Two forms :100micro-Gram unscored and 200 micro-gram scored tablets, which can be Broken to provide approximate 25 and 50 microgram doses. Although misoprostol is Meant for oral administration, the tablets have also been administered Vaginally, Sublingually, buccally and rectally. No data are available about misoprostol Pharmacokinetics during the third trimester ,but studies on the pharmacokinetics of Misoprostol given by various routes for first –trimester abortion have suggested that the Sublingual and oral routes result in significantly higher serum peak concentrations of Misoprostol acid compard with the vaginal route, with significantly shorter times to Peak concentration ..The purpose of this study is to evaluate by means of a systematic Review , the effectiveness and safety of differebdroutes used to administer misoprostol for Induction of labor.

Key Words:

Oral , Vaginal ,Sublingual ,Buccal ,Misoprostol ,Labor Induction.

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LIST OF Abbreviations

ANOVA …… ……...Analysis of variance

AUC ……..Area Under The curve

Bpm…… ……..…Beat per minute

Cmax…….. …….Maximum Plasma Concentration

CTG ……..... …Cardiotocogram

C^0 ……. ……...degree celsius

Gm ……. ……..…gram

HETEs……. …… hydroeicosatetraenoic acids

HPETEs……. ……. hydroperoxyeicosatetraenoic acids

kPas s……. ……Kilo Pascal

LT…… ……. leukotrienes

Mcg……. ……microgram

MmHg……. ……..millimeter mercury

P ……. ……...P value

PGS……..……...Prostaglandins

S.D……Standard Deviation

T 1/ 2……. ……..……Half life

Tmax……..…Time to Maximum Plasma Concentration

INTRODUCTION

Parturition is a multifactorial, physiological process involving numerous interrelated maternal and fetal pathways, which may be both positive feed-forward and negative feedback. The mechanisms that initiate human parturition are not yet fully understood, despite decades of clinical,physiological and biochemical research by many investigators **[Gelisen O., 2005].**

However, it has been proposed that there are a number of stages that promote the myometrium to a contractile state, including the upregulation of receptors, prostaglandin production, and increased formation of intracellular contraction-associated proteins. The exact trigger for uterine contractions and which pathway is pre-eminent is not yet clear. Cervical ripening is independent of the initiation of uterine contractions, although the pathways are not yet fully known, it does involve the release of proinflammatory cytokines, leukocyte infiltration into the cervix, the release and activation of extracellular matrix metalloproteinases, other proteins and glycoproteins **[Gelisen O., 2005].**

Drugs that act upon the pregnant uterus can be thought of as modifiers of these endogenous physiological pathways controlling normal myometrial contractility and cervical ripening. They may be characterized by their sites of action into agents acting upon prostaglandin pathways, progesterone receptors, B-adrenergic receptors, calcium channels and the oxytocin receptor and via nitric oxide. Drugs may also be functionally classified into agents used for the

induction and augmentation of labor, for the termination of pregnancy, to treat postpartum hemorrhage, and to treat threatened preterm labor. **[Gelisen O., 2005].**

Post-term pregnancy is defined as gestation lasting beyond 42 full weeks (>294 days). Diagnosis of every pathological risk that might delay labor is not yet possible, but delay in this physiological event can cause serious fetal and maternal problems. Large surveys have shown that 1.86 and 2.26 per 1000 deliveries are stillbirths at 41 and 42 completed weeks of gestation, respectively **[Ingemarsson and Kallen, 1997].**

Ingemarsson and Kallen (1997), said that 1 fetus out of 300 died during follow-up after 40 weeks despite the availability of surveillance tests. The main concerns about elective induction of labor today are focused on maternal and fetal risks caused by more frequent cesarean delivery and the increased costs of hospitalization these involve. Post-term pregnancies involve increased fetal morbidity, including meconium aspiration, dystocia, and fetal or neonatal mortality **[Ingemarsson and Kallen, 1997].**

One large survey study showed that the odds ratio for stillbirth increases at 41 completed weeks in nulliparas and at 42 completed weeks in multiparas **[Ingemarsson and Kallen, 1997].** Also, compared with deliveries at 40 weeks of gestation, the risk of macrosomia, operative delivery, admission to neonatal intensive care units, and neonatal sepsis increases with every further gestational week **[Alexander et al., 2000]**.A comprehensive review of randomized controlled trials in 1994, before the era of misoprostol, concluded

with the recommendation that labor should be routinely induced once pregnancy has continued beyond 41 full weeks of gestation **[Crowley, 2001].** Many clinicians adopted this practice, and the number of births at or beyond 42 weeks declined significantly **[Roberts et al., 1999].**

Because of the limited resources available, Induction of labor should be used in the most efficient way possible that will result in a favorable obstetric outcome with minimum fetal morbidity , So, elective induction was evaluated in many studies.

After induction at 41 weeks there was a lower incidence of neonatal morbidity without any significant change in abdominal delivery rates or duration of hospital stay. The findings are at odds with those of other studies, which indicate extension of hospital stay and more treatment, higher costs, and higher cesarean delivery rates following elective induction of labor **[Parry et al.,1998 – Seyb et al.,1999 – Maslow and Sweeny , 2000].**

The study of Maslow and Sweeny (2000), differs from these retrospective studies in that thier sole indication for elective labor induction was 41 weeks of gestation, which excluded other possible causes of an increased cesarean delivery rate. Another point of difference from other studies is that they recruited women with strictly unfavorable cervical scores, who they believe are the ones that obstetricians should really be concerned about if their pregnancies extend to 41 completed weeks. Maslow and Sweeny ,[2000] found that in their study ,the time from admission to delivery, was longer when labor was induced than when it was not, which raised the average cost. This is also true for elective induction at

41 weeks of gestation, but tests carried out between the 41 st and 42 nd completed weeks to check on fetal well being and the higher neonatal morbidity were factors that are bound to have increased costs in the follow-up group (2000) **.**

On the other hand, elective induction of labor at or beyond term has been blamed for the increased costs of cesarean delivery and labor in retrospective studies in which oxytocin, misoprostol, or other prostaglandins were used for labor induction **[Parry et al .,1998 – Seyb et al., 1999 – Maslow and Sweeny, 2000].** Furthermore, Menticoglou and Hall,2000, in their commentary, describe induction at 41 weeks of gestation as unacceptable, illogical, and unsupported interference with a normal physiological situation **.**

Induction of labor using medication involves the stimulation of uterine contractions to produce delivery before the onset of spontaneous labor. Two most common prostaglandins analogues (PGs) currently utilized as cervical ripening and labor inducing agents are misoprostol (PGE1) and dinoprostone (PGE2). Misoprostol is an effective agent for cervical ripening and labor induction in mother with viable pregnancies **[Blanchard et al., 2002].**

Labor induction with misoprostol has become an intensely investigated topic. Various authors have reported that the use of misoprostol has an excellent efficacy, minimal side effects and cost saving benifts. **[Blanchard et al., 2002].**They mentioned five primary outcome of ineffectiveness and complication of use of misoprostol such as uterine hyperstimulation with fetal heart rate changes, increased incidence of

ceasarean section,serious neonatal morbidity (seizures, birth asphyxia or perinatal death) , serious maternal morbidity or death and vaginal delivery not achieved with in 24 hours **[Blanchard et al., 2002].**

The use of misoprostol for labor induction with a live fetus was first described in 1992, in the pioneering study by Margulies and his colleagues'(1992). Since then, decreasing doses have been proposed and labor induction with misoprostol has been favorably compared with other methods **[ACOG committee opinion no. 248, 2000& no.228, 1999].**

Rayburn, 1993, said that to reduce the incidence of contractility disturbances and neonatal complications, 25mcg is the recommended dose of vaginal misoprostol for induction of labor **[Rayburn, 1993].** Recent studies have suggested the possibility of sublingual administration of misoprostol for labor induction **[Hofmeyr and Gulmezoglu , 2002 and Fletcher et al., 1993].** In these studies MIsoprostol tablets used were originally manufactured for oral use in 100mcg or 200mcg doses, these tablets had to be broken in smaller pieces to achieve the 25 mcg dosage.

Misoprostol, a synthetic prostaglandin E1 analog, has been given both orally and vaginally for induction of labor at term **[Cullen, 2000]**. The route of administration of misoprostol was noted to be a significant factor when multiple studies indicated that vaginal misoprostol was more effective than oral misoprostol even with equivalent doses **.**There has, however, been the worry of excessive uterine contractility with vaginal doses of 50 mcg or higher **[ACOG committee opinion no. 248,(2000) & no. 228,(1999)] .**

Partly because of issues relating to patient preference, we investigated the sublingual route of administration of misoprostol. This route of administration has been reported previously in the literature. We speculated that sublingual misoprostol could combine the higher efficacy of the vaginal route by avoiding gastrointestinal and hepatic metabolism, but it could have a more restrained effect on uterine contractility by avoiding direct effects on the uterus and cervix.

Aim of the work

The purpose of this study is to evaluate by a comparative way, the effectiveness, complication, safety and patient acceptability of sublingual and vaginal route used to administer misoprostol for induction of labor. It was also our intention to evaluate and compare the fetal and maternal outcomes during the hospital stay.