EFFECIENCY OF CELECOXIB VERSUS MAGNESIUM SULFATE TO ARREST PRETERM LABOR: RANDAMIZED CONTROLLED TRIAL

Thesis
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SUMMARY

Gestational age at birth, together with birth weight, is recognized as a reference standard related to the outcome and prognosis of the preterm infant ***(Moutquin, 2003).***

The aim of tocolysis is to delay preterm delivery to allow time for maternal administration of corticosteroids and in utero transfer to a tertiary perinatal centre, thereby reducing neonatal morbidity and mortality**.**

Based on the best obstetrical assignment of gestational age, death, severe infant morbidity, or both were great before 26 weeks' gestation. The chances of survival increase appreciably at or above 1000 gm birth weight ***(Fanaroff et al., 1995).***

Despite the encouraging results of recent studies demonstrating improved methods to predict prematurity and prevent preterm labor, the incidence of preterm delivery has remained stable during the last 20 years ***(Goldenberg et al., 2001).*** Clearly, new methods to arrest acute preterm labor are needed.

The coxibs are a new group of anti-inflammatory drugs that selectively inhibit COX-2. Thus, they should be at least as effective as nonselective agents for the inhibition of fetal membrane PG synthesis with fewer side effects and

and gratitude to my ever-giving family for their encouragement, support and tender guidance.

Mohammad Khairy

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List of Abbreviations

ACOG	*American college of obstetricians and gynecologists*
ADH	*Anti diuretic hormone*
AMP	*Adenosine mono phosphate*
ATP	*Adenosine tri phosphate*
CP	*Cerebral palsy*
COX-2	*Cyclooxygenase-2*
D&C	*Dilatation and curettage*
FDA	*Food and drug administration*
HMD	*Hyaline membrane disease*
IUFD	*Intra uterine fetal death*
IVF	*In vitro fertilization*
IVH	*Intra ventricular hemorrhage*
LMP ***MgSO4***	*Last menstrual period* *Magnesium sulfate*
NEC	*Necrotizing enterocolitis*
NSAIDs	*Non steroidal anti-inflammatory drugs*
PDA	*Patent ductus arteriosus*
PGS	*Prostaglandins*
PLC	*Phosholipase C*
PPROM	*Preterm pre-labor rupture of membranes*
PVL	*Peri ventricular leukomalacia*
RDS	*Respiratory distress syndrome*
VLBW	*Very low birth weight*

INTRODUCTION

Preterm birth is the leading cause of neonatal mortality and a substantial portion of all birth-related morbidity. Preterm delivery accounts for 65% of all neonatal deaths and 50% of neurological disability in childhood ***(Shenan, 2003).***

Trials of prevention of spontaneous preterm labor received greater interest to prevent associated complications and allow trials to enhance fetal lung maturity ***(Goldenberg, 2002).***

A great number of drugs and other interventions have been used to inhibit preterm labor, but unfortunately, none has been completely effective ***(ACOG, 1995).***

An important intervention for delaying preterm labor is the use of tocolytic drugs. Potential maternal complications of tocolytic drugs cannot be underestimated. ***The American College of Obstetricians and Gynecologists*** has recommended that tocolysis should be used in the presence of regular uterine contractions plus documented cervical change or appreciable cervical dilatation and effacement ***(ACOG, 1998).***

The benefit of keeping the fetus in-utero long enough to enable administration of a full course of corticosteroids to assist in fetal lung maturation, and to organize transfer to

an appropriate neonatal care unit is very important, thus, the primary aim of tocolysis is to delay delivery for at least 48 hours to allow time for these measures to be implemented ***(Carbonne et al., 2002)***.

Magnesium sulfate is one of the most widely used tocolytic agents in the world; it is conceivable that magnesium sulfate tocolysis delay delivery for 24 to 48 hours ***(Patrick et al., 2001)***. Clinical tocolytic effects of magnesium came from the observation that preeclamptic women treated with magnesium sulfate had a greater incidence of prolonged labor (more than 24 hours) as compared to non magnesium treated controls ***(Hall et al., 1959)***.

Prostaglandins play a crucial role in preterm as term labor, and agents that inhibit prostaglandin synthesis are effective tocolytics (***Zuckerman et al., 1974; Slater et al., 1998; Fitz Gerald et al., 2001*)**.

The cox-2 inhibitors are a new group of anti-inflammatory drugs that selectively inhibit COX-2. Thus, they should be at least as effective as non-selective agents for the inhibition of fetal membrane PG synthesis with fewer side effects and may represent new strategy for tocolysis ***(Higby et al., 1993).***

AIM OF THE WORK

The purpose of this study is to compare the efficiency of oral celecoxib, a preferential COX-2 inhibitor, versus magnesium sulfate to arrest preterm labor.

Chapter (1):

PRETERM LABOR

Definition:

Preterm birth complicates 10–15% of all pregnancies. It is the most important cause of neonatal morbidity and mortality and causes 75% of neonatal deaths that are not due to congenital anomalies ***(Alan et al., 2006)***.

In 1935, the American college of pediatrics defined prematurity as alive-born infant weighting 2500 grams or less (***Cone, 1985***). These criteria were used widely until it became apparent that there were discrepancies between gestational age and birth – weight because of restricted fetal growth. The world health organization added gestational age as criteria for premature infants, defined as those born at 37 weeks or less. A distinction was made between low birth weight (2500 grams or less) and prematurity (37 weeks or less than 259 days since the first day of the last menstrual period).

The WHO in 1993 has recommended that preterm is defined as gestational age less than 37 completed weeks of pregnancy or less than 259 days of the LMP, which is further subdivided into:

1- **Early preterm:** Less than 34 week's gestation.

2- **Very early preterm**: Less than 30 week's gestation.

3- **Extremely preterm**: Less than 26 week's gestation.

Also ***the American College of Obstetricians and Gynecologists (ACOG) in 1995*** defined preterm birth as those infants delivered prior to the completion of 37 weeks of gestation.

Gestational age at birth, together with birth weight, is recognized as a reference standard related to the outcome and prognosis of the preterm infant ***(Moutquin, 2003).***

With improved care of ***the Collaborative Group on Antenatal Steroid Therapy (1981)*** reported that the great mortality and serious morbidity from preterm birth is prior to 34 weeks ***(Cunningham et al., 2001).***

Diagnosis of preterm labor:

Early differentiation between true and false labor is difficult before any demonstrable cervical effacement and dilatation. Uterine contractions alone can be misleading because of Braxton Hicks contractions. These contractions, described as irregular, non-rhythmic, and either painful or painless, can cause considerable confusion in the diagnosis of preterm labor. Not frequently, women who deliver before term have uterine activity that is attributed to Braxton Hicks contractions, prompting an incorrect diagnosis of false labor ***(Moutquin, 2003)***.

Because uterine contractions alone may be misleading, ***the American College of Obstetricians and***

Gynecologists has proposed the following criteria to document preterm labor between 20 and 37 weeks' gestation:

1- Contractions occurring at a frequency of four in 20 minutes or eight in 60 minutes plus progressive change in the cervix.

2- Cervical dilatation greater than 1 cm.

3- Cervical effacement of 80 percent or greater ***(ACOG, 1997)***.

Incidence of preterm labor:

In several countries the incidence of preterm labor has been reported to be between 5% and 10% of all births, and this rate has been stable over the past two decades and varies between populations ***(Lumley, 1993).*** Approximately 13 million infants are born preterm each year worldwide ***(Villar& Ezcurra, 1994).***

Etiology of preterm labor:

Spontaneous preterm birth is a common outcome of a broad combination of medical and social factors. In fact, it may be said to be a social disease: it happens much more frequently when the mother is poor, has a low educational level, isolated, single or too young. National data are unequivocal on this major point: preterm birth is closely related to social class.

A wide spectrum of etiologies has been implicated in the delivery of a preterm infant including:

A- Reproductive history.

B- Lifestyle factors.

C- Socio biological factors.

D-Obstetrical factors.

E-Infections.

So premature labor can be understood as a syndrome with a number of underlying-causes including infection, maternal stress, uterine distention, placental hypoxia, bleeding and lack of prostaglandin dehydrogenase. Infection is probably the most important factor at low gestational age, uterine distention and maternal stress increasing in significance. Further on, In the future, the ability to determine the specific reason in each individual case may be better, which may lead to the development of more elective treatment (***Hagberg and Wennerholm., 2000***).

A- Reproductive History:

1- Prior Preterm Birth:

The relative risk of preterm labor increases with the number of previous preterm deliveries. This risk is 2.2% for one preterm delivery, 3.7% for two preterm deliveries, and 4.9% for three or more preterm deliveries. Similarly for

each birth that is not preterm the risk of subsequent preterm birth decreases ***(Bakketeig and Hoffman, 2001).***

2- Previous Abortion:

There is a relationship between the number of prior abortions, whether spontaneous or induced and prevalence of preterm labor. The relative risk of one previous abortion either spontaneous or induced is 1.66 &1.55 respectively, and for two previous abortions either spontaneous or induced is 2.49 & 2.46 respectively, and for three or more abortions either spontaneous or induced is 5.89& 5.58 respectively ***(Lumley, 1993).***

3- Inter-pregnancy interval:

A short interval between two pregnancies has been reported as a risk factor for preterm labor. A significant increase in the incidence of preterm labor was only seen when the interval between the last birth and the menstrual period of the next pregnancy was less than 3 months ***(Lang et al., 1990).***

4- Effect of Infertility:

Women enrolled in IVF programs have high rates of preterm delivery even with singleton pregnancies ***(Hill et al., 1990)***.