INTRODUCTION

Adequate analgesia during labor has a positive influence on the course of labor ***(Keskin et al., 2003).*** Most women who deliver in modern obstetric units request some form of pharmacological and non pharmacological pain relief ***(Thurlow et al., 2002).***

The ideal obstetric analgesic should provide potent analgesic efficacy with minimal maternal and neonatal adverse effects. Epidural analgesia offers the best pain relief for many women in labor. But, where this contraindicated or woman does not wish to have an epidural analgesia, administration of injectable opioids is a simple and less invasive alternative ***(Bricker and Lavaender, 2002).***

Opioids are group of drugs which have been administered for a hundreds of years to allay anxiety and to reduce pain. Opioids can be classified as naturally occurring, semi synthetic, and synthetic ***(Peter et al., 2000).*** Pethidine is one of the most commonly used opioid for labor pain relief ***(Bricker and Lavander, 2002).***

Pethidine exerts its effect through acting as agonist on opioid receptors. It can be administered orally or parentrally. When used intramuscularly, its analgesic effect starts within

10-20 minutes and its duration is shorter than that of morphine, lasting for 2-4 hours ***(Clark et al., 1995).***

Many authors hypothesized that there is an indirect effect of pethidine on the uterine contractility, through pain relief and subsequent decrease of adrenaline may finally produce an increase in uterine contractility and decrease length of active phase of labor ***(Onur et al., 1989).*** Also, pethidine use was associated with changes in the cervical proteases during labor ***(Mildwisky et al., 1993).***

Studies on pethidine raised concern about its effects on the newborn. This includes increased risk of fetal acidosis at birth, sleepy baby, less successful breast feeding and some recent evidence suggests that babies whose mothers have pethidine in labor are more likely to develop dependence in later life ***(Sosa et al., 2006).***

The maternal side effects of pethidine include central nervous system (dizziness, drowsiness, fatigue, headache, and sedation), gastrointestinal system (nausea, vomiting, and constipation), cardiovascular system (orthostatic hypotension), respiratory depression, delayed gastric emptying and aspiration ***(Tsui et al., 2004).***

Tramadol is a synthetic analog of codeine and a weak opioid agonist, acting centrally by modifying transmission of pain impulse by altering mono amine reuptake mechanisms, Tramadol can be administrated orally, rectally, intravenously

or intramuscularly, and it is principally metabolized in the liver and 90% of it is excreted in urine ***(Lee et al., 1993).***

Tramadol has the same range of side effects as pethidine, but when administered intramuscularly it does not causes respiratory depression, and intravenous administration causes far less respiratory depression than pethidine ***(Lee et al., 1993).***

Central and respiratory depressant effect of Tamadol is due to high doses and may be antagonized by naloxone. Tramadol crosses the placenta, and it's concentration in the umbilical venous serum is approximately 80% of maternal level ***(Fieni et al., 2000).***

These concerns about maternal and fetal side effects of pethidine have led to an exploration of advantage and disadvantage of tramadol as an alternative to pethidine comparing there effects on the duration of labor and maternal pain relief.

AIM OF THE WORK

The aim of the present study is to compare the effect of Pethidine versus Tramadol on the duration of labor in primigravidae (including active phase of 1st stage and 2nd stage of labor), degree of analgesia achieved during labor and early postpartum, maternal side effects, and postpartum maternal satisfaction.

NORMAL LABOR

Labor refers to the chain of physiologic events that allows a term fetus to undertake its journey from the uterus to the outside world ***(Liao et al., 2005).***

For parturition to occur, two changes must take place in a woman's reproductive tract. First, the uterus must be converted from a quiescent structure with dyssynchronous contractions to an active coordinately contracting organ with complex interlaced muscular components. The second change is that the cervical connective tissue and smooth muscle must be capable of dilatation to allow the passage of the fetus from the uterus ***(Norwitz et al., 1999).***

Parturition can be divided into four uterine phases which correspond to the major physiological transitions of myometrium and cervix during pregnancy ***(MacDonald and Casey, 1996).***

Uterine phase 0 of parturition:

It is a remarkably effective period of myometrial quiescence that is imposed on the uterus which is characterized by myometrial smooth muscle tranquility with maintenance of cervical structural integrity ***(MacDonald, 1993).***

During this phase the myometrium is rendered unresponsive to natural stimuli and relative contractile

paralysis is imposed against a host of mechanical and chemical challenges that otherwise would promote emptying of the uterine contents while the Cervix remains firm and unyielding which is essential to the success of phase 0 of parturition ***(Iams et al., 1996).***

Factors affecting uterine phase 0 of parturition:

It is likely that all manner of biomolecular systems (neural, endocrine, paracrine and autocrine), calling upon multiple cell-signaling processes, are implemented and coordinated to impose a state of relative uterine unresponsiveness. Moreover, a complementry fail-safe system that protects the uterus against agents that could perturb the tranquil state of phase 0 also must be in place. The actions of estrogen and progesterone via intracellular receptors, myometrial cell plasma membrane receptor, mediated increase in cyclic adenosine monophosphate (cAMP), the generation of cyclic guanosine monophosphate (cGMP), and other systems (modifications in myometrial cell ion channels) may be all operative in phase 0 of human parturition. Individually, some of these processes may be redundant, that is, pregnancy may continue in the absence of one or more processes that normally contribute to the fail-safe system of pregnancy maintenance ***(Cunningham et al., 2001).***

Estrogen acting directly or indirectly, promotes a variety of myometrial changes that enhance the capacity of

the myometrium to generate powerful contractile force and coordinated contractions. For example, estrogen may act to increase gap junctions between myometrial cells and calcium channels must be opened to facilitate contractions. Estrogen, also, acts in promoting progesterone responsiveness. In many responsive tissues, the estrogen receptors induce the synthesis of progesterone receptors ***(Pepe and Albrecht, 1995).***

As regard progesterone, either acting directly or indirectly, it seems to impose contractile unresponsivness. Also, progesterone action causes striking increase in the activities of enzymes that degrade or inactivate endogenously produced uterotonins. Most likely, estrogen and progesterone act in concert to contribute to the effectiveness of phase 0 of parturition ***(Germain et al., 1994).***

Uterine phase 1 of parturition:

During this phase the myometrium shows specific modifications in uterine function with the suspension of uterine phase 0 as ***(Fuchs et al., 1982):***

1) A striking 50 fold or more increase in the number of myometrial oxytocin receptors.
2) An increase in uterine contractile responsiveness to oxytocin and to other uterotonins.
3) An increase in gap junctions between myometrial cells before the onset of labor, continue to increase during labor, and then decrease quickly after delivery.

5) Transition from a contractile state characterized predominantly by occasional painless contractions to one in which more frequent contractions develop.
6) Formation of the lower uterine segment associated with descent of the fetal head to or even through the maternal inlet of the pelvis, a distinctive event referred to as lightening.

As regard the cervix, it shows cervical softening associated with two complementry changes which are collagen breakdown and rearrangement of the collagen fibres associated with alterations in the relative amounts of the various glycosaminoglycans. Near term, there is a striking increase in the relative amount of hyaluronic acid in cervix, with a concomitant decrease in dermatan sulfate. This hyaluronic acid is associated with the capacity of a tissue to retain water ***(Winkler and Rath, 1999).***

Factors affecting uterine phase 1 of parturition:

It was generally accepted that successful pregnancy in all mammalian species was dependent upon the action of progesterone to maintain uterine quiescence until near the end of gestation. This assumption was supported by the finding that in the majority of mammalian pregnancies studied, progesterone withdrawal (whether naturally occurring or surgically or pharmacologically induced) precedes the initiation of parturition. In many of these

species, a decline, sometimes precipitous, in the levels of progesterone in maternal plasma normally begins after approximately 95 percent of pregnancy. Moreover, the administration of progesterone to these species late in pregnancy delays the onset of parturition ***(Cunnigham et al., 2001).***

In primate pregnancy (including humans), however, progesterone withdrawal does not precede the initiation of parturition. The levels of progesterone in the plasma of pregnant women increase throughout pregnancy, declining only after delivery of placenta, the site of progesterone synthesis in human pregnancy ***(Challis and Lye, 1994).***

Parturition theories:

Presently, there appear to be two general theories which are:

(1) The retreat from pregnancy maintenance hypothesis.

(2) The uterotonin induction of parturition theory ***(Cunningham et al., 2001).***

So, labor at term may best be regarded physiologically as an event initiated by the removal of inhibitory effects of pregnancy on the myometrium rather than as an active process governed by uterine stimulants ***(Norwitz et al., 1999).***

For example, in vitro studies have shown that a quiescent myometrium obtained from term uteri and placed

in an isotonic solution contract vigorously and spontaneously without added stimuli ***(Lopez Bernal et al., 1995)***, however, in vivo, it is likely that both mechanisms are important ***(Norwitz et al., 2001).***

Some researchers also speculate that the mature human fetus, in some undefined fashion, is the source of the initial signal for the commencement of the parturition process. This has little experimental support in human parturition ***(Thorburn, 1993).***

Other investigators, suggest that one or another uterotonin, produced in increased amount or in response to an increase in its myometrial receptors, is the proximate cause of the initiation of human parturition. Indeed, an obligatory role for one or more uterotonins is included in most parturition theories, either as a primary or a secondary phenomenon in the final events of childbirth. It is unlikely, however, that the initial signal for the initiation of parturition is a uterotonin such as oxytocin, prostaglandins, or endothelin-1. Rather, it is more likely that the uterus first must be prepared for labor before a uterotonin can be optimally effective ***(Casey and MacDonald, 1994).***

Finally, the potential role of the intrauterine tissues that means amnion, chorion leave, and decidua parietalis has been studied to define the participation if any of each tissue in promoting the initiation of parturition; but presently, an alternative role for these tissues appears to be more likely ***(Germain et al., 1994).***

Fetal contribution to initiation of parturition:

Considerable evidence suggests that the fetus is in control of the timing of labor. Around the time of Hippocrates, it was believed that the reason the fetus presented head first was so that it could kick its legs up against the fundus of the uterus and propel itself through the birth canal. Although we have moved away from this simple and mechanical concept of labor, the idea that the fetus plays a central role in the initiation of labor remains and has been supported by experimental data in other viviparous mammalian species ***(Nathanielsz et al., 1997).***

Cross breeding experiments with horses and donkeys in the 1950s, for example, demonstrated a gestational length intermediate between those of the parent species, which suggested a critical role for the fetal genotype in determining the onset of labor and the duration of gestation ***(Liggins, 1989).***

In domestic ruminant, such as sheep and cows, the mechanism by which the fetus triggers labor at term has been elucidated elegantly and involve glucocorticoid-mediated activation of a placental enzyme, 17hydroxylase/17,20-lyase, which catalyzes the conversion of progesterone to estradiol. This switch in the progesterone:estrogen ratio lead to uterine prostaglandin production and labor ***(Matthews and Challis, 1996).***

Similarly, secretion of surfactant protein-A from the lungs into the amniotic fluid at the end of pregnancy has been shown to be important for the initiation of labor in a murine model ***(Condon et al., 2004).***

Unfortunately, there is as yet insufficient evidence to suggest that any of these factors are critical for the onset of labor in humans. For example, the human placenta does not contain glucocorticoid – inducible 17 alpha hydroxylase/17, 20 – lyase enzyme ***(Liggins, 1989).***

Although the precise signal varies, the final common pathway towards labor seems to be activation of the fetal hypothalamic-pituitary-adrenal axis and is probably common in all viviparous species. In humans activation of the fetal hypothalamic-pituitary-adrenal axis results in the release of dehydroepiandrostenedione, which serves as an essential precursor for estriol production ***(Challis, 1994).***

Regardless of whether the signal for labor begins with the mother or the fetus, the final common pathway for labor ends in the maternal tissues of the uterus and is characterized by the development of regular phasic uterine contractions ***(Liao et al., 2005).***

In brief, labor is a multifactorial physiologic event that involves an integrated set of changes within the uterus that occur gradually over a period of days to weeks. Such changes include, but are not limited to, an increase in prostaglandin

synthesis and release within the uterus, an increase in myometrial gap junction formation and up regulation of myometrial oxytocin receptors. When the myometrium and the cervix have been prepared appropriately, endocrine or paracrine / autocrine factors from the fetoplacental unit bring about a switch in the pattern of myomerial activity from contractures to contractions. The fetus may coordinate this switch in myometrial activity through its influence on placental steroid hormone production, through mechanical distention of the uterus, and through secretion of neurohypophyseal hormones and other stimulators of prostaglandin synthesis ***(Liao et al., 2005).***

Contribution of intrauterine tissues to parturition:

The fetal membranes and deciduas are part of an important tissue shell around the fetus that serves as a physical, immunological and metabolic shield that protects against the untimely initiation of parturition.

(1) Amnion:

A number of bioactive peptides and polypeptides, which are effective smooth muscle relaxants, are synthesized in amnion: CRH, and atrial natriuretic peptide. Specific receptors for these agents are present in myometrial tissue during pregnancy. A mechanism has not been established, however, whereby these vasoactive peptides can be transported from amnion to the myometrium without degradation. It is more likely that

these agents act on contiguous tissues, such as the chorionic vessels of the placenta, or after inspiration or swallowing into the fetal lungs or gastrointestinal tract ***(Casey and MacDonald, 1988).***

(2) Chorion laeve:

The chorion leave is enriched in enzymes that inactivate uterotonins such as prostaglandin dehydrogenase, oxytocinase, and enkephalinase ***(Germain et al., 1994).***

(3) Decidua parietalis:

There are several lines of evidence that decidual activation is an accompaniment of human parturition. However, the central question is whether activation of deciduas precedes or follows the onset of labor ***(MacDonald et al., 1991).***

The process of activation of decidua appears to be localized to the exposed decidual fragments lining the forebag. So, trauma, hypoxia, exposure of forebag to endotoxin lipopolysaccharides, micro-organisms, and IL-1B in the vaginal fluids provokes an inflammatory reaction, which is an inevitable and consistent sequelae of labor ***(Cunnigham et al., 2001).***

Uterine phase 2 of parturition:

Phase 2 is synomynous with active labor, that is, the uterine contractions that bring about progressive cervical

dilatation and delivery of the conceptus. Phase 2 of parturition is customarily divided into three stages of labor ***(Cunningham et al., 2001):***

1) First stage of labor (stage of cervical effacement and dilatation).
2) Second stage of labor (stage of expulsion of the fetus).
3) Third stage of labor (stage of separation and expulsion of the placenta).

Factors affecting uterine phase 2 of parturition:

Once phase 0 is suspended and uterine phase 1 processes are implemented, a number of uterotonins may be important to the success of phase 2, active labor. Many uterotonins known to cause myometrial contractions of smooth muscle in vitro have been proposed such as oxytocin, prostaglandins, serotonin, histamine, platelet activating factor (PAF), angiotensin 2, and many others ***(Cunnigham et al., 2001).***

The endothelins are very powerful inducers of myometrial smooth muscle contraction and endothelins receptors are demonstrable in myometrial tissue. However, the researchers have found that the potential contribution of myometrial endothelin to phase 2 of parturition is not defined ***(Word et al., 1990).***