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Ain Shams University
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EVALUATION OF INTRAVENOUS INFUSION OF PARACETAMOL AS INTRAPARTUM ANALGESIC IN THE FIRST STAGE OFLABOUR: ADOUBLE-BLIND RANDOMIZED TRIAL

Thesis

Submitted for partial fulfillment of Master Degree in Obstetrics and Gynecology

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List of Contents

List of Tables

List of Figures

Abbreviations

AUC	Plasma concentration-time curve
CGRP	Calcitonin gene related peptide
CRF	Case record form
CSE	Combined Spinal-Epidural Analgesia
DRG	The dorsal root ganglia
GCP	Good clinical practice
HTM	High-threshold mechano-receptors
IASP	The international association for study of pain
NAPQI	N-acetyl-p-benzoquinone
NRM	The nucleus raphe magnus
NRS	Numerical rating scale
PAG	The periaqueductal grey
PFS	The pain face scale
PGE	Pathway involved in prostaglandin
PMN	Polymodal nociceptors
SG	The substantia gelatinosa
SRT	Spinoreticular tracts
SSC	The somatosensory cortex
STT	The spinothalamic tract
TENS	Transcutaneous electrical nerve stimulation
VAS	Visual analogue scale
VRS	Verbal rating scale

Introduction

Childbirth is an important experience in a woman's life ***(Goodman et al., 2004),*** nevertheless labor is considered to be one of the most intense and stressful experiences ***(Melzac, 1993).*** Adequate analgesia during labor has a positive influence on the course of labour ***(Keskin et al., 2003),*** so most women who deliver in modern obstetric units request some form of pharmacological and non-pharmacological pain relief ***(Thurlow et al., 2002).***

Epidural analgesia using opioids is the most potent method for women in labour in need of effective analgesia ***(Paech, 1991),*** however it prolongs the duration of the second stage of labor by 15 to 30 minutes and may increase the rate of instrument-assisted vaginal deliveries as well as that of oxytocin administration ***(Halpern et al., 2004; Liu and Sia, 2004).*** Intramuscular administration of narcotics can also reduce the pain of labor pain but this method is limited by negative side effects such as maternal drowsiness, nausea and vomiting as well as neonatal respiratory depression ***(Simkin and Dickersin, 1996).***

Paracetamol has been widely used for over a century as an effective analgesic and as an antipyretic agent ***(Malaise et al., 2007).*** Its efficacy and tolerability are well established and in contrast with other analgesics, it has a favorable safety profile

(Graham et al., 2003). It can be administered orally or rectally ***(Bektas et al., 2009)***. At therapeutic doses, it is associated with fewer adverse effects than either opioids or nonsteroidal anti-inflammatory drugs ***(Hyllested et al., 2002).*** Labour pains are among the most severe pain that the human being experience and are compared in its intensity to severe cancer pain or pain from the amputation of a digit, therefore adequate intrapartum analgesia has a positive influence on the course of labour ***(Melzack, 1984; Keskin et al., 2003).*** Although Paracetamol has been widely used as an effective and safeanalgesic medication ***(Graham, 2005; Malaise et al., 2007)*** there is a paucity of studies assessing its intrapartum use. The 1st one was a pilot single-arm trial in Ain Shams University Hospital, Cairo, Egypt, provided reassuring data regarding this new use of the drug, but it did not have a comparison arm ***(Elbohoty & El-Shorbagy, 2010).*** Another study was also done in Ain Shams University Hospital comparing Intravenous infusion of paracetamol versus intravenous pethidine as an intrapartum analgesic in the first stage of labor which showed a comparable effect between both medicines, but paracetamol had fewer adverse effects ***(Elbohoty et al., 2012).***

The aim of the present study was to evaluate the efficacy and adverse effects of an intravenous infusion of 1000 mg of paracetamol during the active phase of labor as compared with a placebo as a method for intrapartum analgesia.

Primary objective:-

To assess the efficacy of intravenous infusion of paracetamol in comparison with placebo (sterile water for injection) in pregnant women undergoing labor, as demonstrated by the degree of pain relief during the labor process and subsequent need of additional analgesia.

Secondary objective:-

1. To document safety and evaluate adverse events recorded during the study either maternal or fetal.
2. To correlate with the duration of labor either the first or the second stage.

The pain

Definition of pain:

The international association for study of pain (IASP), defined pain as: an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage ***(Merskey and Bogduk, 1994).***

Nature of pain:

Pain is described as an unpleasant sensation associated with a specific part of the body ***(Melzak and Katz, 2006).*** It is produced by processes that either damage or are capable of damaging the tissues. Such damaging stimuli are called ‘‘noxious’’ and are detected by specific sensory receptors called ‘‘nociceptors’’ which are free nerve endings with cell bodies in the dorsal root ganglia (DRG) and terminate in the superficial layers of the dorsal horn of the spinal cord which relay messages by releasing neurotransmitters such as glutamate ***(Jeftinija et al., 1991).*** Substance P and calcitonin gene related peptide (CGRP***) (Lawson et al., 2002).*** These pain neurotransmitters will result in the activation of the second-order neuron via their corresponding receptor Which crosses the spinal cord to the contralateral side and travels up the spinothalamic tract (STT) until it reaches the thalamus hence the third-order neuron is activated, traveling from the thalamus to the somatosensory

cortex (SSC), which allows for the perception of pain ***(Lawson et al., 2002).***

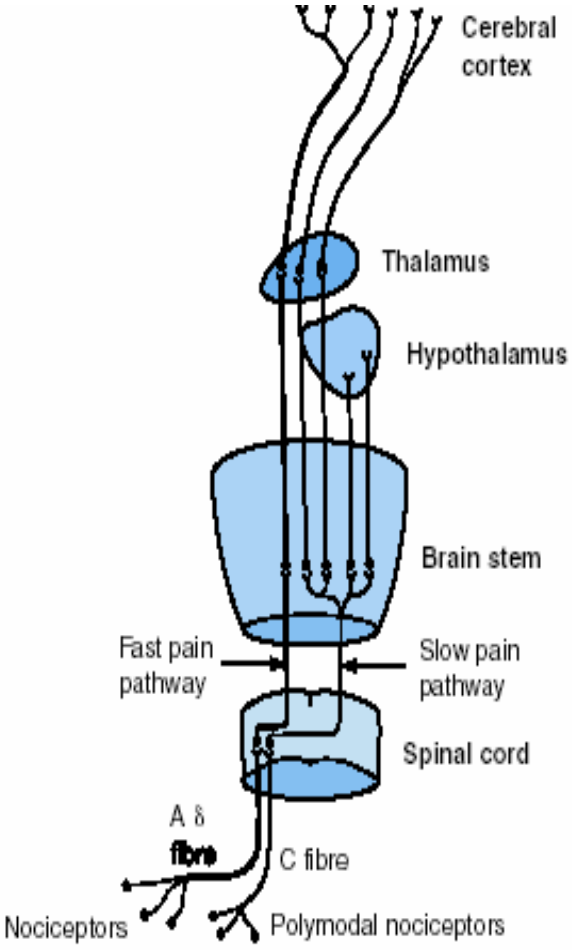

Fig. (1): Ascending tracts of spinal cord ***(Marchand, 2008).***

Sources of pain:

1-Nociceptive pain: Results from damaged tissues.

- **Visceral pain.**
- **Somatic pain:** (Peripherally – Centrally).

2-Neuropathic pain: Results from nerve damage or disease ***(Macintyre and Schug, 2007).***

Types of pain:

1. Visceral pain:

Pain arising from viscera has a number of characteristic features:

- Poorly localized, associated with nausea and autonomic disturbance.
- May be colicky, often referred to another part of the body.
- Pain is elicited by distension, ischemia and inflammation ***(Catterine et al., 1998).***

Pain is mediated via A δ and C fibres, which travel with autonomic afferents that enter the spinal cord at the thoracic, upper lumbar and sacral segments. Because pathways are shared, activity in postsynaptic cells produced by visceral afferent activity is interpreted as arising from converging somatic afferents and pain may be referred to the corresponding somatic tissue ***(Catterine et al., 1998).***

2. Somatic pain :

Sharp, stabbing pain and usually well localized to the area of injury, It results from injury of skin, mucosa, muscles, bone, tendons, arteries, ligaments and joints ***(McCaffrey et al., 2003)***

● *Central nervous system and pain:*

1. Primary afferent conduction:

Nociceptor terminations join to form axons whose cell bodies are in the dorsal root ganglia or trigeminal ganglion. The central terminations of these fibres are in the dorsal horn of the spinal cord ***(Catterine et al., 1998)***

2. Dorsal horn of spinal cord:

The dorsal horns of the cord are divided into laminae on the basis of their histological appearances. Laminae 2 and 3 constitute the substantia gelatinosa (SG), where most of the modulation and sensory processing occurs ***(Dwarkanath, 1991).*** (Fig. 2)

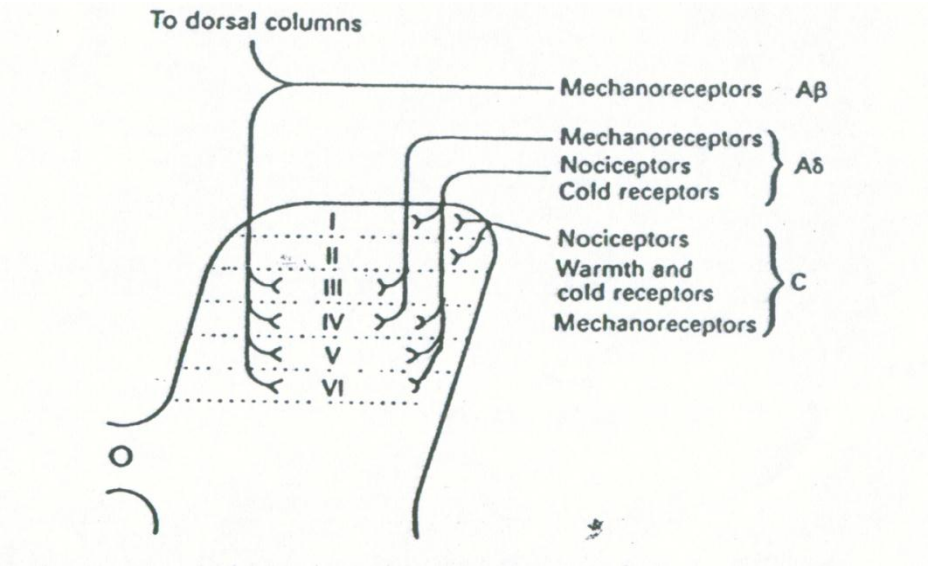

Fig. (2) : Schematic representation of the termination of the 3 types of primary afferent neurons in the various layers of the dorsal horn of the spinal cord ***(Ganong, 1989).***

The impulses from spinal nerves reach the spinal cord via the dorsal spinal root (A-delta and C fibres), where they enter the region of the dorsal horn. Some of the sensory fibres pass directly through the dorsal horn and cross to the contralateral spinothalamic tract ***(Bonica, 1990).***

3. Ascending tracts:

From the dorsal horn, nociceptor neurones ascend in the contralateral spinothalamic and spinoreticular tracts (SRT) in the anterolateral white matter of the spinal cord. The spinothalamic tract sends collateral branches to the periaqueductal grey (PAG) matter in the midbrain. This is well organized to provide discrete information ***(Catherine et al., 1998).***

The spinoreticular pathway ascends in the anterolateral cord and reaches the nuclei of the brain stem reticular formation, where they project to the thalamus, hypothalamus and thalamic intralaminar nuclei which projects diffusely to the whole cerebral cortex and involved in the perception of affective-motivational aspects of pain **(*Dwarkanath, 1991).***

4. Descending modulation of pain:

Electrical stimulation of the midbrain PAG produces profound analgesia which receives input from the thalamus, hypothalamus, the cortex and collaterals from the spinothalamic tract and so is important center for descending control of pain ***(Woolf et al., 2004).***