Efficacy of pregabalin as adjuvant analgesia to diclofenac sodium in laparotomies for benign gynaecological diseases: A Randomized Controlled Trial

Thesis

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List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
ATP	*Adenosine triphosphate*
BMI	*Body Mass Index*
CI	*Confidence interval*
COX	*Cyclooxygenase*
COX-1	*Cyclooxygenase-1*
GABA	*Gamma amino butyric acid*
GABA	*Gamma-amino-butyric acid*
HPβCD	*Hydroxypropyl-β-cyclodextrin*
NSAIDs	*Non-steroidal anti-inflammatory drugs*
PAG	*Peri-Aqueductal Grey matter*
PG	*Prostaglandin*
TENS	*Transcutaneous Electrical Neural Stimulation*
VAS-100	*Visual analogue scale*
VMM	*Ventromedian medulla*
WDR	*Wide dynamic range cells*

INTRODUCTION

Abdominal surgeries tend to be the most painful among all types of surgeries and 70% of the patients suffer from severe pain in the postoperative period ***(Sommer et al., 2008).***

Post-operative pain and fatigue are two of the key causes of prolonged convalescence following abdominal surgery ***(Bekker, 2013).***

The current predominant approach of multimodal postoperative analgesia is mostly based on a combination of opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and perioperative administration of local anesthetics. Each of these approaches comes with its own set of complications ***(Cashman et al., 2004).***

The emerging concepts of pre-emptive analgesia, a drug that has analgesic properties, opioid sparing effects, which possibly reduces opioid tolerance, relieves anxiety and is not associated with adverse effects typical for the traditional analgesic would be an attractive adjuvant for post-operative pain management ***(Kelhet et al., 2003).***

Non-steroidal anti-inflammatory drugs (NSAIDS) like diclofenac exert their action via inhibition of prostaglandin (PG) synthesis by inhibiting cyclooxygenase-1 (COX-1) and COX-2 enzymes with relative equipotency ***(Gan, 2010).***

Previous studies have demonstrated the safety and efficacy of single- and multiple-dose of hydroxypropyl-β-cyclodextrin (HPβCD)-diclofenac in postsurgical patients ***(Chelly, 2013)*** and the management of mild to moderate pain and moderate to severe pain, alone or in combination with opioid analgesics ***(Hospira Inc., 2016)***.

Pregabalin is an attractive adjuvant for perioperative analgesia in this regard as it can be taken on an empty stomach, does not lead to gastrointestinal bleeding, and is generally welltolerate ***(Hindmarch et al., 2005).***

The administration of oral pregabalin preoperatively has been reported to reduce acute postoperative pain ***(Clarke, 2015)*** and to prolong the duration of anesthesia produced by single-injection peripheral nerve blockade ***(Cegin, 2016).***

The efficacy of pregabalin in treating acute postsurgical pain has been demonstrated in numerous studies. A recent metaanalysis has suggested that pregabalin, at all doses and administration regimens, has opioid-sparing effects and reduces pain scores in the postsurgical setting ***(Mishriky et al., 2015).***

Pregabalin is a structural analogue of gamma amino butyric acid (GABA). It acts through presynaptic binding to the alpha-2-delta subunit of voltage gate calcium channels that are widely present in both the spinal cord and the brain. Therefore, it modulates the release of many excitatory neurotransmitters,

such as glutamate, norepinephrine, substance-P, and calcitonin gene related peptide. It causes inhibitory modulation of overexcited neurons and restores them to a normal state. Centrally, pregabalin is able to decrease the hyper excitability of the dorsal horn neurons that is caused by tissue damage ***(Imani, 2012).***

AIM OF THE WORK

Primary objective:

The study aims to asses the efficacy of pregabalin as adjuvant analgesic to diclofenac sodium.

Hypotheses:

In women undergoing laparotomies pregbalin is effective as post-operative analgesia.

Research question:

In women undergoing laparotomies is pregbalin effective as post-operative analgesia?

Chapter 1

ANATOMY AND PHYSIOLOGY OF PAIN

The "standard" definition of pain is that of the international association for the study of pain "An unpleasant sensory and emotional experience, associated with actual or potential tissue damage, or described in terms of such damage" ***(IASP, 2012).***

Many people report pain in the absence of tissue damage or any likely patho-physiological cause; usually this happens for psychological reasons. There is no way to distinguish their experience from that due to tissue damage ***(Pati et al., 2016).***

Classification of pain:

a) The term "nociception", which is derived from noci (Latin for harm or injury), is used only to describe the neural response to traumatic or noxious stimuli. All the nociception produces pain, but not all pain results from nociception. Many patients experience pain in the absence of noxious stimuli, it is therefore clinically useful to divide pain into one of two categories: ***(Baltantyne et al., 2006)***

1. Acute pain, which is primarily due to nociception.

2. Chronic pain, which may be due to nociception but in which psychological and behavioral factors often play a major role.

Pain can also be classified according to: ***(Marchand, 2008).***

- Pathophysiology (e.g. nociceptive or neuropathic pain).
- An etiology (e.g. postoperative or cancer pain).
- Affected area (e.g. headache or low back pain).

Such classifications are useful in the selection of treatment modalities and drug therapy ***(Hall, 2000).***

1. Acute pain

Acute pain can be identified as "that which is caused by noxious stimulation due to injury, a disease process, or abnormal function of muscle or viscera", it is always nociceptive, which is pain serves to detect, localize, and limit tissue damage ***(Renn and Dorsey, 2005, Meyr and Steinberg, 2008).***

This type of pain is typically associated with neuro-endocrine stress that is proportional to intensity ***(Marchand, 2008).*** It's most common forms include post-traumatic, postoperative, and obstetric pain as well as that associated with acute medical illness, such as myocardial infarction, pancreatitis, and renal calculi ***(Kalso et al., 2002).***

Two types of acute (nociceptive) pain - somatic and - visceral are differentiated based on origin and features: ***(Hall, 2000).***

b) Somatic pain: results from injury of skin and mucosa, muscles, bone, tendons, arteries, ligaments and joints ***(Kalso et al., 2002)***

c) Visceral pain: results from stimulation of nociceptors in internal organs as stomach, bladder, intestine etc as result of tissue damage as distension, infection, obstruction, ischemia ***(Hall, 2000; Kalso et al., 2002).***

2. Chronic pain:

Chronic pain is defined as "that which persists beyond the usual course of an acute disease or after a reasonable time for healing to occur", this period varies between 1 and 6 months in most definitions ***(Renn and Dorsey, 2005).*** Chronic pain' may be nociceptive, neuropathic, or combination of both ***(Wallace and Staats, 2005).***

Although acute pain may have survival value (causing e.g., removal of the injured limb from harmful stimulus), chronic pain is of no value, and is a major scourge of humanity ***(Kalso et al., 2002; Wallace and Staats, 2005).***

Pain pathway:

Previously, pain pathways had three components: ***(Carabine et al., 2002; Serpell, 2005).***

1. First order neuron (cell body in dorsal root ganglion) which transmits pain from a peripheral receptor to….

2. Second order neuron in the dorsal horn of the spinal cord, which crosses the midline to ascend in the spinothalamic tract to the thalamus where ....

3. Third order neuron projects to the postcentral gyrus (via the internal capsule).

(Carabine et al., 2002; Serpell, 2005)

But now, the following will be considered components of pain pathways: ***(Rawal, 2002; Carabine et al., 2002).***

1. Peripheral receptors.
2. Neural pathways.
3. Spinal cord mechanisms and long tracts.
4. Brain stem, thalamus, cortex, and other areas.
5. Descending pathways.

1. <u>Peripheral receptors:</u>

Most receptors on the peripheral endings of afferent nerves respond to a variety of stimuli. Their shape, location,

and field of reception indicate that they are able to perceive one type of stimulus more efficiently than many other types ***(Janifer et al., 2008).*** The specific receptor type that is incriminated in the reception of the pain is said to be un-encapsulated nerve ending ***(Carabine et al., 2002).*** Although this receptor has a thin myelin covering, it is usually referred to as unmyelinated or "naked" nerve ending ***(Rawal, 2000).***

There are two distinct responses to a painful stimulus, a "first pain" and a "second pain", the first pain is well localized and brief, while the second is more diffuse and protracted ***(Westlund, 2005).***

First pain is described as sharp, and "pricking", it localizes to a well-defined part of the body surface, the receptors for this first pain are high threshold mechanoreceptor ***(Prain, 2008).*** They appear to be specific "nociceptors" which mediate pain, and ONLY pain ***(Westlund, 2005).***

Second pain is due to stimulation of receptors that exist in many tissues (but not in, paradoxically, the brain), it is often described as dull aching, and poorly localized, receptors for this second pain are termed polymodal nociceptors ***(Julius and Basbaum, 2001).*** This pain tends to last beyond the termination of an acute painful stimulus ***(Westlund, 2005).***