THE EFFECT OF PRE-OPERATIVE PREGABALIN ON POSTOPERATIVE PAIN AND MORPHINE CONSUMPTION AFTER OPEN GYNAECOLOGICAL SURGERY

by

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LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
APS	Acute Pain Service
BP	Blood Pressure
BPI	Brief Pain Inventory
FLACC	Faces, Legs, Activity, Cry, Consolability
GA	General Anaesthesia
GAD	Generalised Anxiety Disorder
HR	Heart Rate
IV	Intravenous
MEAC	Minimum Effective Analgesic Concentration
MPQ	McGill Pain Questionnaires
MTC	Minimum Toxic Concentration
NRS	Numerical Rating Scale
NSAIDS	Non steroidal Anti Inflammatory Drugs
OT	Operation Theater
PCA	Patient-Controlled-Analgesia

PACU	Post Anesthesia Care Unit
PONV	Post-Operative Nausea and Vomiting
RASS	Richmond Agitation Sedation Scale
SD	Standard Deviation
SpO2	Oxygen Saturation
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale

ABSTRAK

Tajuk:

KESAN PREGABALIN SEBELUM PEMBEDAHAN PADA TAHAP KESAKITAN DAN PENGGUNAAAN MORFIN SELEPAS PEMBEDAHAN SAKIT PUAN

Latar Belakang:

Penggunaan pregabalin sebelum waktu pembedahan telah dibukti dapat mengurangkan tahap kesakitan dan penggunaan morfin di kalangan pesakit surgical yang tertentu. Kami mengkaji kesan pregabalin yang dibagi sebelum pembedahan terhadap tahap kesakitan selepas pembedahan di kalangan pesakit yang menjalani pembedahan sakit puan.

Objektif:

Penyelidikan ini bertujuan untuk menilai kesan Pregabalin 150mg yang diberi sebelum pembedahan kepada pengurangan dalam penggunaan ubat opioid dan pengurangan kesakitan selepas pembedahan sakit puan.

Metodologi:

60 pesakit yang menjalani pembedahan sakit puan yang memenuhi kriteria kemasukan telah direkrut di Hospital Universiti Sains Malaysia dan dibahagi secara rambang ke dalam dua kumpulan. Oral pregabalin 150mg 1 jam sebelum pembedahan diberi kepada kumpulan Pregabalin (n=30) manakala placebo diberi kepada kumpulan kawalan (n=30). Regimen pembiusan yang standard diberi kepada kedua-dua kumpulan dan dua kumpulan

tersebut diberi morfin intravena selepas pembedahan melalui alat analgesia kawalan pesakit. Markah kesakitan selepas pembedahan dalam keaddan rehat dan bergerak telah dicatat menggunakan skala analog visual pada 0, 1, 4, 24 jam selepas pembedahan. Penggunaan morfin juga dicatat pada jangka masa tersebut.

Keputusan:

Didapati tiada perbezaan ketara di antara markah kesakitan ketika rehat (p= 0.083), markah kesakitan semasa bergerak (p= 0.680) atau pengunaan morfin (p= 0.740) di antara kumpulan pregabalin dan kumpulan kawalan pada 24 jam selepas pembedahan.

Kesimpulan:

Penggunaan oral pregabalin 150mg satu jam sebelum pembedahan didapati tidak menunjukkan pengurangan dalam penggunaan ubat opioid dan pengurangan markah kesakitan selepas menjalani pembedahan sakit puan.

Kata Kunci:

Pregabalin, morfin, kesakitan selepas pembedahan, rasa loya selepas pembedahan, muntah selepas pembedahan, selepas laparotomy.

ABSTRACT

Title:

THE EFFECT OF PRE-OPERATIVE PREGABALIN ON POSTOPERATIVE PAIN AND MORPHINE CONSUMPTION AFTER OPEN GYNAECOLOGICAL SURGERY

Introduction :

Preoperative pregabalin has been shown to reduce postoperative pain scores and morphine consumption in certain surgical groups. We studied the effect of preoperative pregabalin on post operative pain relief among patients undergoing open gynaecological operation.

Objective:

This was a prospective, randomised, double blinded study on the efficacy of preoperative oral pregabalin 150mg in reducing postoperative morphine consumption and pain scores after undergoing open gynaecological operation..

Methodology :

60 patients undergoing open gynaecological operation that fulfilled inclusion and exclusion criteria were recruited in Hospital Universiti Sains Malaysia and randomized into two groups. Oral pregabalin 150mg was given to the pregabalin group (n=30) one hour prior to operation while placebo was given to the control group (n=30). A standardized regime of general anaesthesia was given to both groups and intravenous morphine was delivered via a patient controlled analgesia machine. Post operative pain scores at rest and movement were recorded using numeric rating scale at 0, 1, 4 and 24

hours postoperatively. Total morphine usage was also recorded at those intervals.

Results:

There were no significant differences in resting pain scores (p= 0.083), moving pain score (p= 0.680) or morphine consumption (p= 0.740) at 24 hours postoperatively between pregabalin and control group.

Conclusion :

The use of 150mg oral pregabalin preoperatively given one hour prior to operation did not decrease post-operative pain score and morphine consumption for patients who underwent open gynaecological operation under general anaesthesia.

Keywords :

pregabalin, morphine, postoperative pain, postoperative nausea, postoperative vomiting, post laparotomy

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Pain is a consistent and predominant complaint of most individuals following surgical interventions. Poorly controlled postoperative pain is a cause of much morbidity in the surgical patient. Postoperative pain not only increases physiological and psychological complications, it also causes the increase in number of follow up visits and patient dissatisfaction (Joshi and Ogunnaike, 2005). This is a recognized fact and our recent campaigns and programs targeted at managing pain as a fifth vital sign proves that. However, effective control of postoperative pain is still a major challenge. It is thought to be inadequately treated in one half of all the surgical procedures (Agarwal et al., 2008).

Recent studies have pointed out that peripheral and central neuronal sensitization play an important role in the development of hyperalgesia and allodynia at the postoperative site in the acute setting and if uncontrolled, may lead to subsequent persistent postoperative pain or chronic pain (Vadivelu et al., 2010). The initial intensity and duration of pain leads to both peripheral and central sensitizations that synergistically exacerbate pain perception (Voscopoulos and Lema, 2010). A review of predictive factors relating to chronic pain noted that acute postoperative pain and the number of doses of postoperative analgesics were the best predictors of persistent pain following surgery (Perkins and Kehlet, 2000).

This understanding had led to the use of antihyperalgesic drugs, pre-emptive analgesia and an NMDA receptor antagonists to combat postoperative pain (Dirks et al., 2002; Richmond et al., 1993).

Pregabalin is a structural analogue of the inhibitory neurotransmitter g-aminobutyric acid, but it is not functionally related to it (Ben-Menachem, 2004). Like its predecessor, gabapentin, it binds to the α-2-δ subunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization (Shneker et al., 2005; Chizh et al., 2007). Pregabalin has anticonvulsant, anti-hyperalgesic, and anxiolytic properties similar to gabapentin, but it has a more favourable pharmacokinetic profile, including dose-independent absorption (Guay, 2005; Frampton et al., 2005). It is also several times more potent than gabapentin while producing fewer adverse effects (Ben- Menacham, 2004).

In the US, Pregabalin is indicated for the treatment of neuropathic pain associated with diabetic peripheral neuropathy, spinal cord injury, postherpetic neuralgia, fibromyalgia, and as an adjunctive theraphy for adult patient with partial onset seizure. In the European Union, pregabalin is indicated for peripheral and central neuropathic pain, epilepsy, and generalized anxiety disorder (Agarwal et al., 2008).

In view of these properties of pregabalin, multiple trials have been carried out on the use of this drug in the perioperative period with the objective of preventing central sensitization and thereby reducing postoperative pain. A systematic review of 11 trials in 2010 showed

that pregabalin effectively reduce postoperative opioids consumption and opioids related adverse effects after surgery (Zhang et al., 2011).

According to Zhang et al. (2011), patients who were given pregabalin ranging from 150mg- 600mg 1-2 hour preoperatively showed reduction in post-operative opioid consumption and visual analogue scale. The studies included in this systemic review showed that this opioid sparing effect of pregabalin stretched across a diverse range of surgeries (laparoscopic cholecystectomy, laparoscopic hysterectomy, laparoscopic sleeve gastrectomy, abdominal hysterectomy and total hip arthroplasty). Specifically, studies have shown that pregabalin premedication effectively lowers postoperative pain score for laparoscopic cholecsyectomy (Agarwal et al., 2008), laparoscopic sleeve gastrectomy (Cabrera Schulmeyer et al., 2010) and abdominal hysterectomy (Ittichaikulthol et al., 2009). However, many study has shown that 300mg-600mg of preoperative pregabalin causes more sedation than placebo group (Joleka et al., 2008; Mathiesenet al., 2008; Chang et al., 2009; Kim et al., 2010).

None of these trials investigated the role of preoperative single dose administration of 150mg pregabalin in attenuating postoperative pain and opioid consumption after open gynaecological operation. The present study was therefore designed to evaluate the role of preoperative single dose of pregabalin for attenuating postoperative pain and analgesic consumption in patients undergoing open gynaecological operation.

1.2 PROBLEM STATEMENT

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events. The introduction of Pregabalin into the Malaysian health care system in recent years has opened up another option for preemptive analgesia.

Currently the use of Pregabalin is not routinely practiced as preemptive analgesia in hospitals in Malaysia. Nevertheless, pregabalin has been shown to reduce postoperative pain score and opioid consumption in numerous types of operation.

1.3 JUSTIFICATION OF THE STUDY

This study was designed to determine the efficacy of preoperative oral pregabalin 150mg in reducing post operative pain score and morphine consumption after undergoing open gynaecological operation.

1.4 OBJECTIVE OF THE STUDY

1.4.1 GENERAL OBJECTIVE

The objective of this study is to measure the effects of oral pregabalin 150mg as compared to no pregabalin with regards to post operative pain relief when given preoperatively to patients undergoing open gynaecological operation.

1.4.2 SPECIFIC OBJECTIVES

1. To evaluate the opioid sparing effects of preoperative oral pregabalin 150mg quantified by a reduction in morphine consumption at 1 hour, 4 hours and 24 hours postoperatively.
2. To compare postoperative pain scores between the two treatment groups (oral Pregabalin 150mg vs No Pregabalin) as measured using the numeric rating scale at 0 hour, 1 hour, 4 hours and 24 hours postoperatively.

1.5 STUDY HYPOTHESIS

Null Hypothesis:

Single preoperative dose of pregabalin would not reduce postoperative morphine requirements and pain score after open gynaecological surgery.

Alternative Hypothesis:

Single preoperative dose of pregabalin would reduce postoperative morphine requirements and pain score after open gynaecological surgery.

CHAPTER 2: LITERATURE REVIEW

2.1 PHYSIOLOGY OF ACUTE PAIN

Pain is defined by the International Association for the Study of Pain (IASP) as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Merskey & Bogduk, 1994).

Many neural processes occur before a person experiences the sensation of acute pain. Initially, primary afferent nociceptors are activated upon contact with noxious stimuli and change these stimuli into electrical signals in a process called transduction (Leon-Casasola, 2007).

Noxious stimuli are then transmitted from the primary afferent nociceptors and relayed to the thalamus followed by the cortex. This process of transmission is mainly done by 2 types of nociceptive neurons which are A-delta fibers and C fibers (Leon-Casasola, 2007).

A-delta fibers are 2-5 microns in diameter, myelinated and conduct at the velocity of 6-30 meters per second. These fibers are activated by high intensity mechanical stimulation-these are called high threshold mechanoreceptors. Some of them are responded to thermal stimuli and are therefore called mechano-thermal receptors (Leon-Casasola, 2007).

C-fibers are less than 2 microns in diameter, unmyelinated and conduct at velocity of 0.5-2 meters per second. These fibers transmit a variety of noxious stimuli which include mechanical, thermal and chemical stimuli and therefore are called C- polymodal nociceptors (Leon-Casasola, 2007).

At the spinal cord level, these fibers travel along the dorsal root and enter the dorsal horn laterally. These small myelinated fibers mainly terminated in the superficial dorsal horn (lamina I) and lamina V. Unmyelinated fibers terminate in lamina II. Some of these fibers ascend and descend in Lissauer's tract before terminating in the spinal cord. The noxious stimuli then transmitted to the cortex through spinothalamic tract (Leon-Casasola, 2007).

The noxious stimuli is also processed and is termed modulation. This mainly happen in spinal cord. Descending neural tract can selectively inhibit or facilitate transmission of signals received at the dorsal horn of the spinal cord. In the dorsal horn itself, nociceptive signals are modulated by endogenous and exogenous agents which act on opioid, alpha adrenoceptors, GABA and glycine receptors (Leon-Casasola, 2007)

Noxious stimuli not only result in tissue damage but also the release of intracellular contents from damage cells and inflammatory cells which leads to inflammation. Neurogenic inflammatory response also takes place and causes the release of substance P, neurokinin A and calcitonin gene-related peptides from the nociceptive afferent fibers. These peptides then change the excitability of sensory and sympathetic nerve fibers and lead to vasodilatation and release of chemical mediators from inflammatory cells. This

causes peripheral sensitization and increased responsiveness to mechanical and thermal stimuli (Latremoliere and woolf, 2009).

In neural injury or inflammation, there will be an increment to the membrane excitability and synaptic efficacy of the nociceptive pathways and leads to central sensitization. The effect of central sensitization is to recruit previously subthreshold synaptic inputs to nociceptive neurons and generating an increased or augmented action potential output. Central sensitization is responsible to the changes in pain sensibility in acute and chronic clinical pain settings (Latremoliere and woolf, 2009).

2.2 DEVELOPMENT OF CHRONIC POST SURGICAL PAIN

A prolonged experience of acute pain in which long-standing changes are seen within and external to the central nervous system creates chronic pain with a histological and pathological basis (Ready and Laird, 1998).

Neuroplasticity, or the physical remodelling of neuronal cytoarchitecture, occurs shortly after the onset of persistent acute pain and leads to the transition from acute pain into a chronic pain state. Due to peripheral lesion that persistently generates pain impulses to the spinal cord, inhibitory interneurones responsible for modulating painful nerve transmission impulses eventually die. In addition, glial cells remodel neuronal synapses to intensify nociceptive transmission. These pain-transmitting neurones become more sensitive, react

more intensely to stimuli, and grow more connections to second-order neurones within the CNS. This process leads to central sensitization in which activity dependent phenotypic changes are seen in the dorsal horn neurones and other CNS structures including higher centres (Torebjork, Lundberg and LaMotte, 1992). Preceding long-term central sensitization, secondary hyperalgesia occurs within central nervous system and it is said to be responsible for chronic postsurgical pain (Eisenach, 2006).

Figure 2.1 graphically summarizes the proposed mechanism of acute pain develops into chronic pain. The initial tissue injury which activates nociceptor then causes peripheral sensitization or primary hyperalgesia. While acute pain is usually modulated at the spinal cord level, prolonged and intense noxious transmission causes long lasting modifications to the central nervous system. This causes prolonged activation of C- fibers and followed by enhancement of NMDA receptor. This in turn leads to an up-regulation of cyclo-oxygenase-2, nitric oxide synthetase and followed by increased prostaglandin synthesis and cannabinoid breakdown. As a result, neural and glial cells remodeling occurs and followed by long term potentiation of the nociceptive pathways. This in turn leads to development of chronic pain (Voscopoulos and Lema, 2010).

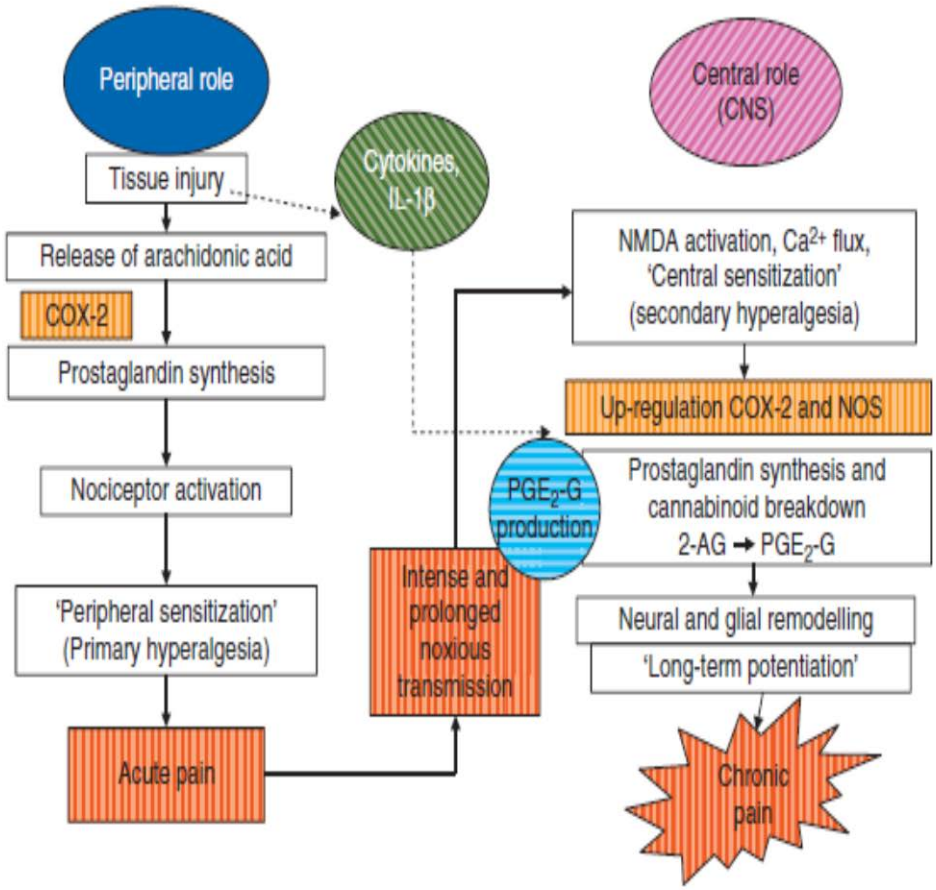

Figure 2.1. Peripheral and central roles of prostaglandin and cyclo-oxygenase-2 in pain perception and sensitization (Adopted from Voscopoulos and Lema, 2010)

Most of the chronic pain syndrome is due to neuroplastic changes after injury, nevertheless, the exact mechanisms for the development of chronic post-surgical pain remain complex and poorly understood. Voscopoulos and Lema (2010) listed down chronic pain predisposing factors:

a. Preoperative pain at the site of surgery or other body regions
b. Psychosocial and mood factors
c. Coping skills

d. Surgical factors

- Nerve damage (complicated aetiology likely than just nerve injury alone)
- Factors predisposing to prolonged inflammatory states (foreign materials)
- Volume of surgeries performed per year for given operation
- Recurrence of operation
- Type of surgery
- Length of surgery (lasting more than 3 hours)

e. Genetic predisposition

f. Acuity of postoperative pain

g. Prolonged postoperative pain/inflammatory responses

h. Duration of postoperative pain treatment

i. Anaesthetic factors (general vs regional, type of general anaesthesia)

j. Gender (female)

k. Type of disease

l. Recurrence of malignancy

m. Adjuvant therapy: radiation, chemotherapy

n. Age

Among these factors, Perkins and Kehlet (2000) showed that the severity of postoperative pain is a strong predictor of subsequent chronic pain.

2.3 CONCEPTS IN PERI-OPERATIVE PAIN MANAGEMENT

Peri-operative pain is an anticipated consequence of surgical procedure. More than 80% of patients who have undergone surgery complain of moderate to severe pain within the first few days after the procedure (Apfelbaum et al., 2003). In a survey, Filos et al. 1999 reported that 50% of surgical patients say that they received inadequate pain relief after their operation.

The concept of multimodal analgesia was introduced more than a decade ago as a technique to improve analgesia and reduce the incidence of opioid-related adverse events. The rationale for this strategy is to achieve sufficient analgesia with the additive or synergistic effects between different classes of analgesics. This allows for a reduction in the individual drugs dosage in addition to a lower incidence of adverse effects from any particular medication used for perioperative pain management. A lower incidence of adverse effects and improved analgesia has been demonstrated with multimodal analgesia techniques, which may provide for shorter hospitalization times, improved recovery and function (Buvanendran et al., 2003; White et al., 2007) and possibly decreased healthcare costs. Currently, the American Society of Anesthesiologists Task Force on Acute Pain Management advocates the use of multimodal analgesia (Ashburn et al., 2004).

Figure 2.2 shows available modalities for the treatment of pain and site upon pain pathway at which these interventions act. Thus, an understanding of the mode and site of analgesic acts can help in better pain control for the patient. For instance, a patient going for total

knee replacement might receive epidural cocktail which consist of opioid and local anaesthetic in addition to oral NSAIDS, paracetamol and opioids in post-operative period. Recently, Elvir-Lazo and White (2010) summarized that improvements in patient outcome related to pain control can best be achieved by using a combination of analgesic technique involving both centrally and peripherally acting analgesic drugs.

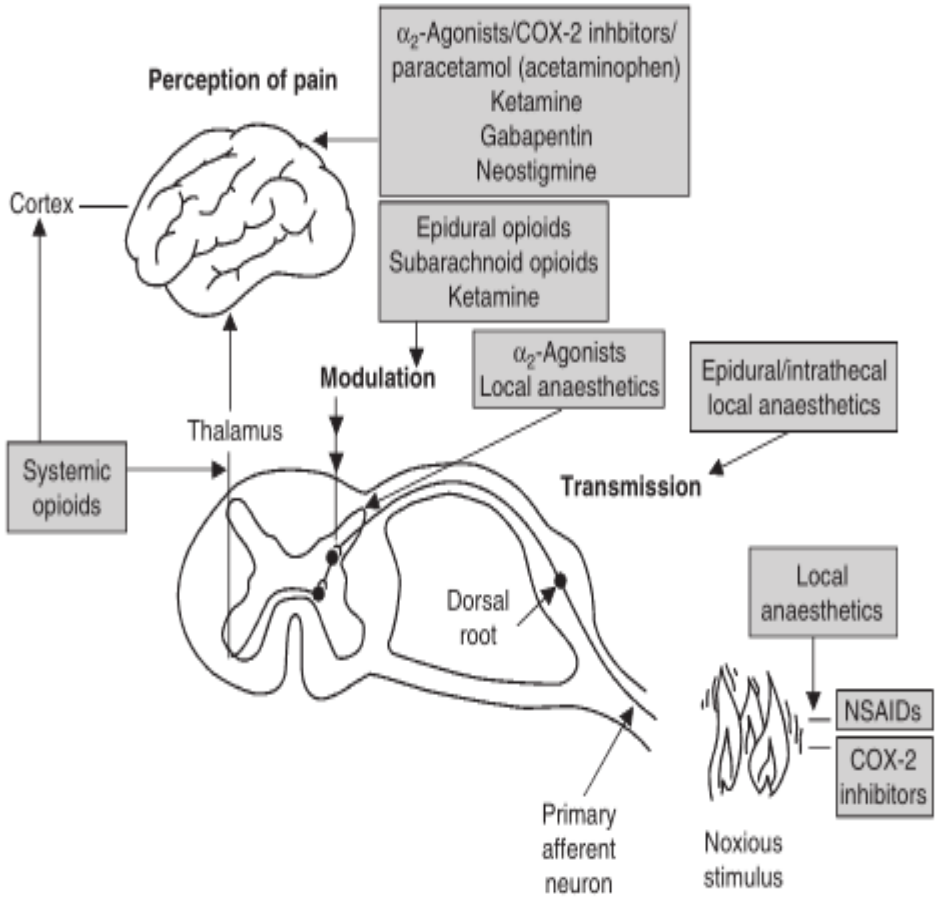

Figure 2.2. The pain pathway and interventions that can modulate activity at each point (Adapted from Ashburn et al., 2004)

As discussed earlier, severity of acute post-surgical pain predicts development of chronic post-surgical pain (Perkins and Kehlet, 2000). The pathophysiology of chronic pain development involves a cascade of sensitization involving the peripheral nervous system till central nervous system. In order to prevent this sensitization, the concept of preemptive analgesia was proposed. By preventing neuronal traffic in nociceptive fibers carrying pain signals to the central nervous system, it is possible to prevent central sensitization in ways that reduce both acute and chronic pain (Woolf and Chong, 1993). The main aims for preventive analgesia are to prevent spinal sensitization, reduce incidence of inflammatory or chronic pain and decrease pain after injury (Senturk, 2002).

Instead of focusing on the treatment of physiological pain to noxious stimuli as practised in conventional perioperative analgesia regime, preemptive analgesia targets on the prevention or reversal of central and peripheral sensitization that may end up with hyperalgesia or pathological pain (Kissin, 2000).

According to Kissin (2000), there are 3 different definitions used to define preemptive analgesia. These include treatment that (1) starts before surgery; (2) prevents establishment of central sensitization caused by incisional injury; and (3) prevent establishment of central sensitization caused by incisional and inflammatory injuries. Compared to conventional perioperative analgesia, preemptive analgesia is only centered on the prevention of pathological pain.

Preemptive analgesia uses drugs and local or regional anaesthesia. In keeping with pathophysiology of sensitization, analgesia should be given before noxious stimuli arise (Grape and Tramer, 2007). Nonetheless, the preemptive technique must also be multimodal, maintained and accompanied by active pain management during perioperative period. This is crucial for preemptive analgesia to be effective (Redmond et al., 2003).

2.4 PATIENT CONTROLLED ANALGESIA

Patient-controlled analgesia (PCA) is a delivery system in which patients self-administer predetermined doses of analgesic medication to relieve their pain. Since its introduction in the early 1980s, the daily management of postoperative pain has been extensively optimised. Morphine is the most studied and most commonly used intravenous drug for PCA (Grass 2005). In spite of the fact that it is the 'first choice' for PCA, other opioids have been successfully used for this option. These include diamorphine, meperidine, fentanyl and tramadol. However, there is no evidence from clinical studies that any particular opioid is more effective or associated with lower incidence of opioid side effects (Grass 2005).

The pharmacokinetic basis of PCA is that patients titrate their plasma opioid concentrations to values above the minimum effective analgesic concentration (MEAC) but below the minimum toxic concentration (MTC), the so-called analgesic window. Although this is a useful concept to explain PCA, it is important to remember that the log

dose– response curve for opioid analgesia is not linear but a steep sigmoidal curve. This means that, once the analgesic threshold is reached, small increases in plasma concentration may result in effective analgesia. Further increases may lead to opioid side-effects rather than further improvements in analgesia. In some patients (e.g. elderly, obese patients undergoing upper abdominal surgery), the difference between MEAC and MTC may be so small that it will be very difficult to provide analgesia without significant opioid side-effects, including respiratory depression (MacIntyre, 2001).

PCA devices have been developed and evolved enormously in technological sophistication, ease of use, flexibility and portability (Grass, 2005). PCA is now routinely used in post-operative care throughout much of the developed world (Warfield and Kahn, 1995; Carr, Miaskowski et al., 1998). PCA devices are programmable by the healthcare provider to deliver a specific amount of medication upon each request by the patient. A continuous 'background' infusion may or may not be co-administered in addition to patient controlled bolus doses. Bolus doses are limited by programmed 'lockout interval' within which subsequent requests are ignored or a cumulative limit to drug dose permitted in a fixed interval, such as one or four hours (Carr, Miaskowski et al., 1998).

The use of PCA in hospitals has been increasing because of its proven advantages over conventional intramuscular injections which is round the clock analgesia prescription . These include improved pain relief, greater patient satisfaction, less sedation and fewer postoperative complications. Patients using PCA obtain better pain relief than those using

conventional analgesia, without an increase in side effects and no difference in duration of hospital stay (Ballantyne, Carr et al., 1993; Hudcova, McNicol et al., 2006).

Nevertheless, there are incidences of equipment-related PCA complications, operator-related or drug-related problems, device design and malfunctions being reported. The improvement on technology and staff training has greatly overcome these complications with equipment related PCA complications being less common than operator related complications (MacIntyre, 2001). With the introduction of an Acute Pain Service, management of postoperative pain by using PCA can be improved.

In summary, PCA is a safe and popular method for postoperative pain control (Tuncer, Tosun et al., 2002).

2.5. PAIN ASSESSMENT TOOLS

Pain, like many phenomena within human sensory experience, cannot be measured by external means and a patient report must be used. Pain measurement scales exploit aspects of the patient report that can yield reproducible data relating to the severity of the patient's pain and the effects of treatment. A clinically useful pain scale must be easy for both patients and healthcare professionals to use and interpret whilst maintaining validity across a variety of disease states and cultures (Jensen et. al., 1992; Matthews et. al.,1990)].

In 2008, the Malaysian Ministry of Health implemented "Pain as the 5th Vital Sign" in hospitals across the country. Making pain a vital sign ensures the measuring and documenting of pain scores in all patients.

By objectively gauging pain using various pain-scoring systems, the difficulties in quantifying pain intensity and the problem of inter-observer perception can be overcome. Most scales make pain measurable, and can tell providers if the pain is mild, moderate or severe. The investigator can also follow the trend of the patient's pain making it easier to find appropriate treatment (Huskisson, 1974).

The pain assessment scales are either unidimensional or multidimensional scales.

2.5.1 UNIDIMENSIONAL SCALE

Unidimensional scales are easy to use and provide quick feedback on the effectiveness of the intervention made. These scales assess a single dimension of pain and measures pain intensity through self-reporting measures;

a. Numerical Rating Scale (NRS)

b. Visual Analog Scale (VAS)

c. Verbal Rating Scale (VRS)

2.5.1.1 NUMERICAL RATING SCALE (NRS)

Numerical rating scales (NRS) take the two extremes of the pain experience (for example, ‘no pain’ and ‘worst pain imaginable’) and assign numbers to levels of pain in between. It is assumed that each number represents a proportional increase in the pain severity. NRS are robust and reproducible pain scales. They are simple for patients to understand and there is evidence that the elderly find them easier to use than visual analogue scores. Recording data from the scores is also straightforward as numbers can simply be read off the marked scales (Jensen et. al., 1992; Matthews et. al.,1990).

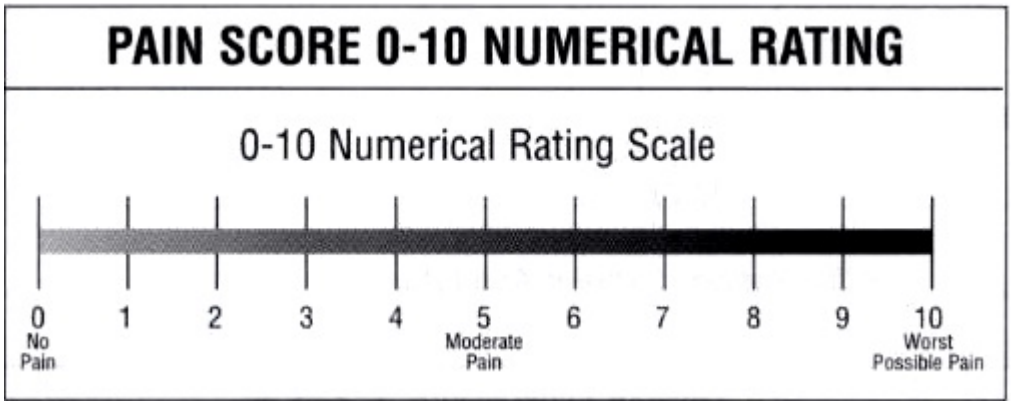

Figure 2.3. Numeric Rating Scale (Adapted from Jensen et. al., 1992)

2.5.1.2 VISUAL ANALOG SCALE (VAS)

A Visual Analogue Scale (VAS) is a measurement instrument that tries to measure a characteristic or attitude which is presumed to range across continuous values and cannot be easily measured directly. VAS is usually presented as a horizontal line, 10 cm in length,

explained by word descriptors at each end (as shown below). The patient marks at the point on the line that they feel represent their perception of current state of pain (Wong DL, Perry SE, Hockenberry MJ *et al.* 2002).

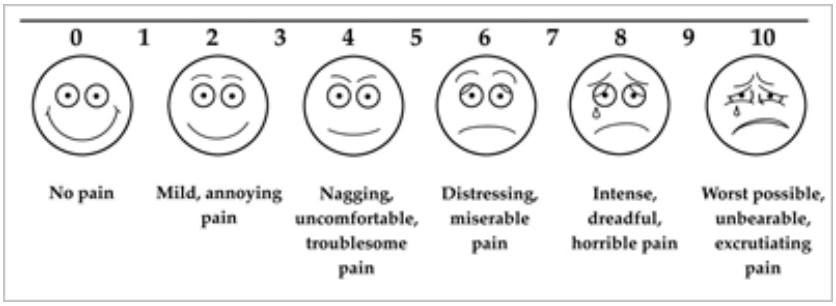

Figure 2.4. Visual Analog Scale (Adapted from Wong DL et. al. 2002)

2.5.1.3 VERBAL RATING SCALE (VRS)

Verbal rating scales (VRS) aim to stratify pain intensity according to levels of severity represented by commonly used adjectives. Such scales may be simple and consist of as few as 3 levels, associated with adjectives such as ‘mild’, ‘moderate’ and ‘severe’. More levels can be used, but problems tend to arise due to inter-patient differences in the interpretation of the adjectives used. VRS are widely applied and there is no doubt that a 3 or 4 level scale is the easiest for patients to use (Jensen et. al., 1992; Matthews et. al.,1990).

2.5.2 MULTIDIMENTIONAL SCALE

Multidimensional scales measures intensity, nature and location of pain as well as the impact pain is having on patient activity and mood. These scales are useful for patients with persistent acute or chronic pain.

a. Brief Pain Inventory (BPI)

b. McGill Pain Questionnaire (MPQ)

c. Memorial Pain Assessment Card

The Wong-Baker Faces Scale and the FLACC (Faces, Legs, Activity, Cry, Consolability) scale is used in children or patients with cognitive impairment.

Pain in infants is assessed using the CRIES scale. This scale uses 5 variables. Crying, Requirement of oxygen, Increased vital signs, Expression and Sleeplessness to assess postoperative pain (van Dijk *et al.*, 2000).

In this study, Numerical Rating Scale was chosen mainly due to the author preference.

2.6 PREGABALIN

2.6.1 INTRODUCTION

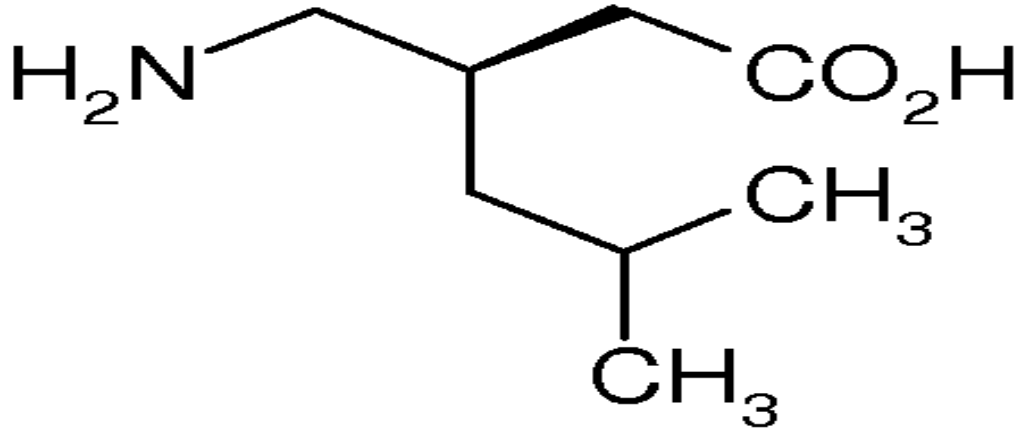

Figure 2.5. Structure of Pregabalin

Pregabalin (S-[+]-3 isobutylgaba) was designed as a lipophilic GABA (γ-aminobutyric acid) analogue substituted at the '3' position to facilitate diffusion across the blood-brain barrier. It has structural analogue of the inhibitory neurotransmitter g-aminobutyric acid, but it is not functionally related to it (Ben-Menachem, 2004). Pregabalin is the pharmacologically active S-enantiomer of 3-aminomethyl-5-methyl-hexanoic acid, and has a similar pharmacological profile to gabapentin (Frampton and Foster, 2005). Though the precise mode of action of pregabalin has not been fully elucidated, it does interact with the same binding site and like its predecessor, gabapentin, it binds to the α-2-δ subunit of voltage-gated calcium channels, reducing the release of several excitatory

neurotransmitters and blocking the development of hyperalgesia and central sensitization (Snheker et al, 2005; Chizh et al., 2007).

Pregabalin appears to produce an inhibitory modulation of neuronal excitability, particularly in areas such as the neocortex, amygdala, and hippocampus. Pregabalin has anticonvulsant, anti-hyperalgesic, and anxiolytic properties similar to gabapentin but several times more potent than gabapentin while producing fewer adverse effects (Ben-Menacham, 2004).

2.6.2 ANTINOCICEPTIVE MECHANISM OF ACTION

The exact mechanism of how Pregabalin works is still unknown. Although it is an analogue of gamma-aminobutyric acid (GABA), it is neither active at $GABA_A$ or $GABA_B$ receptors nor metabolically converted to GABA (Piechan et al., 2004). Nevertheless, in cultured neurons, prolonged application of pregabalin increases the density of GABA transporter protein and increases the rate of functional GABA transport. Pregabalin does not block sodium channels, is not an opiate receptors agonist and does not alter cyclo-oxygenase enzyme activity. It is also inactive at serotonin and dopamine receptors (Piechan et al., 2004).

Pregabalin binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels) in central nervous system tissues. Results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin)