COMPARISON ON THE EFFICACY OF IMMEDIATE RELEASE OXYCODONE AND TRAMADOL IN REDUCING POSTOPERATIVE PAIN, NAUSEA AND VOMITING IN POST LAPAROTOMY PATIENTS WEANED FROM PCA MORPHINE

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TABLE OF CONTENTS

Page

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES continued

LIST OF SYMBOLS AND ABBREVEATIONS

APS Acute Pain Services

ASA American Society of Anaesthesia

BMI Body Mass Index

CRS Combination Rating Scale

CTZ Chemoreceptor Trigger Zone

cAMP Cyclic adenosine monophosphate

DOP Delta orphanin peptide

GDP Guanosine diphosphate

GIT Gastrointestinal system

GTP Guanosine triphosphate

IASP International Association for the Study of Pain

IR Immediate Release

KOP Kappa orphanin peptide

MOP Mu orphanin peptide

MEAC Minimum Effective Analgesiac Concentration

MTC Minimum Toxic Concentration

NOP	Nociceptin orphanin peptide
NRS	Numerical Rating Scale
PCA	Patient Controlled Analgesia
PONV	Postoperative Nausea and Vomiting
VAS	Visual Analogue Scale
VC	Vomiting Centre
δ	Delta

ABSTRAK

PERBANDINGAN KEBERKESANAN OXYCODONE IR DAN TRAMADOL DALAM MENGAWAL KESAKITAN SELEPAS PEMBEDAHAN DAN INSIDEN LOYA & MUNTAH DI KALANGAN PESAKIT LAPAROTOMI YANG DISAPIHKAN DARI PCA MORFIN

Pengenalan: Pengenalan oxycodone ke dalam sistem penjagaan kesihatan Malaysia pada kebelakangan ini telah membuka satu lagi pilihan untuk menghilangkan rasa sakit selepas pembedahan (*post-operative*). Kami menilai keberkesanan klinikal oxycodone dalam mengurangkan kesakitan serta loya dan muntah serta membandingkannya dengan tramadol dalam kajian ini.

Objektif: Kajian ini merupakan satu kajian prospektif dan rawak ke atas keberkesanan oxycodone dalam mengurangkan kesakitan selepas pembedahan, keperluan analgesik dan kejadian loya dan muntah pada pesakit selepas laparotomi setelah disapihkan daripada PCA morfin. Kajian ini telah dijalankan di Hospital Universiti Sains Malaysia.

Metodologi: Kami mengumpulkan 40 pesakit yang menjalani laparotomi elektif untuk pembedahan sakit puan. Pesakit ini telah dipilih secara rawak untuk menerima tab. oxycodone IR setelah disapihkan dari PCA morfin 48 jam selepas pembedahan.. Satu kumpulan pesakit lain menerima tab. tramadol. Skor kesakitan *post-operative* dinilai menggunakan Combination Rating Scale dan keperluan analgesia tambahan pada 2 jam, 6 jam, 24 jam (hari pertama) dan pada hari ketiga direkodkan. Insiden loya telah didokumenkan bersama dengan keperluan antiemetic penyelamatan pada jangkamasa yang sama. Penilaian itu dibuat oleh jururawat yang bertanggungjawab untuk perkhidmatan APS dan data dimasukkan dengan menggunakan Statistical Package for Social Science (SPSS) Versi 22.

Keputusan: Kajian ini mendedahkan bahawa pesakit yang menerima oxycodone mempunyai skor kesakitan jauh lebih rendah iaitu kurang dari 4 dalam masa 6 jam selepas rawatan dimulakan. Skor ini hanya dicapai dalam kumpulan tramadol selepas rawatan selama 24 jam. Ini adalah keputusan signifikan dengan nilai *p value* <0.001 berdasarkan masa dan kesan rawatan. Keperluan analgesia penyelamat pertama dan kedua adalah signifikan antara kumpulan. Sejumlah 10% daripada kumpulan oxycodone dan 60% daripada kumpulan tramadol memerlukan penyelamatan pertama dan 5% daripada kumpulan oxycodone berbanding 40% kumpulan tramadol memerlukan penyelamatan analgesia. Insiden loya adalah jauh lebih rendah dalam kumpulan oxycodone, hanya pada tempoh 2 jam dengan nilai *p value* 0.022. Keperluan ubat tahan muntah penyelamat yang pertama dan kedua adalah lebih rendah dalam kumpulan oxycodone; bagaimanapun ianya kekal pada tahap tidak ketara dengan nilai *p value* > 0.05. Akhir sekali, skor kepuasan min untuk pesakit kumpulan oxycodone adalah 6.85 berbanding 5.75 daripada skor 10 dengan perbezaan min yang signifikan, iaitu *p value* <0.001.

Kesimpulan: Pengenalan oxycodone IR untuk mengawal kesakitan selepas pembedahan dikalangan pesakit laparotomi yang disapihkan dari PCA Morfin menunjuk skor kesakitan dan keperluan analgesia yang lebih rendah. Terdapat pengurangan signifikan dalam kejadian loya pada jam kedua. Walau bagaimanapun, tiada perbezaan yang signifikan dalam keperluan antiemetics antara kedua-dua kumpulan. Kepuasan keseluruhan adalah lebih baik pada kumpulan pesakit oxycodone.

Kata kunci : oxycodone IR, tramadol, kesakitan selepas pembedahan, mual dan muntah selepas pembedahan, laparotomi

ABSTRACT

COMPARISON ON THE EFFICACY OF IMMEDIATE RELEASE OXYCODONE AND TRAMADOL IN REDUCING POSTOPERATIVE PAIN, NAUSEA AND VOMITING IN POST LAPAROTOMY PATIENTS WEANED FROM PCA MORPHINE

Introduction : The introduction of oxycodone into the Malaysian health care system in recent years has opened up another option for postoperative pain relief. We assess the clinical efficacy of oral oxycodone IR in reducing pain as well as nausea and vomiting and compare it to oral tramadol in this postoperative study.

Objective: This was a prospective, randomised, double blinded study on the efficacy of oxycodone IR as oral maintenance analgesia in reducing postoperative pain, analgesic requirement and incidence of nausea and vomiting in patients post laparotomy after PCA morphine is weaned off. This study was conducted in Hospital Universiti Sains Malaysia.

Methodology : We recruited 40 patients undergoing an elective laparotomy for gynaecological surgery. These patients were randomly selected to receive oral oxycodone IR once PCA morphine was weaned off 48 hours post surgery. The other group of patients received the standard oral tramadol. Postoperative pain scores were assessed using the Combination Rating Scale and requirement of rescue analgesia at 2 hours, 6 hours, 24 hours and on day 3 of oral analgesia. Incidence of nausea was documented along with the requirement of rescue antiemetics at the same intervals. Assessment was made by pain services nurses and data was entered using Statistical Package for Social Science SPSS Version 22.

Results: This study revealed that patients receiving oral oxycodone IR had significantly lower pain scores of less than 4 which was achieved within 6 hours of treatment. This level was only achieved by the tramadol group at 24 hours of treatment. This is significant with a *p value* < 0.001 based on time and treatment effects. Requirement of 1st and 2nd line rescue analgesia was significant between groups. 10% of the oxycodone group and 60% of the tramadol group needed 1st line rescue and 5% of the oxycodone group against 40% of the tramadol required rescue analgesia. Incidence of nausea was significantly lower in the oxycodone group only at 2 hours with a p value of 0.022. The requirement of 1st and 2nd line rescue antiemetics was lower in the oxycodone group however remained insignificant with a *p value* of > 0.05. Finally the mean satisfaction score for patients on oxycodone was 6.85 compared to 5.75 over a score of 10 with a significant mean difference of *p value* < 0.001.

Conclusion : The introduction of oral oxycodone IR in the postoperative period for post laparotomy patients who were weaned from PCA morphine showed better pain scores and less analgesic requirement. These patients also had reduced incidence of nausea at 2 hours and better overall patient satisfaction scores compared to the tramadol group. However, there was no significant difference in the antiemetic requirement between the two groups.

Keywords : oxycodone IR, tramadol, postoperative pain, postoperative nausea, postoperative vomiting, post laparotomy

CHAPTER 1

INTRODUCTION

1.1 Background of the study

1.1.1 Postoperative pain

Pain is a major postoperative adverse outcome causing a decrease in a patient's quality of recovery, prolonging hospital stay, and increasing the incidence of admission after surgery. Effective postoperative pain control is therefore necessary to reduce morbidity in postoperative patients (Apfelbaum *et al.*, 2003). It is an essential component of medical care.

Adequate management of postoperative pain relieves suffering and leads to early mobilisation, shortened hospital stay and increase patient satisfaction. In the 2007 survey by the National Audit on Postoperative Pain, the incidence of moderate or severe postoperative pain was reported at 74% in the first 24 hours postoperatively (Breivik *et al.*, 2008).

The use of multimodal strategies to improve postoperative recovery is becoming an essential tool to achieve this goal. The combination of two different classes of analgesics act synergistically to increase their analgesic effect. Combining analgesics which act on different sites or have different mechanisms of action can reduce the dosage required of the drug and also lower the risk of potential side effects and toxicity. Likewise, combining short and long acting agents will result in different durations of analgesic coverage (Breivik *et al.*, 2008).

Since laparotomy is categorised as major surgery, patients are most likely to experience moderate to severe pain. Patients suffering from post-laparotomy pain usually experience pain that persists for several days to weeks and is usually poorly controlled.

Poorly controlled pain can contribute directly or indirectly to postoperative complications namely, myocardial ischemia, pulmonary dysfunction, reduced gastric motility and delayed return of gastrointestinal functions. Good analgesia can reduce these deleterious effects (Ramsay, 2000).

Studies have shown that pain is a significant determinant of patient satisfaction. It has been recognised that there are a vast majority of patients that are actually undertreated for the pain they experienced postoperatively. However, satisfaction to the analgesic therapy received is subjective and differs from one individual to another (Carr *et al.*, 2001).

1.1.2 Oxycodone

Oxycodone is an opioid that contains two chemical classes of alkaloids, phenantrene and benylisoquinolines. Oxycodone was derived from thebaine in 1916 and introduced into clinical practice in 1917. Oxycodone is similar to morphine where in that it is liposoluble. It is a mu-opioid receptor specific ligand with less binding affinity compared to morphine and methadone (Kalso, 2005).

The metabolism of oxycodone in humans is poorly defined. Countries like Finland have been using oxycodone as the primary opioid analgesic for postoperative pain. Oxycodone has also been used vastly for the treatment of cancer related pain and chronic non cancer pain (Kalso, 2005).

1.1.3 Tramadol

Tramadol is a synthetic centrally acting analgesia agent which acts as an opioid agonist as well as an inhibitor of monoamine neurotransmitter reuptake. Several studies have proven that tramadol effectively relieves moderate to severe postoperative pain. Its overall analgesic efficacy is similar to that of morphine and alfentanil. Peak analgesic effects of oral tramadol 100mg occurs one to four hours after administration with analgesia persisting for three to six hours (Scott and Perry, 2000).

The analgesic efficacy of oral tramadol has been established in multiple clinical trials as reducing pain intensity by 46.8 to 57.6% within four to six hours on assessment with a Visual Analogue Scale (Scott and Perry, 2000).

1.2 Patient Controlled Analgesia

Patient Controlled Analgesia (PCA) is a method of administrating analgesics by means of a pump. The patient controls the amount or dosage of drug required to relieve pain. The patient is taught basic skills to understand and benefit from this pain control method (Grass, 2005).

Of all the commonly used opioids, morphine has been the most successful and remains the gold standard for intravenous PCA preparations in the United States of America. The production of analgesia and sedation is due to the morphine active metabolite morphine-6-glucoronide which is mainly eliminated by glucoronidation (Grass, 2005).

1.3 Problem statement

Despite years of advancement in the management of pain, the mainstay of treatment of postoperative pain is still mainly opioids (Silvasti *et al.*, 1999). The introduction of oxycodone into the Malaysian health care system in recent years has opened up another option for postoperative pain relief.

Currently the use of oral Oxycodone IR is not routinely practiced as postoperative analgesia in hospitals in Malaysia although oxycodone has been in clinical use since 1917. Oxycodone has been proven to achieve and provide a more stable pain control with a rapid onset of effects compared to Tramadol.

1.4 Justification of the study

This study is designed to determine the analgesic efficacy of oral Oxycodone IR and to compare the role of IR Oxycodone with Tramadol as maintenance analgesia for reducing pain as well as the effect on nausea and vomiting postoperatively after 48 hours on PCA Morphine.

CHAPTER 2

LITERATURE REVIEW

2.1 Pain

Pain is an experience. It is a perception that signals the individual that tissue damage has occurred or may be occurring. It is subjective and very complex.

The word "pain" comes from the Latin word "poena" meaning a fine or a penalty. Aristotle who probably was the first to distinguish the five physical senses considered pain to be the passion of the soul that somehow resulted from the intensification of other sensory experiences(Merskey and Bogduk, 1994).

The International Association for the Study of Pain defines 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).

Inadequate management of pain is common although pain is a predictable factor in postoperative experience. Unrelieved postoperative pain results in psychological and clinical changes which increases costs and decreases quality of life (Apfelbaum *et al.*, 2003). These changes increase mortality and morbidity of the individual.

The response to pain can vary between individuals and even in the same individual at different times. There is an interplay between the objective, physiological sensory aspect of pain and its subjective, emotional and psychological components (Carr *et al.*, 2001)

Normal pain perception depends on specialized neurons that function as receptors, detecting the stimulus, and then transducing and connecting it to the central nervous system (Morgan *et al.*, 2002).

The term ‘clinical pain’ is used to describe ongoing discomfort and abnormal sensitivity. This pain has three general features:- spontaneous pain, exaggerated pain or hyperalgesia and pain produced by a stimuli which would normally not cause it known as allodynia. Pain should be assessed based on whether it is acute or chronic, and if it is inflammatory pain or neuropathic pain (Woolf, 1995).

2.2 Theory of pain

The New Theory of Pain or the Gate Control Theory was published by Wall and Melzack in 1965. The theory states that the transmission of pain from the peripheral nerve through the spinal cord is subject to modulation by both intrinsic neurons and controls emanating from the brain. Excitation and inhibition are independently controlled (Dickenson, 2002).

The Gate Control Theory proposes that small C fibres activate excitatory systems that excited output cells. These cells had their activity controlled by large A-beta fibre mediated inhibitions. These are under the control of the descending system (Dickenson, 2002).

This theory asserts that non-painful input closes the "gates" to painful input, which prevents pain sensation from traveling to the central nervous system. Therefore,

stimulation by non-noxious input called nonnociceptive fibers are able to interfere with signals from pain fibers, thereby inhibiting pain (Melzack and Wall, 1967).

These connections determine if and when painful stimuli goes to the brain. When no input comes in, the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).

Normal somatosensory input happens when there is more large-fiber stimulation (or only large-fiber stimulation). Both the inhibitory neuron and the projection neuron are stimulated, but the inhibitory neuron prevents the projection neuron from sending signals to the brain (gate is closed).

Nociception (pain reception) happens when there is more small-fiber stimulation or only small-fiber stimulation. This inactivates the inhibitory neuron, and the projection neuron sends signals to the brain informing it of pain (gate is open).

Descending pathways from the brain close the gate by inhibiting the projector neurons and diminishing pain perception (Melzack and Wall, 1967).

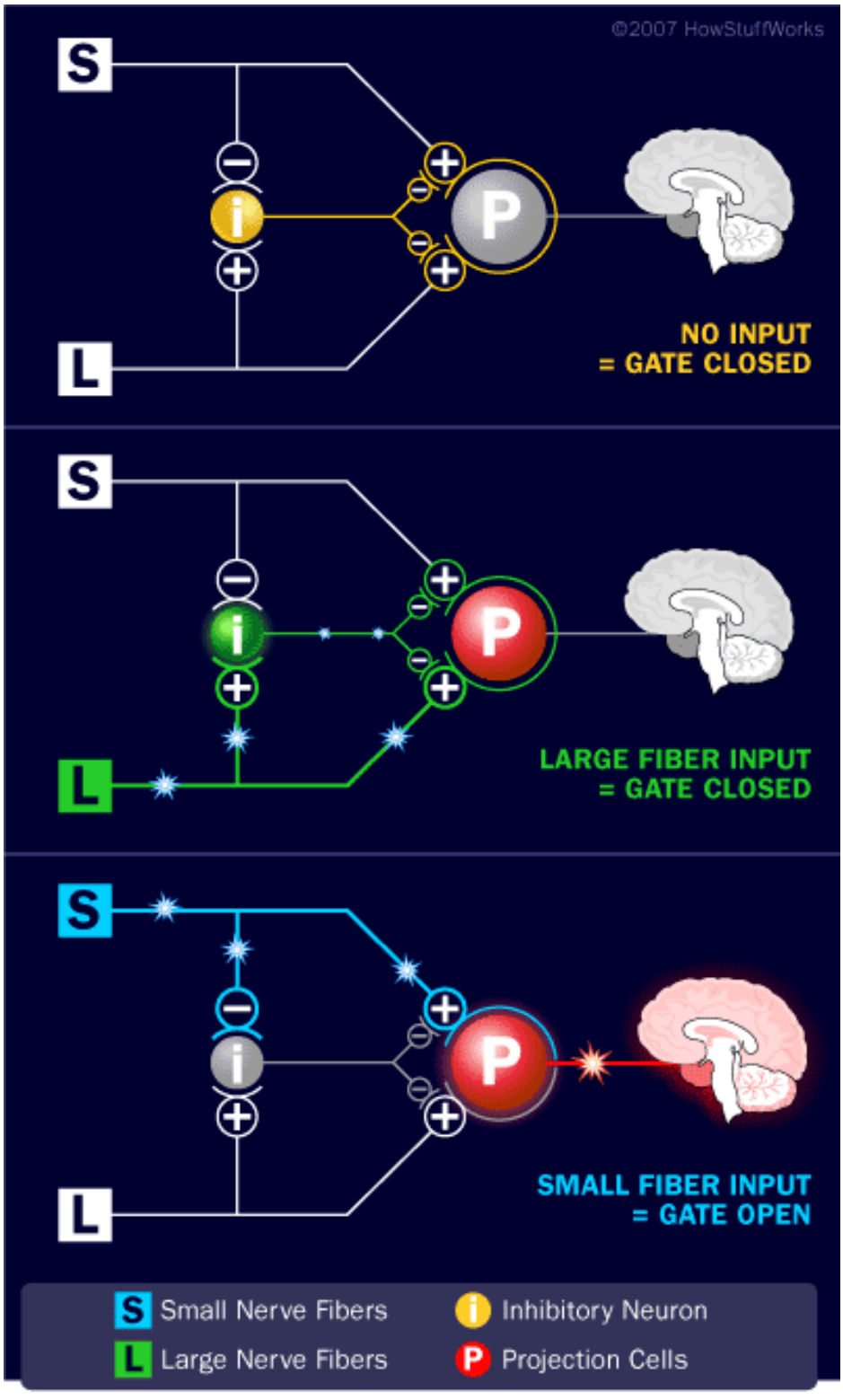

Figure 1.0 : Descending pathways from the brain close the gate (Melzack and Wall, 1967)

2.3 Pain Pathway

Pain is conducted along 3 neuronal pathways. These pathways transmit noxious stimuli from the periphery to the cerebral cortex. The cell bodies of the primary afferent neurons are located in the dorsal root ganglia. These are in the vertebral foramina at each spinal cord level. Each neuron has one axon that bifurcates. One end goes to the peripheral tissue which it innervates and the other end into the dorsal horn of the spinal cord.

First-order neurons mainly send the proximal end of their axons into the spinal cord via the dorsal spinal root at each level. This is a sensory spinal root. Once in the dorsal horn, it would synapse with second order neurons, interneurons, sympathetic neurons and ventral horn motor neurons. The second order neurons, synapses at the ipsilateral side of the dorsal column and crosses the midline to ascend via the contralateral spinothalamic tract to reach the thalamic nuclei.(Morgan *et al.*, 2002)

Spinal cord gray matter was divided by Rexed into ten laminae. The first six laminae make up the dorsal horn. They receive all afferent activity and represent the principle site of modulation of pain by the ascending and descending neural pathways. The outer layer which is Lamina I contains the central terminal of thinly myelinated sensory fibres that respond to high threshold mechanical and noxious thermal stimuli (Jessell, 1982).

Lamina II, also called the substantia gelatinosa, contains the terminals of unmyelinated fibres, most of which can equally be activated by noxious mechanical, thermal and chemical stimuli. Lamina II is believed to play a major role in processing and modulating nociceptive input from cutaneous receptors (Jessell, 1982).

The third order neurons which are located in the thalamus send fibres to the postcentral gyrus of the parietal cortex and also the sylvian fissures. Perception and discrete localization of pain takes place in these areas (Morgan *et al.*, 2002).

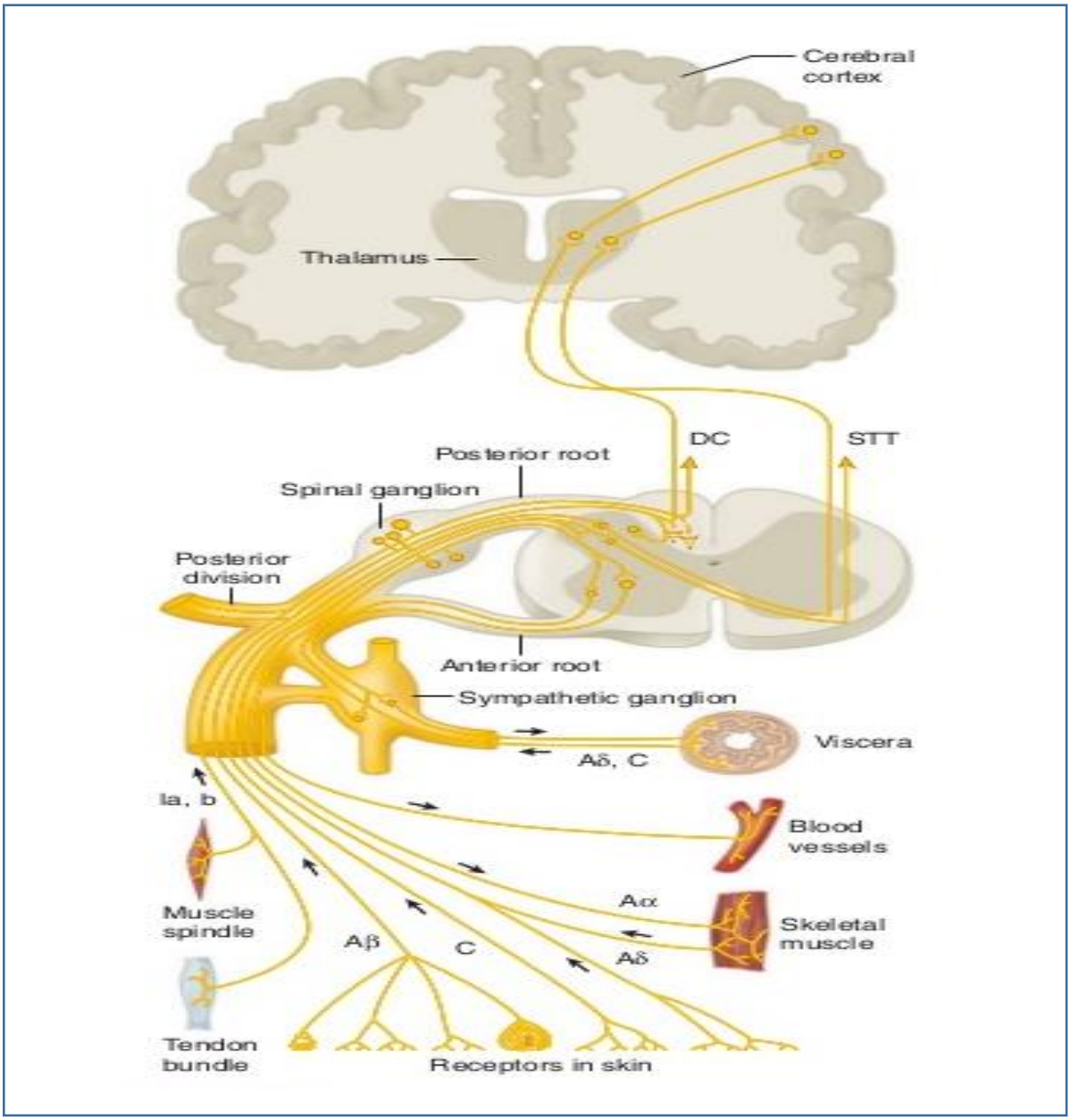

Figure 1.1 : Pain pathway (Morgan *et al.*, 2002)

2.4 Classification of pain

2.4.1 Acute pain

Acute pain is a type of pain that begins suddenly and is usually sharp in quality. It serves as a threat to the body. Acute pain typically lasts less than 3 to 6 months. Acute pain is self-limiting or resolves with treatment in a few days or weeks. It gradually resolves as the injured tissues heal (Kam and Power, 2012).

Acute pain is caused by noxious stimulation due to injury, a disease process or the abnormal function of muscle or viscera. It is usually nociceptive. Acute pain has an adaptive function which is protective by enabling healing to occur without interruption. This is achieved by ensuring minimal contact to external stimuli by making the injured area of the body along with the surrounding tissue hypersensitive to all stimuli (Woolf, 1995).

There are two types of acute pain which are somatic and visceral. These are differentiated based on origin and features.

Somatic pain can be further classified as superficial and deep. Superficial pain is due to nociceptive input which arises from the skin and subcutaneous tissue. It is well localised and sharp pricking or throbbing. Deep pain on the other hand arises from muscle, bone, fascia or periosteum. This type of pain is less well localised compared to superficial pain and is also dull aching (Morgan *et al.*, 2002).

Nociceptive pain serves to detect, localize and limit tissue damage. Four physiological processes are involved; transduction, transmission, modulation and perception (Morgan *et al.*, 2002).

Two principle zones of pain are associated with cutaneous tissue damage. The first zone known as the zone of primary hyperalgesia encompasses the region of tissue damage and is characterised by increased sensitivity to stimuli and spontaneous pain. Surrounding this area is the undamaged zone of secondary hyperalgesia. In this area, there is an increase in mechanical but not heat stimuli. Increased sensitivity implies a decrease in stimulus threshold necessary to elicit a response (Millan, 1999).

Visceral pain also differs from somatic pain as it is colicky in nature and is accompanied by nausea and autonomic disturbance (Mitra and Sinatra, 2004). It is due to the disease process and involves internal organs and the layers that cover it like the pleura or peritoneum (Morgan *et al.*, 2002).

There are four subtypes of visceral pain, namely;

i) True localised visceral pain

ii) Localised parietal pain

iii) Referred visceral pain

iv) Referred parietal pain

True visceral pain is recognised as originating from the midline and is dull and diffuse. This pain is described as either anterior or posterior; an example being a myocardial infarction (McMahon *et al.*, 1995). Parietal pain is sharp and stabbing. Generally, it is viewed as either localised to the area surrounding an organ or referred to another site (Morgan *et al.*, 2002).

2.4.2 Chronic pain

Chronic pain is caused collectively by central, peripheral and psychological mechanisms (Morgan *et al.*, 2002). This type of pain lasts longer than acute pain and is generally somewhat resistant to medical treatment. It is usually associated with a long-term illness and can be the result of damaged tissue, but mostly is attributable to nerve damage (Kam and Power, 2012).

Chronic pain can either be spontaneous or provoked. Spontaneous pain occurs in most chronic pain conditions but is a particular feature of denervation syndromes. Provoked pain is elicited by a peripheral stimulus but the response is usually exaggerated (Kam and Power, 2012).

Both acute and chronic pain can be debilitating, and both can affect and be affected by a person's state of mind. However the nature of chronic pain being that it is ongoing and sometimes constant can make the individual who has it more susceptible to psychological consequences such as depression and anxiety. At the same time, psychological distress can amplify the pain (Ashburn and Staats, 1999).

Breakthrough pain occurs in about 70% of people with chronic pain treated with pain medications. Breakthrough pain refers to flares of pain that occur even when pain medication is being used regularly. It can be spontaneous or set off by a seemingly insignificant event such as standing up. And sometimes it may be the result of pain medication wearing off before it is time for the next dose (Ashburn and Staats, 1999).

Neuropathic pain is produced by damage to the nervous system. It involves complex mechanisms which are central neural and peripheral-central. These are in association with partial or complete lesions of peripheral nerves or more central structures (Morgan *et al.*, 2002).

There are three types of pathological changes produced by nerve lesions. Firstly, a sustained state of central sensitization occurs secondary to ectopic C-fibre input. Then, decreased inhibition occurs as a result of impaired inhibitory transmission and finally A-mediated pain due to a reorganization of synaptic connection in the spinal cord (Woolf, 1995). Neuropathic pain may be continuous or episodic and associated with allodynia which is pain from a normally non-painful stimuli or dysesthesia which refers to abnormal sensations (Merskey and Bogduk, 1994).

Cancer pain or cancer-related pain refers to pain that is the result of primary tumour growth, metastatic disease or toxic effects of radiotherapy or chemotherapy (Ashburn and Staats, 1999). Cancer pain can either be acute pain following an operation which would subside once the wound heals or chronic which is caused by the tumour compressing a nerve or nerve changes due to treatment (Ashburn and Staats, 1999).

2.5 Pain Assessment Tools

Pain is highly subjective and pain assessment is critical to optimal pain management interventions. Although valid and reliable assessment of pain is essential for both clinical trials and effective pain management, the nature of pain makes objective measurement impossible (Sjöström *et al.,* 1997).

In 2008, the Ministry of Health Malaysia 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.

The analgesic corridor is the range of plasma concentration of opioid analgesic within which there is pain relief. The patient experiences pain when the plasma concentration of the administered analgesic falls below the analgesic corridor. Our aim would be to achieve a plasma concentration of opioids within the analgesic corridor so that the patient has adequate pain relief without the consequence of serious side effects (Leykin, 2005).

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, thus making it easier to find appropriate treatment (Huskisson, 1974).

The pain assessment scales are either unidimensional or multidimensional scales.

2.5.1 Unidimensional scales

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. Verbal Analogue Scale (VAS)

c. Visual Rating Scale (VRS)

NRS and VAS are equally sensitive in assessing acute pain after surgery (Huskisson, 1974). They are superior to the VRS and function better for expressing subjective feeling of present pain intensity. The verbal categories of mild, moderate and severe pain may correspond to different values on the VAS in the same individual (Breivik *et al.*, 2008).

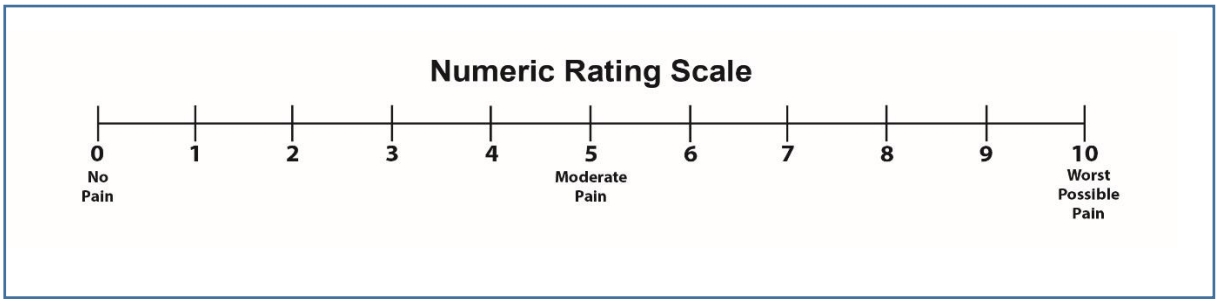

Figure 2.0 : Numerical Rating Scale (Huskisson, 1974)

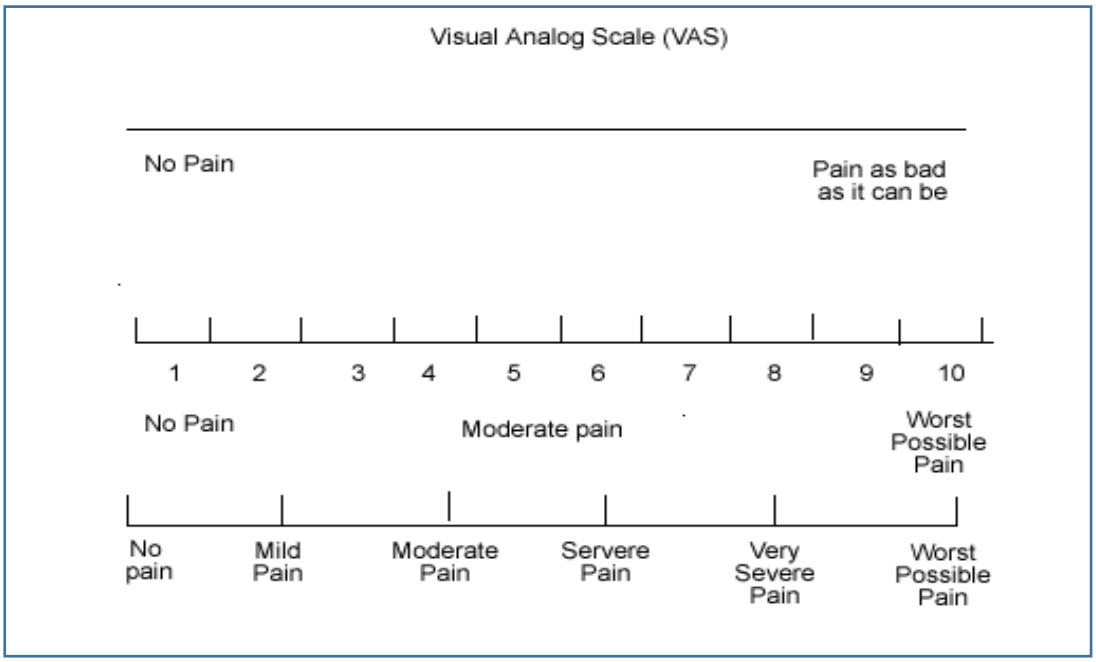

Figure 2.1 : Visual Analogue Score (Hawker *et al.*, 2011)

2.5.2 Multidimensional scales

Multidimensional scales measure intensity, nature and location of pain as well as the impact pain is having on patient's 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).

2.5.3 Combined Rating Scale

The Combined Rating Scale (CRS) is a combination of the VAS and the NRS which is the recommended scale by the Ministry of Health Malaysia.

The VAS has been proven to be satisfactory in the subjective measurement of pain. It consists of a 10cm long straight line with the endpoints defining extreme limits of "No Pain" and "Worst Pain Imaginable".

The NRS is a line represented by an 11 point scale numbered from left to right numbers ranging from 0 to 10, with 0 corresponding to "No Pain" and 10 representing "Worst Pain Imaginable" (Scott and Huskisson, 1976). This scale is a commonly used clinical measure of pain. The patients is asked to indicate the intensity of pain by reporting a number that best represents their pain.(Bijur *et al.*, 2003)

Patients are asked to rate their pain according to this standard pocket sized chart. The number and intensity of pain felt by the patient is recorded as the pain score.

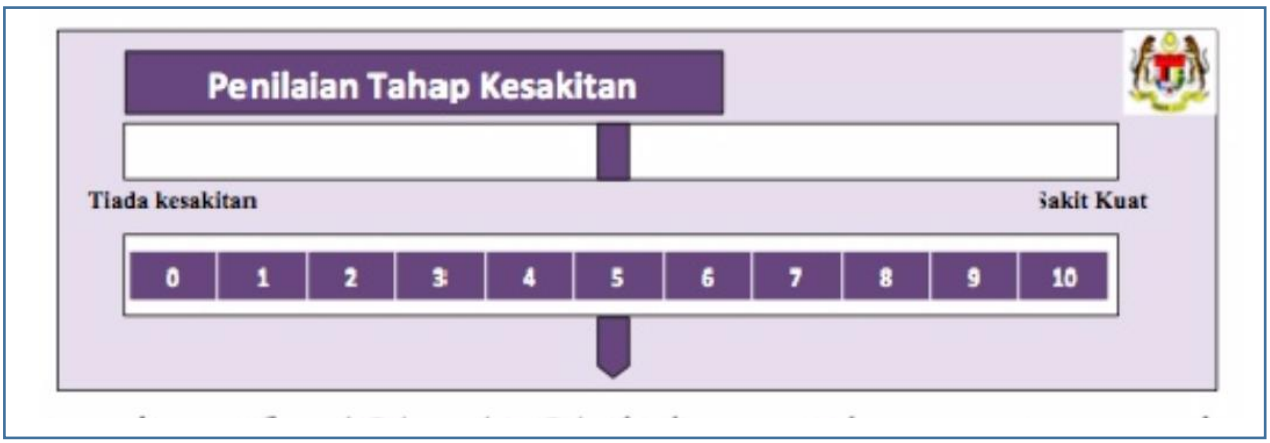

Figure 2.2: Numerical Rating Scale for Ministry of Health, Adapted from the Pain Management Handbook by Ministry of Health Malaysia, 2013

Figure 2.3 : Combined Rating Scale is the tool of choice for this study. Adapted from the Pain Management Handbook by Ministry of Health Malaysia, 2013

2.6 Postoperative nausea and vomiting (PONV)

2.6.1 Definition

Postoperative nausea and vomiting (PONV) is defined as nausea, retching or vomiting occurring during the first 24-48 hours after surgery in inpatients. It is one of the most common causes of dissatisfaction in patients after anaesthesia and remains a common clinical problem. PONV has been also surveyed to be the anaesthetic outcome patients would most want to avoid (Pierre and Whelan, 2013).

There is a rate of up to 30% and is one of the most feared side effects of anaesthesia and surgery, even above pain. Although usually self-limiting, there is delayed discharge from the recovery room, increased chances of readmission and increase risk of complications with each episode of vomiting (Blackburn and Spencer, 2015).

Despite multimodal approaches which have been taken to minimise the occurrence, there is still no guarantee that the individual will not experience any PONV (Öbrink *et al.,* 2015).

2.6.2 Pathophysiology of nausea and vomiting

The physiology of nausea and vomiting is a complex one and not fully understood or discovered.

Nausea is the feeling of impending vomiting. This includes activation of central, sympathetic and parasympathetic responses. Vomiting on the other hand is the involuntary, rapid and forceful oral expulsion of gastric contents through the mouth. This consists of two phases. The pre-ejection retching phase and the ejection or expulsion phase (Blackburn and Spencer, 2015).

It begins with a deep inspiration. The glottis and nasopharynx are initially closed. A large retrograde intestinal contraction that is initiated by central, peripheral and enteric nervous systems forces intestinal contents into the stomach. The esophagus, lower esophageal sphincter and the body of stomach relaxes (Kam and Power, 2012).

This is followed by the contraction of the abdominal and thoracic muscles with the diaphragm descending at the same time. These events cause a marked rise in intraabdominal pressure that forces the gastric contents into the esophagus and subsequently out of the mouth (Kam and Power, 2012).

There is also retrograde contraction of the intestinal muscles with relaxation of the gastric fundus along with the contraction of external anal and urethral sphincter muscles (Pleuvry, 2006).

The vomiting centre and the chemoreceptor trigger zone (CTZ) are two key areas of the brain important in the action of vomiting. The vomiting centre (VC) lies in the lateral reticular formation of the medulla and receives afferent impulses via the vestibulocochlear nerve (CN VIII) in the vestibulocochlear apparatus in the middle ear, carotid baroreceptor impulses (CN IX), gastrointestinal chemo and stretch receptors (CN X) and aortic baroreceptors (CN X). The VC also receives afferents from higher cortical centres and coordinates actions of the smooth and striated muscles involved in vomiting via CN V, VII, IX, X and XI. These innervate the muscles of the face, neck and oropharynx. Motor, sympathetic and parasympathetic outflow to the gastrointestinal tract (GIT) are carried by the autonomic general visceral efferents of CN II, VII, IX, X. Finally, the efferent branches from the VC travel via the spinal nerves to the diaphragm and the abdominal muscles (Blackburn and Spencer, 2015).

The CTZ is located bilaterally on the floor of the 4th ventricle in the area postrema near the vagal nuclei. The CTZ lies outside the blood brain barrier and is sensitive to chemical stimulation such as drugs and toxins. Its efferents act directly on the CTZ (Kam and Power, 2012).