PERIOPERATIVE INTRAVENOUS PARACETAMOL AS ADJUNCTIVE TREATMENT FOR POSTOPERATIVE PAIN RELIEF AFTER ORTHOPAEDIC SURGERY INVOLVING LOWER LIMB BONE FRACTURE

By

DR MOHD IZWAN AZMI BIN MUDA

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ABSTRAK

Latarbelakang: Penggunaan intravena paracetamol semasa pembedahan telah didapati mengurangkan tahap kesakitan dan penggunaan morfin di kalangan pesakit surgikal tertentu. Kami mengkaji kesan intravena paracetamol semasa pembedahan terhadap tahap kesakitan selepas pembedahan di kalangan pesakit yang menjalani pembedahan ortopedik selepas patah tulang paha, betis atau kaki. Matlamat utama kami adalah pengurangan tahap kesakitan and penggunaan morfin sehingga 6 jam selepas pembedahan.

Cara: 62 pesakit yang menjalani pembedahan ortopedik yang melibatkan kepatahan tulang paha, betis atau kaki yang memenuhi kriteria telah direkrut di Hospital Sains Malaysia dan dirawakkan dalam dua kumpulan. Kumpulan intravena paracetamol (n = 31) telah menerima intravena paracetamol 1 g (100 ml) ketika tamat pembedahan manakala kumpulan placebo (n = 31) telah menerima intravena normal saline (100 ml) ketika tamat pembedahan. Kedua-dua kumpulan telah menerima protokol pembiusan am yang teratur dan menerima intravena morfin selepas pembedahan menggunakan Alat Analgesia Kawalan Pesakit. Tahap kesakitan, penggunaan morfin dan kesan sampingan selepas pembedahan direkod pada 30 minit, 3 dan 6 jam selepas pembedahan.

Keputusan: Mean tahap kesakitan adalah lebih rendah dan terbukti berbeza untuk kumpulan intravena paracetamol berbanding dengan kumpulan placebo untuk masa rehat (mean ± SD = 4.23 ± 1.63 VS 5.42 ± 2.41 at 30 min, p = 0.015; 2.81 ± 1.58 VS 4.19 ± 2.09 at 3 hours, p = 0.005; 2.23 ± 1.20 VS 3.23 ± 1.86 at 6 hours, p = 0.015) and moving (mean ± SD = 6.45 ± 1.69 VS 7.26 ± 2.21 at 30 min, p = 0.111; 5.00 ± 1.79 VS

6.48 ± 1.86 at 3 hours, p = 0.002; 4.35 ± 1.38 VS 5.35 ± 1.70 at 6 hours, p = 0.014). Didapati tiada perbezaan yang ketara dalam penggunaan morfin untuk kumpulan intravena paracetamol dan placebo walaupun jumlah terkumpul penggunaan morfin adalah lebih rendah untuk kumpulan intravena paracetamol berbanding kumpulan placebo (mean ± SD = 14.65 ± 10.12 VS 20.61 ± 14.33, p = 0.063). Kekerapan kesan sampingan didapati sama untuk kedua-dua kumpulan.

Kesimpulan: Kajian ini menunjukkan kebaikkan terhadap penggunaan intravena paracetamol sebagai analgesia pelbagai semasa pembedahan untuk pesakit yang mengalami kepatahan tulang paha, betis dan kaki. Kami menyarankan penggunaan intravena paracetamol dalam analgesia pelbagai untuk merawat kesakitan selepas pembedahan.

ABSTRACT

Backgraound: Perioperative intravenous paracetamol has been shown to reduce postoperative pain scores and morphine consumption in certain surgical populations. We studied the effects of perioperative intravenous paracetamol on postoperative pain relief among patients undergoing orthopaedic surgery for lower limb bone fractures. Our primary end points were a reduction in postoperative pain score and cumulative morphine consumption 6 hours postoperatively

Methods: 62 patients undergoing orthopaedic surgery involving lower limb bone fractures that fulfilled inclusion and exclusion criteria were recruited in Hospital Universiti Sains Malaysia and randomized into two groups. The intravenous paracetamol group (n = 31) received intravenous paracetamol 1 gram (100 ml) at skin closure while the placebo group (n = 31) received intravenous normal saline (100 ml) at skin closure. Both groups received a standardized regimen of general anaesthesia and were given intravenous morphine postoperatively via a Patient Controlled Analgesia Device. Postoperative pain score, cumulative morphine consumption and side effects were recorded using a visual analogue scale at 30 minutes, 3 and 6 hours postoperatively.

Results: The mean pain scores were significantly lower in intravenous paracetamol group compare to placebo group in resting (mean ± SD = 4.23 ± 1.63 VS 5.42 ± 2.41 at 30 min, p = 0.015; 2.81 ± 1.58 VS 4.19 ± 2.09 at 3 hours, p = 0.005; 2.23 ± 1.20 VS 3.23 ± 1.86 at 6 hours, p = 0.015) and moving (mean ± SD = 6.45 ± 1.69 VS 7.26 ± 2.21 at 30 min, p = 0.111; 5.00 ± 1.79 VS 6.48 ± 1.86 at 3 hours, p = 0.002; 4.35 ± 1.38 VS 5.35 ± 1.70 at 6 hours, p = 0.014). There were no significant different in cumulative morphine

consumption between intravenous paracetamol and placebo group despite total cumulative morphine consumption for intravenous paracetamol group was lower than placebo group (mean ± SD = 14.65 ± 10.12 VS 20.61 ± 14.33, p = 0.063). Incidence of side effects was similar between the two groups.

Conclusion: This study show beneficial effects of perioperative intravenous paracetamol as part of multimodal analgesia for patients who have lower limb bone fractures going for orthopaedic procedures. We recommended the use of intravenous paracetamol as part of multimodal analgesia in treating postoperative pain.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Acute postoperative pain is a common and still the major complaint encounter after surgery even with current standard of care. In a survey of adults who had undergone surgical procedures in the United States, Warfield and colleagues noted that 77% reported pain after surgery with 80% of affected individuals experiencing moderate to severe pain (Warfield & Kahn, 1995). In another study, in adult who had a variety of surgical procedure, Apfelbaum et al. reported approximately 80% of patient experiences moderate to severe pain postoperatively (Apfelbaum, Chen, Mehta, & Gan, 2003). Inadequate pain relief and control is associated with multiple problems. If it is not managed effectively, postoperative pain can lead to prolonged rehabilitation, poor surgical outcomes and higher rate of medical complication including increased risk of cardiovascular, pulmonary complication and venous thromboembolic disease (Joshi & Ogunnaike, 2005; H Kehlet & Holte, 2001). As a consequences all of complications lead to delayed recovery and prolonged hospital stay (Morrison et al., 2003).

Among the different type of surgical procedure, orthopaedic procedure may induce more intense pain than other surgical procedures because bone pain is more painful than soft tissue injury (Ekman & Koman, 2004). A study by Chung et al. on postoperative pain showed that patient, who had underwent orthopaedic surgery had highest incidences of severe pain in the post anaesthesia care unit and 24 hour postoperatively (Chung, Ritchie, & Su, 1997). For orthopaedic patients, poorly controlled postoperative pain may be associated with delay in ambulation, longer inpatient hospital stays, and decreased patient satisfaction (Joshi & Ogunnaike, 2005) (Morrison et al., 2003). In addition, long-term complications may occur from poorly

controlled postoperative pain, such as limited range of motion and chronic pain syndrome (Joshi & Ogunnaike, 2005) (Perkins & Kehlet, 2000).

The usual treatment for postoperative pain in orthopaedic patients has been oral or intravenous opioid medication. Unfortunately, these medications are frequently associated with multiple adverse reactions, especially nausea and vomiting, pruritus, ileus, and constipation. At routine doses in elderly patients and higher doses in other postoperative patients, opioid analgesics may be associated with respiratory depression, hypotension, dizziness, confusion, and even delirium. These complications usually delay patient mobilization with physical therapy, and increase length of hospital stay (Pizzi et al., 2012) (Oderda et al., 2007). Thus, opioid mono-therapy is not an adequate or appropriate strategy to improve pain management in postoperative patients

Over the past decade, multimodal analgesia has gained recognition for being an effective strategy in managing postoperative pain (Elvir-Lazo & White, 2010; Henrik Kehlet & Dahl, 1993). Using different classes of analgesics each with different pathways and receptor, multimodal analgesia optimizes analgesic efficacy using lower doses of each of respective agents, thus limiting the risk of dose-related adverse events (Buvanendran & Kroin, 2009). Many clinician and anaesthesiologist find this approach beneficial, particularly when using regimens that allow lower doses of opioids. Consequently multimodal analgesia can improved recovery after surgery and ensure rehabilitation and reduced hospital length of stay, thus reducing the overall costs. In addition to opioids and NSAIDs, multimodal analgesics also include gabapentanoids, ketamine, alpha-2 agonists including clonidine and dexmetomidine, and local anaesthetics. Intravenous paracetamol is only recently available in our set up. It is considered a safe drug and only available for a decade in oral, syrup and suppository

form. Now, intravenous paracetamol is considered a fundamental component of the multimodal approach to which opioids, NSAIDs and other drugs are added.

Intravenous paracetamol is only recently available in Malaysia for clinical use. It has been use for the management of mild pain, the management of moderate to severe pain with adjunctive opioid analgesics and the reduction of fever. Several studies have noted its clinical benefit by providing reduced pain scores, opioid consumption, and postoperative side effects when used as a postoperative analgesic.

Several literature review and meta-analysis were done regarding usage of intravenous paracetamol intraoperative and postoperative. Marcario and Royal performed a literature review of randomized clinical trials of intravenous paracetamol for acute postoperative pain. Sixteen articles from nine countries published between 2005 and 2010 met inclusion criteria and had a total of 1464 patients. In seven of the eight studies where intravenous paracetamol was compared with an active comparative medication, intravenous paracetamol was found to have similar analgesic outcomes. Three of the eight studies also found intravenous paracetamol resulted in significant reduction in mean opioid consumption. Twelve of 14 placebo-controlled studies found that intravenous paracetamol patients had improved pain relief (Macario & Royal, 2011).

Another systemic review of clinical trial done by Bright et al. regarding intravenous paracetamol reduces postoperative opioid consumption after orthopaedic surgery. Eight articles were chosen after review of inclusion and exclusion criteria and analysed. Five clinical trials reported that there is significant reduction in opioid consumption in the postoperative period. However one study did not find any reduction in opioid requirement after spinal surgery in children and adolescents. Studies that reported a significant decreased in opioid consumption were done in adult population. Three of

them were done in lower limb surgeries, one in a mixed orthopaedic and rest is a spinal surgery. Six clinical trials reported a better pain score when paracetamol has been used but other three trials denied. They concluded that postoperative intravenous paracetamol is a safe and effective component of multimodal analgesic regimen, and it reduces postoperative opioid consumption after orthopaedic surgery (Jebaraj, Maitra, Baidya, & Khanna, 2013)

Most of the clinical trials studied the use of intravenous paracetamol alone compare with placebo or active comparator, therefore the use of intravenous paracetamol is consider mono-therapy approach for postoperative pain control. A few clinical studies used intravenous paracetamol as adjunctive to morphine and use multiple drug combination for the treatment of postoperative pain and added intravenous paracetamol as a new combination.

With the concept of multiple modal approaches for postoperative pain management and to differentiate from previous study, this study plan to use multi drugs regimes (opioids, NSAIDs and local anaesthetics) for pain management and plan to investigate the use of additional intravenous paracetamol in reducing postoperative pain and morphine consumption postoperatively. To establish this study, orthopaedic surgery involving bone fracture for lower limb is choose because this type of surgery we anticipate moderate to severe pain postoperatively.

1.2 OBEJECTIVE OF THE STUDY

General Objective:

The objective of this study was to evaluate the effects of intravenous paracetamol as compared to placebo with regards to postoperative pain relief when given perioperatively to patients undergo orthopaedic surgery for lower limb bone fractures.

Specific Objectives:

1. To evaluate effect of perioperative intravenous paracetamol in reducing postoperative visual analogue scale at 30 minutes, 3 hours and 6 hours postoperatively

2. To study the adjunctive effect of intravenous paracetamol in reducing morphine consumption over 6 hours postoperatively

3. To evaluate effect of perioperative intravenous paracetamol on side effects of morphine.

CHAPTER 2: REVIEW OF LITERATURE

2.1 PHYSIOLOGY OF ACUTE PAIN

In 1996 the International Association for the 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, 1991). Acute pain is defined as pain of recent onset and probable limited duration. It is typically has an identifiable cause relationship with injury or disease. Chronic pain commonly persists beyond the time of healing of an injury and frequently there may not be any clear identifiable cause (Ready & Edwards, 1992).

Pain is a subjective experience, which cannot be easily measured. It requires consciousness. Describing pain as an ‘experience’ separates pain from ‘nociception’. Nociception is the neural processes underlying the encoding and processing of a noxious stimulus to the brain via a pain pathway (Loeser & Treede, 2008). In addition to these sensory effects, the perception and subjective experience of pain is multifactorial including signalling systems and modulation from higher centres and will be influenced by psychological and environmental factors in every individual.

The nervous system for nociception that alerts the brain to noxious sensory stimuli is separate from the nervous system that informs the brain of innocuous sensory stimuli. Nociceptors are unspecialized, free, unmyelinated nerve endings that convert (transduce) a variety of stimuli into nerve impulses, which the brain interprets to produce the sensation of pain (Steeds, 2013). The nerve cell bodies are located in the dorsal root ganglia, or for the trigeminal nerve in the trigeminal ganglia, and they send one nerve fiber branch to the periphery and another into the spinal cord or brainstem.

The classification of the nociceptor is based on the classification of the nerve fiber of which it is the terminal end. There are two types of nerve fibers, Ad fibers and C fiber. Ad fibers are myelinated, large diameter 2 -3 microns and conduct at the velocity of 6 – 30 meter per second. The Aδ-fiber nociceptors are of two types and respond to mechanical and mechanothermal stimuli. C fibers are unmyelinated, small-diameter less than 2 microns and conduct much slower at the velocity of 0.5 – 2 meters per second. The C-fiber nociceptors respond polymodally to thermal, mechanical, and chemical stimuli. It is well known that the sensation of pain is made up of two categories, an initial fast, sharp pain and a later slow, dull, long lasting pain. This pattern is explained by the difference in the speed of propagation of nerve impulses in the two nerve fiber types described above. The neuronal impulses in fast-conducting Aδ-fiber nociceptors produce the sensation of the sharp, fast pain, while the slower C-fiber nociceptors produce the sensation of the delayed, dull pain (Fein, 2012).

Peripheral activation of the nociceptors (transduction) is modulated by a number of chemical substances including neuropeptides and excitatory amino acids, which are produced or released when there is cellular damage (Table 2.1) (Butterworth, Markey, & Wasnick, 2013). These mediators influence the degree of nerve activity and, hence, the intensity of the pain sensation. Repeated stimulation typically causes sensitization of peripheral nerve fibers, causing lowering of pain thresholds and spontaneous pain, a mechanism that can be experienced as cutaneous hypersensitivity, e.g., in skin areas with sunburn.

In addition, local release of chemicals such substance P causes vasodilation and swelling as well as release of histamine from the mast cells, further increasing vasodilation. This complex chemical signalling protects the injured area by producing behaviours that keep that area away from mechanical or other stimuli. Promotion of

healing and protection against infection are aided by the increased blood flow and inflammation (the "protective function of pain").

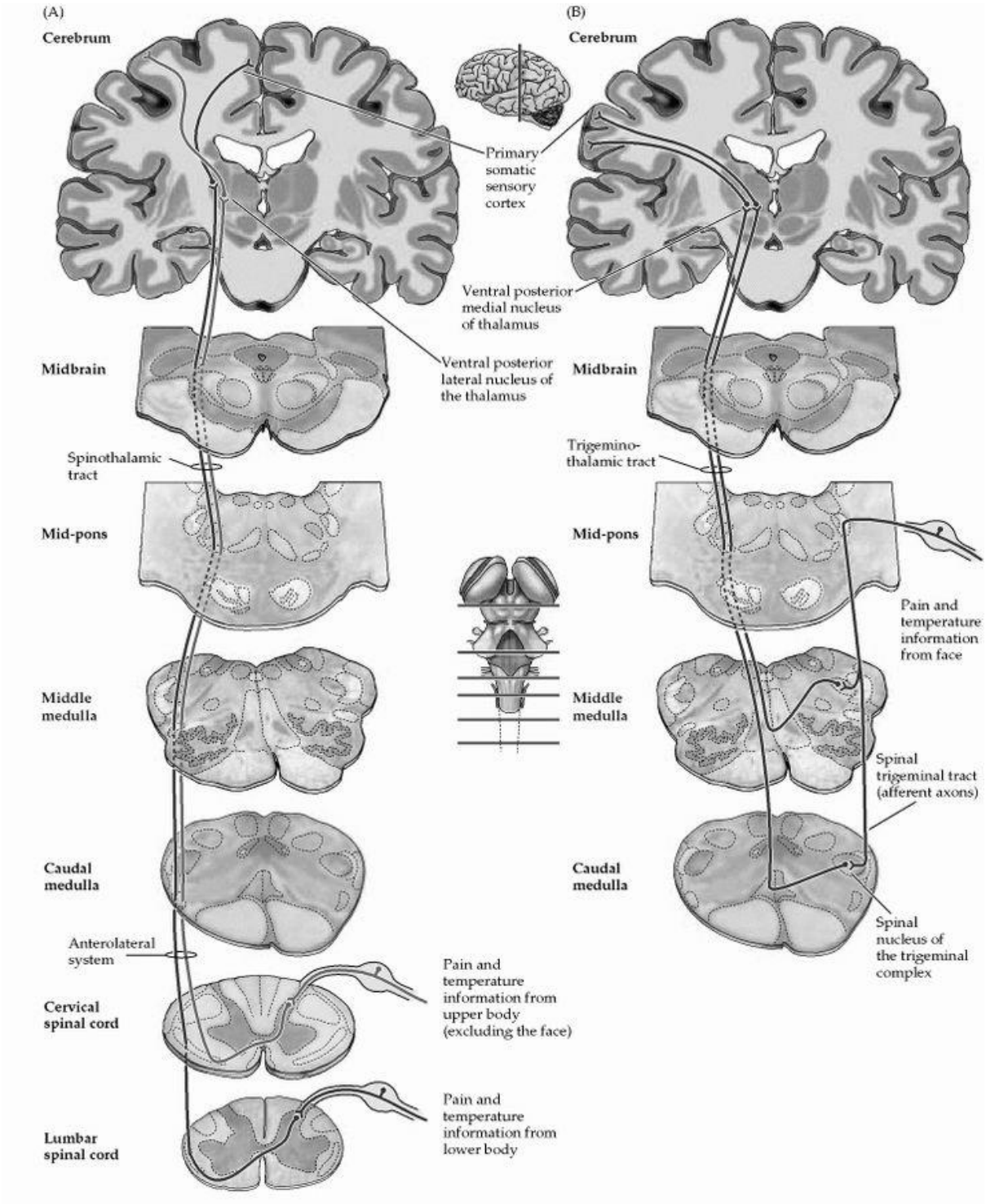
Table 2.1 Major neurotransmitter mediating and modulating pain

Neurotransmitter	Receptor	Effect on Nociception
Substance P	Neurokinin-1	Excitatory
Calcitonin gene-related peptide		Excitatory
Glutamate	NMDA, AMPA, kainite, quisqualate	Excitatory
Aspartate	NMDA, AMPA, kainite, quisqualate	Excitatory
Adenosine triphosphate (ATP)	P1, P2	Excitatory
Somatostatin		Inhibitory
Acetylcholine	Muscarinic	Inhibitory
Enkephalins	μ, δ, κ	Inhibitory
B-Endorphin	μ, δ, κ	Inhibitory
Norepinephrine	α2	Inhibitory
Adenosine	A1	Inhibitory
Serotonin	5-HT1, (5-HT3)	Inhibitory
γ- Aminobutyric acid (GABA)	A, B	Inhibitory
Glycine		Inhibitory

2.1.1 PAIN PATHWAYS

Pain is conducted along three neuronal pathways, first order, second order and third order neuron that transmit noxious stimuli from the periphery to cerebral cortex (Figures 2.1). The majority of first order neuron sends the proximal end of their axon into the spinal cord via the dorsal spinal root. Some unmyelinated afferent fibers enter the spinal cord via the ventral nerve root. Each neuron has a single axon that bifurcates, sending one end to the peripheral tissues it innervates and the other into the dorsal horn of the spinal cord. In the dorsal horn, the primary afferent neuron synapses with the second order neuron. Pain fibers originating from the head are carried by the trigeminal (V), facial (VII), glossopharyngeal (IX) and vagal (X) nerves.

The major nerve routes (second order neuron) for the transmission of pain and normal temperature information from the body and face to the brain are the spinothalamic pathway and the trigeminal pathway. In spinothalamic pathway, the nerve fibers from the dorsal root ganglia enter the spinal cord through the dorsal root and send branches 1–2 segments up and down the spinal cord (dorsolateral tract of Lissauer) before entering the spinal gray matter, where they make contacts with (innervate) the nerve cells in Rexed lamina I (marginal zone) and lamina II (substantia gelatinosa). The Aδ fibers innervate the cells in the marginal zone, and the C fibers innervate mainly the cells in the substantia gelatinosa layer of the spinal cord. These nerve cells, in turn, innervate the cells in the nucleus proprius, another area of the spinal cord gray matter (Rexed layers IV, V, and VI), which send nerve fibers across the spinal midline and ascend (in the anterolateral or ventrolateral part of the spinal white matter) through the medulla and pons and innervate nerve cells located in specific areas of the thalamus. This makes up the spinothalamic pathway for the transmission of information on pain



Figures 2.1 (A) Pain pathways for upper and lower body (B) Pain pathways for face

and normal termal stimuli (<45°C). dysfunctions in the thalamic pathways may themselves be a source of pain, as is observed in patients after stroke with central pain ("thalamic pain") in the area of paralysis (Butterworth et al., 2013).

In the trigeminal pathway, noxious stimuli from the face area are transmitted in the nerve fibers originating from the nerve cells in the trigeminal ganglion as well as cranial nuclei VII, IX, and X. The nerve fibers enter the brainstem and descend to the medulla, where they innervate a subdivision of the trigeminal nuclear complex. From here the nerve fibers from these cells cross the neural midline and ascend to innervate the thalamic nerve cells on the contralateral side. Spontaneous firing of the trigeminal nerve ganglion may be the etiology of "trigeminal neuralgia".

The area of the thalamus that receives the pain information from the spinal cord and trigeminal nuclei is where the third order neuron located. It also the area that receives information about normal sensory stimuli such as touch and pressure. From this area, nerve fibers are sent to somatosensory area I and II in the postcentral gyrus of the parietal cortex and the superior wall of the sylvian fissure. Thus, by having both the nociceptive and the normal somatic sensory information converge on the same cortical area, information on the location and the intensity of the pain can be processed to become a "localized painful feeling."

Appreciating the complexity of the pain pathway can contribute to understanding the difficulty in assessing the origin of pain in a patient and in providing pain relief, especially in chronic pain.

2.1.2 MODULATION OF THE PERCEPTION OF PAIN

It is well known that there is a difference between the objective reality of a painful stimulus and the subjective response to it. The dissociation between injury and pain implies that there is a mechanism in the body that modulates pain perception. This endogenous mechanism of pain modulation is thought to provide the advantage of increased survival in all species. There is three important mechanisms have been described which is segmental inhibition, the endogenous opioid system, and the descending inhibitory nerve system.

In 1965, Melzack and Wall proposed the "gate theory of pain control," which has been modified subsequently but which in essence remains valid. The theory proposes that the transmission of information across the point of contact (synapse) between the Aδ and C nerve fibers (which bring noxious information from the periphery) and the cells in the dorsal horn of the spinal cord can be diminished or blocked. Hence, the perception of the painfulness of the stimulus either is diminished or is not felt at all. The development of transcutaneous electrical nerve stimulation (TENS) was the clinical consequence of this phenomenon (Kopf & Patel, 2010).

The transmission of the nerve impulse across the synapse can be described as follows: The activation of the large myelinated nerve fibers (Aβ fibers) is associated with the low-threshold mechanoreceptors such as touch, which stimulate an inhibitory nerve in the spinal cord that inhibits the synaptic transmission. This is a possible explanation of why rubbing an injured area reduces the pain sensation.

Besides the gating of transmission of noxious stimuli, there is another system modulates pain perception. Since 4000 BCE, it has been known that opium and its derivatives such as morphine, codeine, and heroin are powerful analgesics, and they

remain the mainstay of pain relief therapy today. In the 1960s and 1970s, receptors for the opium derivatives were found, especially in the nerve cells of the periaqueductal gray matter and the ventral medulla, as well as in the spinal cord. This finding implied that chemicals must be produced by the nervous systems that are the natural ligands of these receptors. Three groups of endogenous compounds (enkephalins, endorphins, and dynorphin) have been discovered that bind to the opioid receptors and are referred to as the endogenous opioid system. The presence of this system and the descending pain modulation system (adrenergic and serotoninergic) provides an explanation for the system of internal pain modulation and the subjective variability of pain.

Nerve activity in descending nerves from certain brainstem areas (periaqueductal gray matter, rostral medulla) can control the ascent of nociceptive information to the brain. Serotonin and norepinephrine are the main transmitters of this pathway, which can therefore be modulated pharmacologically. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (e.g., amitriptyline) may therefore have analgesic properties.

2.2 CONCEPT OF MULTIMODAL ANALGESIA

The concept of multimodal analgesia was introduced long time ago as a technique to improve analgesia and reduce the incidence of opioid related adverse events. What is multimodal analgesia? Multimodal analgesia is achieved by combining different analgesics that act by different mechanisms and at different sites in the nervous system (e.g., opioids, NSAIDs, and local anaesthetics), resulting in additive or synergistic analgesia (Henrik Kehlet & Dahl, 1993) (Figure 2.2).

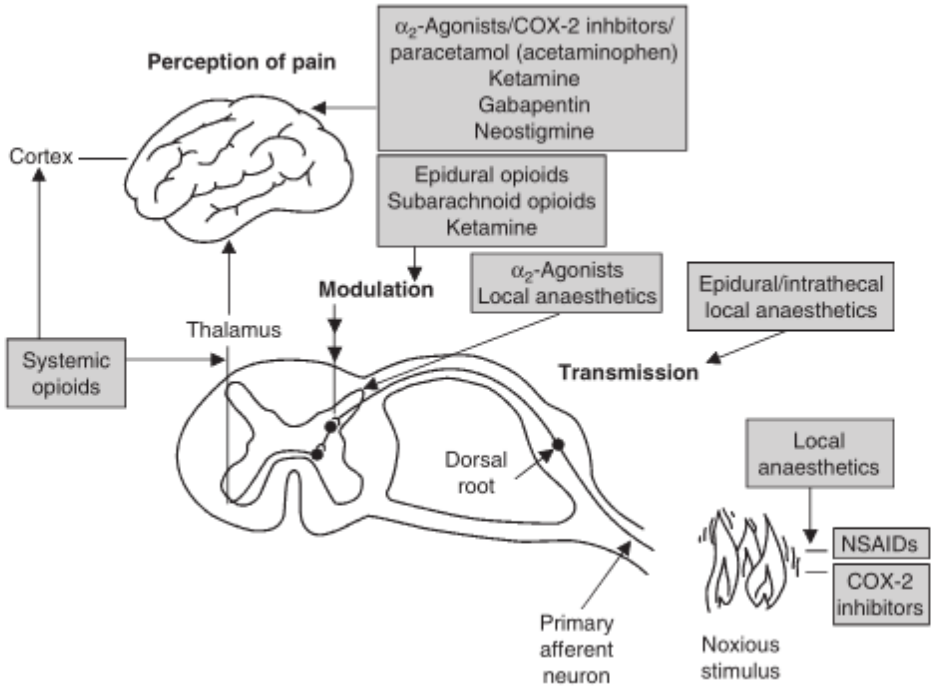


Figure 2.2 Types of Analgesics and Their Site of Action.

The aim of this strategy is to achieve sufficient analgesia, reduce the doses of individual drugs and lower the incidence of adverse drug effects. In a study by Christine et. al, they study the combination of drugs, opioids (mepiridine), NSAID (ketorolac) and local anaesthesia in ambulatory laparoscopic cholecystectomy. They conclude that, the concomitant use of opioid, NSAID and local anaesthesia to be highly effective in

patients, resulting in faster recovery and discharge (Michaloliakou, Chung, & Sharma, 1996). A lower incidence of adverse effects and improved analgesia also has been demonstrated with multimodal analgesia techniques, which may provide for shorter hospitalization times, improved recovery and function and possibly decreased healthcare costs (Buvanendran et al., 2003).

It has been suggested that multimodal analgesia is a rational approach to pain management and is more effective (Carpenter, 1997). Animal studies also demonstrate the synergistic effect between NSAIDs and opioids, and certain other analgesics in clinical pain states (Malmberg & Yaksh, 1993). Therefore, multimodal analgesia is currently recommended for effective postoperative pain control.

2.2.1 OPIOIDS

Opioid are the most effective analgesics, especially for moderate to severe postoperative pain (Claxton, McGuire, Chung, & Cruise, 1997). Their effects are mediated by opioid receptors in the central nervous system that attenuate pain related signal. Peripheral opioid receptors also provide analgesic effects (Stein, 1993). The potency of individual opioids correlates with their affinity for their respective receptors (Stahl, Van Bever, Janssen, & Simon, 1977). The side effect profile of opioids which is nausea, vomiting, sedation, ileus, constipation and respiratory depression should be considered when using it as a sole analgesic for postoperative pain. In order to reduce the dose of opioids, other non-opioids analgesics should be considered.

There are many types and route for opioids is available. Morphine is common opioids used for postoperative pain relieved especially for moderate to severe pain. The common route for morphine in postoperative setting includes intravenous by small boluses titration or via patients controlled analgesia machine (PCA), intramuscular, subcutaneous and neuroaxial. PCA morphine is still superior in the management of postoperative pain especially in ward (Walder, Schafer, Henzi, & Tramer, 2001). And it became a standard of care in procedures where moderate to severe postoperative pain is expected. Another route that are commonly use is neuroaxial morphine. It provides excellent postoperative analgesia for up to 24 hours. However, in those patient received opioids especially morphine, delayed respiratory depression remains a concern and these patients need to be monitored closely postoperatively. Alternatively, fentanyl, a short acting opioids are appropriate than longer acting opioids for PCA and neuroaxial (Gross et al., 2006). Most of the clinical trials of analgesics use opioids as comparator and end objective of study especially morphine.

2.2.2 NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have proved to be valuable in the management of postoperative pain because of their opioid sparing action and anti-inflammatory effects (Cashman, 1996). We know that Prostaglandins, including PGE2, are responsible for reducing the pain threshold at the site of injury, resulting in central sensitization and a lower pain threshold in the surrounding uninjured tissue. The primary site of action of NSAIDs is believed to be in the periphery though recent research indicates that central inhibition of cyclooxygenase-2 (COX-2) may also play an important role in modulating nociception (Buvanendran et al., 2006). NSAIDs inhibit the synthesis of prostaglandins both in the spinal cord and at the periphery, thus diminishing the hyperalgesic state after surgical trauma.

Oral NSAIDs have long been used for treating postoperative pain. However it only used in those patients whose can tolerated orally. Since parenteral preparations of NSAIDs have become available, these drugs have been more widely used in the management of acute perioperative pain.

Early reports suggested that parenteral NSAIDs possessed analgesic properties comparable to the traditional opioid analgesics (Yee, Koshiver, Allbon, & Brown, 1986) without opioid related side effects (Ding & White, 1992). Compared with the partial opioid agonist tramadol, diclofenac produced better postoperative pain relief with fewer side effects after cardiac surgery (Immer et al., 2003). When administered as an adjuvant during outpatient anaesthesia, ketorolac was associated with improved postoperative analgesia and patient comfort compared with fentanyl and dezocine (Ding & White, 1992). Other investigators reported that ketorolac provided postoperative pain relief similar to that of fentanyl but was associated with less nausea

and somnolence, as well as an early return to of bowel function (Wong et al., 1993). In most studies, use of ketorolac has been associated with less frequent incidence of postoperative nausea vomiting then the opioid analgesics. As a result, patients tolerate oral fluids and are fit for discharge earlier than those receiving only opioid analgesics during perioperative period.

Oral and rectal administration of NSAIDs is also effective and less costly in the management of postoperative pain (Forse, El-Beheiry, Butler, & Pace, 1996). For example, when oral naproxen was administered before laparoscopic surgery, postoperative pain scores, opioid requirements and time to discharge were significantly reduced (Rosenblum, Weller, Conard, Falvey, & Gross, 1991) .

Despite the obvious benefits of using NSAIDs in the postoperative period, as with any mixed COX-1/COX-2 inhibitor, the primary concern would be the increased postoperative bleeding that has been documented for NSAIDs because of their COX-1 component (Marret, Flahault, Samama, & Bonnet, 2003).

2.2.3 COX-2 SELECTIVE INHIBITOR

COX-2-selective inhibitors have the advantage over NSAIDs in the perioperative setting of not increasing the risk of bleeding. Multiple clinical studies in surgical patients evaluated the use of celecoxib, rofecoxib and valdecoxib as preventive analgesics. In a study comparing celecoxib versus placebo done in patients undergoing total knee arthroplasty under spinal anaesthesia show lower pain scores and morphine consumption over the first 48h. Celecoxib also increased knee range of motion over the first 3 postoperative days. Incidences of postoperative nausea and vomiting (PONV) did not differ by group. As expected with a COX-2-selective inhibitor, there were no differences in intraoperative or postoperative blood loss between groups (Huang et al., 2008).

Rofecoxib is a COX-2-selective inhibitor that is no longer used due to adverse cardiovascular events. However, clinical trials with acute use of rofecoxib during joint replacement surgery reveal mechanisms by which COX-2 inhibition can reduce postoperative pain. Perioperative use of rofecoxib reduced opioid consumption, pain, vomiting, and sleep disturbance, with improved knee range of motion compared with that of placebo, after total knee arthroplasty (Buvanendran et al., 2003).

Most of the COX-2 selective inhibitor is available only in an oral formulation. A parenteral form of a new COX-2 selective inhibitor which is parecoxib is currently available. Parecoxib is a prodrug which is rapidly converted to valdecoxib. It has been shown to be effective as an analgesic post gynaecological surgery in a 24 hour study with ketorolac as comparators (Barton et al., 2002). Postoperative administration of parecoxib resulted in significant opioid sparing effects, reduced adverse effects and improved quality of recovery and patient satisfaction with postoperative pain

management (Malan Jr et al., 2003). In a 7 day study of parecoxib and ketorolac in elderly patients parecoxib was associated with similar GI effects to placebo, with significantly fewer gastric and duodenal erosions and ulcers than ketorolac (Hubbard et al., 2000).

In view of benefits of NSAIDs and COX-2 selective inhibitor in postoperative pain management, recent practice guidelines for acute pain management in the perioperative setting specifically state ‘unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, COX-2 inhibitors, or acetaminophen’ (Management, 2004).

2.2.4 NMDA ANTAGONISTS

With the discovery of the N-methyl-D-aspartate (NMDA) receptor and its links to nociceptive pain transmission and central sensitization, there has been renewed interest in utilizing non-competitive NMDA receptor antagonists, such as ketamine, as potential anti-hyperalgesic agents. Ketamine has been a well-known general anaesthetic and analgesic for the past 3 decades. Although high doses of ketamine have been implicated in causing psychomimetic effects (excessive sedation, cognitive dysfunction, hallucinations, nightmares), sub-anaesthetic or low doses of ketamine have demonstrated significant analgesic efficacy without these side effects. Low-dose ketamine has not been associated with adverse pharmacological effects on respiration, cardiovascular function, nausea, vomiting, urinary retention, and constipation or postoperative ileus.

There is evidence that low-dose ketamine may play an important role in postoperative pain management when used as an adjunct to opioids, local anaesthetics, and other analgesic agents (Schmid, Sandler, & Katz, 1999; Subramaniam, Subramaniam, & Steinbrook, 2004). A recent review of 70 studies with 4701 patients, confirmed that perioperative opioid consumption was lower, postoperative nausea and vomiting was decreased and that ketamine was especially useful in very painful procedures such as thoracic and major orthopaedic surgery. The analgesic effect of ketamine was independent of the type of intraoperative opioid, timing of ketamine administration and ketamine dose (Laskowski, Stirling, McKay, & Lim, 2011).

2.2.5 ALPHA-2 AGONIST

Alpha-2 adrenergic activation represents an intrinsic pain control network of the central nervous system. The alpha-2 adrenergic receptor has high density in the substantia gelatinosa of the dorsal horn in humans and that is believed to be the primary site of action by which alpha-2 adrenergic agonists can reduce pain. Clonidine and the more selective dexmedetomidine have opioid sparing, sedative and analgesics properties (Smith, 2011). Unfortunately the analgesic doses of these drugs cause significant side effects in the form of sedation, hypotension and bradycardia. They are also very long acting and can cause delay awakening after general anaesthesia.

Due to the many side effects of systemic clonidine administration, the spinal route is preferred. In a study compare epidural clonidine versus placebo for spinal surgery under general anaesthesia, shown PCA morphine use, pain score and PONV incidence was less in the clonidine group than placebo (Farmery & Wilson-MacDonald, 2009). In a study of patients undergoing abdominal total hysterectomy under general anaesthesia were compare between morphine alone or dexmedetomidine plus morphine for postoperative analgesia over 24 h. Patients with dexmedetomidine and morphine required less morphine (23mg) than the morphine alone group (33 mg) over the 0–24 h postoperative period. Postoperative pain scores at rest or with movement and the incidence of nausea during the 4– 24 h period were lower in the dexmedetomidine and morphine group. There was lower blood pressure and heart rate in the dexmedetomidine and morphine group, but the decrease was small (Lin et al., 2009).

2.2.6 GABAPENTANOIDS

Pregabalin and gabapentin used extensively in the treatment of chronic neuropathic pain and seizure, reduce postoperative pain if given pre and postoperatively. Preemptive pregabalin decreases postoperative pain scores, opioid consumption as well as opioid related adverse effects. However postoperative sedation is increased (Peng, Wijeysundera, & Li, 2007). Pregabalin and gabapentin bind to the a2d subunit of voltage-gated calcium channels in the spinal cord and brain (Bian et al., 2006). Earlier clinical trials with gabapentin for early postsurgical pain have recently been reviewed (Gilron, 2007). In patients undergoing laparoscopic cholecystectomy were randomized to receive pregabalin 150mg or placebo orally 1 h before surgery. Opioid consumption and pain score were less in the pregabalin group. However PONV incidence, or sedation, did not differ between the two groups (Agarwal et al., 2008).

2.2.7 LOCAL ANAESTHETICS

Local anaesthetics can be administered for perioperative pain management via different routes either by peripheral nerve blocks or wound infiltration. Peripheral nerve blocks techniques are simple, safe and highly effective approaches to providing perioperative analgesia. The use of long acting local anaesthetics for neural blockage techniques involving the upper and lower extremities can facilitate an early discharge. Extending peripheral nerve blocks using disposable catheter systems to provide continuous perineural blockage has been shown to improve recovery after both upper and lower extremities (White, Issioui, Skrivanek, Early, & Wakefield, 2003).

Infiltrating local anaesthetics into the skin and subcutaneous tissue prior to making an incision may be the simplest approach to analgesia. It is a safe procedure with few side effects and low risk for toxicity. When administered before surgery, this simple technique can also decrease anaesthetic and analgesic requirements during surgery, as well as reduce the need for opioid analgesics postoperatively. In patients undergoing total abdominal hysterectomy under general anaesthesia, bilateral block of the abdominal wall with ropivacaine shown less morphine use over the 48 h period after surgery compare to placebo group. Pain scores at rest and with movement were reduced in the ropivacaine group. The incidence of PONV did not differ between groups, but the incidence of sedation was reduced in the ropivacaine group (Carney, McDonnell, Ochana, Bhinder, & Laffey, 2008).