USM GERAN JANGKA PENDEK

A COMPARATIVE STUDY OF INTRAVENOUS PATIENT-CONTROLLED ANALGESIA MORPHINE AND TRAMADOL IN PATIENTS UNDERGOING MAJOR OPERATION

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IN THE NAME OF ALLAH, THE BENEFICIENT, THE MERCIFUL

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ABSTRAK

PERBANDINGAN DI ANTARA ANALGESIA INTRAVENA KAWALAN PESAKIT (PCA) MORPHINE DENGAN ANALGESIA INTRAVENA KAWALAN PESAKIT (PCA) TRAMADOL DI KALANGAN PESAKIT YANG MENJALANI PEMBEDAHAN MAJOR

Pengenalan: Kejayaan pembedahan major bergantung sebahagiannya kepada keberkesanan pengawalan kesakitan selepas pembedahan. Ianya dapat dicapai dengan pemberian morphine melalui system ' PCA'. Tramadol adalah 'Opioid' penahan sakit yang lemah. Ianya bertindak terutamanya melalui reseptor opioid 'μ'. Tujuan kajian ini adalah untuk menentukan keberkesanan intravena 'PCA' Tramadol berbanding dengan 'PCA' Morphine dari segi kawalan kesakitan, kesan sedasi, dan kesan sampingan yang lain seperti rasa loya, muntah dan kegatalan.

Kaedah: Kajian ini dijalankan secara rawak, dan 'double - blind' ke atas 160 pesakit ASA I dan I I yang terpilih dan telah dibahagikan kepada dua kumpulan melalui kaedah sampul surat tertutup. Selepas pembedahan, kumpulan 'PCA' (M) morphine (n = 80) menerima dos permulaan intravena morphine 0.1 mg/kg diikuti infusi 'PCA' sebanyak 1 mg (1mg/ ml) seperti diperlukan. Kumpulan 'PCA' (T) tramadol (n = 80) menerima dos permulaan 2.5 mg/kg diikuti infusi 'PCA' sebanyak 10 mg (10 mg/ ml) seperti diperlukan. Tempoh jarak kunci keselamatan adalah 10 minit. Semua pesakit tidak menerima basal infusi. Di bilik permulihan, pesakit diberikan oksigen

melalui 'face mask' dan pemerhatian tahap kesakitan mengikut 'Modified Pain Score', tahap sedasi mengikut 'Ramsay Sedation Score', kadar pernafasan, rasa loya, muntah, kegatalan, tekanan darah dan kadar nadi dicatatkan. Pesakit sekali lagi diperiksa selepas 30 minit di bilik pemulihan. Pemerhatian diteruskan di wad selepas 4 jam, 24 jam dan 48 jam pembedahan.

Keputusan: Menunjukkan tiada perbezaan di dalam data demografik di antara dua kumpulan ini ($p > 0.05$). Purata tahap kesakitan bagi kumpulan Tramadol untuk untuk setiap 30 minit, 4 jam, 24 jam dan 48 jam selepas pembedahan adalah 1.32 ± 0.79, 1.04 ± 0.79, 0.35 ± 0.48 dan 0.09 ± 0.33 setiap satu. Manakala purata tahap kesakitan bagi kumpulan Morphine untuk setiap 30 minit, 4 jam, 24 jam dan 48 jam selepas pembedahan adalah 1.35 ± 0.99, 1.14 ± 0.81, 0.40 ± 0.54 dan 0.10 ± 0.34 setiap satu. Tiada perbezaan yang ketara untuk tahap kesakitan bagi setiap tempoh yang dinyatakan di antara kedua dua kumpulan tersebut ($p>0.05$). Purata tahap sedasi bagi kumpulan Tramadol untuk setiap 30 minit, 4 jam, 24 jam dan 48 jam selepas pembedahan adalah 0.90 ± 0.74, 0.56 ± 0.59, 0.08 ± 0.27 dan 0.02 ± 0.16 setiap satu. Manakala purata tahap sedasi bagi kumpulan Morphine untuk setiap 30 minit, 4 jam, 24 jam dan 48 jam selepas pembedahan adalah 0.84 ± 0.70, 0.46 ± 0.64, 0.08 ± 0.27 dan 0.01 ± 0.11 setiap satu. Tiada perbezaan yang ketara untuk tahap sedasi bagi setiap tempoh yang dinyatakan di antara kedua dua kumpulan tersebut ($p>0.05$). Kajian juga menunjukkan tiada perbezaan yang ketara antara kedua-dua kumpulan dari segi kejadian loya, muntah dan kegatalan.

Kesimpulan: Kajian ini menunjukkan 'PCA' Tramadol adalah sama keberkesanannya berbanding dengan 'PCA' morphine dari segi pengawalan kesakitan selepas pembedahan major. Kesan sedasi, rasa loya, muntah atau kegatalan adalah sama di dalam kedua-dua kumpulan.

ABSTRACT

A COMPARATIVE STUDY OF INTRAVENOUS PATIENT- CONTROLLED ANALGESIA MORPHINE AND TRAMADOL IN PATIENTS UNDERGOING MAJOR OPERATION

Introduction: The success of major surgery depends partly on providing effective post-operative pain relief, which can be achieved by morphine administration via PCA system. Tramadol is a weak opioid analgesic, which act mainly on μ-opioid receptor. The purpose of this study was to evaluate the effectiveness of intravenous patient-controlled analgesia (PCA) Tramadol in comparison with PCA Morphine in term of analgesic properties, sedation and other side effects such as nausea, vomiting and pruritus.

Methods: A randomized, double-blinded study was conducted on 160 selected ASA I and II patients who were divided into two groups by a closed envelope technique. Following surgery, the PCA morphine (M) group (n=80) received a loading dose of 0.1 mg/kg of intravenous morphine followed by 1 mg (1 mg/ml) of PCA infusion as required. The PCA tramadol (T) group (n=80) received a loading dose of 2.5 mg/kg of intravenous tramadol followed by 10 mg (10 mg/ml) of PCA infusion as required. The lockout intervals for both groups were 10 minutes. None of the patients received baseline infusion. In the recovery room, patients were given oxygen via facemask and monitored for pain score according to Modified Pain Score, sedation score

according to Ramsay Sedation Score, respiratory rate, nausea, vomiting, pruritus, blood pressure and pulse rate. Patients were evaluated at the end of 30 minutes in recovery room. After 4 hours, 24 hours and 48 hours post operation, patients were again evaluated in the ward.

Results: Showed no difference in the demographic data between the two groups ($p>0.05$). The mean pain score in tramadol group at 30 minutes, 4 hours, 24 hours and 48 hours post operation were 1.32 ± 0.79, 1.04 ± 0.79, 0.35 ± 0.48 and 0.09 ± 0.33 respectively. Whereas, the mean pain score in morphine group at 30 minutes, 4 hours, 24 hours and 48 hours post operation were 1.35 ± 0.99, 1.14 ± 0.81, 0.40 ± 0.54 and 0.10 ± 0.34 respectively. There were no significant differences in the mean pain score between the two groups at each duration of assessment ($p>0.05$). The mean sedation score in tramadol group at 30 minutes, 4 hours, 24 hours and 48 hours post operation were 0.90 ± 0.74, 0.56 ± 0.59, 0.08 ± 0.27 and 0.02 ± 0.16 respectively. Whereas, the mean sedation score in morphine group at 30 minutes, 4 hours, 24 hours and 48 hours post operation were 0.84 ± 0.70, 0.46 ± 0.64, 0.08 ± 0.27 and 0.01 ± 0.11 respectively. There were no significant differences in the mean sedation score between the two groups at each duration of assessment ($p>0.05$). There were also no significant differences between the two groups in the incidence of nausea, vomiting and pruritus.

Conclusion: This study indicates that PCA tramadol is suitable to be used as an alternative to PCA morphine in controlling pain following major surgery. The incidence of sedation, nausea and pruritus were similar in the two groups.

CHAPTER 1: INTRODUCTION

Postoperative recovery after major surgery depends on various factors, such as adequate pain relief, nausea or vomiting and mobilization. After surgery, 20% – 40% of patients would experience pain of moderate intensity and another would experience severe pain (50% - 70%). A reduction in the surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome. The stress response has been termed "the integrated, adaptive lining web of neuroendocrine, immunologic, and intercellular biochemical signals evoked by tissue injury". The dominant neuroendocrine response to pain involved hypothalamic-pituitary adrenocortical and sympathoadrenal interactions (Miller, R.D., 1999).

As afferent neural stimuli and activation of the autonomic nervous system and other reflexes by pain may serve as major release mechanisms of the endocrine metabolic responses and thus contribute to various organ dysfunctions. Segmental reflex responses associated with surgery include increased skeletal muscle tone and spasm with increases in oxygen consumption and lactic acid production (Miller, R.D., 1999).

Sympathetic activation increases efferent sympathetic tone to all viscera and releases catabolic hormone (catecholamines, cortisol and glucagons) and decreases anabolic hormones (insulin and testosterone) from gland hormones. This causes tachycardia, increased stroke volume, cardiac work and myocardial oxygen consumption. Tone is

decreased in the gastrointestinal and urinary tracts. Pain following major operations or trauma has direct effects on respiratory function. Immobilization or bed rest due to pain in peripheral sites can also indirectly affect respiratory as well as hematologic function. (Morgan, G.E. *et al.*, 1996). Moderate to severe acute pain, regardless of site, can affect nearly every organ function and adversely influence postoperative morbidity and mortality. Pain relief may be a powerful technique to modify surgical stress responses (Kehlet, H. *et al.*, 2001).

Despite advances in the knowledge of acute pain mechanisms and treatment, management of acute pain is often ineffective, especially in general ward. The prospect of moderate or severe pain is a common concern of patients when contemplating major operations. The principal intent of pain control is to substantially reduce or possibly eliminate postoperative pain. Pain may also have other physical as well as psychological sequelae, including impaired respiratory function, long term pain depression, and posttraumatic stress reactions. Major operations are stressful psychological and physiological events, and patient may fell traumatized despite otherwise successful operations (Kehlet, H. *et al.*, 2001).

The purpose of postoperative analgesia is to prevent pain and inhibit the transmission of nociceptive stimuli that leads to stress responses and long term changes in sensory function (Wilder-Smith C. H. *et al*, 1999). Most analgesia trials have focused on the intensity or location of pain, rather than assessing whether improved analgesia can modify the traumatic experience

Prevention of postoperative sensitization has been attempted by various method including oral medication, suppositories, intramuscular, intravenous or regional technique with varying outcome (Wilder-Smith, C.H. *et al.*,1999). More recently, patient satisfaction with opioids has improved with the introduction of PCA system (Chen, P.P. *et al*, 2001).

Tramadol has been used in numbers of European countries for many years and has been approved by the Food and Drug Administration (FDA) in the United States (Miller, R.D., 1999). Tramadol is a weak opioid analgesic, mainly act on μ opioids receptor but also has additional analgesic action through the inhibition of neuronal re-uptake of neurotransmitter 5-hydroxytryptamine and noradrenaline as well as stimulation of the released of 5-hydroxytryptamine. Tramadol has not been associated with clinically significant respiratory depression unlike conventional opioids (Bloch, M.B. *et al*, 2002).

Morphine is the most commonly used opioids analgesic in PCA system. The purpose of this study is to evaluate whether an analgesic dose of tramadol using PCA system is similar to conventional opioids, morphine in terms of effectiveness, sedation and common side effects of opioids such as nausea, vomiting and pruritus.

Another aim of this study is to evaluate the suitability of PCA tramadol as an alternative to PCA morphine in acute pain service (APS) in postoperative patients in Universiti Sains Malaysia Hospital (HUSM).

CHAPTER 2: LITERATURE REVIEW

2.1. TRAMADOL

2.1.1 History

Tramadol was first introduced in 1977 in Germany as a weak opioid analgesic. It is a synthetic opioid of the aminocyclohexanol group. It was believed initially to produce analgesic effect, only via μ-receptor. In the late 1980s, it has been discovered that it has another mode of action due to its low risk of respiratory depression, tolerance and dependence (Langford, R.M. *et al*, 1998). Tramadol inhibits re-uptake of neurotransmitters, serotonin and noradrenaline (Bloch , M.B. *et al*, 2002).

It is a racemic mixture of two sinergestic enantiomers, with (+)-tramadol producing greater serotonin reuptake inhibition, whereas (-)-tramadol inhibits noradrenaline reuptake. The administration of tramadol does not induce histamine release, an important factor in anaphylactoid reactions (Roux, L. *et. al*, 2000).

2.1.2 Classification

Tramadol is a synthetic analgesic of the aminocyclohexanol group with features a centrally acting analgesic drug and opioids like effects (Murphy, D.B., *et al.*, 1997).

2.1.3 Physicochemical characteristics

The chemical designation is (+) trans -2- (dimethyl aminomethyl) - (m - methoxyphenyl) – cyclohexanol – hydrochloride (Roux, L. *et al*, 2000). Tramadol is white, odourless powder that dissolves easily in water or alcohol and available in numerous preparation. It provides central analgesic potency of an opioid but lacks most of the opioids critical and unrelated side effects such as respiratory depression, constipation, abuse, dependence or other opioids related problems (Langford, R.M. *et al*, 1998).

2.1.4 Uses

Tramadol is used for pain relief especially in acute pain service or alternatively in chronic pain since it has opioid analgesia with less opioid side effects such as respiratory depression, tolerance and dependence.

2.1.5. Contraindication

Tramadol is contraindicated in patients with history of allergic to tramadol and allergic to sedative or psychotropic drugs. Those who are receiving MAO inhibitors within 14 days and those with alcohol intoxication are also contraindicated.

2.1.6. Dosage

In clinical practice, the loading dose ranges for IV Tramadol administration in pain control are approximately 1-3 mg/kg (Nagaoka, E. *et al.*, 2002) with maximum dose of 100 mg (Silvasti, M. *et al.*, 2000).

2.1.7. Pharmacokinetics

The analgesic effect of Tramadol HCl is produced by both parent drugs (racemix mixture) and the M1 (mono-o-desmethyltramadol) metabolite. Tramadol is being metabolized by hepatic cytochrome P450 to desmethylated compounds. A major metabolite, (+)-O-desmethyl tramadol is responsible for the weak μ-opioid agonist effect and requires sparteine oxygenase enzyme for its formation. (Roux, L. *et al*, 2000)

This sparteine oxygenase enzyme is deficient in up to 7% of Caucasian individuals, leading to the reduced formation of (+)-O-desmethyl Tramadol and reduced analgesic effect in these 'poor metabolizers'(Roux, L. *et al*, 2000). The CYP2D6*10 allele which is particularly associated with these enzyme is common in Asian people (Gan, S.H., *et al*, 2002).

When administered orally, tramadol is rapidly absorbed (Kaye, K., 1998) and reaches peak effect after 2-3 hours. Peak plasma level is achieved in 1 hour (Roux, L. *et al*, 2000). When administered intravenously, the onset of action is within 7 minutes and reaches peak plasma level in 25 minutes (Roux, L. *et al*, 2000). The bioavailability is 73-79%. Tramadol is 20%

protein bound and crosses placenta and blood-brain barrier. The plasma clearance is 6.4 ml/min/kg with 30% excreted unchanged and 60% excreted as metabolite. The volume of distribution (V_D) is 2.6 – 2.9 L/kg and the half-life is about 7 hours (Lehmann, K.A. *et al.*, 1994).

2.1.8. Pharmacodynamics

Initially, it was believed that tramadol produces opioid analgesia only via μ-receptor. The opioid activity of this drug is produced by both low affinity binding of the parent compound and higher affinity binding of the O-demethylated metabolite M1 to μ-receptor. M1 is 6 times more potent than the parent drug. In late 1980s, another mode of action has been discovered due to its low risk of respiratory depression, tolerance and dependence (Roux. L. *et al*, 2000).

It was found that tramadol inhibits the re-uptake of neurotransmitters, serotonin and noradrenaline. It is a racemic mixture of two sinergestic enantiomers, with (+)-tramadol producing greater serotonin reuptake inhibition, whereas (-)-tramadol inhibits noradrenaline reuptake. The analgesic effect of tramadol begins approximately within 7 minutes after intravenous administration (Roux, L. *et al*, 2000). In contrast to morphine, tramadol has not been shown to cause histamine release. At therapeutic doses, tramadol has no effect on heart rate, left – ventricular function or cardiac index (Roux, L. *et al*, 2000).

2.1.8 (a) Central Nervous System

Tramadol causes anxiety, confusion, dizziness, headache, tremor, ataxia, hypertonia, paraesthesia, stupor, migraine and convulsion. Virtually, tramadol has no dependence potential (Vickers, M.D. *et al.*, 1992).

2.1.8 (b) Cardiovascular System

Tramadol can cause hypertension, vasodilatation, syncope, orthostatic hypotension (1%), tachycardia (<1%), abnormal ECG and palpitation.

2.1.8 (c) Gastrointestinal System

Abdominal pain, constipation, diarrhoea, dry mouth, nausea and vomiting may occur.

2.1.8 (d) Respiratory system

In high doses, it can cause dyspnoea. At an equi-analgesic dose, tramadol has much less effect on the respiratory centre than morphine. Thus, it has a higher therapeutic ratio with transient effects on respiratory system (Vickers, M.D. *et al*, 1992).

2.1.8 (e) Skin

Rarely, tramadol can cause vasodilatation and urticaria (< 1%)

2.1.8 (f) Genitourinary System

Albuminuria, micturation disorder, oliguria, urinary retention may occur.

2.1.8 (g) **Special Senses**

Visual disturbances (1%), tinnitus and deafness are rare.

2.1.8 (h) **Miscellaneus**

Some patients may develop hypertonia (1%).

2.1.9. Overdosage

The effects of tramadol overdosage are typical as the overdosage of other opioid analgesics such as miosis, vomiting, cardiovascular collapse, sedation, coma, respiratory depression and/or seizures (Roux. L. *et al*, 2000).

2.1.10. Interactions

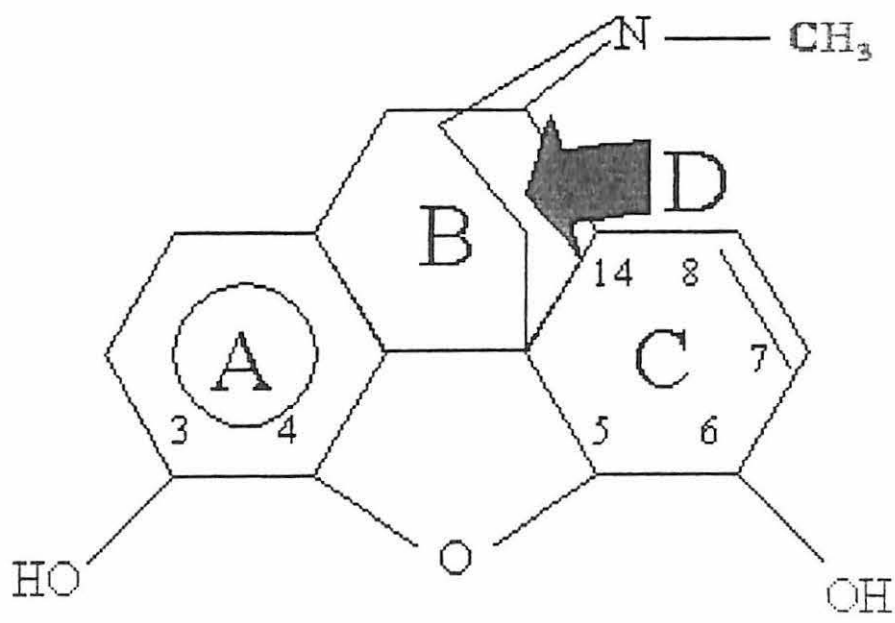
Drugs that inhibit or induce P-450 enzymes can influence the effects of tramadol. Interactions have previously been reported with carbamazepine, cimetidine and quinidine. Patients receiving monoamine oxidase inhibitors are at risk of hypertensive crisis. Tramadol is probably safe to be used in conjunction with anticoagulant therapy (Roux. L. *et al*, 2000).

2.1 MORPHINE

2.2.1 History

Morphine is a prototype opioid agonist to which all other opioids are compared. It is a pure opioid agonist and tertiary amine being isolated from poppy plant in 1805 by Serturner. It acts on the μ & κ receptor. Morphine is a weak base, water soluble in vitro but become poorly lipid soluble in vivo (Stoelting, R.K., 1999).

Figure 2.1: Chemical Structure of Morphine



Morphine

2.2.2. Physical properties

Morphine is available in the form of aqueous morphine sulphate with pKa of 7.9 (basic).

2.2.3 Clinical uses

Morphine can be used as:

1. Analgesic with various method administration including parenteral, intrathecal, and epidural.
2. Supportive treatment for pulmonary oedema.
3. Premedication for surgery.
4. Induction agent for general anaesthesia.
5. Brief relieve of anxiety in serious and frightening disease accompanied by pain such as trauma.

2.2.4 Contraindication

Morphine is contraindicated in patients with asthma, elderly, high intracranial pressure, hypovolaemia, liver and kidney disease and neonates.

2.2.5 Dosage

The intravenous dosage of morphine in an adult is 0.l0mg/kg. When high dose anaesthesia is required, the intravenous dose is 0.5-3 mg/kg. It can cause respiratory depression within

7 minutes if administered intravenously and 30 minutes if administered intramuscularly (Stoelting, R.K., 1999).

2.2.6 Pharmacokinetics

Oral morphine is subject to extensive presystemic or first-pass metabolism and only about 20% of a dose reaches the systemic circulation (Laurence, D.R. *et al*, 1997). Thus, absorption from the gastrointestinal tract is not reliable. Morphine is usually administered intravenously, thus eliminating the unpredictable influence of drug absorption (Stoelting, R.K., 1999). The onset of action is within 10 minutes (Miller, R.D., 1999) and the peak effect after IV administration of morphine requires about 45 minutes. The half-life is about 6 hours. Morphine is 20-35% protein bound. The plasma clearance is 15 ml/min/kg (Miller, R.D., 1999) with 3-4 L/kg volume distribution (V_D) (Stoelting, R.K., 1999). Morphine also crosses the placental membrane and has been found in breast milk.

Morphine is metabolized by both liver and kidney. The conjugated metabolites include morphine-3-glucoruonide, morphine-6-glucuronide (more potent than morphine) and some sulphate (Stoelting, R.K., 1999). Morphine is mainly excreted as morphine-3-glucoronide (M3G) and 10% is excreted unchanged in the urine (Laurence, D.R.*et al*., 1997). A small amount of the glucoronide conjugate is excreted in the bile and 7-10% is excreted in the feces. 90% of excretion occurs in the first 24 hours while the rest is excreted within 48 hours (Stoelting, R.K., 1999).

2.2.7 Pharmacodynamics

Morphine produces its analgesic effects via stereospecific opioid receptors at presynaptic and postsynaptic sites in the central nervous system (principally the brainstem and spinal cord) and outside the central nervous system in peripheral tissue. The mechanism of its analgesic effect is due to μ agonist action.

2.2.7 (a) Central Nervous System

Morphine exerts its potent analgesic properties through its effects on μ_1 (suprespinal and spinal analgesia) receptor and μ_2 (spinal analgesia) receptor causing selective to dull pain and reduce affective response. μ_2 receptors are responsible for hypoventilation, bradycardia, constipation and physical dependence (Stoelting, R.K., 1999). The therapeutic effects of morphine include euphoria, anxiolysis and feelings of relaxation. Morphine causes respiratory depression, in part by a direct effect on the brain stem respiratory centers. Morphine depressed the cough reflex by direct effect on the cough center in the medulla. Other effects of morphine include sedation, increases intracranial pressure (ICP) and decreases cerebral blood flow (CBF). The EEG will show an increased voltage and lowered frequency of wave form pattern (Stoelting, R.K., 1999).

2.2.7 (b) Cardiovascular System

In therapeutic doses, morphine does not usually exert major effects on cardiovascular system. If given in large doses, morphine can decrease blood pressure, decrease heart rate and cause peripheral vasodilatation. The decrease in systemic vascular resistance leads to a decrease in blood pressure. Postural hypotension resulted from peripheral vasodilatation and venous pooling (decrease venous return). The reduction in left ventricular end diastolic (LVED) pressure occurs as a result of dilatation of venous capacitance vessel. Sinus bradycardia may occur due to central vagal stimulation. The release of histamine, centrally mediated parasympathetic pathway, vagal induced bradycardia, direct and indirect venous and arterial vasodilatation and splanchnic sequestration of blood (Stoelting, R.K., 1999).

2.2.7 (c) Gastrointestinal System

Morphine can cause a decrease in prepulsive activity and increase in smooth muscle tone in anal and ileocolic sphincter. The resultant prolongation in gastrointestinal transit time is responsible for the constipating effect of morphine. The lower oesophageal sphincter pressure is decreased, the oesophageal reflux is increased and the hydrochloric acid (HCl) secretion is decreased by morphine (Stoelting, R.K., 1999).

2.2.7 (d) Respiratory system

Bronchoconstriction may occur due to the released of histamine. The respiratory center is depressed due to decrease sensitivity of brainstem respiratory center to $PaC0_2$ leading to periodic breathing and apnoea. 10 mg of intravenous morphine will decrease tidal volume,

respiratory rate and resting $PaC0_2$ to 3 mmHg in a normal subject. In large doses (2mg/kg), it will depress the minute ventilation and increase $ETC0_2$. Morphine also produces dose-dependent depression of ciliary activity in the airways (Stoelting, R.K., 1999).

2.2.7 (e) Skin

Morphine can cause vasodilatation.

2.2.7 (f) Uterus

Morphine crosses placenta and may result in direct depression on the uterus contraction in large doses. It can also cause muscle rigidity.

2.2.7 (g) Genitourinary System

Morphine can increase the ureteric tone, causing contraction of dextrusor and vesicular muscle that may lead to the difficulty in micturition. It also has an antidiuretic effect.

2.2.8 Overdosage

The adverse effects of morphine include miosis, respiratory depression, euphoria and dependence. Rarely, morphine causes muscle rigidity. Overdosage of morphine resulted in marked miosis, asphyxia, severe hypoxaemia and convulsion (Stoelting, R.K., 1999).

2.2.9 Interaction

The ventilatory effect of morphine may be exaggerated by amphetamine, phenothiazine, monoamine oxidase inhibitor and tricyclic anti depressants. This exaggerated response may reflex alteration in the rate or metabolism pathway of the opioid. Sympathomimetic drugs appear to enhance analgesia produced by opioids (Stoelting, R.K., 1999).

2.3 PAIN

"An unpleasant sensory and emotional experience usually associated with actual or potential tissue damage, or described in terms of such damage" (The International Association for the Study of Pain, 1986). Pain is mainly a protective mechanism that occurs when tissues are being damaged. It is an unpleasant sensation and need to be relieved (Stoelting, R.K., 1999).

2.3.1. The importance of pain management

1. Allow early mobilization and early discharge.
2. Reduce hospitalization and nursing care which later will reduce the cost.
3. Promote healing and improve perfusion.
4. Easy pain control by the patient.
5. Reduce personal anxiety especially for the children due to bad experience.
6. Reduce postoperative complication.

(Hutton, P. *et al.*, 2002)

2.3.2. Pain Pathways

Surgery produces local tissue damage with consequence release of inflammatory mediators (prostaglandin, histamine, serotonin, bradykinin, 5-hydroxytriptamine, substance P) and generation of noxious stimuli by A delta and C nerve fiber to the neuroaxis (Miller, R.D., 1999).

2.3.3. First Order Neurons

The first order neurons, send their axon to spinal cord via the dorsal (sensory) spinal root at each cervical, thoracic and sacral level. Some unmyelinated afferent (C) fibers enter the spinal cord via the ventral nerve nerve (Motor) root. In dorsal horn, in addition to synapsing with second order neurons, the axons of first order neuron may synapse with interneurons and ventral horn motor neurons. Pain fibers from head are carried by V, VII, IX and X nerve (Morgan, G.E. *et al.*, 2002).

2.3.4. Second Order Neurons

The second order neurons, segregated according to size, with large, myelinated fibers becoming medial and small, unmyelinated fibers becoming lateral (Morgan, G.E. *et al.*, 2002).

2.3.4 (a) The Spinothalamic Tract

The axon of most second order neurons cross the midline to the contralateral side of the spinal cord before they form the spinothalamic tract and send their fibers to the thalamus, reticular formation, the nucleus raphe magnus and periaqueductal gray. The lateral spinothalamic (Neospinothalamic) tract projects mainly to the ventral posterolateral nucleus of the thalamus that give rise to discriminative pain such as location, intensity and duration of pain.

FAST PAIN (NEOSPINOTHALAMIC):

- Sharp pain, pricking , electric
- Felt within 0.1 sec after stimulation
- Transmitted through A delta fiber at 6-30 m/sec
- Involvement of second order neuron
- Terminated in thalamus-sensory cortex

(Stoelting, R.K., 1999)

The medial spinothalmic (Paleospinothalamic) tract projects to the medial thalamus and give rise to autonomic and unpleasant emotional perceptions of pain (Morgan, G.E. *et al.*, 2002).

SLOW PAIN (PALEOSPINOTHALAMIC):

- Burning, aching, throbbing, chronic
- Begins only after 1 sec or more and sometime even minute
- Widespread in the whole body except brain and spinal cord
- Transmitted through C fiber at 0.5 – 2 m/s
- More than two neurons involved
- Widely terminated in brain stem
- Only 1/10-1/4 sensory cortex involved
- Poorly localized

(Stoelting, R.K., 1999)

2.3.4 (b) The Alternative Pain Pathways

As with epicritic sensation, pain fibers ascend diffusely, ipsilaterally and contralaterally. Hence, some patients can still complaint of pain in spite of ablation of the contralateral spinothalamic tract.

2.3.5. Third Order Neurons

The third order neurons are located in the thalamus and send fibers to somatosensory areas I and II in the post-central gyrus of the parietal cortex and the superior wall of the sylvian fissure. Perception and discrete localization of pain take place in these cortical areas.

2.3.6. Pain stimulus

Pain can be stimulated by various means which include:

- Mechanical
- Thermal
- Chemical

2.3.6 (a) Cerebral Sensory Cortex

The function of cerebral sensory cortex is only to interpret pain. The pain can still persist even after complete removal of this cerebral sensory cortex.

2.3.6 (b) Pain Suppression (Analgesia)

Pain suppression is mediated through opioid receptors. The opioid receptors involved include mu, kappa, delta and gamma. Natural pain suppression in the body are provided by enkephalin, dynorphin and endorphin.

2.3.6 (c) Spinal Cord and Higher Centre

Areas that involved in the regulation of pain are hypothalamus, pituitary, brain stem and multiple areas in the brain.

2.3.7. Pain Sensation

Pain measurement is very subjective and varies greatly from patient to patient. Various methods have been suggested to grade it because pain is complex perceptual experience that can only be quantified indirectly (Stoelting, R.K., 1999).

Since pain has been operationalized in different ways in animal, human laboratory and clinical arenas of investigation has been vary limited. Measurement of pain in diseases should not be confused with measurement of experimental pain (Huskisson, E.C., 1974).

The physical pathology is only one contribution to the experience of pain. Pain is influenced by multiple factors such as cultural conditioning, expectations, social contingencies, mood state and perceptions of control (Turk, D.C., 1993).

It is easier to study experimental pain because it can be measured in terms of the intensity of the stimulus. In case of pathological pain the nature of the stimulus is often unknown, its intensity is usually difficult to measure, and severity of the disease is not clearly related to pain because pain is modified by such factors as the individual patient's pain threshold (Huskisson, E.C., 1974).

In all types of pain, accurate assessment is required to appropriately treat the patient. Unfortunately, the problem is not this simple because there is no direct relationship between physical pathology and the integrity of pain. Pain is a subjective experience and there is no way to objectively quantify it (Turk, D.C., 1993).

2.3.8 Pain scoring system

Various methods have been suggested to grade pain. They include:

- Verbal Numerical Pain Score
- Visual Analogue Score (VAS)
- Functional Score
- Observational Pain Score

2.3.8 (a) Verbal Numerical Pain Score

Patient is asked to give a score of 0 to 10 by which:

0 = no pain at all

10 = worst pain imaginable

In this study we used modified Verbal Numerical Score by using the number 0 to 4. The pain score is given as below:

0 = No Pain

1 = Slight Pain

2 = Tolerable Pain

3 = Bad Pain

4 = Worst Pain

This Modified Pain Score is a simple way, easy for patient to understand and response but may be less sensitive.

2.3.8 (b) Visual Analogue Score (VAS)

Some of the problems with the simple descriptive pain scale can be overcome by using either a visual analogue scale stretching from "no pain" to "pain as bad as it could be" (Huskisson, E.C., 1974). With the graphic rating method the intervals between the descriptive terms must usually be assessed, though it is possible to alter them to correct the abnormal distribution of results that may arise (Chapman, C.R. *et al.*, 1985). This rating scale can be used quickly with minimal instructions to subjects and scored easily.

Because of broad range of psychological experience is compressed into an artificially small continuum, subjects tend to spread responses over the entire scale regardless of the magnitude of the actual sensation (Chapman, C.R. *et al.*, 1985).

Patient is asked to indicate the intensity of pain by marking a 10cm line that labeled " no pain" at one end and "pain as bad as it could be" at the other end (Huskisson, E.C., 1974).