EFFECT IN COMPARISON BETWEEN INTRATHECAL DEXMEDETOMIDINE AND INTRATHECAL FENTANYL ADDED TO BUPIVACAINE IN LOWER LIMB ORTHOPAEDIC SURGERIES

BY

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TABLE OF CONTENTS

CHAPTER 4: METHODOLOGY

CHAPTER 5: RESULTS

LIST OF ABBREVIATIONS

CSF	Cerebrospinal Fluid
CNS	Central Nervous System
LA	Local Anaesthetics
S2	Second sacral vertebrae
BMI	Body Mass Index
FDA	Food and Drug Administration
ICU	Intensive Care Unit
IASP	International Association for the Study of Pain
EAA	Excitatory Amino Acid
NS	Nociceptive specific
WDR	Wide dynamic range
NK	Neurokinin (peptide)
NMDA	N Methyl D Aspartate
AMPA	Alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
SG	Substantia Gelatinosa
POMC	Proopiomelanocortin
Ca^{2+}	Calcium
PAG	Periaqueductal gray
NRM	Nucleus Raphe Magnus
DR	Dorsal Raphe
CN	Caudate Nucleus
Rgc	Reticularisgigantocellularis
GABA	Gamma Amino Butyric acid
cAMP	Cyclic adenosine monophosphate
ACTH	Adrenocorticotrophic Hormone
PACU	Postanaesthesia Care Unit

LIST OF ABBREVIATIONS; continued

VAS	Visual Analog scale
HR	Heart Rate
MAP	Mean Arterial Pressure
Mg	Magnesium

LIST OF FIGURES PAGE

LIST OF FIGURES; continued

LIST OF TABLES PAGE

ABSTRAK

KAJIAN KE ATAS KESAN DEXMEDETOMIDINE DAN FENTANYL DITAMBAH KEPADA BUPIVACAINE UNTUK BIUS SEPARUH BADAN UNTUK PEMBEDAHAN ORTOPEDIK DI BAHAGIAN KAKI

Pengenalan: Kami menyelidik kesan penambahan dexmedetomidine jika dibandingkan dengan fentanyl dalam bius separuh badan dalam mempercepatkan permulaan bius, memanjangkan kesan bius dan mengurangkan penggunaan ubat tahan sakit yang lain selepas pembedahan.

Objektif: Ini adalah kajian prospektif secara rawak di mana kami meletakkan pesakit dalam salah satu kumpulan yang menerima dexmedetomidine atau fentanyl. Pesakit tidak mengetahui samada mereka menerima dexmedetomidine atau fentanyl. Kami menyelidik samada penambahan dexmedetomidine dengan bupivacaine untuk bius separuh badan dapat mempercepatkan permulaan bius, memanjangkan kesan bius, mempunyai kesan buruk yang rendah dan mengurangkan penggunaan ubat tahan sakit selepas pembedahan. Kajian ini dijalankan di Hospital Universiti Sains Malaysia, Kelantan.

Kaedah kajian: : Seramai 64 pesakit dibahagikan secara rawak untuk menerima dexmedetomidine atau fentanyl ditambah dengan bupivacaine untuk bius separuh badan. Kami mengumpul maklumat mengenai masa permulaaan kesan ubat bius keatas kekebasan sehingga T10 dan tiada pergerakan kaki, masa mulanya kekebasan kulit hilang dan adanya pergerakan kaki, kesan buruk seperti loya, muntah, gatal gatal badan, tekanan darah dan degupan jantung rendah serta masa pesakit meminta ubat tahan sakit selepas pembedahan. Kami juga mencatatkan jumlah ubat voltaren yang diminta dalam

24 jam pertama. Penilaian data ini dibuat oleh kakitangan bius yang tidak mengetahui jika pesakit menerima dexmedetomidine atau fentanyl.

Keputusan: Kami mendapati pesakit yang menerima dexmedetomidine mempunyai min masa lebih lama untuk permintaan ubat tahan sakit voltaren iaitu 8.84±0.57 (jam) berbanding fentanyl 7.53±0.57 (jam) ($p<0.001$). Min penggunaan ubat voltaren dalam 24 jam didapati signifikan lebih rendah 51.56±8.84 mg untuk kumpulan dexmedetomidine ($p<0.001$) berbanding fentanyl 92.19±36.17 mg. Bius separuh badan didapati bermula lebih cepat iaitu 2.88±0.71 minit dan lebih lama tempoh bius iaitu 323.75±20.28 minit untuk kumpulan dexmedetomidine secara signifikan($p<0.001$) berbanding fentanyl iaitu hanya 5.09±1.35 minit untuk bermulanya bius dan bertahan selama hanya 256.56±33.76 minit. Didapati tiada perbezaan diantara kedua-dua ubat kajian tersebut dalan kesan sampingannya.

Kesimpulan: Kajian ini mendapati bahawa dengan penggunaan dexmedetomidine untuk tambahan kepada bupivacaine untuk bius separuh badan dapat mempercepatkan permulaan bius, tahan lebih lama dan mengurangkan penggunaan ubat tahan sakit selepas pembedahan terdapat pengurangan ketara dalam skor kesakitan sehingga 2 jam selepas pembedahan ortopedik bahagian kaki.

Kata kunci: dexmedetomidine, ubat bius separuh badan, fentanyl, bupivacaine, pembedahan ortopedik bahagian kaki

ABSTRACT

EFFECT IN COMPARISON BETWEEN INTRATHECAL DEXMEDETOMIDINE AND INTRATHECAL FENTANYL ADDED TO BUPIVACAINE IN LOWER LIMB ORTHOPAEDIC SURGERIES

Introduction: Various adjuvants have been used with local anaesthetics in spinal anaesthesia to avoid intraoperative visceral and somatic pain and to provide prolonged postoperative analgesia. Dexmedetomidine, the new highly selective α2-agonist drug, is now being used as a neuraxial adjuvant.

Objectives: The purpose of this study was to evaluate the onset and duration of sensory and motor block as well as postoperative analgesia and adverse effects of dexmedetomidine or fentanyl given intrathecally with hyperbaric 0.5% bupivacaine for spinal anaesthesia in lower limb orthopaedic surgeries. This study was conducted in Hospital Universiti Sains Malaysia, Kelantan.

Methodology: Sixty four patients classified as American Society of Anesthesiologists (ASA) status I and II scheduled for lower limb orthopaedic surgeries were prospectively studied. Patients were randomly allocated to receive intrathecally either 2.5 mls hyperbaric 0.5% bupivacaine plus 5 µg dexmetedomidine (n=32) or 2.5 mls hyperbaric 0.5% bupivacaine plus 25 mg fentanyl (n = 32), the onset time to reach peak sensory and motor level, the regression time for sensory and motor block, haemodynamic changes, postoperative time to rescue analgesia with total dosage of voltaren in first 24 hours and side effects were recorded by an anaesthetist colleague blinded to the groups.

Results: Patients in the dexmedetomidine group had a significantly longer sensory and motor block time than patients in fentanyl group. The mean time of sensory regression to S1 was 323.75±20.28 min in dexmedetomidine group and 256.56±33.76 min in fentanyl group (P<0.001). The mean regression time of motor block to reach modified Bromage 0 was 271.56±24.64 min in dexmedetomidine group and 202.81±44.09 min in fentanyl group (P<0.001). Postoperative analgesic requirements were less and time to rescue analgesia were prolonged in dexmedetomidine group compared to fentanyl. Mean time to rescue analgesia was 8.84±0.57 minute in dexmedetomidine group compared to 7.53±0.57 minutes in fentanyl group (p<0.001). There were no significant difference in the adverse effect of both the drugs.

Conclusions: Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, haemodynamic stability, and reduced demand for rescue analgesics in 24 h as compared to fentanyl.

Keywords: Bupivacaine, dexmedetomidine, fentanyl, spinal anaesthesia

CHAPTER 1

INTRODUCTION

1.1 Adjuvant drugs

Adjuvant drugs are pharmacological agents possessing little pharmacological effect by themselves and enhance or potentiate the action of other drugs when given at the same time. Neuraxial drug administration describes the technique of delivering analgesics and adjuvant drugs in close proximity to the spinal cord either intrathecally into cerebrospinal fluid (CSF) or epidurally into the epidural space.

Drugs deposited into CSF or epidural space traverses different meningeal layers to gain access to receptors located in the spinal cord gray matter. Drugs absorbed by the systemic circulation also reach the central nervous system (CNS) to produce its effects (Bakshi, Chatterjee et al. 1984).

Neuraxial analgesia is achieved in the perioperative period with local anaesthetic (LA) drugs. Adjuvant drugs modify LA effects and reduce side effects. Perioperatively these drugs affect:

1. Latency i.e. time of onset of LA block
2. Duration of analgesia i.e. duration of sensory and motor block
3. Quality of analgesia i.e. complete, incomplete (partial or patchy analgesia requiring supplemental drugs)

Postoperatively adjuvant drugs affect:

1. Analgesic gap i.e. time interval between subsequent doses administered

2. Quality of analgesia i.e. patient satisfaction of pain relief

3. Side effects i.e. reduction of untoward effects of LA drugs

Neuraxial anaesthesia and analgesia provide solid analgesic effect by inhibiting nociceptive transmission from peripheral to central neuronal system (Wu, Wang et al, 2014). However, their analgesic advantages might be limited by the short life of current local anaesthetics (LAs), and, especially, be weakened during postoperative pain control. The analgesic duration can be prolonged by increasing the dose of LA, with accompanied increased risk of systemic and potential neurotoxicity.

Therefore, adjunct analgesic strategy is an alternative to prolong duration of analgesia and decrease the potential risk of side effects by reducing the dose of individual LA. Several neuraxial adjuvants, including clonidine, dexmedetomidine, opioids, dexamethasone, ketamine, magnesium and midazolam have demonstrated the synergistic analgesic effect with LAs with varying degrees of success.

Knowledge and use of adjuvant drug therapy has rendered neuraxial analgesia more effective in the management of both acute and chronic pain conditions.

1.2 Subarachnoid block

The use of subarachnoid block has become an established and reliable method of providing anaesthesia for lower abdominal and lower limb surgery. Even though present with the risk of paralysis, subarachnoid block still remains a very effective and safe anaesthetic technique for lower abdominal and lower limb surgery. This technique is affordable and effort should be made to increase patient awareness and its acceptability in the new millennium.

Spinal anaesthesia has progressed greatly since 1885 and is used successfully in a number of different clinical situations. However, anatomy, choice of local anaesthetic, physiologic effects of spinal anaesthesia, patient positioning, and the approach to spinal anaesthesia procedure must all be considered. The patient should be aware regarding the possible side effects and complications that can occur from performing a spinal anaesthetic in order to obtain informed consent before the procedure. If all of these factors are conducive for the patient to receive a spinal anaesthetic, care must be taken to prevent complications. Learning how to perform spinal anaesthesia is an invaluable skill that all anaesthesiologists should have in their armamentarium.

There are absolute and relative contraindications to spinal anaesthesia. The absolute contraindications includes patient refusal, infection at site of injection, hypovolaemia, indeterminate neurologic disease, coagulopathy and increased intracranial pressure. Relative contraindications include sepsis distinct from the anatomic site of puncture (e.g., chorioamnionitis or lower extremity infection) and unexpected prolonged duration of surgery. In the latter case, if the patient is on antibiotics and the vital signs are stable, spinal anaesthesia may be considered.

In reviewing the functional anatomy of spinal anaesthesia, an intimate knowledge of the spinal column, spinal cord, and spinal nerves must be present. This chapter reviews briefly the curves of the vertebral column, the ligaments of the spinal column, membranes and length of the spinal cord, and passage of the spinal nerves from the spinal cord.

The vertebral column consists of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 4 coccygeal segments. The vertebral column usually contains three curves. The cervical and lumbar curves are convex anteriorly, and the thoracic curve is convex posteriorly. The vertebral column curves, along with gravity, baricity of local anaesthetic, and patient position, influence the spread of local anaesthetics in the subarachnoid space.

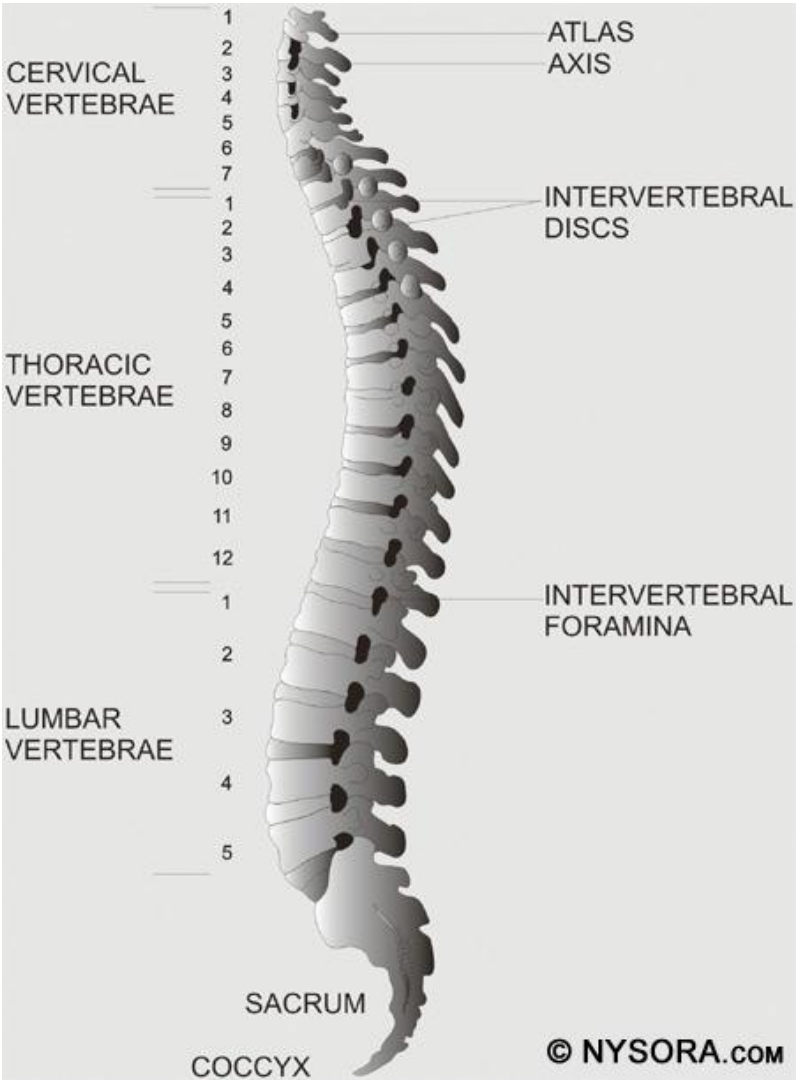

Figure 1.1: The spinal column is seen from a lateral view. All of the vertebrae, intervertebral discs, and intervertebral foraminae are shown.

Five ligaments hold the spinal column together. The supraspinous ligaments connect the apices of the spinous processes from the seventh cervical vertebra (C7) to the sacrum. The supraspinous ligament is known as the ligamentum nuchae in the area above C7. The interspinous ligaments connect the spinous processes together. The ligamentumflavum, or yellow ligament, connects the laminae above and below together. Finally, the posterior and anterior longitudinal ligaments bind the vertebral bodies together.

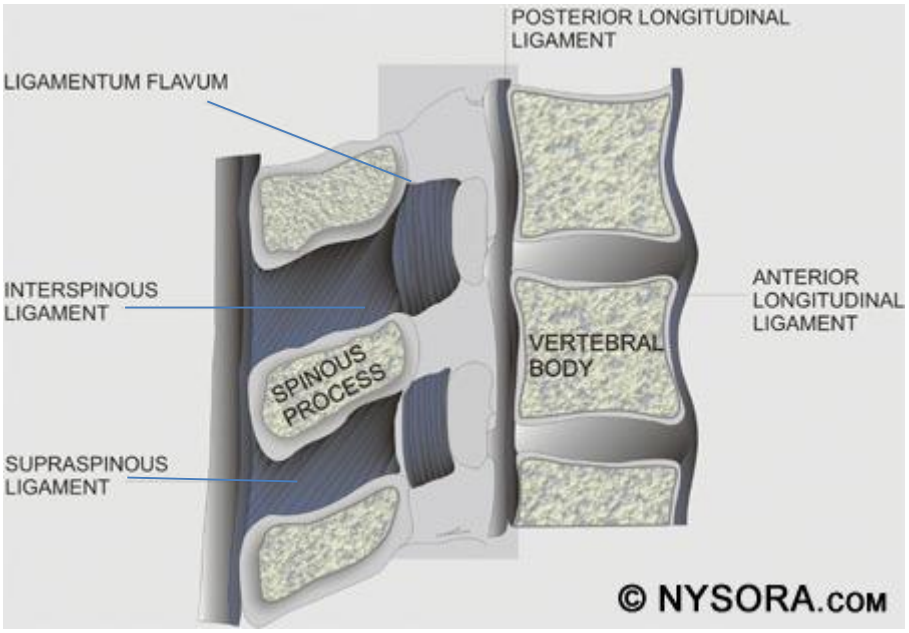

Figure 1.2: A cross section of the spinal canal is shown with the ligaments, vertebral body, and spinous processes.

The three membranes that protect the spinal cord are the dura mater, arachnoid mater, and pia mater. The dura mater, or tough mother, is the outermost layer. The dural sac extends to the second sacral vertebra (S2). The arachnoid mater is the middle layer, and the subdural space lies between the dural mater and arachnoid mater. The arachnoid mater, or cobweb mother, also ends at S2, like the dural sac. The pia mater, or soft mother, clings to the surface of the spinal cord and ends in the filumterminale, which helps to hold the spinal cord to the sacrum. The space between the arachnoid and pia mater is known as the subarachnoid space, and spinal nerves run in this space, as does CSF.

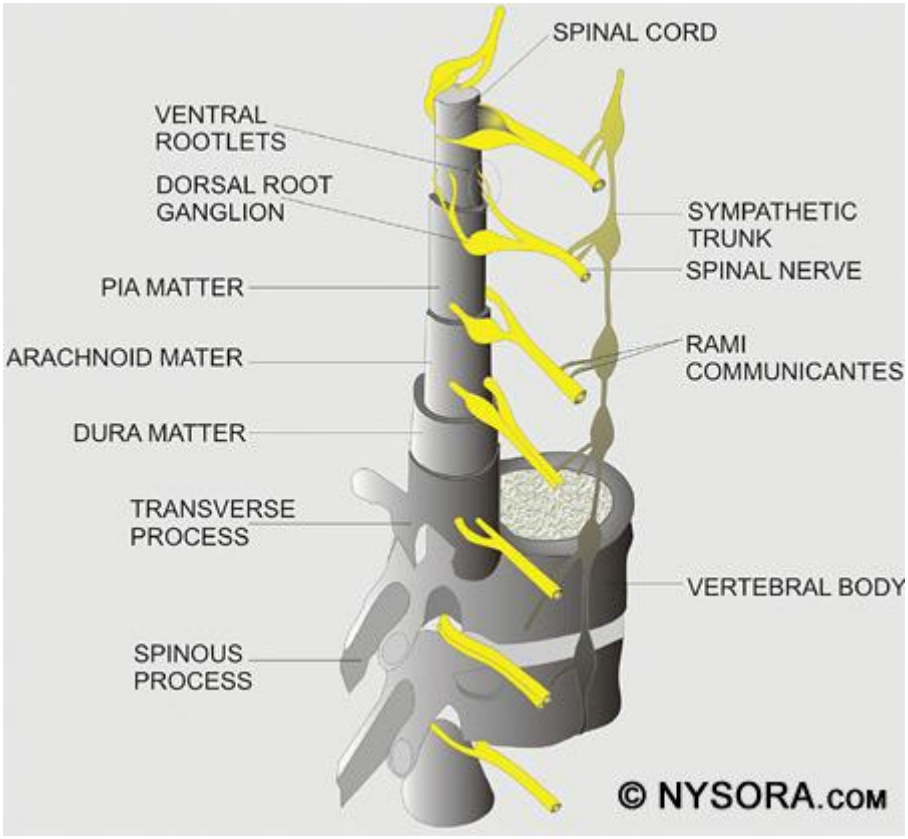

Figure 1.3: The spinal cord is shown along with the dorsal root ganglia and ventral rootlets, spinal nerves, sympathetic trunk, rami communicantes, and pia, arachnoid, and dura mater.

When performing a spinal anaesthetic using the midline approach, the layers of anatomy that are traversed (from posterior to anterior) are skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum, dura mater, subdural space, arachnoid mater, and finally the subarachnoid space.

When the paramedian technique is applied, the spinal needle should traverse the skin, subcutaneous fat, ligamentum flavum, dura mater, subdural space, arachnoid mater, and then pass into the subarachnoid space.The spinal nerve roots and spinal cord serve as the target sites for spinal anaesthesia.

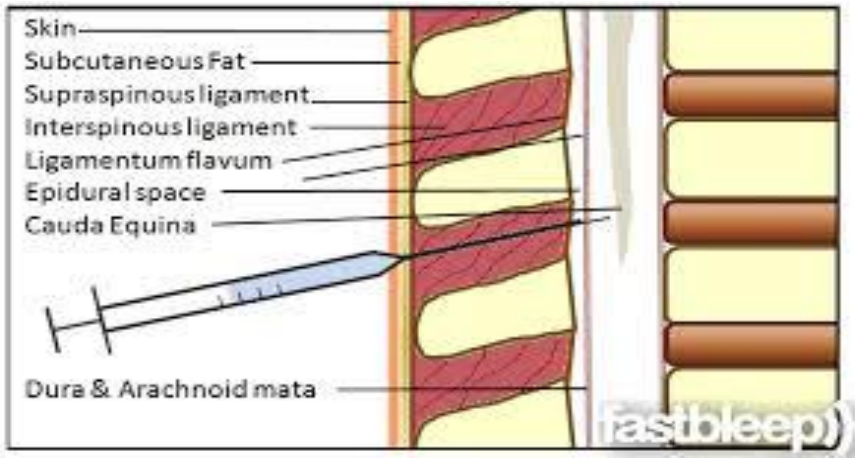

Figure 1.4: The layers that are passed through during insertion of spinal needle

When preparing for spinal anaesthetic blockade, it is important to find landmarks on the patient. The iliac crests usually mark the interspace between the fourth and fifth lumbar vertebrae, and a line can be drawn between them to help locate this interspace. Care must be taken to feel for the soft area between the spinous processes to locate the interspace. Depending on the level of anaesthesia necessary for the surgery and the ability to feel for the interspace, the L3-4 interspace or the L4-5 interspace can be used to introduce the spinal needle. Because the spinal cord ends at the L1 to L2 level, it would not be wise to attempt spinal anaesthesia at or above this level.

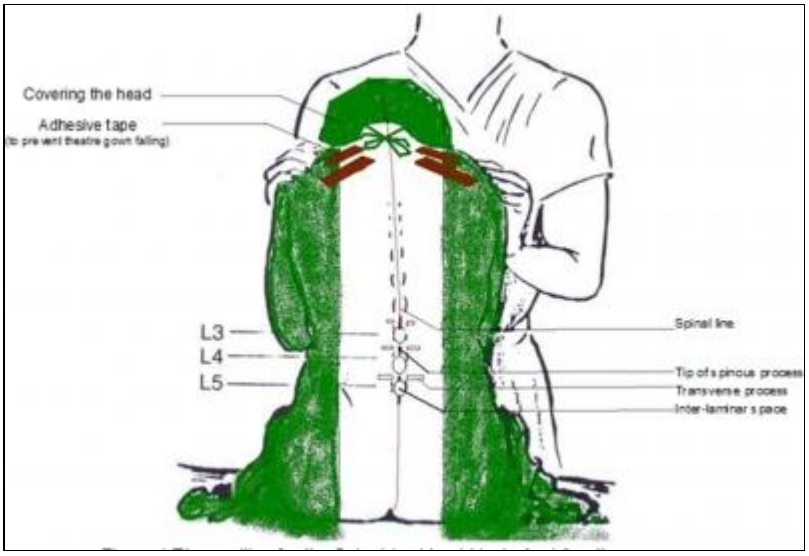

Figure 1.5: Correct positioning of patient during spinal anaesthesia

Table 1.1: Clinical Pearls of spinal anaesthesia:
The tenth thoracic (T10) dermatome corresponds to the umbilicus.
The sixth thoracic (T6) dermatome corresponds to the xiphoid.
The fourth thoracic (T4) dermatome corresponds to the nipples.

It would be incomplete to discuss surface anatomy without mentioning the dermatomes that are important for spinal anaesthesia. A dermatome is an area of skin innervated by sensory fibres from a single spinal nerve. The tenth thoracic (T10) dermatome corresponds to the umbilicus, the sixth thoracic (T6) dermatome the xiphoid, and the fourth thoracic (T4) dermatome the nipples. Figure 1.5 illustrates the dermatomes of the human body. To achieve surgical anaesthesia for a given procedure, the extent of spinal anaesthesia must reach a certain dermatomal level. Dermatomal levels of spinal anaesthesia for common surgical procedures are listed in Table 1.2.

Figure 1.6: The dermatomes of the human body

Table 1.2: Dermatomal Levels of Spinal Anaesthesia for Common Surgical Procedures

PROCEDURE	**DERMATOMAL LEVEL**
Upper abdominal surgery	T4
Intestinal, gynaecologic and urologic surgery	T6
Transurethral resection of the prostate	
Vaginal delivery of a fetus, and hip surgery	T10
Thigh surgery and lower leg amputations	L1
Foot and ankle surgery	L2
Perineal and anal surgery	S2-S5 (saddle block)

1.3 Local Anaesthetics

The choice of local anaesthetic is based on potency, onset, duration of anaesthesia, and side effects of the drug. Two distinct groups of local anaesthetics are used in spinal anaesthesia, esters and amides, which are characterized by the bond that connects the aromatic portion and the intermediate chain.

Esters contain an ester link between the aromatic portion and the intermediate chain, and this includes drugs like procaine, chloroprocaine, and tetracaine. Amide groups contain an amide link between the aromatic portion and the intermediate chain, and this includes bupivacaine, ropivacaine, etidocaine, lidocaine, mepivacaine, and prilocaine. The drug metabolism is important in determining the activity of local anaesthetics, lipid solubility, protein binding, and pKa.

Lipid solubility relates to the potency of local anaesthetics. Low lipid solubility indicates that higher concentrations of local anaesthesia must be given to obtain adequate blockade. High lipid solubility produces anaesthesia at low concentrations. Higher protein binding drugs results in longer duration of action.

The pKa of a local anaesthetic is the pH at which ionized and nonionized forms are present in equilibrium in a solution.The nonionized form allows the local anaesthetic to diffuse across the lipophilic nerve sheath and reach the sodium channels in the nerve membrane. The onset of anaesthesia relates to the amount of local anaesthetic available in the base form. The lower the pKa level of an anaesthetic drugs the faster the onset of action.

Pharmacokinetics of local anaesthetics includes uptake and elimination of the local anaesthetic. Four factors play a role in the uptake of local anaesthetics from the subarachnoid space into neuronal tissue;

(1) concentration of local anaesthetic in CSF,

(2) the surface area of nerve tissue exposed to CSF,

(3) lipid content of nerve tissue, and

(4) blood flow to nerve tissue.

The uptake of local anaesthetic is greatest at the site of highest concentration in the CSF and is decreased above and below this site. Both the nerve roots and the spinal cord take up local anaesthetics after injection into the subarachnoid space. The wider surface area of the nerve root exposed, the greater the uptake of local anaesthetic.

The spinal cord has two mechanisms for uptake of local anaesthetics. The first mechanism is by diffusion in the most superficial portion of the spinal cord, which is a slow process, from the CSF to the pia mater and into the spinal cord.

The second method of local anaesthetic uptake is by extension into the spaces of Virchow-Robin, which are the areas of pia mater that surround the blood vessels penetrating the central nervous system.

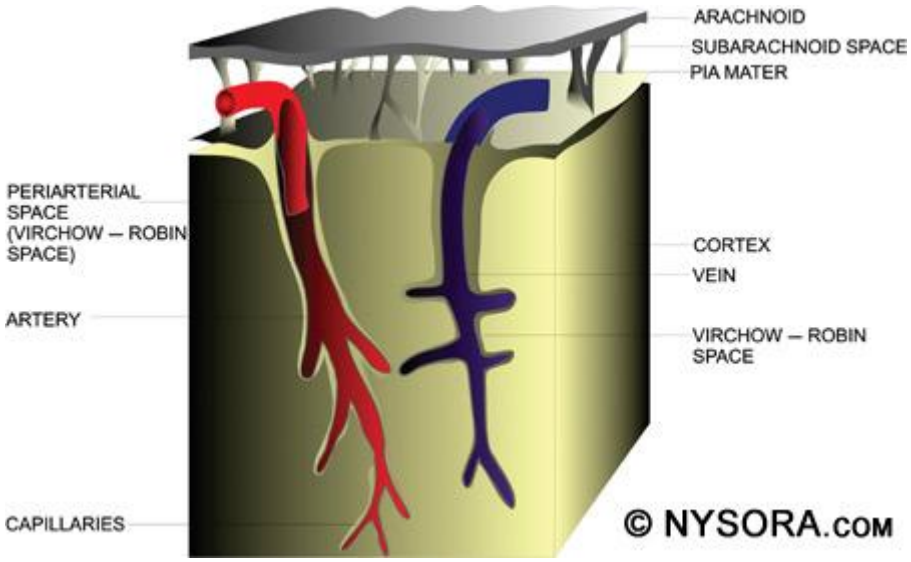

Figure 1.7: Representation of periarterial Virchow-Robin spaces around the spinal cord.

Many factors affect the distribution of local anaesthetics in the subarachnoid space. The three most important factors for determining spread of local anaesthesia in the subarachnoid space are baricity of the local anaesthetic solution, position of the patient during and just after injection, and dose of the anaesthetic injected.

Hypobaric solutions are less dense than CSF and tend to flow against gravity. Isobaric solutions are as dense as CSF and tend to remain at the level at which they are injected. Hyperbaric solutions are denser than CSF and tend to follow gravity after injection.

Dose and volume both play a role in the spread of local anaesthetics after spinal injection. Concentration of local anaesthetic before injection has no bearing on distribution because after injection, due to the mixing of the CSF and local anaesthetic, there will be a new concentration.

Multiple factors affect the distribution of local anaesthesia after spinal blockade, one being CSF volume. Carpenter showed that lumbosacral CSF volume correlated with peak sensory block height and duration of surgical anaesthesia. Higuchi found that CSF density and lumbosacral CSF volume correlates to peak sensory block level, and onset and duration of motor block. However, due to the wide variability in CSF volume the ability to predict the level of the spinal blockade after local anaesthetic injection is very poor, even if body mass index (BMI) is calculated and used.

Spinal anaesthesia is the most commonly used technique for lower limb surgeries as it is very economical and easy to administer. However, postoperative pain control is a major problem due to spinal anaesthesia being only a temporary spinal blockade and thus early analgesic intervention is needed in the postoperative period. Few number of adjuvant drugs such as clonidine, midazolam and others have been proven in studies to prolong the effect of spinal anaesthesia.

A common problem during lower limb surgeries under spinal anaesthesia is nausea and vomiting. The addition of fentanyl to hyperbaric bupivacaine improves the quality of intraoperative and early postoperative subarachnoid block. The addition of opioids to local anaesthetic solution has disadvantages such as pruritus and respiratory depression.

Dexmedetomidine, a new highly selective α2-agonist, is still under study as an alternative neuraxial adjuvant as it provides stable haemodynamic conditions, good intraoperative block coverage and prolonged postoperative analgesia with minimal side

effects. Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short term sedative for mechanically ventilated intensive care unit (ICU) patients.

Based on earlier human studies, it is hypothesized that intrathecal 5 µg Dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects. Till date, there has been no study comparing the addition of Dexmedetomidine to hyperbaric bupivacaine with fentanyl to hyperbaric bupivacaine, although various studies have compared Dexmedetomidine and fentanyl with isobaric bupivacaine.

This study aims to investigate the effect of intrathecal administration of dexmedetomidine on the duration of sensory and motor block and postoperative analgesic requirements produced by spinal bupivacaine in lower limb orthopaedic surgery.

CHAPTER 2

LITERATURE REVIEW

2.1 Pain

2.1.1 Definition

The "standard" definition of pain is that of the International Association for the Study of Pain (IASP):-

"An unpleasant sensory or emotional experience associated with actual or potential tissue damage. Pain is subjective, different perception in different individual. Each individual learns the application of the word through experiences related to injury in any stage of life. It is a sensation in a part of the body, but it is unpleasant, and therefore is also known as an emotional experience. Many people present with pain in the absence of any tissue damage; usually this happens for psychological reasons. There is no way to picturise their experience from that due to tissue damage, if we take this as a subjective statement". (Wolff 1980)

This definition is extremely broad and by concentrating on the subjective nature of pain, this definition allows us to conveniently ignore individuals whose physical findings are not at all consistent with a diagnosis of "pain", but who cannot relate a subjective feeling of pain. Indeed, it tells us that (appearances to the contrary) such people are *not in pain*!

2.1.2 Pain fibres

Cutaneous sensation is mediated by specific sensory receptors that are located in the skin layer. These are broadly classified into low and high threshold primary afferents. The low threshold afferents are myelinated fibres with specialised nerve endings that convey innocuous sensations such as light touch, vibration, pressure (all Ab) and proprioception (Aa). High threshold afferents are thin myelinated (Ad) or unmyelinated (C) fibres located in the dermis and epidermis, which conveys pain and temperature sensation.

Table 2.1: Comparative properties of primary afferent fibres

Fibre class	**Threshold**	**Main transmitters**	**Main receptor activated**	**Laminar location**	**Target spinal cord neurones**	**Normal sensation**	**Pathological sensation**
C	High	Peptides	NK1,2	I-II, V	NS	Slow pain	Hyperalgesia
Ad		EAA	NMDA AMPA mGlu		WDR	Fast pain	Allodynia
Ab	Low	EAA	AMPA	III-VI	LT WDR	Touch vibration pressure	Mechanical allodynia

Key: EAA = Excitatory amino acids; NS = Nociceptive specific; LT = Low threshold; WDR = wide dynamic range; NK = neurokinin (peptide) receptor; NMDA, AMPA, mGlu are different types of glutamate receptors

Pain and temperature afferents are polymodal free nerve endings and do not have any specialised receptors. They respond to more than one stimulus, e.g. chemical, thermal or mechanical stimuli. Free nerve endings are present in all parts of the body except the interior of the bones and the interior of the brain itself.

In the cornea of the eye, only free nerve endings are found and abrasions of the cornea can be extremely painful. Most responds only to tissue damaging stimuli and are called nociceptors. Pain sensations can be broadly classified into sharp, stabbing, dull, throbbing and aching types.

Ad fibres mediate the former or ‘fast’ pain, C-fibres signal the latter or ‘slow pain’. Not all Ad and C fibres are nociceptors as some of them responds to low threshold stimuli such as touching or brushing of the skin. C fibres are thermoreceptors, and responds to warm or cold.

Although pain results from damage to free nerve endings, but in reality the pain is a result of substances released by the damaged tissues: prostaglandins, histamine and peptides which activates the receptors located on the free nerve ends.(Cervero 1994)

2.1.3 Spinal cord

The spinal cord consists of a grey and white matter. White matter contains ascending and descending fibres while the grey matter contains cells and central terminals of primary afferents from the periphery.

The dorsal horn is divided into 6 layers (laminae) and processes sensory information. Lamina I is the most dorsal and consist of a thin layer of large cells and small inhibitory interneurons. The axons from this large cells forms a part of the spinothalamic tract.

The second layer is lamina II or known as the "substantia gelatinosa". Most of the cells here are inhibitory but excitatory cells are present as well. This layer is believed to control the "connectivity" of the other laminae in the dorsal horn. Together, laminae I-II are known as the superficial dorsal horn and receives input from the nociceptors high threshold C and Ad fibres and contain cells that are nociceptive specific, NS (respond only to noxious stimuli) or wide dynamic range, WDR (respond to both innocuous and noxious stimuli).

Laminae III-VI receives input from the cutaneous Ab non-nociceptive afferents and contains cells with low-threshold (LT) receptive fields that responds to innocuous stimuli. Some lamina V cells are WDRs that receive input from both low-threshold (Ab) sensory fibres and high-threshold (C, Ad) fibres as their dendrites project dorsally into laminae I-II.

The dorsal horn is not only transmits innocuous and noxious messages, it also has an important role in modulating pain transmission through spinal and supraspinal mechanisms. This regulatory circuit involves the primary afferents, spinal interneurons and descending fibres. (LIght and Perl 1980)

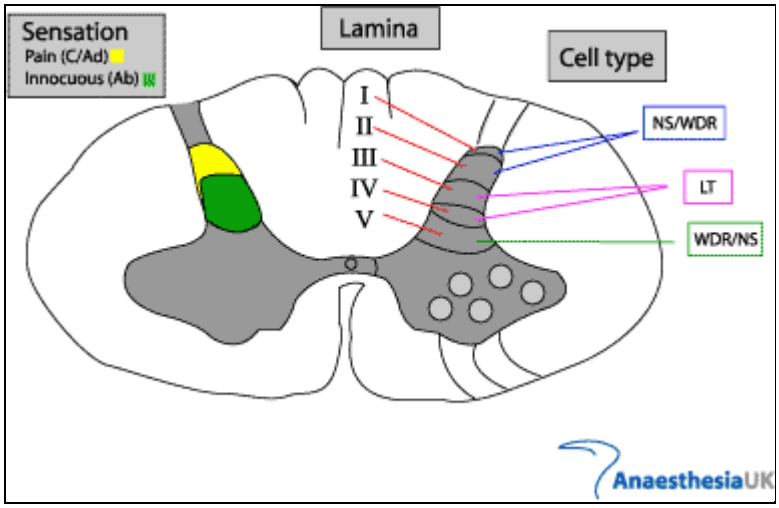

Figure 2.1: Spinal cord transverse section showing lamina levels I -V

2.1.4 Pain pathways

The first pain modulatory mechanism called the "Gate Control" theory was coined by Melzack and Wall in the mid 1960 whereby the concept states that non-painful input closes the gates to painful input, which prevents the transmission of pain from travelling to CNS (i.e., non-noxious input [stimulation] suppresses pain). (Melzack and Wall 1967).

The theory suggests that collaterals of the large sensory fibres carrying cutaneous sensory input activate inhibitory interneurons, which inhibit (modulate) pain transmission information carried by the pain fibres.

Non-noxious input suppresses pain, or sensory input “closes the gate” to noxious input. The gate theory predicts that at the spinal cord level, non-noxious input will lead to presynaptic inhibition on dorsal root nociceptor fibres that synapse on nociceptors spinal neurons (T), and this presynaptic inhibition will block incoming noxious information from reaching the CNS (i.e., will close the gate to incoming noxious information).

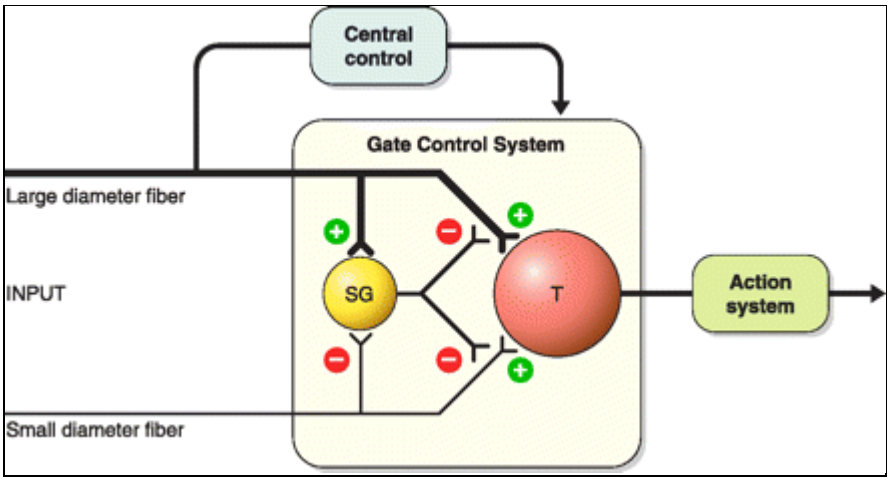

Figure 2.2: Gate control theory of pain. This figure shows the inhibitory interneurons (yellow) located in the substantia gelatinosa (SG) would determine whether nociceptive input from the periphery would be relayed through the spinal transmission system (red, T) to higher CNS areas whereby pain would be consciously perceived(Willis Jr 1985).

Three classes of opioid receptors have been identified: μ-mu, δ-delta and κ-kappa(Paterson, Robson et al. 1983) which are widely distributed in the brain. Genes encoding each one of them have been cloned and noted to be members of the G protein receptors. Three major classes of endogenous opioid peptides that interact with the above opiate receptors have also been recognized in the CNS: β-endorphins, enkephalins and the dynorphins. These opioid peptides are derived from a large protein precursor by three different genes: the proopiomelanocortin (POMC) gene, the proenkephalin gene and the prodynorphin gene.

These opioid peptides modulate the nociceptive input in two ways:

1) it blocks neurotransmitter release by inhibiting Ca2+ influx into the presynaptic terminal, or

2) open up the potassium channels, which hyperpolarizes neurons and inhibits spike activity.

They act on various receptors in the brain and spinal cord. These opioid peptides, enkephalins are considered as the putative ligands for the δ receptors, β endorphins for the μ-receptors, and dynorphins for the κ receptors. The opioid receptors are distributed differently within the central and peripheral nervous system and there are functional differences in these receptors in various structures. This explains the side effects following opiate treatments. For example, mu (μ) receptors are found widespread in the brain stem, parabrachial nuclei, which is a respiratory center and inhibition of these neurons elicits respiratory depression.

Central or peripheral terminals of nociceptive afferent fibres contain opiate receptors where exogenous and endogenous opioids could act to modulate the ability to transmit nociceptive senasation. High densities of opiate receptors are found in periaqueductal gray (PAG), nucleus raphe magnus (NRM), and dorsal raphe (DR) in the rostral ventral medulla, in the spinal cord, caudate nucleus (CN), septal nucleus, hypothalamus, habenula and hippocampus. (Mansour, Khachaturian et al. 1988)