A Comparison of Plain Ropivacaine 0.5% with Plain Bupivacaine 0.5% In Spinal Anaesthesia for Orthopaedic Surgery.

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TABLE OF CONTENT

LIST OF TABLES

LIST OF FIGURES

ABSTRAK

Perbandingan pembiusan separa spinal di antara Ropivacaine 0.5% dan Bupivacaine 0.5% untuk pembedahan ortopedik.

PENGENALAN

Ropivacaine, ejen local anaesthetic baru yang berkongsi struktur dan farmakologi dengan bupivacaine, mempunyali kelebihan dari segi kadar toksik untuk jantung yang minima serta keupayaan fungsi daya gerakan kembali ke tahap normal selepas pembiusan adalah lebih pantas. Ini adalah kerana ropivacaine mempunyai ciri S (-) enantiomer tulen.

METODOLOGI

Seramai 72 pesakit ASA grade I-II yang dijadualkan untuk pembedahan orthopedic anggota kaki, dibahagikan secara rawak kepada kumpulan yang menerima 15 mg ropivacaine 0.5% atau 15 mg bupivacaine 0.5% untuk pembiusan secara spinal.

KEPUTUSAN

Purata jangkamasa hilang daya rasa pada paras T12 adalah 4 minit (SD ±3.4) untuk kumpulan bupivacaine dan 5.1 minit (SD ±3.3) untuk kumpulan ropivacaine ($P<0.207$). Untuk menghalang daya rasa sehingga ke paras T10 memerlukan 6.4 minit (SD ±3.3) bagi kumpulan bupivacaine dan 9.3 minit (SD ±5.2) bagi kumpulan ropivacaine ($P<0.015$). Sementara itu untuk menghalang daya rasa ke tahap T4, kumpulan bupivacaine mengambil masa 6.9 minit (SD ±3.7) manakala 15 minit (SD ±4.1) untuk kumpulan ropivacaine ($P<0.001$). Purata lama masa daya rasa hilang dari awal pembiusan diberi adalah 5.4 jam

(SD ±1.2) untuk kumpulan bupivacaine dan 6.5 jam (SD ±2.4) untuk kumpulan ropivacaine (P<0.02). Purata masa untuk daya pergerakan hilang mengikut "Modified Bromage Score" (MBS) adalah seperti berikut: MBS 1 – 1.4 minit (SD ±0.8) bupivacaine, 2.1 (SD ±1.5) ropivacaine (P<0.01); MBS2 – 1.6 minit (SD ±0.9) bupivacaine, ropivacaine 3 minit (SD ±2.0) (P<0.001); MBS 3 – 2.1 minit (SD ±1.1) bupivacaine, 3.6 minit (SD ±1.8) ropivacaine (P<0.001). Masa yang diambil untuk daya pergerakan hilang dari permulaan pembiusan adalah 4.7 jam (SD ±1.1) untuk kumpulan bupivacaine dan 3.5 jam (SD ±1.4) untuk kumpulan ropivacaine (P<0.001).

KESIMPULAN

15 mg ropivacaine 0.5% sesuai untuk menghalang daya rasa dan daya pergerakan di bawah paras T12 dalam jangkamasa yang singkat serta menghindar. Rasa sakit untuk satu tempoh yang panjang samping membolehkan daya pergerakan kembali normal dalam tempoh yang singkat.

ABSTRACT

A Comparison of Plain Ropivacaine 0.5% with Plain Bupivacaine 0.5% in Spinal Anaesthesia for Orthopaedic Surgery.

INTRODUCTION

Bupivacaine is a popular local anaesthetic drug used for spinal anesthesia, it is relatively cardiotoxic and has a longer duration of motor blockade leading to longer discharge time, research for newer local anaesthetic with less cardiotoxicity and minimal motor blockade is aimed. Ropivacaine is a relatively new long-acting local anesthetic used in spinal anaesthesia, which is structurally and pharmacologically closely related to bupivacaine. However, unlike bupivacaine, which is synthesized as a racemic mixture, ropivacaine is synthesized as a pure S (-) enantiomer. This characteristic feature of the drug may contribute to its faster return of motor function than bupivacaine, and with lower risk of cardiotoxicity.

METHODOLOGY

A double blind randomized clinical trial on 72 ASA grade I- II patients who were scheduled to undergo orthopedic surgery of the lower limb with duration of operation less than 3 hours were included in the study. These patients received an intrathecal injection of either: 15 mg of 0.5% plain ropivacaine (3 ml), or 15 mg of 0.5% plain bupivacaine (3 ml) for the above procedure.

RESULTS

The mean onset of sensory block at T12 dermatome was 4 minutes (SD ±3.4) in bupivacaine group and in ropivacaine group it was 5.1 minutes (SD ±3.3) ($P<0.207$).

Where as to reach T10 in bupivacaine group was 6.4 minutes (SD ±3.3) and in ropivacaine group reached in 9.3 minutes (SD ±5.2) (P<0.015). Regarding sensory block at T4, 20 patients (55.5%) in bupivacaine group reached this level with mean onset of sensory block in 6.9 minutes (SD ±3.7). Where as only 4 patients (11%) in ropivacaine group were able to reach the level of T4 in 15 minutes (SD ±4.08) (P<0.001). The duration of sensory block was assessed by the patient's first request for analgesia. In bupivacaine group the mean duration of time of sensory block was 5.4 hours (SD ±1.2) and in ropivacaine group it was 6.5 hours (SD ±2.44) (P<0.02). The mean onset of motor block to reach Modified Bromage Score (MBS1) in bupivacaine group was 1.4 minutes (SD ±0.8) and in ropivacaine group it was 2.1 minutes (SD ±1.5) (P<0.01). And to reach MBS2, in bupivacaine group and in ropivacaine group was 1.6 minutes (SD ±0.9) and 3.0 minutes (SD ±2.0) respectively (P<0.001). While to reach MBS3 bupivacaine group was 2.1 minutes (SD ±1.1) and in ropivacaine group it was 3.6 minutes (SD ±1.8) (P<0.001). In the bupivacaine group the mean duration of motor block was 4.7 hours (SD ±1.1) and in ropivacaine group was 3.5 hours (SD ±1.4) (P<0.001).

CONCLUSION

Ropivacaine in a dose of 15 mg as 0.5% solution can be used with an acceptable onset of sensory and motor blockade with a longer duration of analgesia and early mobilization for lower limb orthopedic surgery of duration less than three hours and a level of lower than T12 dermatome.

CHAPTER ONE

1. INTRODUCTION

Bupivacaine is a popular drug for spinal anaesthesia, but because of its cardiotoxicity and longer duration of motor blockade leading to longer discharge time (Pavlin 1998), the laboratory research programme was aimed at identifying a local anesthetic with a similar clinical profile, but with less cardiotoxicity than bupivacaine. The research for alternatives to bupivacaine has concentrated on amide-linked agents. Ropivacaine and levobupicaine are two relatively new amide local anaesthetic agents that have been produced in order to address the issue of bupivacaine cardiotoxicity (Whiteside JB et al. 2001).

Ropivacaine is a relatively new long acting local anaesthetic, which is structurally and pharmacologically closely related to bupivacaine. However, unlike bupivacaine, which is synthesized as a racemic mixture, ropivacaine is synthesized as a pure S (-) enantiomer. It has 10-fold less lipid solubility than bupivacaine, which may decrease its accumulation in certain tissues, including myelinated A-alpha motor fibers. This characteristic may contribute to its faster return of motor function than bupivacaine. Clinical pharmacological studies also showed that ropivacaine has a lower risk of cardiotoxicity. These two advantages have currently made the use of ropivacaine more popular for epidural anaesthesia especially in postoperative analgesia and in the management of labor pain (Levin A. 1998).

The use of ropivacaine in spinal anaesthesia is relatively new and limited studies have been done. Because of its less dense motor blockade, most of the studies first focused more on its possible benefits in ambulatory surgery (Gautier Ph.E et al. 1999), cesarean delivery (Kim SK et al. 2002), and then they started to study its effect on other type of procedures like orthopedic and general surgery in its two forms; hyperbaric (Whiteside J.B et al. 2003) or plain (isobaric) (Mc Namee D.A et al. 2002).

We would like to study the use of plain ropivacaine in spinal anaesthesia of the lower limb orthopedic surgery and compare its characteristics with that of plain bupivacaine in term of onset of both sensory and motor block as well as duration of block with the maximum cephalad spread, quality of analgesia and muscle relaxation and its safety in use.

2. OBJECTIVES

The main objective of this study is to compare plain ropivacaine in a dose of 15 mg as 0.5% solution with plain bupivacaine in a dose of 15 mg as 0.5% solution in orthopedic surgery for lower limb of duration less than three hours.

1.1. To compare the onset and duration of sensory block to T10 with plain ropivacaine 15 mg as 5% solution and plain bupivacaine 15 mg as 0.5% solution.

1.2. To compare the onset and duration of motor block using plain ropivacaine and plain bupivacaine with the above dosage.

1.3. To compare the maximum block spread of plain ropivacaine with plain bupivacaine with the above dosage

1.4. To assess the quality of analgesia with the use of plain ropivacaine and plain bupivacaine with the above dosage

1.5. To assess muscle relaxation induced by plain ropivacaine and plain bupivacaine using the above dosage

1.6. To assess intraoperative and postoperative complications of plain ropivacaine and plain bupivacaine using the above dosage

CHAPTER TWO

LITRATURE REVIEW

2.1 PHARMACOLOGY OF LOCAL ANAESTHETICS

The first local anaesthetic to be discovered was cocaine, an alkaloid form of leaves of the plant Erythroxylon coca, found in the highlands of Peru. Pure alkaloid was first isolated by Neimann. In 1880, von Anrep was the first to describe the sensory anaesthetic action of subcutaneous injection and recommended its use as such, however this was not acted upon. In 1884, Carl Koller made the first documented use of local anaesthesia for surgery, when he introduced its topical use into ophthalmology. In the same year, Hall introduced its use into dentistry. In the following year, Halsted demonstrated its efficacy in blocking conduction in nerve trunks (William et al. 1996). Corning, in 1885, induced spinal anaesthesia in dogs, and in 1895, Corning injected cocaine 110 mg at the level T11/T12 to treat habitual masturbation. In 1898, Bier performed the first spinal anesthesia, and described the first postdural puncture headache (Turnbull D.K et al. 2003). However, the search for chemical substitutes for cocaine began in 1892, with the work of Einhorn and colleagues and procaine resulted in 1905 (Brown D.L et al. 2000). Lofgren synthesized lidocaine in 1943, and since then, with the exception of chloroprocaine, all new local anaesthetics introduced into clinical practice have been amino-amides (William et al. 1996). So for utilization of these agents, the safe and effective use depends on the understanding of the pharmacokinetics and pharmacodynamics of the various local anaesthetics available today.

2.1.1 MECHANISM OF ACTION

The generation and propagation of impulses in nerve axons to carry afferent (sensory) and efferent (motor, sympathetic) information requires the flow of specific ionic currents through channels in the plasma membrane. These channels open and close depending on the electrical potential of the cell membrane. The major determinant of the depolarization of nerve fibers is dependent on the specific influx of sodium ions through sodium channels in nerve cell axons. Local anaesthetic agents reversibly bind to and block the sodium channels, thereby preventing the initiation or propagation of the electrical impulses required for nerve conduction (Stoelting RV. 1999).

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It now appears that although the uncharged form of a local anaesthetic is more likely to cross into the cell membrane, either form may bind to the sodium channel. Sodium channels exist in activated-open, inactivated-closed, and rested-closed states during various phases of the action potential. In the resting nerve membrane, sodium channels are distributed in equilibrium between the rested-closed and inactivated-closed states. By selectively binding to sodium channels in inactivated-closed states, local anesthetic molecules stabilize these channels in this configuration and prevent their change to the rested-closed and activated-open states in response to nerve impulses. Sodium channels in the inactivated-closed state are not permeable to sodium, and thus conduction of nerve impulses in the form of propagated action potentials cannot occur. It is speculated that local anesthetics bind to specific sites located on the inner portion of sodium channels (internal gate) as well as obstructing sodium channels near their external openings to maintain these channels in inactivated-closed states (Butterworth & Strichartz. 1990).

Sodium ion channels tend to recover from local anaesthetic-induced conduction blockade between action potentials and to develop additional conduction blockade each time sodium channels open during an action potential (frequency-dependant blockade). Hence, local anaesthetic molecules can gain access to receptors only when sodium channels are in activated-open states. For this reason, selective conduction blockade of nerve fibers by local anaesthetics may be related to the nerve's characteristic frequencies of activity as well as to anatomical properties. So sensory fibers, especially pain fibers, have a high firing rate and relatively long action potential duration than motor fibers, and thus are more sensitive to low concentration of local anaesthetics. Frequency- and voltage-dependence is also the mechanism of anti-arrhythmic effects of local anaesthetics on cardiac cells (Bromage et al. 1974).

Local anaesthetics have differential conduction blockade properties in which it prefers to block small nerve fibers; this is because distance of passive propagation of impulses in the small fibers is shorter, in general, small unmyelinated C-fibers (pain) and small myelinated Aδ-fibers (pain and temperature) are blocked before larger myelinated Aα, Aβ and Aγ fibers (postural, touch, pressure and motor signals), also in nerve bundles, fibers that are located circumferentially are affected first by local anaesthetics. So in the large nerve trunks, motor nerves are usually located circumferentially and may be affected before the sensory fibers. In the extremities, proximal sensory fibers are located more circumferentially than distal sensory fibers. Thus, loss of sense may spread from proximal to distal part of the limb. Local anaesthetics action is affected by the pH of the application site. It also is uncertain whether local anaesthetics cross into the cell through the cell

membrane or actually through the sodium channel, either way, the local anaesthetic initiates block of the channel by binding to the receptor inside the cell (William et al. 1996).

2.1.2 CLASSIFICATION

Local anaesthetics are commonly classified by the duration of their clinical actions. Structurally, based on the linkage between the aromatic portion and the amine portion of the compound, they can be classified as either esters or amides. The various local anaesthetic agents differ in terms of their potency, onset, and duration of action, depending in general on their physico-chemical properties as outlined below (Stoelting RV. 1999).

The correlation between the physical properties and biologic properties are especially true for in *vitro* compared with in *vivo* nerve models. Recently, with the introduction of ropivacaine, chirality's has become yet another way to describe local anesthetics. A chiral carbon is one in which the four bonding atoms (or groups of atoms) are all different. This leads to the potential for that molecule to exist in two different three-dimensional mirror-image configurations: the S (sinister, l, levo, or left) or R (rectus, *d,* dextro, or right) isomers. Each stereoisomer has different physicochemical properties that potentially can be exploited for its unique pharmacological properties (Whiteside JB et al. 2001).

Ropivacaine became the first synthetic local anaesthetic marketed that exists only as the S isomeric formulation and although all local anesthetics with the exception of Lignocaine potentially can be formulated as a pure isomer, all of them currently are racemic mixtures (Whiteside JB et al. 2001).

The potential advantages of having pure isomers are that perhaps a larger degree of toxicity or potency is due just to one of the isomers and the favorable one can be sought. This certainly appears to be true for ropivacaine where the R-enantiomer is three times more cardiotoxic than the S-enantiomer. The S-isomer of bupivacaine is being studied currently because of its more favorable side-effect profile compared with the R-isomer formulation. Results of this study could potentially lead to a new bupivacaine with all the desirable properties that minimizes the side-effects (Moller R & Cavino BG. 1990).

2.1.2, (a). Esters

Cocaine as described above was the first local anaesthetic and is also an ester. Albert Niemann, who noted the passionate chewing of the Coca leaves by the native Indians, discovered it in the 1850s. The first chemically synthesized ester was procaine. Procaine is still used for local infiltration, and although many other ester local anaesthetics have been synthesised as chloroprocaine, and tetracaine remain in clinical use (William et al. 1996). Ester linkage is relatively unstable, as a result ester local anaesthetics have a shorter shelf-life and are sensitive to high temperatures. Esters are rapidly hydrolyzed having the half life of 1-3 minutes in plasma by the cholinesterase enzymes (plasma pseudocholinesterases and red blood cell esterase), with para-amino benzoic acid being one of the primary metabolites. Para-amino benzoic acid (as in lotion) is probably responsible for the majority of allergic reactions reported in a small number of patients who use ester-type drugs (Stoelting RV. 1999).

2.1.2, (b). Amides

Dibucaine was the first amide-type local anaesthetic synthesized, but its clinical use was limited secondary to its toxicity. Dibucaine is now used only for the diagnosis of cholinesterase deficiency and for quizzing residents and medical students. Lidocaine was introduced in I943. It was the first amide class of local anaesthetic used widely in clinical practice. The other amide in order of synthesis is mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine and levobupivacaine. The amides are extremely stable compounds and have long shelf-lives. They undergo degradation in the liver with plasma half-lives between 2 and 3 hours and allergic reactions to these compounds are rare. It is important that there is no cross-reactivity to allergies between esters and amides (Whiteside JB et al. 2001).

2.1.3. BUPIVACAINE

Bupivacaine is classified as an amide local anaesthetic, which used as a local anaesthetic, presented as a clear, colorless solution containing 0.25%, 0.5%, and 0.75% of bupivacaine hydrochloride. The 0.25% and 0.5% solutions are available combined with 1: 200,000 adrenaline. A 0.5% (heavy') solution containing 80 mg/ml of glucose is also available.

2.1.3, (a). Pharmacokinetics

Absorption of bupivacaine is similar to lignocaine but the addition of adrenaline does not prolong the duration of action of bupivacaine. Regarding distribution, it is 95% protein-bound in the plasma; volume of distribution is 73 liters.

Metabolism occurs in the liver by N-dealkylation, primarily to pipcolyl oxylidine. Some 5% of the dose is excreted in the urine as pipcolyl-oxylidine; 6% is excreted unchanged. The clearance is 0.47 L/min and the elimination half-life is 210 minutes. The drug can be administered by infiltration, intrathecally, epidurally and for major nerve blockade, 0.125 - 0.25% with or without adrenaline may be used for infiltration analgesia and the onset of action is reasonably rapid, and the duration of action is 240 minutes (480 minutes with adrenaline). The onset of action for peripheral nerve block is about 20 minutes. 0.5% bupivacaine is used for surgical anaesthesia and when extra volume is needed, a more dilute (0.375%) may be used. The upper limit of safe dosage in the adults is 2-mg/kg body weights (Stoelting RV. 1999).

2.1.3, (b). Pharmacodynamics

Bupivacaine causes reversible peripheral neural blockade. Bupivacaine diffuse in their uncharged base form through neural sheaths and the axonal membrane to the internal surface of the cell membrane's sodium channels; where they combine with hydrogen ions to form a cationic species which enter the internal opening of the sodium ion channel and combines with a receptor. This produces blockade of the sodium ion channel, thereby decreasing sodium ion conductance and preventing depolarization of the cell membrane. In general, the actions are similar to lignocaine but it is markedly cardiotoxic, binds specifically to myocardial proteins. R-bupivacaine is also more arrhythmogenic, and slows ventricular conduction 4.6 times as much as S-bupivacaine. The decrease in cardiotoxicity due to S-bupivacaine's steroselectivity is the subject of a recent review. Given in toxic doses, it decreases myocardial contractility and the peripheral vascular resistance producing hypotension and possibly cardiovascular collapse (Stoelting RV. 1999).

2.1.3, (c). Contraindications and precautions

Hypersensitivity reactions to bupivacaine may occur but are extremely rare. Caution should be taken in patients with fixed cardiac output state and shunts during performance of central neural axis blockade. Allergy to amide local anaesthetic is extremely rare (Stoelting RV. 1999).

2.1.3, (d). Adverse effects and side effects

Side-effects are similar to lignocaine, such as convulsion, dizziness, perioral numbness, tinnitus and neurotoxic (neuritis), conduction blockade, arrhythmias, depression of myocardial contractility and hypotension but it is more cardiotoxic than lidocaine (Stoelting RV. 1999).

2.1.4 ROPIVACAINE

Ropivacaine is the new long-acting amino-amide local anaesthetic combines the anaesthetic potency and long duration of action of bupivacaine with a toxicity profile intermediate between bupivacaine and lidocaine. It is presented as clear solution of 2%, 5%, 7.5% and 10%. Ropivacaine is manufactured as the pure S-enantiomer in order to take advantage of the decreased cardiotoxicity (Whiteside JB et al. 2001).

2.1.4, (a). Pharmacokinetics

Ropivacaine has a chiral center and is the pure S- (-)-enantiomer. Ropivacaine has a pKa of 8.1. The metabolites have a pharmacological activity that is less than that of ropivacaine. The plasma concentration of ropivacaine depends upon the dose, the routes of administration and the vascularity of the injection site, metabolism in the liver by aromatic hydroxylation and N-dealkylation (Stoelting RV. 1999). About 3% of the metabolites are excreted in the urine. Ropivacaine has total plasma clearance of 440 ml/min, an unbound plasma clearance of 44 L/min, a renal clearance of 1 L/min, a volume of distribution at steady state of 41 liters and an elemination half-life of 108 minute after IV administration (Stoelting RV. 1999).

2.1.4, (b). Pharmacodynamics

Ropivacaine is the first long-acting, amide-type local anaesthetic with both anaesthetic and analgesic effects. At high doses it produces surgical anaesthesia, while at lower doses it produces sensory block with limited and non-progressive motor block. Onset and duration of the local anaesthetic effect of ropivacaine depends on the dose and site of administration, while the presence of a vasoconstrictor has little, if any influence. Ropivacaine, like other local anaesthetic, causes reversible blockade and similar affects on other excitable membranes e.g. brain and myocardium, but with lower cardiac toxicity compared to bupivacaine (Whiteside JB et al. 2001).

2.1.4, (c). Contraindications and precautions

Caution should be taken in patients with fixed cardiac output states and shunts during performance of central neural axis blockade. Allergy to amide local anaesthetics is extremely rare (Stoelting RV. 1999).

2.1.4, (d). Adverse effects and side effects

The adverse reactions of ropivacaine are similar to those of bupivacaine as neurotoxicity, hypotension, bradycardia and urinary retention. The needle puncture may cause spinal haematoma, headache or may aid in introducing microorganisms as meningitis and abscess formation but with less incidence of cardiac toxicity than bupivacaine (Stoelting RV. 1999).

2.2 SPINAL ANESTHESIA

2.2.1. HISTORY

In 1761, Colugno described the presence of a collection of water around the brain and inside the spinal column. In 1825, Magendie was credited with appreciating that this fluid circulated around the brain and the spinal column. By 1811, Zophar Jayne of Illinois had designed a syringe attached to a small, sharp, and hollow beak with an opening on the side near the tip. Subsequently, in 1853, Daniel Ferguson developed a syringe and hollow platinum trochar with an oblique opening on one side encased in outer tubing. Also with an oblique opening, Wood was credited for developing the first hollow hypodermic needle in 1853 (William et al. 1996).

The first local anaesthetic to be discovered was cocaine, an alkaloid form of leaves of the plant Erythroxylon coca, found in the highlands of Peru. So the history of the development of the spinal needle tip is one of trial and error, misattribution and unsolved problems. From the early hollow needles (1853), through the cutting bevel design (1900-1927-1993), to the current pencil-point needles (1951-1987-1996), the same initial problems are still evident today, albeit less commonly: postdural headaches, failed blocks and neurological damage (Calthorpe N et al. 2004). In 1880 von Anrep, was the first to describe the sensory anaesthetic action of subcutaneous injection and recommended its use as such, however this was not acted upon. And Carl Koller made the first documented use of local anaesthesia for surgery on 1884, when he introduced its topical use into ophthalmology. In the same year Hall introduced its use into dentistry (William et al. 1996).

John Leonard Corning in 1885 produced spinal anaesthesia in dogs. In 1895 same Corning inject cocaine 110 mg at level T11/T12 to treat habitual masturbation. Bier in 1898 performed the first spinal anaesthesia, and he also described the first postdural puncture headache (Turnbull DK et al. 2003). So the search for chemical substitutes for cocaine began in 1892, with the work of Einhorn and colleagues. The result of the work is procaine in 1905 (Brown DL et al. 2000). Lofgren synthesized lidocaine in 1943 and since then, with the exception of chloroprocaine, all new local anesthetics introduced into clinical practice have been amino-amides.

2.2.2. ANATOMY OF SPINAL CANAL

The spinal canal is occupied by the spinal cord, which begins at the level of the foramen magnum and extends to the first or second lumbar vertebrae. It is continuous with the medulla oblongata above and ends below as the conus medullaris, from which the cauda equina (collection of segmental nerve fibers) and the filum terminale continue to the coccyx. At birth, the spinal cord ends at the third lumbar vertebrae before rising to the more cephalic adult level. The cauda equina is suspended in spinal fluid allowing sufficient mobility to deviate from spinal needle tip, which enters the subarachnoid space. The spinal cord could be pierced by a needle that enters the spinal canal at level higher than L 1, this leads to greater popularity of the lumbar approach to neuraxial blockade.

As the tip of the needle enters the spinal canal and approaches the spinal cord or cauda equina, the following structures are sequentially encountered: the epidural space, the dura mater, the subdural space, the arachnoid mater and the subarachnoid space containing cerebrospinal fluid and spinal cord (the spinal cord is covered by the pia mater). First, the needle enters the epidural space. The posterior epidural space is located between the dura mater anteriorly, the ligamentum flavum posteriolaterally, and the connective tissue of the laminea of the vertebrae laterally. The thin narrow anterior epidural space is situated between the posterior longitudinal ligament and the anterior spinal dura.

The epidural space extends from the base of the skull to the sacrococcygeal ligament of the sacral hiatus. It is filled with fatty tissue, loose connective tissue, lymphatics, arteries, a rich venous plexus and segmental nerve roots traversing the lateral boundaries. After penetration into and through the posterior epidural space the needle tip next encounters the three protective coverings of the spinal cord and cauda equina.

The outermost meningeal layer, the dura mater is compromised of longitudinally organized fibers that extend down the vertebral column as a fibroelastic tube and terminate at the inferior border of S2. For subarachnoid placement of local anaesthetics, the dura mater provides the characteristic "pop" which usually indicates that the subarachnoid space has been entered. Between the dura and arachnoid mater, immediately subdurally, there is a potential space that contains lymph and capillaries. In rare cases (0.1% to 0.2%) the needle tip and deposition of drugs may open this subdural space.

This may result in either a total spinal when epidural doses of drugs are administered or may be one of the potential causes of a failed spinal. This potential cavity extends to the nerve roots and ganglia with communication to the cranial cavity but once again, has no direct accessibility to the cerebral spinal fluid. Directly adjacent to the dura mater which is the arachnoid mater, a nonvascular connective tissue covering, is the middle meningeal membrane. With the dura mater, this meningeal layer also extends to the inferior border of the S2 vertebra.

After passing through the arachnoid mater, the needle tip enters the subarachnoid space. This space contains the cerebrospinal fluid and is confined to the area between the pia and arachnoid mater. The pia mater is a fragile vascular membrane, closely attached to the spinal cord, the cauda equina and the spinal nerve roots. The spinal cord and spinal nerve roots are bathed in cerebrospinal fluid. As the spinal nerve roots penetrate beyond spinal dura and enter the epidural space, they retain all three meningeal layers.

The subarachnoid space continues along both nerve roots (dorsal and ventral), ending at the dorsal root ganglia. Deeper penetration of the needle tip at the level of the cauda equine disperses the segmental nerves, which are covered by pia mater and leaves the subarachnoid space to enter into the anterior dura. At the spinal cord level, deeper penetration of the needle tip will encounter the pia mater before injuring the spinal cord.

2.2.3 DRUGS USED

The choice of local anaesthetic to be used for intrathecal anaesthesia is usually based on the expected duration of surgery and need for early patient discharge. Because of changes in health care system organization, a significant increase in the number of surgical procedures performed on an out patient basis and intrathecal anaesthesia have also become regular and very popular for day-case procedures.

2.2.3 (a). Short Acting Agents

Lidocaine both as plain and heavy solutions in doses ranging from 50 to 100 mg is widely used for surgical procedures that last up to one hour. For shorter procedures the dose can he reduced to 40 mg, which provides an adequate surgical block with times for complete regression of spinal block of approximately 2 hours, meaning that the patient may be discharged from hospital 3 hours after intrathecal injection of doses of spinal lidocaine as low as 20 mg has been described for outpatient procedures, with high patient satisfaction and very rapid recovery and discharge, but only with the addition of small doses of fentanyl (Ben-David B et al. 2001).

Nonetheless, despite its broad use and lengthy history, the overwhelming evidence of transient neurological symptoms associated with spinal lidocaine raised concerns regarding its use, especially for day-case procedures (Freedman JM et al. 1998).

Mepivacaine is another amide local anaesthetic with a clinical profile similar to that of lidocaine; however, it is also associated with a similarly high incidence of transient neurologic symptoms (Hiller A et al. 1997).

Procaine and prilocaine could theoretically be good alternatives to lidocaine for short-lasting spinal anaesthesia, but they are not extensively available for intrathecal administration around the world (Liu SS et al. 2001) In comparison with 100 mg lidocaine 5%, the same dose of procaine 10% provides a similar onset time, shorter resolution of nerve block, and lower incidence of transient neurological symptoms (Le Truong HH et al. 2001).

However, spinal procaine has also been reported to be associated with a higher failure rate and higher incidence of nausea as compared to lidocaine, resulting in delayed discharge times. Prilocaine used at the same dose as lidocaine provides a similar clinical profile, with the advantage of a lower incidence of transient neurological symptoms (Hampl KF et al. 1998).

2.2.3 (b). Long-Acting Agents

Long-acting agents, such as bupivacaine with doses ranging between 10 and 20 mg of either plain or hyperbaric solutions and tetracaine with doses ranging between 8 and 16 mg of either plain or hyperbaric solutions are extensively used to provide intrathecal anaesthesia for surgical procedures that last up to 2-2.5 hours (Brown DL et al. 2000). The use of long-acting agents is associated with a lower risk for transient neurological dysfunction (Freedman JM et al. 1998). With increasing concerns regarding the development of neurological dysfunction after spinal lidocaine, the use of small doses of long-acting agents to provide reliable spinal anaesthesia for short procedures has been investigated (Liu SS et al. 1996).

Bupivacaine, 5-8 mg (used as plain hypobaric or hyperbaric solutions) has been demonstrated to provide reliable spinal anaesthesia for out-patients, with recovery times comparable to those with 40-60 mg lidocaine (Pittoni G et al. 1995). Because it has been demonstrated that most of the toxic effects of bupivacaine are related to the D-enantiomer, the pharmaceutical research has recently focused on pure S-enantiomers. Two new long-acting local anaesthetics have been developed ropivacaine and levobupivacaine (Whiteside JB et al. 2001).

The efficacy and safety of intrathecal administration of both plain and hyperbaric solutions of ropivacaine have been evaluated in different clinical settings, including orthopedic, urologic surgery, cesarean sections and labor pain (Chung, C. J. et al. 2001). As for other agents, the use of hyperbaric solutions results in a faster onset and higher maximum sensory level, with shorter duration of nerve block (Khaw, K. S. et al. 2002).

Ropivacaine is also 40--60% less potent than bupivacaine, Because of its lower lipophilicity (Polley LS et al. 1999). In a study conducted in volunteers, McDonald et al. 1999 demonstrated that ropivacaine is associated with a shorter recovery time than is bupivacaine (when the two agents are used at similar doses). Thus, the use of small doses of ropivacaine could potentially confer some advantages over bupivacaine for outpatient procedures (Gautier P et al. 1999). Gautier compared the use of 8 mg ropivacaine with 8 mg bupivacaine for outpatient knee arthroscopy and demonstrated that ropivacaine allows for earlier recovery of motor function and discharge than does the same dose of bupivacaine (Gautier P et al. 1999).

2.2.3 (c). Additives

Several drugs other than local anaesthetics can be injected into the subarachnoid space, either alone or more frequently in addition to local anaesthetic solutions. There are two primary reasons for using additives with spinal local anaesthetics; first is to improve the quality and duration of spinal block and to minimize the dose of local anaesthetic injected, secondly to reduce the severity cardiac toxicity and to improve its clinical profile.

- **Epinephrine**

Epinephrine in a dose (0.1-0.2 mg) is widely used in addition to local anaesthetic both to minimize the systemic absorption of local anaesthetic and to prolong the duration of spinal block. However the addition of a potent vasoconstrictor may lead to transient neurological symptoms (Hashimoto et al. 2001).

- **Opioids**

Several reports have shown beneficial effect of adding a small dose of opioids such as fentanyl, sufentanil, and morphine to intrathecal local anaesthetic solutions on the prolongation of the duration of analgesia. The pain pathway is interrupted by two distinct mechanisms. The opioids inhibit pain transmission in the dorsal horn, and the local anaesthetic blocks the conduction in the nerve root and spinal cord (Bernadette Th et al. 1998). Adding 10-20 μg fentanyl, 1-10 μg sufentanil, or 0.1-0.2 mg morphine to either bupivacaine or lidocaine provides adequate intraoperative surgical block for lower limb or laparoscopic gynecologic outpatient procedures with very short times to discharge (Ben-David B et al. 2000).

Because of its hydrophilicity, morphine has increased potential for rostral migration in the cerebrospinal fluid possibly leading to delayed respiratory depression. Lipophilic opioids such as fentanyl and sufentanil, has a faster onset of action and little risk for delayed respiratory depression (Hamber EA et al. 1999).

- **Clonidine**

Clonidine is a selective α_2 adrenergic agonist and given intrathecally has been shown to prolong the duration of surgical anaesthesia produced by local anesthetic agents and extend the postoperative analgesia beyond the period of anaesthesia. At spinal level, its analgesic effect is believed to be mediated by postsynaptically situated alpha-2 adrenoreceptors in the dorsal horn. This mechanism is separate from that of local anaesthetic. In addition, it may also have a direct effect on neural transmission (Bernadette Th et al. 1998). Premedication with oral clonidine does prolong sensory and motor block from spinal anesthesia with tetracaine, lidocaine, and bupivacaine (Bernadette Th et al. 1998).

The prolongation of local anaesthetic block is more pronounced with 150μg clonidine, than with 200μg epinephrine. Addition of 150 μg clonidine to spinal injection does not increase the incidence of hypotension associated with spinal anaesthesia; a dose of 200-400 μg may cause cardiovascular depression (Bernadette Th et al. 1998).

2.3. PHYSIOLOGY OF SPINAL ANESTHESIA

A thorough understanding of the physiology of spinal anaesthesia is essential for its safe and effective administration. The degree to which these physiological effects impact on the surgical patient and lead to adverse outcomes is dependent on patient co-morbidity, surgical operation, clinical setting (inpatient versus ambulatory) and spinal anaesthetic technique. Awareness of, and attention to, the factors that potentially cause these physiological effects to become complications is important to ensure proper patient selection and preparation prior to induction of anaesthesia.

2.3.1 CENTRAL NERVOUS SYSTEM PHYSIOLOGY

It is often assumed that local anaesthetics act where they bind with greatest avidity: superficial layer of the spinal cord and the dorsal root. Nevertheless, the sites of greatest local anaesthesia binding change over time, during which the only obvious change in the quality or extent of spinal anaesthesia may be a 1 or 2 spinal segment change in the most rostral extent of block. This argues against our attaching great significance to the macroscopic extent of local anaesthesia binding in the spinal cord (Butterworth J 1998). It is generally assumed that inhibition of nerve conduction during spinal anaesthesia will only occur when local anaesthetic concentration exceeds some minimal blocking concentration.

Differences among neurons in local anaesthetic susceptibility could explain the differential block seen in the more rostral spinal segments of a spinal anaesthesia. During clinical spinal anaesthesia, kinesthetic sensibility is often inhibited in more rostral dermatomes than light touch, which in turn is inhibited in more rostral dermatomes than pinprick sensibility.

The classic data, reported by Greene in 1958, demonstrated that there was typically a 2 spinal- segment separation between the more rostral inhibition of cold sensation and that of pinprick anaesthesia. Freund et al 1967 used electromyography techniques to compare the rostral extent of motor and sensory block, showing a median 2.5 segment differential between the two. Finally, Chamberlain used thermograph during lidocaine or tetracaine spinal anaesthesia to define a wide margin of differential block between sympathetic and somatic sensory fibers. These authors found a mean 6-7 segments between the rostral margins of the two modalities (Butterworth J 1998)

2.3.2 CARDIOVASCULAR PHYSIOLOGY

The cardiovascular effects of spinal anaesthesia depend primarily on the rostral extent of sympathetic block and secondarily on the degree of sedation. Hypotension and bradycardia are both well-recognized side-effects of spinal anaesthesia, although their clinical presentations are usually mild and respond rapidly to treatment. However, a systole and cardiac arrest can occur suddenly and may lead to significant morbidity or even mortality.

2.3.2, (a). Hypotension

The underlying mechanisms of spinal anaesthesia- induced hypotension have been studied both in animals and in patients. Butterworth et al. used a canine model with cardiopulmonary bypass to separate spinal anaesthesia effects on the arterial and venous circulations from those on the heart. Decreases in the blood volume contained by the venous reservoir (of the bypass circuit) denoted increases in venous capacitance.