"COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE BETWEEN EQUIPOTENT DOSES OF 0.75% PLAIN ROPIVACAINE AND 0.5% PLAIN LEVOBUPIVACAINE IN LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA- A ONE YEAR RANDOMIZED CLINICAL STUDY"

By

(REG. NO. BA0112001)

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

APRIL – 2015

KLE UNIVERSITY, BELGAUM, KARNATAKA

ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that this dissertation entitled **"COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE BETWEEN EQUIPOTENT DOSES OF 0.75% PLAIN ROPIVACAINE AND 0.5% PLAIN LEVOBUPIVACAINE IN LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA- A ONE YEAR RANDOMIZED CLINICAL STUDY"** is a bonafide research work done by **REG. NO. BA 0112001.**

Dr. S.N SURESH MD,DA
Professor and Head,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. (Mrs.)N.S. MAHANTSHETTI MD(Paed.)
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologists
C	-	Cervical
T	-	Thoracic
Mcg	-	Microgram
cc	-	Cubic centmeter
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ED	-	Effective dose
FDA	-	Food and Drug Administration
GA	-	General anaesthesia
HCO3	-	Bicarbonate
HR	-	Heart rate
Bpm	-	Beats per minute
IV	-	Intravenous
HCL	-	Hydrochloric Acid
KCl	-	Potassium chloride
kg	-	Kilogram
L	-	Lumbar
m	-	Meters
MAP	-	Mean arterial pressure
mg	-	Milligram
v/s	-	Versus

Mins	-	Minutes
ml	-	Millilitre
NIBP	-	Non invasive blood pressure
O_2	-	Oxygen
$PaCO_2$	-	Partial pressure of carbon dioxide
S	-	Sacral
SAB	-	Subarachnoid block
SBP	-	Systolic blood pressure
SD	-	Standard deviation
Sec	-	Second
SpO_2	-	Peripheral saturation of oxygen
TNS	-	Transient neurological symptoms
α	-	Alpha
β	-	Beta
δ	-	Delta
μ	-	Micro

ABSTRACT

Background and Objectives

Epidural anaesthesia is being routinely practiced and has been the anaesthetic technique of choice for most of the abdominal and lower limb surgeries. Newer long-acting local anesthetics namely ropivacaine and levobupivacaine, introduced recently for clinical use claim benefits over racemic bupivacaine in the form of reduced cardiac and CNS toxicity on overdose. Hence the present study was undertaken to compare the clinical efficacy of 0.75% Ropivacaine with 0.5% Levobupivacaine for epidural anaesthesia in patients undergoing lower abdominal surgeries.

Methods

The present one year randomized clinical study was conducted between January 2013 to December 2013 on 90 ASA grade I and II patients of either gender, aged between 20 to 60 years who were allocated to receive either 15ml of 0.75% plain ropivacaine or 15 ml of 0.5% plain levobupivacaine epidurally for elective lower abdominal surgeries at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Results

The groups were statistically similar as regards demographic data and pre anaesthetic characteristics. The mean times for onset of sensory block in Group R and Group L were 17.93 ± 2.98 min and 18.62 ± 3.09 min respectively. The mean duration of sensory block in group R (196.78 ± 20.31 min) was longer than that

in group L(189.56 ± 19.53 min) although the difference was statistically insignificant. (p=0.067). Two patients in group R and three patients in group L developed a sensory block level upto T6 dermatomal level. The mean onset of motor block in group R was similar to that in group L (24.09 ± 3.07 v/s 25.47 ± 4.13; p=0.076) while duration of motor blockade was observed to be shorter in group R (111.53 ± 16.70min) as compared with group L (118.53 ± 18.14 min) though it was statistically insignificant (p=0.056). Ropivacaine provided a longer duration of post operative analgesia than levobupivacaine (263.0 ± 22.77 vs 253.78 ± 24.43 minutes) although the difference remained statistically insignificant.

Conclusion and interpretation

It can be concluded that both 0.75% ropivacaine(15ml) and 0.5% levobupivacaine(15ml) when administered epidurally for elective lower abdominal surgeries, provide adequate and comparable sensory and motor blockade with minimal haemodynamic disturbances. Ropivacaine results in a shorter duration of motor blockade and provides a longer duration of sensory blockade and post operative analgesia.

Keywords

Ropivacaine; Levobupivacaine; Epidural anaesthesia.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

Chapter 1

Introduction

INTRODUCTION

“Pain is a more terrible lord of mankind that even death itself” – Albert Schweitzer.

The principal function of an anaesthesiologist in patient care is not only to save lives but also to relieve pain and suffering.

As the practice of anaesthesiology has extended into the peri operative period, the expertise in acute pain management is highly valued. The type of anaesthesia during the intraoperative period plays a significant role in providing effective postoperative analgesia, which significantly reduces morbidity following surgery.

Neuraxial blockade, especially epidural anaesthesia is being commonly and routinely practiced and has been the anaesthetic technique of choice for most of the abdominal and lower limb surgeries as it has the added advantage of excellent pain relief in the post operative period.

The history of neuraxial anaesthesia goes back as far as the 19th century. Early animal experiments by Corning and self-experiments by Bier, explored the anaesthetic effect of this technique and progressive scientific research and development to this date has led to the application of this technique to a vast array of clinical situations.[1]

Also, the lack of pain and opioid-related side effects results in a shortened hospital stay. Regional anaesthesia also reduces intraoperative bleeding resulting in improved operating conditions for the surgeon.

Epidural blockade is more versatile than spinal anaesthesia, giving the clinician an opportunity to provide adequate anaesthesia and analgesia, for extended duration of surgical needs and at the same time enabling excellent pain management well into the post operative period. It also provides hemodynamic stability due to minimal sympathetic blockade, as it produces segmental blockade unlike spinal anaesthesia. [1]

Bupivacaine, since its synthesis by Ekenstam in 1956 and introduction in 1963 by L.J Teluvio, has been extensively in use for epidural anaesthesia as it produces an adequate sensory and motor blockade.[1] However it has its own disadvantages and side-effects such as cardiac and central nervous system toxicity, more commonly seen with infusion of large doses.[2, 3]

These adverse effects have prompted a search for drugs with lesser toxicity.

Newer long-acting local anesthetics namely ropivacaine and levobupivacaine have recently been introduced for clinical use. The claimed benefits of these are reduced cardiac toxicity on overdose and more specific effects on sensory rather than motor nerve fibres.[4,5] Ropivacaine, first registered for clinical use in 1966 was found to have less cardio toxicity than bupivacaine in animal models. Unlike bupivacaine, ropivacaine has been developed and marketed as the pure S (-) enantiomer of the parent chiral molecule propivacaine. It is less lipophilic than bupivacaine. This property is associated with a decreased potential for CNS toxicity and cardiotoxicity.[6]

Numerous experimental studies were conducted to identify the fine cellular mechanism of the local anesthetic toxicity which refined the understanding of their action. The identification of optically active isomers of the mepivacaine family led to the selection of ropivacaine, a pure S-(-) enantiomer, whose toxicology was selectively and extensively studied before its introduction into the market in 1996. During the rapid and extensive use of ropivacaine in anaesthetic practice, unwanted side-effects have been found to be very limited.[7]

Besides being well tolerated and safe, ropivacaine has a short time to onset of anesthesia and results in a sensory and motor blockade of duration adequate for the procedure.

Levobupivacaine, in contrast to bupivacaine, which is available as racemate containing equal amounts of the R (+) - and S (–)-enantiomers, contains only the pure S (–)-enantiomer.[8] In recent years levobupivacaine has emerged as a safer alternative for regional anaesthesia. It demonstrated less affinity and strength of depressant effects on myocardial and central nervous vital centres in pharmacodynamic studies, and a superior pharmacokinetic profile.[9,10]

However, to date very few studies in literature have compared levobupivacaine and ropivacaine for epidural anaesthesia. Hence the present study is planned to compare the onset and duration of motor and sensory blockade in patients undergoing lower abdominal surgeries under epidural anaesthesia.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

Primary objective: To compare the onset and duration of motor block, onset, level and duration of sensory block.

Secondary objective: To compare the duration of postoperative analgesia and haemodynamic changes,

between 0.75% (plain) Ropivacaine and 0.5% (plain) levobupivacaine in patients posted for lower abdominal surgeries under epidural anaesthesia.

BASIC SCIENCES

Applied Anatomy

Sound knowledge of vertebral column anatomy and its contents is essential to all the anaesthesiologists for safe and successful administration of epidural anaesthesia, not only in terms of performance but also in terms of spread of drug in epidural space and level of block achieved.

Vertebral column

Main function of vertebral column is to protect the spinal cord. There are 33 vertebrae in vertebral column which includes[41]

- Cervical - 7
- Thoracic - 12
- Lumbar - 5
- Sacrum - 5 (fused)
- Coccyx - 4 (fused)

Curves of spine

In adults, curves of vertebral column have significant effect on spread of drugs in subarachnoid space and these curves are: [41]

- Cervical curve - Convexity anterior
- Thoracic curve - Concave anterior
- Lumbar curve - Convexity anteriorly

Cervical (C) five and lumbar (L) five are the highest points of cervical and lumbar curves in supine position and the lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively.[41]

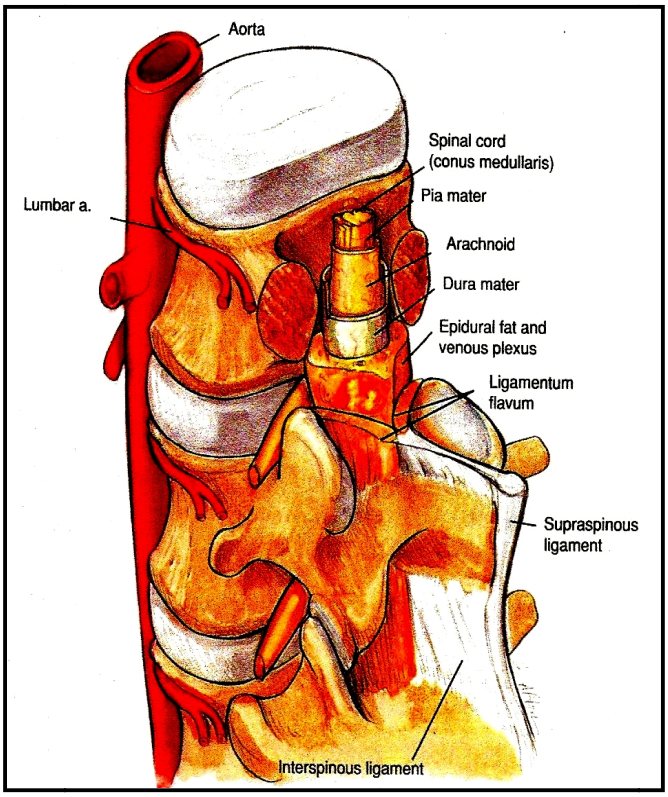


Fig 1: Vertebral Column

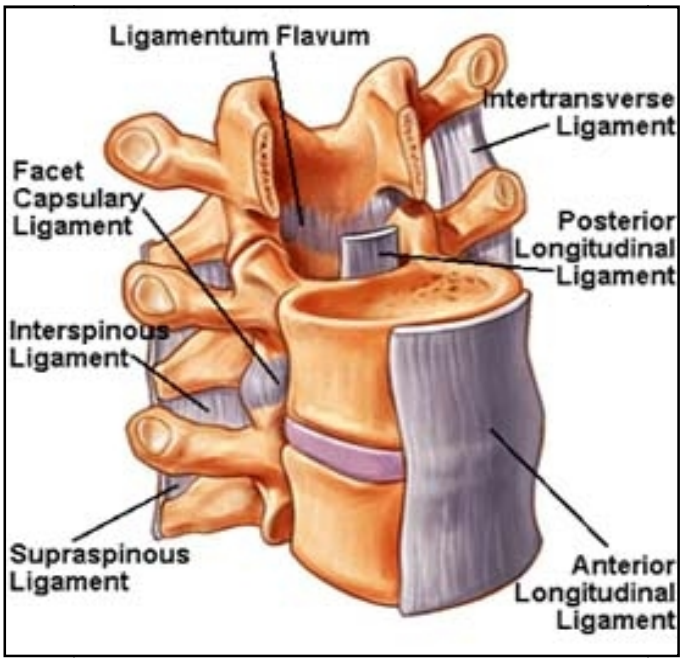


Figure 2: Spinal Ligaments

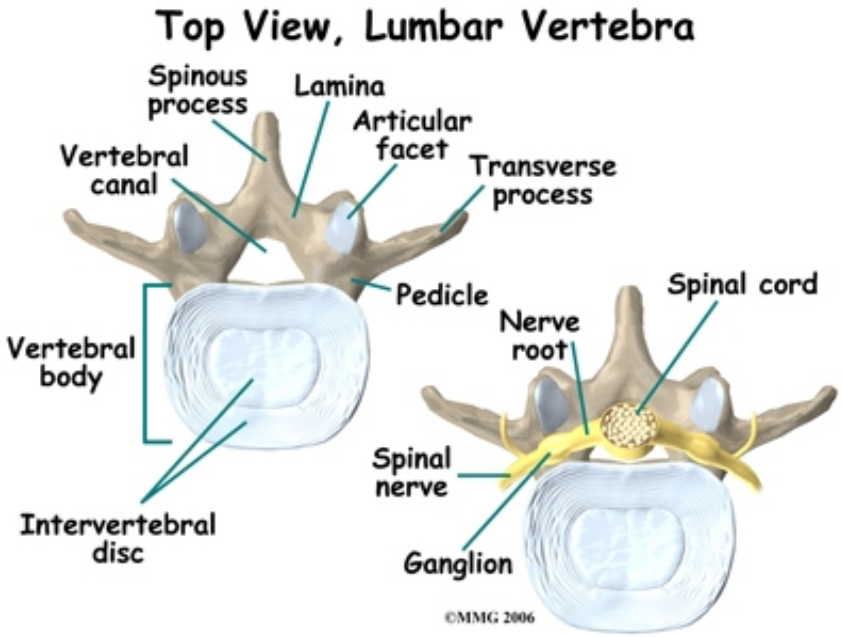


Figure 3: Typical Lumbar Vertebra

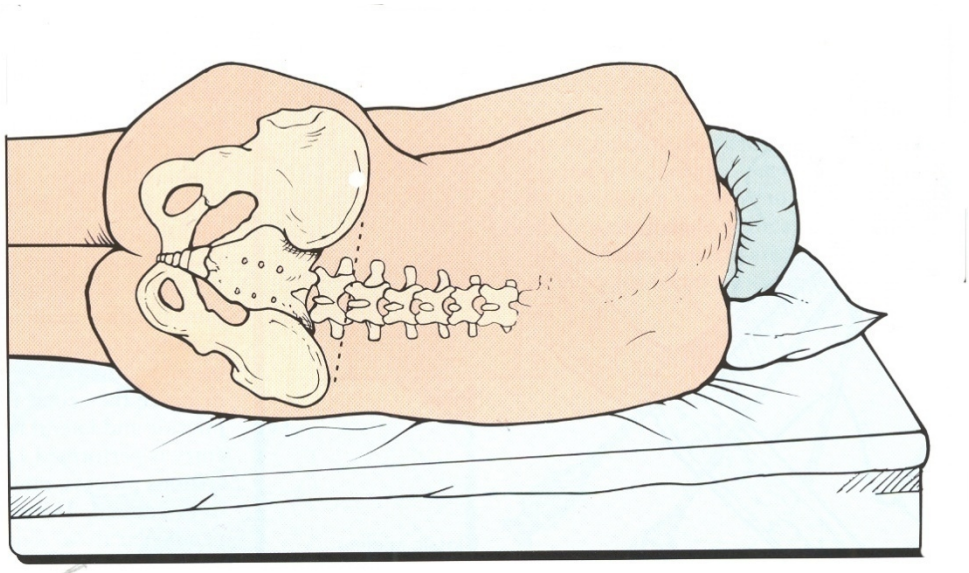


Figure 4: Line of Tuffier

Vertebral ligaments[41]

Following are the ligaments which give stability to the vertebral column:

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from sacrum to cervical five where it is continued as the ligamentum nuchae (Figure 2).

Interspinous ligament: This is a thin membranous ligament which connects spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament (Figure 2).

Ligamentum flavum: This ligament comprises yellow elastic fibres and connects adjacent laminae. Laterally, this ligament begins at the root of articular processes and extends posteriorly and medially to the point where laminae join to form spinous process (Figure 2).

Longitudinal ligaments: There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together

Intervertebral Discs[42]

These are principle connecting link between vertebral bodies. They form about 25% of the length of the spine. They have two parts. The outer fibrous part called the *annulus fibrosus* is made up of fibrous tissue, while the *nucleus pulposus* is the softer core. (Figure 3)

Topographical Line of Tauffier[42]

This is a horizontal line across the back between the crests of the iliac bone passing over the spine of the 4th lumbar vertebra in the upright position. In a patient lying in the lateral position it may also pass through L4 and L5 interspaces. The superior iliac crest is used to identify the L4 and L5 interspace during epidural anesthesia (Figure 4).

Lumbar vertebrae[42]

A typical lumbar vertebra consists of (Figure 3);

- A kidney shaped body.
- Two pedicles directed backwards from the upper part of the body.
- Two transverse processes
- Two laminae meeting posteriorly and enclosing the triangular vertebral foramen.
- Spinous processes which are thick, broad and quadrilateral in shape.
- Two upper and lower articular processes which prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Vertebral canal

- Spinal cord
- Spinal nerve roots
- Meninges
- Cerebrospinal fluid
- Vessels
- Fat
- Loose areolar tissue

Spinal cord[41]

The average length of the spinal cord in males is 45 centimetres (cms) and in females it is 42 cms. The average weight is approximately 30 gm.

The spinal cord is a continuation of the medulla oblongata below the level of foramen magnum and it tapers off into a conical extremity known as conus

medullaris. Filum terminale descends to the back of first segment of coccyx from apex of conus medullaris.

At birth, Spinal cord ends at the level of lower border of lumbar (L) three vertebra and in adults, it is as follows;

- Lower border of L1 - 50%
- Upper border of L2 - 40%
- Upper border of L3 - 3%

From the spinal cord arise 31 pairs of spinal nerves, made of a ventral and a dorsal root. These anterior and posterior roots after crossing the subarachnoid space, pass through the dura and extradural space independently and unite at the level of intervertebral foramen to form spinal nerve trunks, which further divide into anterior and posterior primary divisions.

The amount of white matter declines progressively from the cervical region down to the lumbar region. The gray matter is greatly increased in the both the lumbar and cervical enlargement.

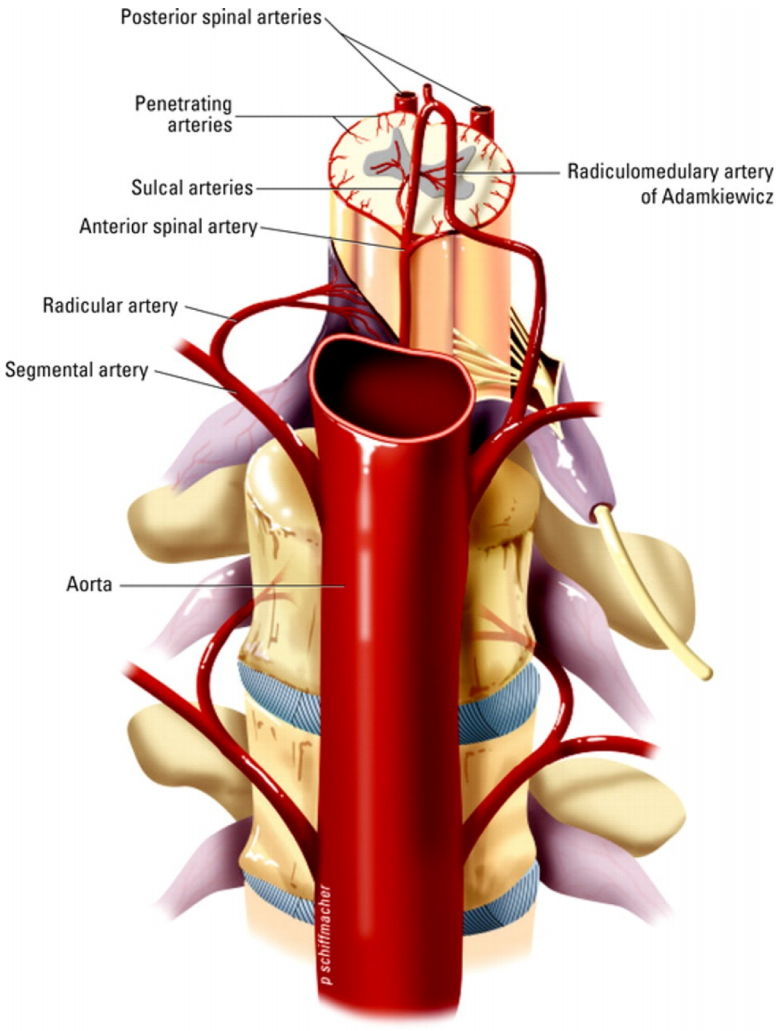


Figure 5: blood supply of spinal cord

Blood Supply of Spinal Cord[42]

The arterial supply is from the anterior and posterior spinal arteries. The anterior spinal artery is a single vessel lying in front of the anterior median fissure. It is formed by two small arteries, one given off from each vertebral artery at the level of the foramen magnum. It receives small communications from the intercostal and lumbar arteries; to provide the extra blood supply needed in the cervical, thoracic and lumbar enlargements.

There are two posterior spinal arteries-one on each side. They are derived from the vertebral artery or more often from a primary branch of each vertebral artery. They supply the posterior one-third of the spinal cord. This supply is augmented by

spinal branches of vertebral, ascending cervical, posterior intercostals, lumbar and lateral sacral arteries, which pass through the intervertebral foramina.

Venous drainage is through a plexus of anterior and posterior veins in the neck, azygous veins in the thorax, lumbar veins in the abdomen, and lateral sacral veins in the pelvis. There is no anastomosis between the anterior and posterior spinal arteries.

The longest of the feeder arteries is the radicularis magna (artery of Adamkiewicz), which supplies the anterior spinal artery in the area of the lumbar enlargement of the cord. It enters by way of a single intervertebral foramen (78% of the time on the left) between the T8 and L3 foramina.

Meninges[43]

The spinal cord is covered by three membranes from inward to outward, they are the pia mater, the arachnoid mater and the dura mater. The dural sac is the continuation of meningeal layer of the cranial dura mater. It is a circular sac or sleeve surrounding the spinal cord. Above, it is attached firmly to the circumference of the foramen magnum.

Duramater[44]

It is the outermost membrane, the fibres of which run longitudinally. Although continuous, it can be described in two parts: the cranial and the spinal. The cranial dura consists has two layers, outer endosteal layer, which lines the skull, and an inner meningeal layer, which invests the brain and folds inward to form the falx cerebri and tentorium cerebelli.

Arachnoid Mater[43]

The arachnoid mater is a delicate non-vascular membrane applied closely to the dura mater. The lower extent of dural sac is as follows;

- S2 vertebra 35%
- Below S2 40%
- Above S2 25%

Below this the dura continues as the filum terminale. The subarachnoid space is the space between the arachnoid and pia mater. This space is traversed by the cranial and spinal nerves and by the cobweb trabeculae. The space is annular in the cranial and thoracic vertebrae and is about three mm deep. Below the first lumbar vertebrae it is circular.

Epidural space[45]

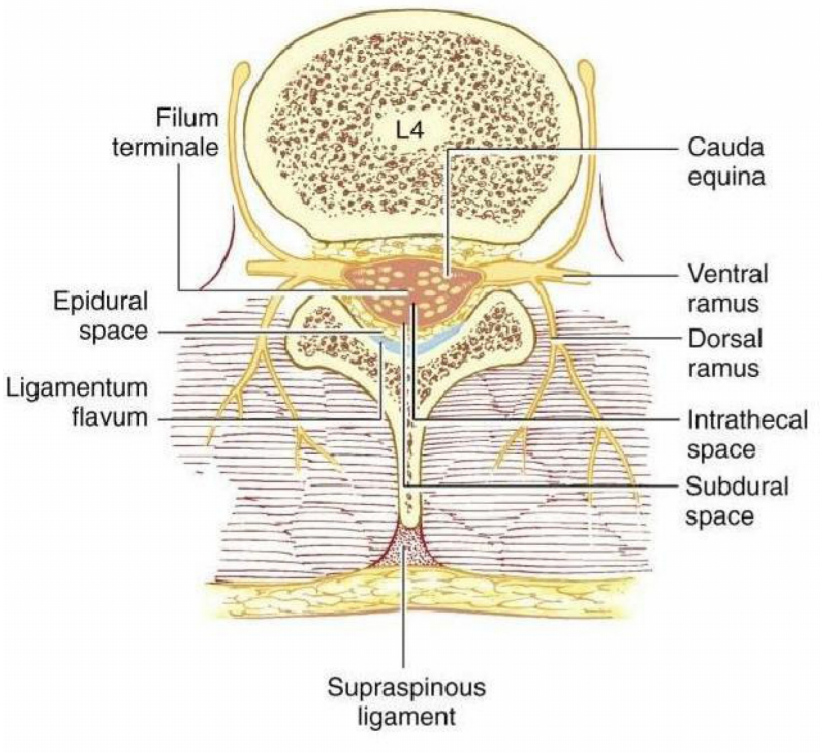


Figure 6: Epidural space

Measurement: The epidural space is most roomy at the upper thoracic levels. The epidural space at the posterior space in the adult measures about 0.4 mm at C7-T1, 7.5 mm in the upper thoracic region, 4.1 mm at T11-12 region and 4-7 mm in the lumbar region. The space is far greater than that of the subarachnoid space at the same level.

Shape and size: These are largely determined by the shape of the lumbar vertebral canal and the position and size of the dural sac within it. It has been suggested that though merely a potential space, it could be up to 5 mm in depth.

Types of epidural space[45]

The epidural space can be categorized into cervical, thoracic, lumbar and sacral epidural spaces. These spaces can be defined according to their margins. At the cervical epidural space, there is a fusion of the spinal and periosteal layers of dura mater at the foramen magnum to lower margin of the 7th cervical vertebra. While the thoracic epidural space is formed by the lower margin of C7 to the upper margin of L1, the lumbar epidural space is formed by the lower margin of L1 vertebra to the upper margin of S1 vertebra. The sacral epidural space is formed by the upper margin of S1 to sacrococcygeal membrane.

Boundaries of the epidural space

The epidural space is bounded superiorly by the fusion of the spinal and periosteal layers of the dura mater at the foramen magnum. Inferiorly, it is bound by the sacrococcygeal membrane. The space is bounded anteriorly by the posterior longitudinal ligament, vertebral bodies and discs while the pedicles and intervertebral foraminae form the lateral boundary. The ligamentum flavum, capsule of facet joints and the laminae form the posterior boundary of the epidural space.

The contents of the epidural space

This space contains semi-liquid fat, lymphatics, arteries, loose areolar connective tissue, the spinal nerve roots, and extensive plexus of veins. The epidural contents are contained in a series of circumferentially discontinuous compartments separated by zones where the dura contacts the wall of the vertebral canal.

Fat[46]

The epidural space contains abundant epidural fat that distributes along the spinal canal in a predictable pattern. Fat cells are also abundant in the dura that forms the sleeves around spinal nerve roots but they are not embedded within the laminae that form the dura mater of the dural sac. The fat in the epidural space buffers the pulsatile movements of the dural sac and protects nerve structure, creates a reservoir of lipophilic substances, and facilitates the movement of the dural sac over the periosteum of the spinal column during flexion and extension. The epidural fat has a continuous pattern of distribution that assumes a metameric pattern especially in the adult human. Drugs stored in fat, inside dural sleeves, could have a greater impact on nerve roots than drugs stored in epidural fat, given that the concentration of fat is proportionally higher inside nerve root sleeves than in the epidural space, and that the distance between nerves and fat is shorter. Similarly, changes in fat content and distribution caused by different pathologies may alter the absorption and distribution of drugs injected in the epidural space. The fat is largely distributed along the dorsal margin of the space, where it assumes triangular capsular shapes and linked to the midline of the ligamentum flavum by a vascular pedicle. The clinical significance of the fat distribution is related to the pharmacokinetics of drugs including local anesthetics injected into the space leaving a minute quantity of the agent to react with the nerve roots, and the slight resistance experienced during the insertion of an epidural catheter.

Lymphatics

The lymphatics of the epidural space are concentrated in the region of the dural roots where they remove foreign materials including microorganisms from the subarachnoid and epidural spaces.

Vertebral venous plexus[47]

The internal vertebral venous plexus has been extensively studied and found to be located in the epidural space. This plexus of veins is thought to be frequently involved in a bloody or traumatic tap during needle placement in the epidural space. The internal vertebral venous plexus consists of four interconnecting longitudinal vessels, two anterior and two posterior. The external vertebral plexus (EVP) in contrast, lies peripheral to the vertebrae and is made of the anterior and posterior external vertebral plexuses. The EVP is situated anterior to the vertebral bodies and in relation to the laminae, spinous processes, transverse processes and articular processes respectively. These veins communicate with the segmental veins of the neck, the intercostal, azygos and lumbar veins. With the veins of bones of the vertebral column, the internal and external vertebral plexuses form Batson's plexus. These veins are predominantly in the antero-lateral part of the epidural space, and ultimately drain into the azygous system of veins. As the whole system is valveless, increased intrathoracic or intra-abdominal pressure (e.g. ascites, pregnancy) can lead to major congestion and vessel enlargement within the spinal canal. The epidural venous plexus is surrounded by sparse quantity of fat.

The anterior epidural space is entirely occupied by a rich venous plexus (valveless system of veins). The plexus communicates with the intracranial sigmoid, basilar venous sinuses, basivertebral vein, occipital vein, and the azygous system. The plexus is linked to the abdominal and thoracic veins by the intervertebral foramina and through this connection transmit intraabdominal and intrathoracic pressure to the epidural space. The rich venous plexus is also connected to the iliac veins through the sacral venous plexus. Obstruction of the inferior vena cava, advanced pregnancy or intra abdominal tumors can cause distension of the venous plexus leading to an

increased risk of being traumatized during needle and/or catheter placement in the epidural space.

Epidural arteries[48]

The epidural arteries located in the lumbar region of the vertebral column are branches of the ilio-lumbar arteries. These arteries are found in the lateral region of the space and therefore not threatened by an advancing epidural needle.

Pharmacokinetics Of Epidural Blockade[49]

Epidural anaesthesia results from the interaction of local anaesthetics with nerve structures, primarily those located within the epidural space. Local anaesthetics can reach the sites of action along various distribution pathways. Uptake into extraneural tissues (in particular epidural fat) and systemic absorption compete with neural tissue distribution thereby affecting the clinical potency and duration of action. Consequently, epidural doses must be much higher than spinal doses.

Specifically, drugs may a) exit the intervertebral foramina to reach the paraspinous muscle space, b) drugs may diffuse into epidural fat, c) drugs may diffuse into ligaments and finally, d) drugs may diffuse across the spinal meninges.

The only mechanism by which drugs redistribute from the epidural space to the spinal cord is diffusion through the spinal meninges and the cellular arachnoid mater is the principal meningeal barrier to diffusion accounting for 95% of the resistance to meningeal permeability.

Meningeal permeability is not the only determinant of a drug spinal cord bioavailability after epidural administration. Drugs can partition into various environments in the epidural space and be unavailable for transfer across the spinal meninges.

Epidural fat may serve as a sequestration site for lipid soluble drugs. The dura mater is an important site of drug clearance. The human dura mater is a highly vascular structure. Because lipid soluble molecules traverse capillaries more readily than do more hydrophilic molecules, one can assume that lipid soluble drugs may be cleared by this mechanism more readily than less lipid soluble drugs.

Meninges contain multiple enzyme systems, which are capable of drug metabolism. In addition, the meninges express enzymes capable of metabolizing neurotransmitters, including epinephrine, norepinephrine, acetylcholine and neuropeptides. After epidural administration, local anesthetics need to cross the spinal meninges to reach their site of action

Epidurally administered drugs that reach the CSF, also can diffuse back across the meninges into the epidural space, but unless and until the drug concentration in the epidural space falls below that in the CSF, net drug transfer will be directed from the epidural space into the CSF. Diffusion depends mainly of the drug's physicochemical properties, particularly, lipid solubility.

Physiological Effects Of Epidural Blockade[41]

With currently available local anaesthetic agents, spinal epidural blockade implies sympathetic blockade accompanied by somatic blockade, which may involve sensory and motor blockade alone or in combination. Some of the most important (but not all) physiological effects of epidural blockade can be discussed in relation to either sympathetic blockade of vasoconstrictor fibres (below T4) and/or of cardiac sympathetic fibres.

Zone of differential blockade

Sensory

In intradural block sympathetic fibres are blocked two or three segments higher than sensory fibres. In extradural block, the relationship is complex. Level of sympathetic block is the same as (or lower than) sensory with epidural blockade. Sympathetic block will be greater when more concentrated solutions are used or when adrenaline added, as this has similar effect.

Motor

In intradural block, the difference between sensory and motor block is slight (two segments). In extradural block, the difference in levels is greater, depending on nature of local anaesthetic solution.

All types of nerve fibers are affected by local anaesthetics, but within any one fiber type, there is tendency for small, slower conducting fibers to be more readily blocked than large, fast conducting fibers. Between fiber types however, these rules do not hold good. Myelinated preganglionic B fibers which have a faster conduction time are about three times more sensitive to local anaesthetics than the slower non-myelinated post ganglionic C fibers.

Sensory Aα fibers appear to be more sensitive to blockade than motor Aβ fibers, although of the same conduction velocity, this may be because sensory fibers conduct at a higher frequency. It has been suggested that this selectivity for sensory fibers exhibited by Bupivacaine and Ropivacaine is a function of frequency dependent block, a property not shared by Etidocaine and Amethocaine.

Cardiovascular System

There are different ways in which intra and extradural block can influence the cardiovascular system.

1. Vasodilatation of resistance and capacitance vessels. Block of cardiac efferent sympathetic fibers from T1 and T4 resulting in loss of chronotropic and Inotropic drive and fall in cardiac output.
2. The arterial or Bainbridge reflex causing-bradycardia.
3. The operation of Marey's law causing tachycardia.
4. Depression of vascular smooth muscle and β adrenergic blockade of myocardium with fall in cardiac output.
5. Adrenaline effect (if used) following absorption, resulting in β stimulation and associated rise in cardiac output and reduction in peripheral resistance.

The overall effect is likely to be greater fall in mean arterial pressure than if adrenaline had not been used. Block not extending above T4 is not always associated with fall of blood pressure in fit young adults although the elderly may suffer significant hypotension when moderate volumes are injected into the epidural space Slowing heart rate is caused if any of the anterior roots carrying sympathetic cardiac accelerator fibers are blocked, as may happen in higher spinal blockade above T4, T5. A further cause of slow pulse rate is the lowering of blood pressure in the right atrium consequent on diminished venous return [Bainbridge (1874-1921) effect]. On the other hand, tachycardia during spinal analgesia may result from the operation of Marey's Law (a pulse of low tension is fast). Bradycardia is the more frequent effect.

Theories of causation of fall in blood pressure

1. Diminished cardiac output consequent on reduction of venous return to heart, and lack of muscular propulsive force on veins.
2. Dilatation of post arteriolar capillaries and small venules due to paralysis of vasoconstrictors, compensatory vasoconstriction takes place in areas not anaesthetized via carotid sinus reflexes. In high spinal blocks, majority of

vasoconstrictor fibers including those to arm (T2-T10), are paralyzed, hence low blood pressure. Total peripheral resistance decreases by only 18% following complete sympathetic block in healthy young adults.

3. Paralysis of sympathetic nerve supply to heart T1-T4. Bradycardia may give rise to fall in cardiac output.
4. Paralysis of sympathetic nerve supply to adrenal glands splanchnic nerves, with consequent catecholamine depletion.
5. Absorption of drug into circulation. This is more likely to be a cause of hypotension after extradural than after intradural analgesia because of the large amount of analgesic drug injected Ischemia and hypoxia of vital centres.
7. Hypovolemia, if present, may give rise to fall in blood pressure if central neural blockade is employed.
8. Compression of great vessels within abdomen, by the pregnant uterus, abdominal tumours or abdominal packs may cause severe hypotension in presence of central neural blockade.

Respiratory system

The phrenic nerve supplying diaphragm arises from the anterior roots of C3, C4, C5 and should not be encroached on in spinal anaesthesia, but phrenic nerve paralysis can occur.

Apnea may be due to medullary ischemia or to a toxic effect of the drug in extradural blocks. During epidural anaesthesia breathing becomes quiet and tranquil. This is not only due to motor blockade, but also to differentiation with reduction of sensory input to respiratory center.

Lowered arterial and venous tone also lessens the work of heart and tends to relieve any pre existing pulmonary congestion. The ventilation perfusion during

extradural block is not greatly altered and effects on respiratory functions are relatively small with no evidence on FRC or V/Q ratio. The pulmonary gas exchange is preserved.

The effect of block is largely on cardiovascular system. Vital capacity and force expiratory volume may be reduced, especially in cigarette smokers. Intercostal muscle paralysis is compensated for by descent of diaphragm, which is made easier by the lax abdominal wall. This not accompanied by hypoxia and hypercapnia although the ability to cough forcibly to expel secretion is impaired.

The patient may stop breathing so that respiratory support by IPPV and, if necessary the tracheal intubation required. Causes may be:

- Inadequate medullary blood flow due to inadequate cardiac output-a serious situation demanding immediate cardiorespiratory support.
- Massive epidural spread.
- Accidental subdural injection
- Toxic effects of local analgesic drug.
- Injecting narcotic analgesic drugs

Gastrointestinal system

Pre ganglionic sympathetic fibers from T5 to L1 are inhibitory to gut, there is no effect on oesophagus, the innervations of which is vagus. The small gut is contracted as the sympathetic inhibitory impulses are removed, the vagus being all powerful, Sphincters are relaxed and peristalsis is active although not more frequent. Pressure within the bowel lumen is increased.

Nausea and vomiting due to the hypotension may occur and usually come on in waves-lasting a minute or so and then passing away spontaneously. Stimuli arising in the upper abdomen may ascend along the unblocked vagi and perhaps the phrenic

nerve, and cause discomfort, if the patient is conscious. Infiltration of local anesthetic solutions may prevent this by blocking vagal afferents.

Colonic blood supply and oxygen availability are increased, perhaps an important factor in the prevention of anastomotic breakdown following gut resection.

Theories of causation of nausea and vomiting:

1. Hypotension, correction using a pressor drug may relieve nausea
2. Increased peristalsis
3. Traction on nerve endings and plexuses, especially via vagus
4. Presence of bile in stomach due to relaxation of pyloric and bile-duct sphincters
5. Narcotic analgesics (premedication)
6. Psychological factors
7. Hypoxia

Gastric emptying time is quicker when extradural block is employed for postoperative pain relief than when narcotic analgesics are used

Liver

There are no specific effects of significance. The degree of hypotension that compromises liver function is not known. Liver disease may interfere with the metabolism of local anaesthetic drugs.

Endocrine system

The usual increase of ADH during surgery is suppressed. Neuraxial block delays adrenal response to trauma, whereas operations under GA cause a rise in steroids.

In any case, either regional or general, there is no difference in the postoperative period once the effects of the block are discontinued. Spinal block suppresses the hyperglycemic response to surgery and stress and so is useful in

diabetic patients but this does not extend into postoperative period. The response to insulin is augmented and anaesthetist should be aware of possibility of hypoglycemia. Extradural block prevents lymphopenia and granulocytosis after operation, thus inhibiting the metabolic endocrine response to surgery and preventing immune depression.

Genitor urinary system

Sympathetic supply of kidney is from T11 to L1 via the lowest splanchnic nerves. Any effects on renal function are due to hypotension. Auto regulation of renal blood flow is impaired if mean arterial pressure falls below 50 mmHg. These changes are transient and disappear when blood pressure rises again. Sphincters of bladder are not relaxed, so soiling of table by urine is not seen and tone of ureters is not greatly altered. The penis is often engorged and flaccid due to paralysis of the Nervi erigentes (S2 and S3). This is a useful positive sign of successful block. Retention of urine may be moderately prolonged as L2 and L3 contain small autonomic fibers and their paralysis lasts longer than of the larger sensory and motor fibers.

Body temperature

Vasodilatation favors heat loss. Absence of sweating favors hyperpyrexia in hot environments. Catecholamine secretion is depressed, hence less heat is produced by metabolism. Extradural space is a temperature sensitive zone, whereas intradural space is not. Cold solutions injected into extradural space may induce shivering

1. Because the large veins act as exchangers.
2. As a result of sensory input.
3. Possibly because of the existence of thermal sensors

ROPIVACAINE

Introduction

Ropivacaine is a new long acting local anaesthetic drug that belongs to the amino amide group. Though it was synthesized by Ekenstam[50] in 1957 and belongs to the same group as that of bupivacaine and mepivacaine, ie pipecoloxylidides local anaesthetics, ropivacaine was introduced to clinical practice in 1996.

It was found that "propyl derivatives" of pipecoloxylidides were less toxic than 'butyl derivatives' (bupivacaine). Thus, Ropivacaine was developed since bupivacaine was found to be associated with significant number of cardiac arrests.[2] Despite being in the market for close to three decades internationally, it was only introduced into the Indian market very recently.

It is the first local anaesthetic to be presented as an almost pure S-enantiomer (> 99% pure).[7] It is commonly used for infiltration, peripheral nerve blocks, epidural, spinal anaesthesia and also for caudal epidural in children for surgical pain relief.

Chemical Structure[51]

Ropivacaine is an amino-amide class of local anaesthetic chemically described as S-(-)-1-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate. The International Union of Pure and Applied Chemistry name is (S)-N-(2,6-dimethylphenyl)-1-propylpiperidine-2-carboxamide. The drug substance is a white crystalline powder, with a molecular formula of $C_{17}H_{26}N_2O \cdot HCl \cdot H_2O$ and a molecular weight of 328.89. The chemical structure is given in the figure 7.

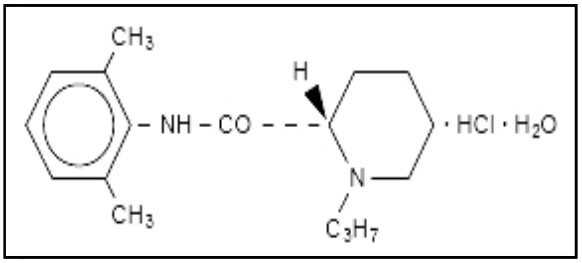


Fig : 7. Chemical structure of ropivacaine

Physical Properties

At 25°C ropivacaine HCL has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1). However, ropivacaine has a lower lipid solubility (substitution of pipecoloxylidine with a 3-carbon side chain instead of a 4–carbon side chain)[23] compared to bupivacaine and mepivacaine. Usually sodium hydroxide or hydrochloric acid is added to adjust pH of the compound. Ropivacaine is preservative free and is available in single dose containers in 2 (0.2%), 5 (0.5%), 7.5 (0.75%) and 10 mg/mL (1%) concentrations .The specific gravity of solutions range from 1.002 to 1.005 at 25°C.

Mechanism of Action[52,53]

Ropivacaine reversibly interferes with the entry of sodium in nerve cell membranes, leading to decreased permeability to sodium and thus

a. Block generation and conductance of nerve impulses.
b. Slows propagation of nerve impulses
c. Reduces the rate of rise of action potential

Most local anaesthetics block the unmyelinated C and myelinated Aδ fibers that transmit pain impulses at the same rate. However the rate of blockade of Aα and Aβ (that carry motor impulses) depends on the physicochemical properties, Pka and lipid solubility of the individual local anaesthetic drugs. As ropivacaine is less lipid soluble when compared to bupivacaine , the blockade of Aα and Aβ is slow and hence produce less motor blockade than bupivacaine. Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block while the motor block produced

by ropivacaine is slower in onset, less in intensity and short in duration. Clinically the order of blockade of nerve fibres is autonomic, sensory and motor, while the disappearance occurs in reverse order. The order of the loss of nerve function is

1. Pain
2. Temperature
3. Touch
4. Proprioception and
5. Skeletal muscle tone.

Pharmacokinetics[53,54]

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug given, the route of administration, the patient's haemodynamic condition and the vascularity of the site of administration. Absorption of ropivacaine from the epidural space is complete and biphasic. The half lives of the 2 phases (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively.

Distribution

After intravascular infusion, ropivacaine has a steady state of distribution of 41 ± 7 litres. It is a 94% protein bound, mainly to α1-acid glycoprotein. Ropivacaine readily crosses the placenta.

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome P450 1A to 3-hydroxy ropivacaine. After a single IV dose, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentration of 3-hydroxy ropivacaine have been found in the plasma. An additional metabolite, 2-hydroxy-methyl-ropivacaine has been identified but not quantified. N-de-alkylated metabolite of ropivacaine and 3OH-ropivacaine are the major metabolites excreted in urine

during epidural infusion.

Elimination

Ropivacaine metabolites are mainly excreted via kidney. After I.V administration 86% of the dose is excreted in urine of which only 1% is in unchanged form. Following I.V administration ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min and a renal clearance of 1 mL/min. The mean ± SD terminal half life is 1.8 ± 0.7 h and 4.2 ±1.0 h after I.V and epidural administration respectively.

Adverse effects

Excessive plasma levels are due to over dosage, unintentional intravascular injection or slow metabolic degradation. The mean doses at which CNS symptoms of toxicity begin to occur in human beings are 4.3 and 0.6µg/mL of total and free plasma concentrations respectively. When prolonged blocks are used the risks of reaching a toxic plasma concentration or inducing local neural injury are increased. Various possible side effects include

a. Injection site pain
b. **Cardiovascular system toxicity:** Vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities.
c. **Gastrointestinal system toxicity:** Fecal incontinence, tenesmus, nausea, vomiting.
d. **Central nervous system toxicity:** Tremor, Horner's syndrome, dyskinesia, neuropathy, vertigo, convulsion and coma. Because of depressant effect of ropivacaine on medulla, excitatory stage of CNS might not occur.
e. **Liver and Biliary system toxicity:** Jaundice
f. **Metabolic disorders:** Hypomagnesemia

LEVOBUPIVACAINE

Introduction

In recent years levobupivacaine, the pure S (−)-enantiomer of bupivacaine, emerged as a safer alternative for regional anesthesia than its racemic parent. It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centers in pharmacodynamic studies, and a superior pharmacokinetic profile. Clinically, levobupivacaine is well tolerated in a variety of regional anesthesia techniques both after bolus administration and continuous postoperative infusion.

Chemical structure[9]

Levobupivacaine ([2S]-1-butyl-N-2 6-dimethylphenyl] piperidine-2-carboxamide) is an amino-amide local anesthetic drug belonging to the family of n-alkyl substitute pipecoloxylidide. Its chemical formula is C_{18} H_{28} N_2 O. (Figure 8)

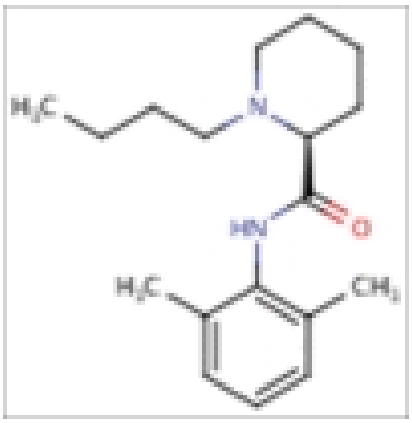


Figure 8 : Chemical structure of levobupivacaine

Physical Properties

Levobupivacaine HCL is a white crystalline solid that is soluble in water. Levobupivacaine injection is a sterile, non pyrogenic aqueous solution with a pH of 4-6.5. The pKa of levobupivacaine is approximately the same as bupivacaine (8.1). It has a similar lipid solubility as bupivacaine and mepivacaine and is >97% bound to plasma

proteins. Usually sodium hydroxide or hydrochloric acid is added to adjust pH of the compound. Levobupivacaine is preservative free and is available in single dose containers in 2.5 (0.25%), 5 (0.5%), and 7.5 (0.75%) concentrations.

Mechanism of Action [55]

Levobupivacaine exerts its pharmacological action through reversible blockade of neuronal sodium channels. Myelinated nerves are blocked through exposure at the nodes of Ranvier more readily than unmyelinated nerves; and small nerves are blocked more easily than larger ones.

In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of the affected nerve fibers. Specifically, as bupivacaine, but with a superior pharmacokinetic profile.

Clinically, levobupivacaine has been observed to be well-tolerated in regional anesthesia techniques both after bolus administration and continuous post-operative infusion. The incidence of adverse drug reactions (ADRs) is rare when it is administered correctly.

Pharmacokinetics[8,9]

Absorptiom

The dose as well as the route of administration of levobupivacaine determines the plasma concentration following therapeutic administration as the absorption is dependent upon the vascularity of the tissue.

After epidural administration of levobupivacaine, the absorption is biphasic, with rapid absorption of a small quantity of drug into the circulation and slower absorption of the remainder of the drug. It has been observed that peak levels of levobupivacaine in the blood reaches approximately 30 min after epidural administration and doses up to 150 mg had resulted in mean C_{max} levels up to 1.2

g/mL. The epidural absorption gets affected by age as the fraction absorbed decreases and the fast absorption phase is shorter in older (aged < 70 years) compared with the younger (aged 18-44 years) patients. The older patients also have a higher spread of analgesia by ~ 3 dermatomes. Therefore, in the elderly patients a lower dose of levobupivacaine, according to their physical status is recommended.

Distribution

The volume of distribution is estimated at 66.91 ± 18.23 L (after intravenous administration of 40 mg in healthy volunteers). The pKa of levobupivacaine is 8.1, similar to the pKa of the racemic bupivacaine. The half-life is 3.3h. The rate of clearance is 39.06 ± 13.29 L/h (after intravenous administration of 40 mg in healthy volunteers).

Alpha1-glycoprotein is the main binding site for levobupivacaine. Protein binding of levobupivacaine is more (97%) than that of racemic bupivacaine (95%). Less than 3% of the drug circulates free in plasma. The free proportion of the drug can have an action on the other tissues, causing unwanted side-effects and toxic manifestations. In newborns and in protein-deficient states like under nutrition and nephrotic syndrome, lesser amount of protein is available for binding, causing higher levels of free drug, resulting in toxic effects at lower doses.[55]

Metabolism

Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. *In vitro* studies using (14 C) levobupivacaine showed that cytochrome (CYP) CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to inactive metabolites, desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively.

Elimination

In vivo, the 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates, which are excreted in urine. Metabolic inversion of levobupivacaine to R (+)-bupivacaine was not evident both *in vitro* and *in vivo*.[55]

Following intravenous administration, recovery of the radio-labeled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 h. Of this 95%, about 71% was in urine while 24% was in feces.

Systemic toxicity

Recent evidence, as described below, suggests that the systemic toxicity of levobupivacaine is less than that of the R(+)-bupivacaine or racemic bupivacaine.[2] Differences in CNS-toxicity between levobupivacaine and racemic bupivacaine has been studied in animal and humans. Symptoms of excitatory CNS-toxicity, like convulsions, occurred at a lower dose infused for bupivacaine than for levobupivacaine in a sheep animal model.[28] There was a distinct difference in the cell firing rate in the tractus solitarius of the rat after rapid intravenous injection of S(–)-bupivacaine and R(+)-bupivacaine, the latter being the strongest inhibitor. This neuronal inhibition may be an additional factor involved in the origin of cardiotoxicity of local anaesthetics. In human volunteers, the CNS-depressant effects on the EEG were less after intravenous infusion (40 mg) of levobupivacaine than bupivacaine.[29]

Management of complications

Discontinuation of drug administration should be done at the first sign of toxicity. As no specific antidote is available, symptomatic and supportive management should be done promptly. Any change in mentation need oxygen

administration. Secure airway and provide assisted ventilation if any signs of respiratory depression are observed. Convulsions can be treated with barbiturates, specific anticonvulsants or neuromuscular blockers. In case of cardiac arrest, prolonged resuscitative efforts might be required.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Epidural anaesthesia was introduced into clinical practice in the first years of the 20th century, about 50 years after the discovery of inhalation anaesthesia. In 1921, Fidel Pagés described the injection of local anaesthetic into epidural space in lumbar and thoracic regions, and this markedly increased the possibility of epidural block.[11] The subsequent improvements in needles, catheters, new drugs and a better understanding of physiology and pharmacology contributed to the development of the epidural block, which nowadays is an essential technique in anaesthesiology.

Most of the local anaesthetics synthesized during the initial period were amino ester agents which were relatively unstable. In addition, the hydrolysis of amino esters by enzyme pseudo cholinesterase resulted in the formation of para amino benzoic acid which was responsible for reported allergic reactions. [12]

A major breakthrough in the chemistry of local anesthetic agents occurred in 1943 when Loefgren and Lundquist synthesized lidocaine, which was an amide derivative of diethylamino acetic acid. Similarly, several other drugs like mepivacaine, bupivacaine, prilocaine were later introduced into clinical practice.

These amide local anesthetics exhibited a number of advantages over amino esters which included better stability when in solution and a longer shelf life. They were not influenced by repeated exposures to high temperature and thus could be re-sterilized. In addition, their metabolites did not include p-amino benzoic acid resulting in a decreased likelihood of allergic reactions.[13]

In the beginning of 1990, a number of cases were published reporting cauda equina syndrome observed with continuous spinal anaesthesia with hyperbaric 5% lidocaine.

In 1993, a new adverse effect, 'transient neurologic toxicity', was described in patients recovering from spinal anaesthesia with lidocaine.[14, 15]

Chiang YY et al [16] reported lignocaine toxicity in a healthy young male, weighing 65 kg, undergoing circumcision for phimosis under penile block with 2% lidocaine (600 mg) who developed headache, tinnitus, visual and auditory disturbances twenty minutes after injection followed by muscle twitching of angle of mouth, trismus and rigidity of extremities. The adverse event was believed to be lidocaine-induced CNS intoxication.

Bupivacaine, an amino amide local anesthetic was first synthesized in Sweden by A.F Ekenstam and his colleagues in 1957. First report of its use was in 1963 by L.J Teluvio. It is one of the long acting local anesthetic agents available, which is extensively used for intrathecal, extradural and peripheral nerve blocks. But a number of deaths from cardiac arrest were reported in association with regional anaesthesia using bupivacaine. Most appeared to be caused by accidental intravenous injection of this long acting local anaesthetic agent. The doses required to produce cardiotoxicity seemed to be close to the convulsant doses.[17]

George. A.N. Albright stated that bupivacaine might result in almost simultaneous seizures and cardiovascular collapse without antecedent hypoxia from typical clinical doses following inadvertent intravascular administration.[2]

One of the specific clinical features of bupivacaine is that clinical evidence of accumulation of the drug in plasma may not be appreciated until a fairly late stage because of its high affinity for plasma protein binding sites. The free concentration of the drug in plasma remains low until all the protein-binding sites are fully occupied, after which toxicity can occur without exhibiting signs of CNS toxicity before CVS collapse[17,18]

Bupivacaine has also been shown to have selective cardiac effects related to the slow rate at which it dissociates from the sodium channel.[19] An important aspects of this toxicity is that it involves a significant degree of stereo specificity, with the S (–) isomer showing significantly less cardio toxic effect[20]

Thus with the disadvantages of lignocaine and bupivacaine clearly known, the need to develop a safer drug was clear and evident.

Two newer, long-acting local anaesthetics have been developed after the evidence of bupivacaine-related severe toxicity: levobupivacaine and ropivacaine. Both these agents are pure left-isomers and based on their three-dimensional structure, they have less toxic potential both on the central nervous system and on the heart. Several clinical studies have evaluated their toxicology and clinical profiles.

Ropivacaine is a newer amide local anaesthetic agent that has been produced as a pure S(–) isomer which is the propyl analogue of bupivacaine having a butyl group in same position.[21,22] In animal studies ropivacaine was found to be intermediate in its depressant effects on V_{max} between bupivacaine (highest) & lidocaine (lowest).[23,24] A favourable cardio toxic profile of ropivacaine was confirmed in rabbits[25] & pigs with greater safety margins between convulsive & lethal doses. Ropivacaine administered by intravenous infusion was found to be less toxic than bupivacaine in human volunteers. Mild CNS symptoms & minor cardiovascular toxicity as measured by changes in contractility & conductivity, occurred at lesser dosage & lower plasma concentration with bupivacaine compared to ropivacaine.[26]

Similarly, Levobupivacaine demonstrated less affinity and strength of inhibitory effect on the inactivated state of cardiac sodium channels than the racemic parent or dextro bupivacaine in in-vitro animal tissue experimental studies[27] A recent study has confirmed a better neurotoxic profile of levobupivacaine when compared to

racemic bupivacaine, and this is indicative of a safer profile of levobupivacaine in clinical practice. Similarly, in vivo animal studies showed that the cardiotoxic dose of intravenous bupivacaine and its pure S (−)-enantiomers followed the order ropivacaine >levobupivacaine >bupivacaine [28]

In human volunteers studies, the mean dose of intravenous levobupivacaine and bupivacaine associated with central nervous system symptoms was similar, ie 56–68 mg and 48–65 mg, respectively[29]. At this similar dose, levobupivacaine showed significantly less myocardial contractility and atrio-ventricular conduction depressant effect than bupivacaine. Although pharmacokinetics of ropivacaine and levobupivacaine has been determined after intravenous infusion[29] the number of available studies on their clinical profile in spinal and epidural anaesthesia is limited.

Thus with the experimental studies demonstrationg the safety profile of levobupivacaine and ropivacaine, several studies were undertaken to determine their efficacy in clinical practice.

In a study conducted by **Crosby E. et al**,[30] 60 patients posted for caesarean section were enrolled to receive 22ml of 0.5% bupivacaine or 22ml of 0.5% ropivacaine epidurally. The median onset time for sensory block, within dermatomal levels relevant for surgery (T6-S3), varied between 7.5 and 25 min in the ropivacaine group and 5 and 17.5 min in the bupivacaine group. The median duration of sensory block within dermatomal levels relevant for surgery varied between 1.7 and 4.2 hr for ropivacaine and 1.8 and 4.4 hr for bupivacaine. The median onset time for motor block with ropivacaine was 15 min and for 12.5 min for bupivacaine.. The median duration times for motor block for ropivacaine and bupivacaine were 2.1h and 2.4h respectively.

In a similar study conducted by **Wolff A.P et al**, [31] which recruited 126 patients undergoing elective hip replacement to receive either 20 ml of epidural 0.5%, 0.75%, or 1% ropivacaine or 0.5% bupivacaine. The onset times of analgesia appropriate for surgery (T10-S3) were largely less than 30 min in all groups and were not statistically significant. Duration of sensory blockade was 4.3 hrs, 5.3hrs, 6.9hrs and 4.8hrs for 0.5%, 0.75%, 1.0% ropivacaine and 0.5% bupivacaine respectively. Duration of motor block was 3hrs, 3.1hrs, 4.6hrs, and 3.3hrs for 0.5%, 0.75%, 1.0% ropivacaine and 0.5% bupivacaine respectively.

In another study conducted by **Guler G et al** [32] in which 81, ASA I-II males, aged 60-80 years, undergoing transurethral resection of prostate were randomly assigned to three groups receiving epidural ropivacaine as Group I(15 ml) of 0.75% solution, group II (10ml) of 0.75% solution, and group III (10 ml) of 0.5% ropivacaine. The duration of sensory block was more in group I (172min), and the time to achieve the T10 level was least in group I (17min). Duration of motor block was significantly less in group III (87min) than in groups I (95.8min) and II (91.6min).

In another study conducted by **Korula S. et al** [33] 61 patients undergoing bilateral inguinal mesh hernioplasty were randomised to receive 15 ml of either 0.5% bupivacaine and 0.75% ropivacaine epidurally. The mean time for onset of sensory block to T_6 was longer in 0.5% bupivacaine (18 +/- 5.77min) compared to both 0.75% ropivacaine (15.66 +/- 6.91min). The sensory block lasted for a longer duration with 0.75% ropivacaine group (352 +/- 41.63min) than bupivacaine group (334 +/- 41.23 min) but the difference being statistically insignificant. After the main dose of study drug 40% of patients in the ropivacaine group and 50% of patients in the bupivacaine group achieved grade 3 block within 30 min. The duration of motor blockade was

comparable with 0.5% bupiavaine (131.61 +/- 29.56 min) and 0.75% ropivacaine (144.64 +/- 34.61 min).

Based on findings that the cardiotoxicity observed with racemic bupivacaine is more pronounced with the R(+)-enantiomer, the S(-)-enantiomer (levobupivacaine) has been developed for clinical use as a long acting local anaesthetic. The majority of studies indicate that levobupivacaine has similar potency to bupivacaine. However, levobupivacaine had a lower risk of cardiovascular and CNS toxicity than bupivacaine in animal studies.[9]

Cox CR et al, [34] in their study conducted on 88 patients undergoing elective lower limb surgeries under lumbar extradural anaesthesia who were randomised to receive 15 ml of 0.5% or 0.75% levobupivacaine, or 0.5% bupivacaine observed the onset of sensory block to be longer in 0.5% levobupivacaine (8min) as compared to both 0.75% levobupivacaine (7min) and 0.5% bupivacaine (7min). The sensory block lasted for a longer duration with 0.5% levobupivacaine group (377min) but the difference being insignificant. The onset of motor block with 0.5% levobupivacaine (25min) was similar to 0.75% levobupivacaine (27min) and 0.5% bupivacaine (18min). The motor block duration of 0.5% levobupivacaine (185min) too, was similar to 0.5% bupivacaine (192min).

In a similar sudy, **Faccenda KA et al**, [35] conducted a prospective, controlled, double-blinded study on 62 ASA I-II obstetric patients undergoing elective Caesarean Section under extradural anesthesia, who were randomized to receive either 25 ml of 0.5% bupivacaine or 0.5% levobupivacaine. The mean time for onset of block adequate for surgery was 10 minutes for levobupivacaine and 8.4 minutes for bupivacaine. Mean duration of sensory block was 486 and 463 minutes for levobupivacaine and bupivacaine respectively. The mean duration of motor block was

significantly longer in the levobupivacaine group (206.5 minutes) compared with 163.5 minutes for bupivacaine.

In another study conducted by **Kopacz DJ et al**, [36] 56 patients undergoing elective lower abdominal surgery under epidural anaesthesia were randomised to receive 20 ml of either 0.75% levobupivacaine or 0.75% bupivacaine. The mean time for onset of sensory block was similar in both levobupivacaine and bupivacaine groups (13.6 +/- 5.6 min vs 14.0 +/- 9.9 min) respectively. The sensory block lasted for a longer duration with 0.75% levobupivacaine group (550 +/- 87.6min) than bupivacaine group (505.9 +/- 71.1 min) indicating that the sensory and motor block produced by 0.75% levobupivacaine is equivalent to that of 0.75% racemic bupivacaine.

There are very sparse studies in literature comparing epidural levobupivacaine and ropivacaine.

In a study conducted by **Casati A et al,** [37] 45 ASA I-III patients were randomly allocated to receive epidural block with 15 ml of 0.5% levobupivacaine, 0.5% bupivacaine, or 0.5% ropivacaine . The onset time of sensory block observed was (31 +/- 16 minutes) with levobupivacaine, (25 +/- 19 minutes) with bupivacaine, and (30 +/- 24 minutes) with ropivacaine ($p = 0.98$). Recovery of pinprick sensation occurred after (214 +/- 61 minutes) with levobupivacaine, (213 +/- 53 minutes) with bupivacaine and (233 +/- 34 minutes) with ropivacaine ($p = 0.26$). It was thus concluded that, Levobupivacaine 0.5% produces an epidural block of similar onset, quality, and duration as the one produced by the same volume of 0.5% bupivacaine, with a motor block deeper than that produced by 0.5% ropivacaine.

In another randomised study by **Peduto V. A et al,** [38] 65 patients received 15ml of 0.5% levobupivacaine or 15ml of 0.75% ropivacaine epidurally for lower

limb procedures. The time for onset of sensory block with levobupivacaine, was (29 +/- 24 min), and with ropivacaine was (25 +/- 22 min) (P = 0.41). The time for complete resolution of motor block with levobupivacaine was (105 +/- 63 min) and with ropivacaine, was (95 +/- 48 min; P = 0.86). The time for regression of sensory block to T12 with levobupivacaine was (185 +/- 77 min) and with ropivacaine, it was (201 +/- 75 min; P = 0.46). It was thus concluded that 15ml of 0.5% levobupivacaine produces an epidural block with the same clinical profile as 15ml of 0.75% ropivacaine .

Yang et al, [39] in a similar study conducted on 62 parturients undergoing elective caesarean section under epidural anaesthesia who were randomised to receive 20 ml of either 0.5% levobupivacaine or 0.75% ropivacaine observed that the mean time for onset of sensory block upto T_6 was longer in 0.5% levobupivacaine (15.5 +/- 9.7min) compared to both 0.75% ropivacaine (11.8 +/- 8.6 min). The sensory block lasted for a longer duration with 0.5% levobupivacaine group (224 +/- 66.6min) than ropivacaine group (176 +/- 32.8 min) the difference being statistically significant($p < 0.05$). The mean times for onset of motor blockade of bromage 3 in ropivacaine group was (24.9 +/- 13.3 min) as compared to (31.0 +/- 14.4 min) in levobupivacaine group. The duration of motor blockade was comparable with 0.5% ropivacaine and 0.5% levobupivacaine (126.3 +/- 86.6 min vs 106.6 +/- 67.7 min).

In another study conducted by **Santorsola R et al**,[40] 45 patients undergoing hallux valgus repair under femoral nerve block were randomised to receive 20 ml of either 0.5% levobupivacaine, 0.5% bupivacaine or 0.5% ropivacaine. The mean time for onset of sensory block was 15min with 0.5% levobupivacaine, 15min with 0.5% ropivacaine and 30min with 0.5% bupivacaine. The sensory block lasted for a duration of 16hrs with 0.5% levobupivacaine group, 17hrs with ropivacaine group and

14hrs with bupivacaine group. The times of onset and duration of motor blockade were comparable in all the groups.

Thus, with studies in literature demonstrating adequate clinical efficacy and safety profile of levobupivacaine and ropivacaine, the present study is aimed to determine the clinical effects of ropivacaine and levobupivacaine in patients undergoing lower abdominal surgeries under epidural anaesthesia.

Chapter 4

Methodology

MATERIAL & METHODS

The present study titled "COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE BETWEEN EQUIPOTENT DOSES OF 0.75% PLAIN ROPIVACAINE AND 0.5% PLAIN LEVOBUPIVACAINE IN LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA- A ONE YEAR RANDOMIZED CLINICAL STUDY"was conducted in the Department of Anaesthesiology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2013 to December 2013.

Source of Data

Patients aged between 20 to 60 years of either gender, belonging to ASA Grade I and II scheduled for elective lower abdominal surgeries under epidural anaesthesia were studied.

Inclusion Criteria:-

- Patients aged between 20-60 years.
- Patients of either sex.
- Patients with ASA Grade I and II

Exclusion Criteria:-

- Patient refusal.
- Contraindications to epidural.
- Pre-existing neurological deficits in the lower extremities, and

- Cardiorespiratory diseases,
- neurological or psychological disease,
- hepatic, or renal disease.
- Bleeding diathesis

Sample Size

A total of 90 patients distributed into two groups of 45 each scheduled for elective lower abdominal surgeries under epidural anaesthesia were enrolled.

Randomization procedure: randomisation was performed using a computer generated randomization table.

Sample Size and sampling method: Using the results of previously conducted studies and the duration of motor block as the parameter to determine the sample size in the standard formula mentioned below;

$$\text{Sample Size}(n) = \frac{2 \text{ X } (Z\alpha + Z\beta)^2 (\ ^2)}{(X_1 - X_2)^2}$$

Level of significance is taken as 5%

Power of the test used is taken as 80%

Hence, $Z\alpha = 1.66$

$Z\beta = 0.84$

X_1= 185

X_2= 225

☞ = 75

Thus, $n = \frac{2[1.65 + 0.84]2 \times 752}{(185\text{-}225)^2}$

n = 44

Where:

- X_1 is duration of motor block in levobupivacaine group
- X_2 is duration of motor block in ropivacaine group

for ease of calculation, a sample size of 45 in each group was obtained.

Study Group:-

After having obtained the approval of Institutional ethical committee and informed consent of the patients and having met inclusion and exclusion criteria, patients were randomized based on computer generated randomization table into one of the two groups.

- Group L –15ml of 0.5% Levobupivacaine
- Group R – 15ml of 0.75% Ropivacaine

All study drugs were prepared in identical syringes with either 15ml of 0.75% plain ropivacaineor15 ml of 0.5% levobupivacaine. Study drugs were prepared by an anaesthesiologist not involved with subsequent administration and patient assessment.

Procedure:-

A thorough pre-anaesthetic check-up was done for all patients, a day before surgery. Basic investigations like haemoglobin, total & differential WBC count, RBS, bleeding & clotting time, HIV &HBsAg, ECG and urine routine were carried out in all the patients. Written informed consent was obtained before the surgery after explaining the patients about the drug and epidural anaesthetic procedure. All the patients were educated about the verbal numerical scale to grade the pain in the post operative period.

Once the patient‘s nil oral status was confirmed, an intravenous access with 18 gauge IV Cannula was secured and the patient was preloaded with Ringer‘s Lactate fluid @ 10 ml/kg over 30 minutes in the pre anaesthetic room.The patient was then shifted to operation theatre where monitors were attached and base line heart rate, BP(systolic & diastolic, mean arterial blood pressure), respiratory rate and SpO2 were recorded.

Under strict aseptic precautions, the skin and subcutaneous tissues at the L2-3 or L3-4 interspace were infiltrated with 2ml of 2% Lidocaine. The epidural space was identified with patients in the lateral decubitus position by using an 18-gauge Tuohy needle and a loss of resistance to air technique. Initial test dose of 2% lignocaine with adrenaline was given after negative aspiration of blood of csf, followed by injection of 15 ml of either 0.5% levobupivacaine or 0.75% ropivacaine.

The time at which epidural injection of the study drug was completed was considered as zero (t=0).

(A) Sensory blockade:-

Sensory blockade was assessed by pin prick method using the blunt end of a 27-gauge needle. Adequate block to initiate surgery was a bilateral sensory block uptoT_{10} dermatome.

1) Onset of sensory blockade:- Time (in mins) at which there is loss of pain to pinprick atT10 levels after complete injection of the study drug.

2) Highest level of sensory block: - Highest cephalad dermatomal sensory blockade achieved.

3) Duration of sensory blockade: - Time from onset of sensory block till two segment regression from highest level of blockade..

4) Duration of post operative analgesia:-Time (in mins) between injection of study drug to the first supplemental analgesic administered.

(B) Motor blockade:-

Motor block was assessed by modified Bromage scale. Onset time and duration of motor blockade was tested bilaterally using modified Bromage scale (Proposed by Bromage and modified by Logan-Smith).

Scale	Criteria	Degree/Grade of block
0	Free movement of legs, feet with ability to raise extended leg	none
1	Inability to raise extended led and knee flexion is decreased but full extension of feet and ankles are present	Partial 33%
2	Inability to raise leg or flex knees, but flexion of ankle and feet present	Partial 66%
3	Inability to raise leg, flex knee or ankle or move toes	Complete paralysis

1) Onset of motor blockade: -Time (in mins) to achieve Bromage scale III block after complete injection of the study drug..

2) Total duration of motor blockade: - Time(in min) to recede to Bromage scale score 0 from maximum Bromage scale achieved.

Sensory and motor block were assessed at time intervals: 0, 5, 10, 15, 30, 45, 60, 90, 120 minutes after injection. The assessments were continued at 30 minutes interval thereafter until the motor block regressed completely (i.e modified bromage score=0). All durations were calculated considering the time of injection as time zero.

(C) Haemodynamic and other vital parameters:-

Blood pressure and heart rate were recorded at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and every 15 minutes thereafter till the end of surgery.

Hypotension was defined as decrease in systolic B.P by 30% from baseline values or a systolic B.P less than 90 mm of Hg and was treated with incremental intravenous boluses of mephentermine 5 to 10 mg and a bolus administration of 250ml of ringer lactate solution over 10 mins.

Bradycardia was defined as decrease in heart rate less than 60 beats per minute and was treated with intravenous Atropine 0.6 mg. Supplementary oxygen was given through face mask.

(D) Post operative period:-

All patients were observed and monitored for vital signs in the post anaesthesia recovery room and in the ward until complete recovery from sensory and motor blockade and duration of post operative analgesia & any side effects if present were recorded. Inj tramadol 100mg ivwas given when patient complained of mild pain (VAS score > 3) and the time noted. Patients were also observed for the next 24 hours after the procedure. Time for the first supplemental analgesic in the post operative period was considered as the duration of post operative analgesia.

(E) Statistical Methods

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Fisher's exact test. $P<0.05$ was considered statistically significant.

Chapter 5

Results

RESULTS

This one year randomized clinical trial was conducted in the Department of Anaesthesiology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum during the period of January 2013 to December 2013.

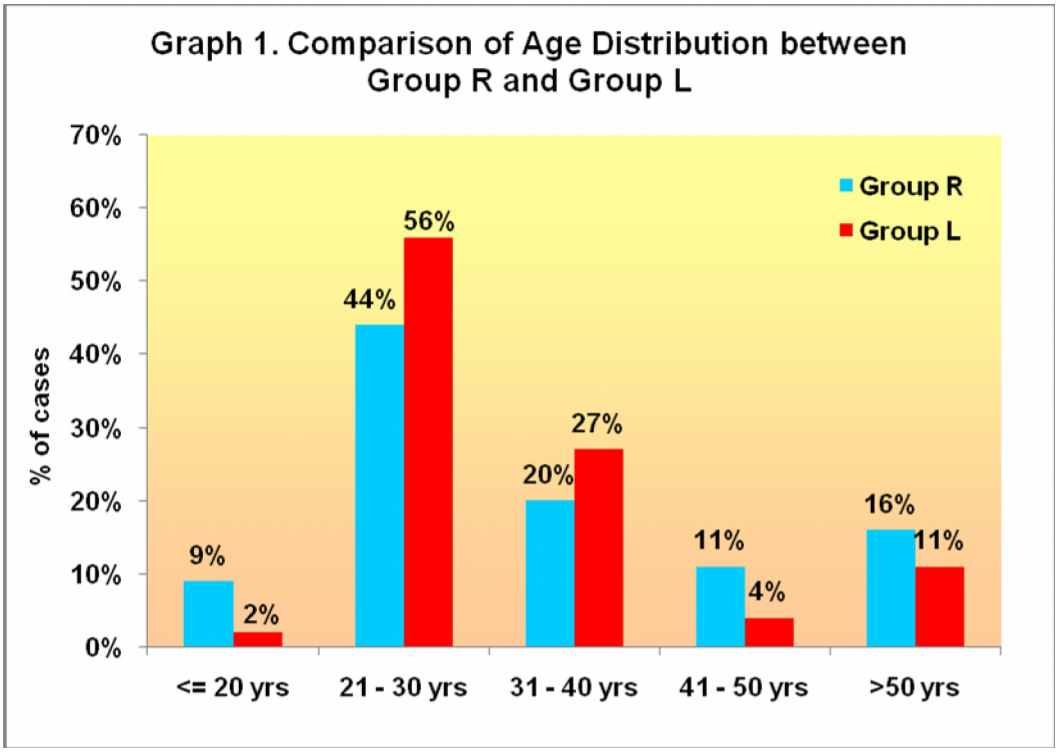
A total of 90, ASA Grade I and II patients of either gender aged between 20 to 60 years undergoing elective lower abdominal surgeries under epidural anaesthesia were randomly distributed into two groups of 45 each,

Group R	0.75% Ropivacaine
Group L	0.5% Levobupivacaine

The data obtained was analysed and the final observations and results were tabulated as below.

Table 1. Age distribution

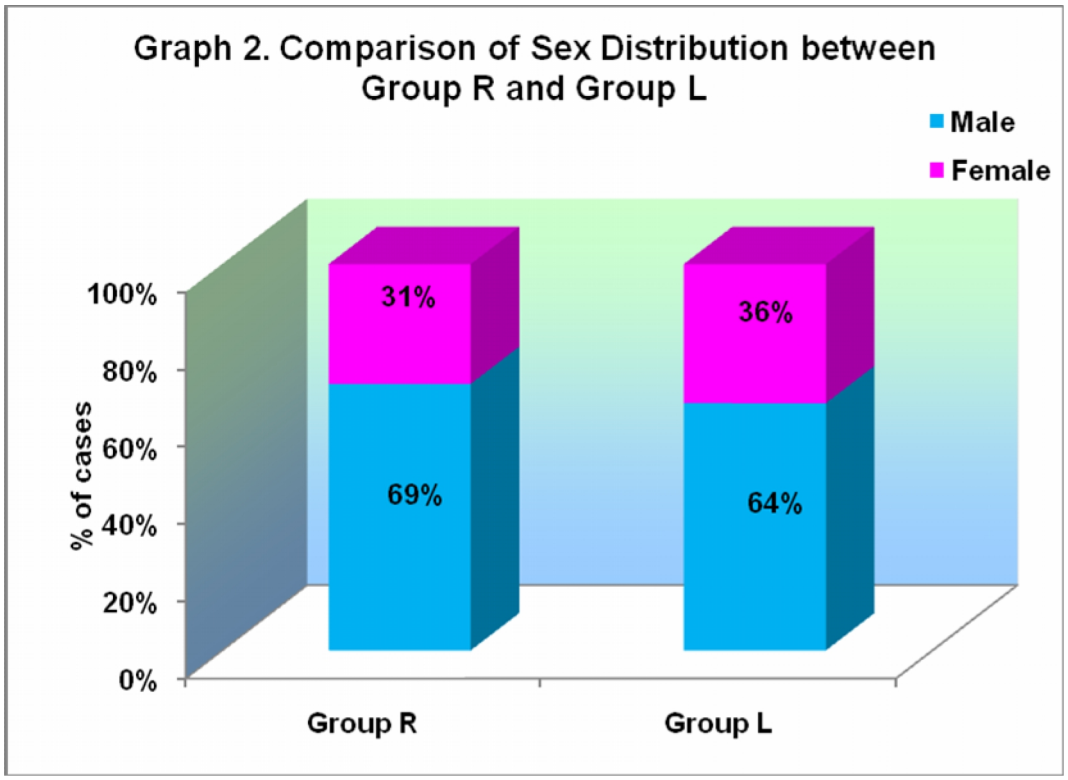
Age	Group R		Group L		P Value
	Frequency	%	Frequency	%	
<= 20 yrs	4	9%	1	2%	**0.354**
21 - 30 yrs	20	44%	25	56%	
31 - 40 yrs	9	20%	12	27%	
41 - 50 yrs	5	11%	2	4%	
>50 yrs	7	16%	5	11%	
Total	45	100%	45	100%	
Mean ± SD	34.76 ± 11.71		33.60 ± 10.61		**0.625**



In this study there was no statistically significant difference in the age distribution between both the groups. (most of the patients in group L (56%) and group R (44%) were aged between 20 to 30 years.)

Table 2. Sex distribution

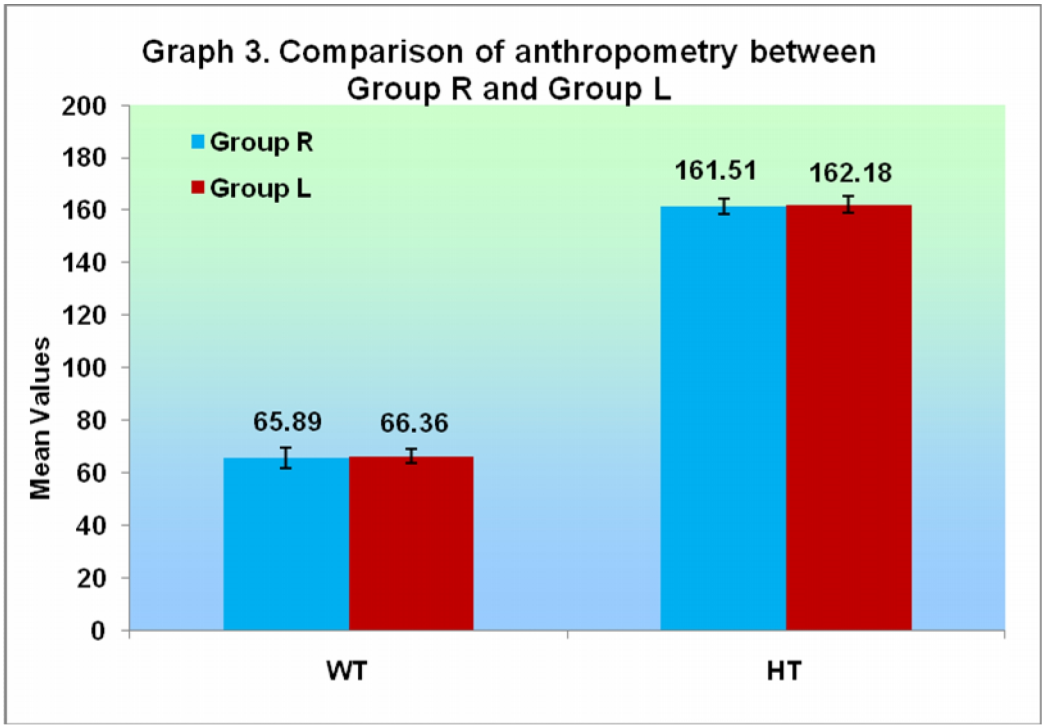
Sex	Group R		Group L		P Value
	Frequency	%	Frequency	%	
F	14	31%	16	36%	**0.655**
M	31	69%	29	64%	
Total	45	100%	45	100%	



In the present study, 31% of patients in group R were females compared to 36% in group L. However the sex distribution in group R and L was comparable (p =0 .655).

Table 3. Anthropometry

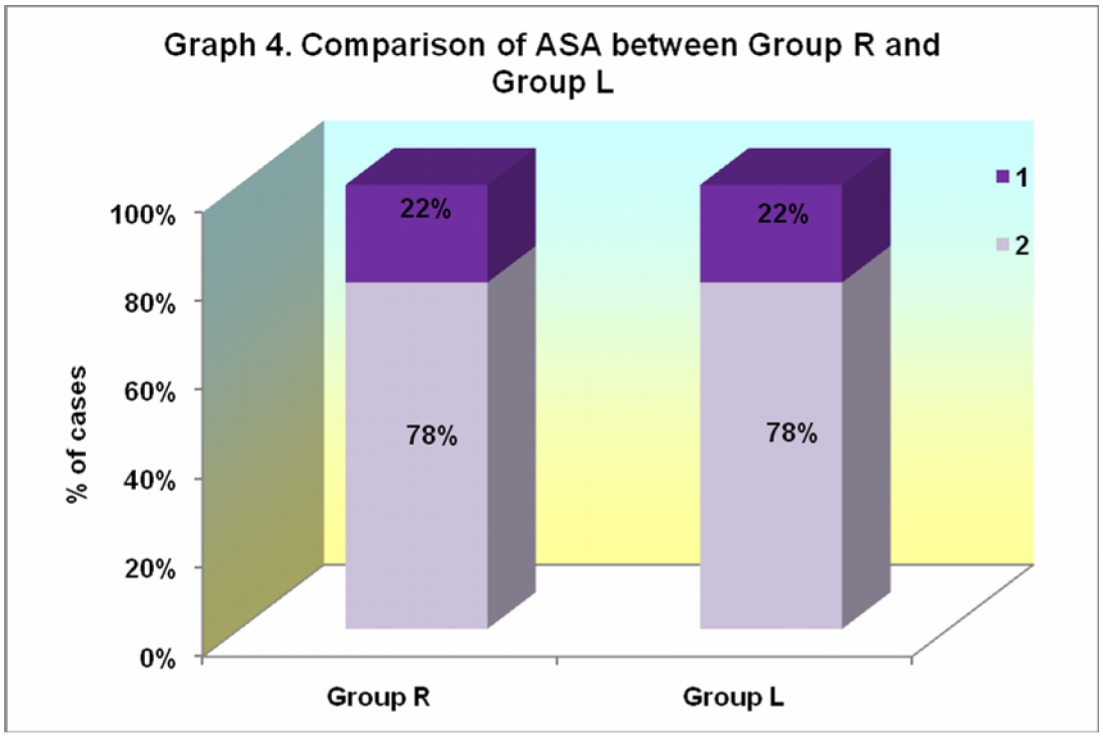
	Group R	Group L	P Value
	Mean ± SD	Mean ± SD	
WT	65.89 ± 3.94	66.36 ± 2.70	**0.514**
HT	161.51 ± 2.86	162.18 ± 2.99	**0.282**



In the present study no statistically significant difference was observed between group L and group R with regard to mean weight (66.36 ± 2.70 and 65.89 ± 3.94 Kgs respectively; p = 0.514) and mean height (162.18 ± 2.99 and 161.51 ± 2.86 Cms respectively; p = 0.282)

Table 4. ASA grade

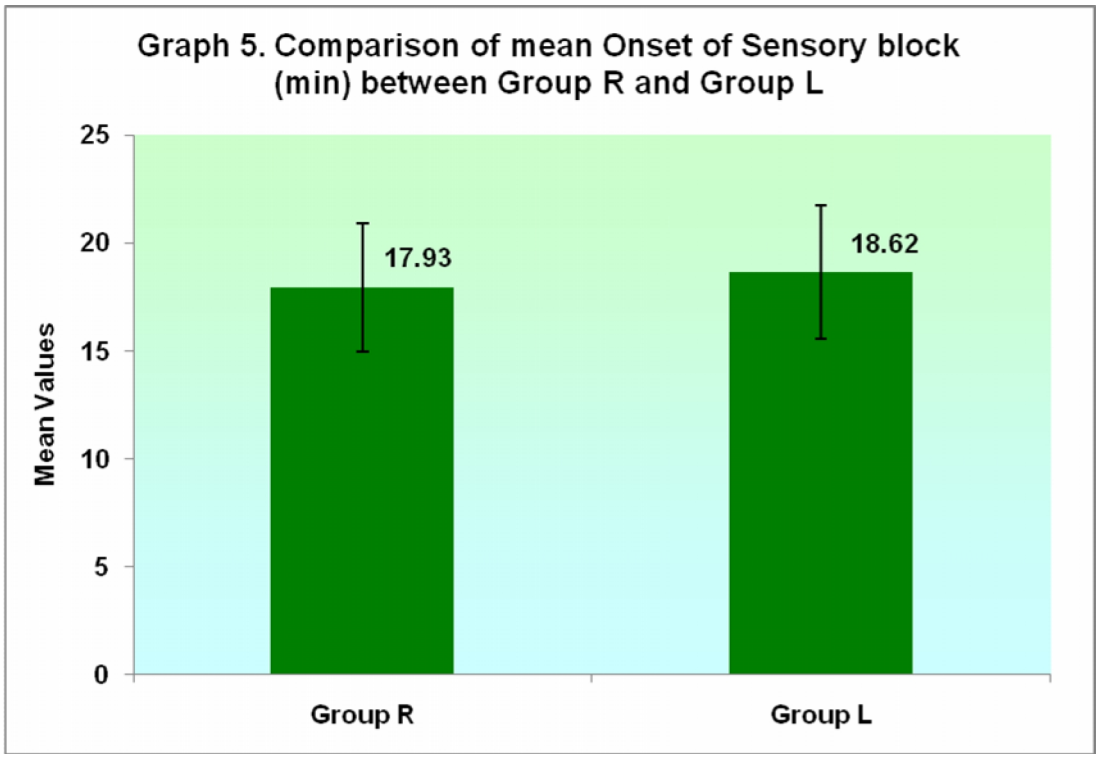
ASA	Group R		Group L		P Value
	Frequency	%	Frequency	%	
1	10	22%	10	22%	**1.000**
2	35	78%	35	78%	
Total	45	100%	45	100%	



In this study, no statistically significant difference was observed with regard to ASA grade (22% patients were ASA class I in both group R and group L.)

Table 5. Comparison of mean onset of sensory block

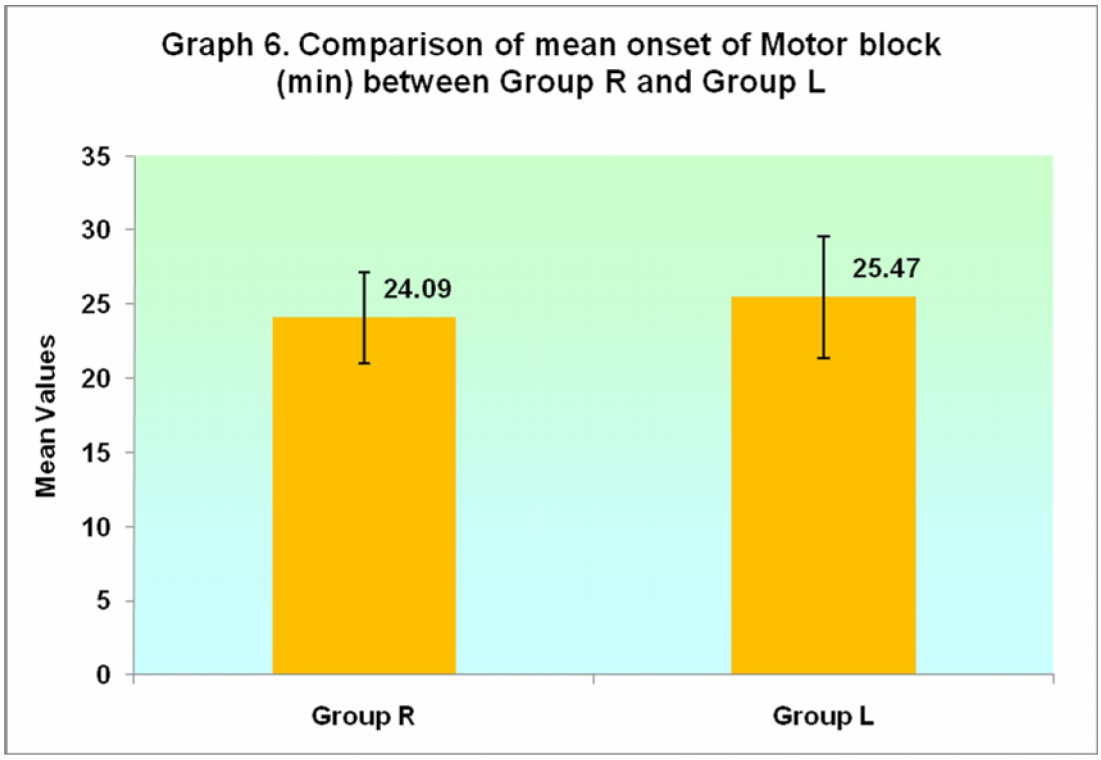
	Group R	Group L	P Value
	Mean ± SD	Mean ± SD	
Onset of Sensory block (min)	17.93 ± 2.98	18.62 ± 3.09	**0.285**



In this study, mean onset time of sensory block was slightly earlier in group R compared to group L but no statistical significance was noted (17.93 ± 2.98 v/s 18.62 ± 3.09 minutes; p= 0.285).

Table 6. Comparison of mean onset of motor block

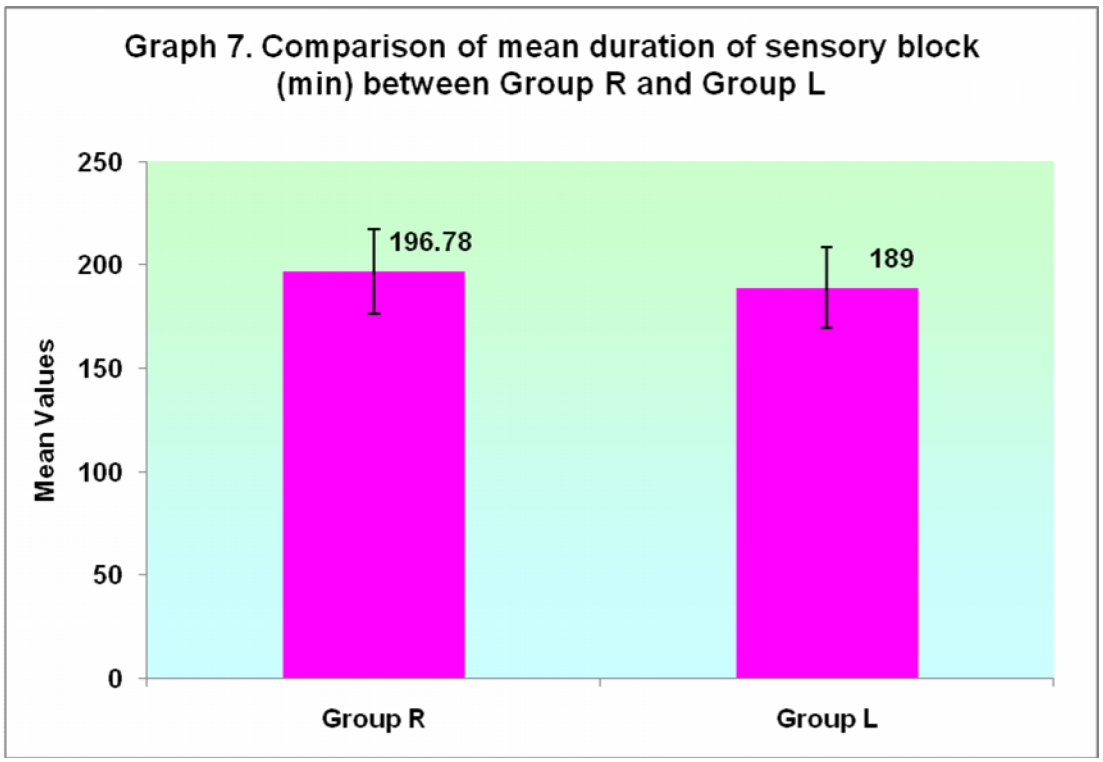
	Group R	Group L	P Value
	Mean ± SD	Mean ± SD	
Onset of motor block (min)	24.09 ± 3.07	25.47 ± 4.13	**0.076**



In this study, mean onset time of motor block was slightly delayed in group L compared to group L (24.09 ± 3.07 v/s 25.47 ± 4.13 minutes; p = 0.076), but it was statistically insignificant.

Table 7. Comparison of mean duration of sensory block

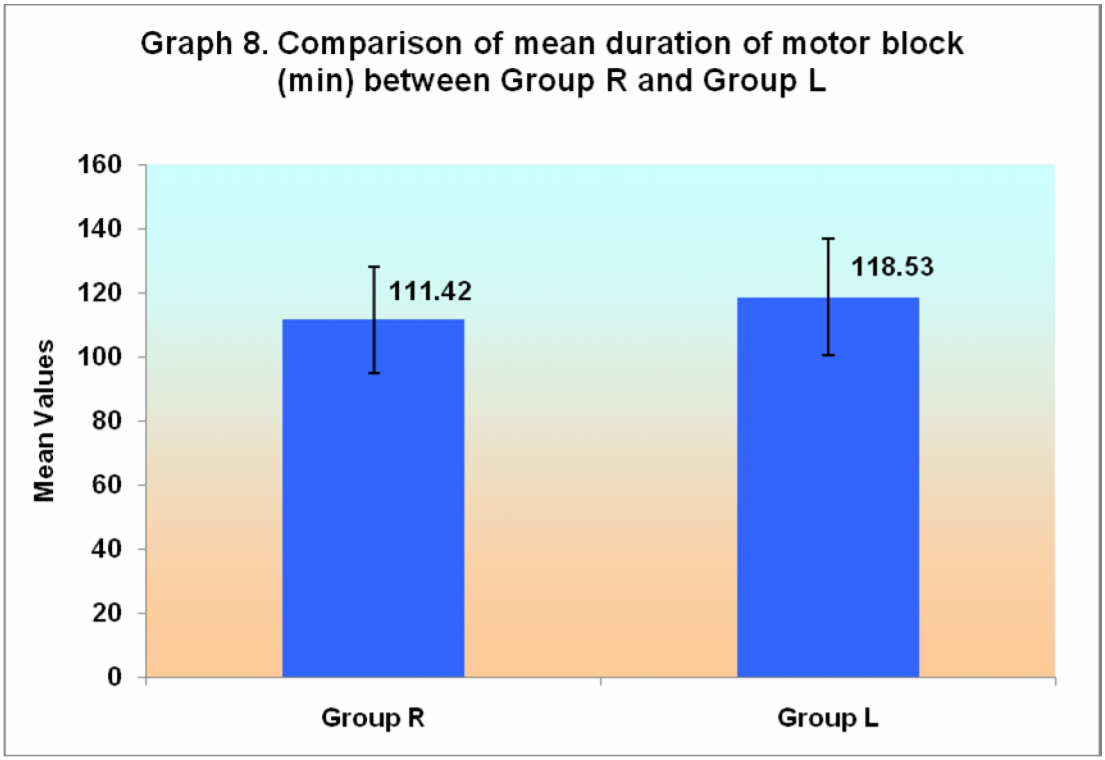
	Group R	Group L	P Value
	Mean ± SD	Mean ± SD	
Duration of Sensory block (min)	196.78 ± 20.31	189.0 ± 19.53	**0.067**



In this study, mean duration of sensory block was slightly more in group R compared to group L (196.78 ± 20.31 v/s 189.0 ± 19.53 minutes; p = 0.067), but the difference was statistically insignificant.

Table 8. Comparison of mean duration of motor block

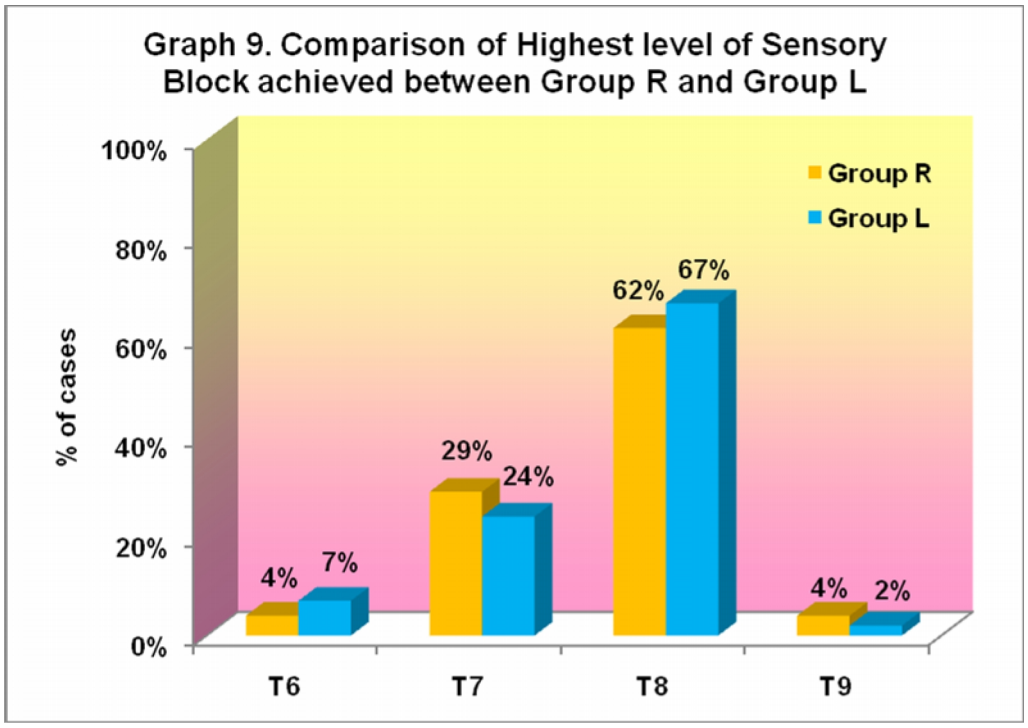
	Group R	Group L	P Value
	Mean ± SD	Mean ± SD	
Duration of motor block (min)	111.42 ± 16.70	118.53 ± 18.14	**0.056**



The duration of motor block was found to be lesser in group R(111.42 ± 16.70 min) compared to that in group L(118.53 ± 18.14 min), the difference being statistically insignificant (p=0.05)

Table 9. Comparison of highest sensory block level

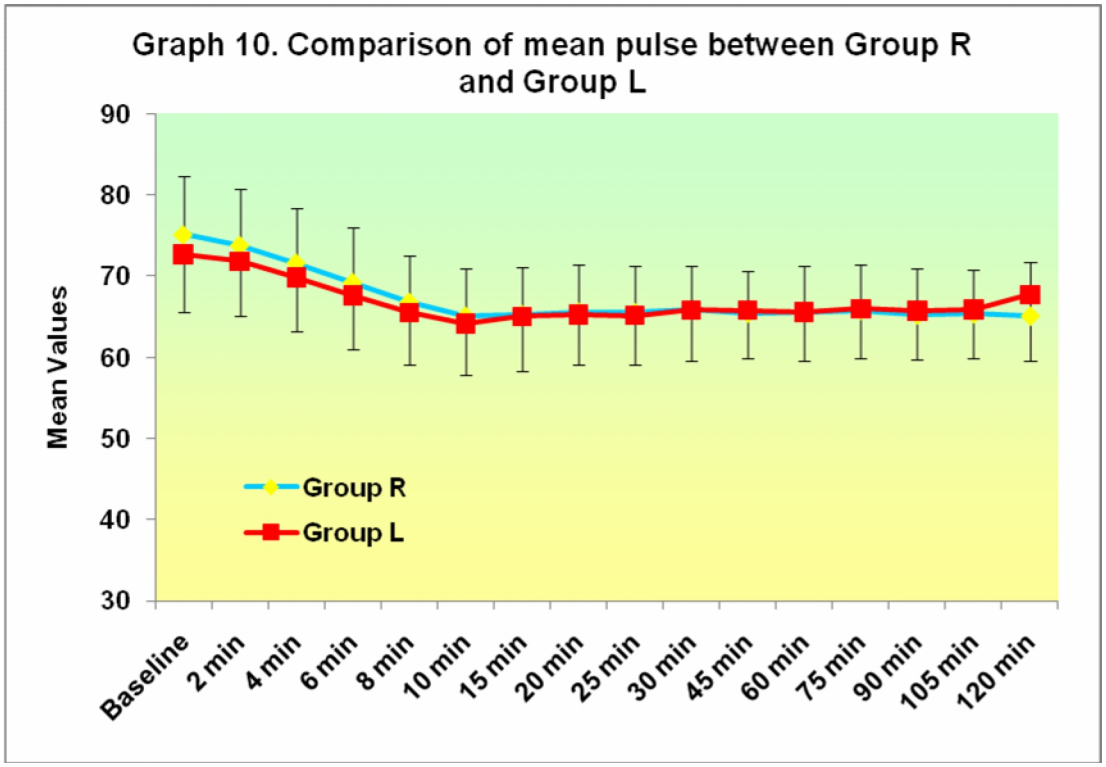
Highest level of Sensory Block achieved	Group R		Group L		P Value
	Frequency	%	Frequency	%	
T6	2	4%	3	7%	0.857
T7	13	29%	11	24%	
T8	28	62%	30	67%	
T9	2	4%	1	2%	
Total	45	100%	45	100%	



In the present study, the number of patients that had a block level of T_7 and T_8 was 29% and 62% patients in group R compared to 24% and 67% in group L respectively (p = 0.857). Only 4% patients in group R and 7% in group L attained a sensory block upto T6, and 4% in group R and 2% in group L attained a level of T9. Thus the highest level of block achieved was similar in both groups.

Table 10. Comparison of mean pulse rate at different intervals (bpm)

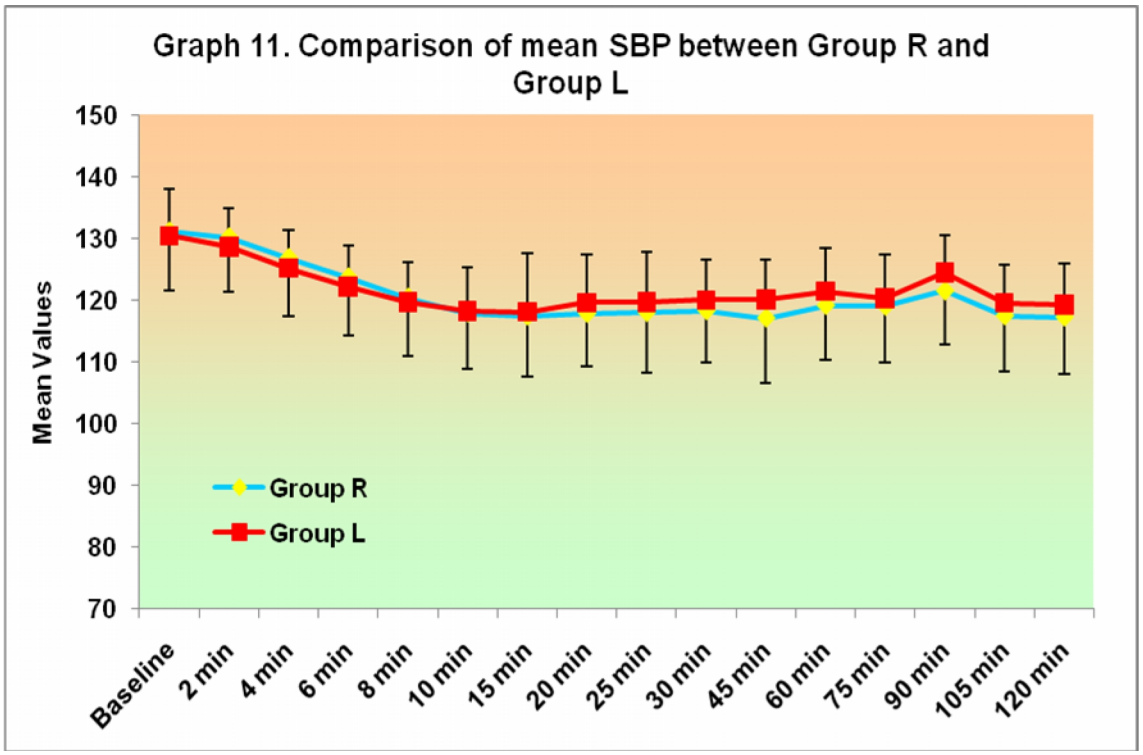
Pulse Rate	Group R (n=45)	Group L (n=45)	P Value
	Mean ± SD	Mean ± SD	
Baseline	75.13 ± 7.24	72.67 ± 7.08	0.106
2 min	73.80 ± 6.87	71.84 ± 6.78	0.178
4 min	71.64 ± 6.70	69.80 ± 6.64	0.193
6 min	69.24 ± 6.77	67.64 ± 6.71	0.263
8 min	66.82 ± 5.77	65.51 ± 6.47	0.313
10 min	65.09 ± 5.86	64.13 ± 6.36	0.461
15 min	65.29 ± 5.88	65.04 ± 6.71	0.855
20 min	65.60 ± 5.75	65.29 ± 6.20	0.806
25 min	65.53 ± 5.68	65.16 ± 6.11	0.762
30 min	65.84 ± 5.39	65.82 ± 6.29	0.986
45 min	65.47 ± 5.14	65.78 ± 5.93	0.791
60 min	65.58 ± 5.61	65.56 ± 5.96	0.986
75 min	65.80 ± 5.62	65.98 ± 6.14	0.886
90 min	65.24 ± 5.70	65.73 ± 6.09	0.695
105 min	65.39 ± 5.36	65.89 ± 6.06	0.712
120 min	65.11 ± 6.57	67.71 ± 8.15	0.306



In this study the mean pulse rate between the two groups at different time intervals was comparable with no statistical difference noted. ($p > 0.05$)

Table 11. Comparison of mean systolic blood pressure at different intervals (mm of Hg)

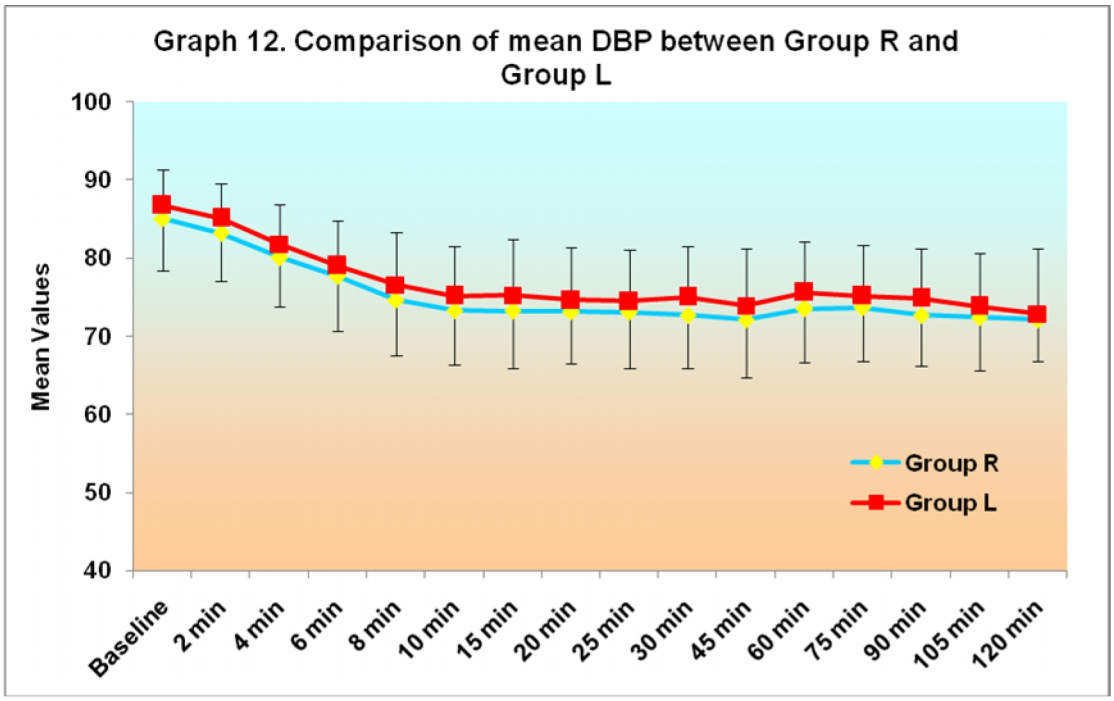
SBP	Group R (n=45)	Group L (n=45)	P Value
	Mean ± SD	Mean ± SD	
Baseline	131.11 ± 9.50	130.44 ± 7.66	0.715
2 min	130.18 ± 8.76	128.67 ± 6.12	0.345
4 min	126.84 ± 9.46	125.20 ± 6.17	0.331
6 min	123.69 ± 9.46	122.22 ± 6.53	0.394
8 min	120.40 ± 9.51	119.69 ± 6.35	0.678
10 min	117.91 ± 9.12	118.27 ± 7.08	0.837
15 min	117.38 ± 9.81	118.13 ± 9.45	0.711
20 min	117.82 ± 8.61	119.60 ± 7.71	0.305
25 min	117.96 ± 9.82	119.64 ± 8.17	0.378
30 min	118.27 ± 8.30	120.04 ± 6.52	0.261
45 min	117.07 ± 10.39	120.09 ± 6.51	0.102
60 min	119.11 ± 8.80	121.42 ± 7.00	0.171
75 min	118.98 ± 9.09	120.36 ± 7.09	0.425
90 min	121.47 ± 8.63	124.47 ± 6.07	0.060
105 min	117.43 ± 9.07	119.56 ± 6.18	0.251
120 min	117.22 ± 9.13	119.29 ± 6.56	0.448



In this study, the mean systolic blood pressure between the two groups at different time intervals was comparable with no statistical difference noted. ($p > 0.05$)

Table 12. Comparison of mean diastolic blood pressure at different intervals (mm of Hg)

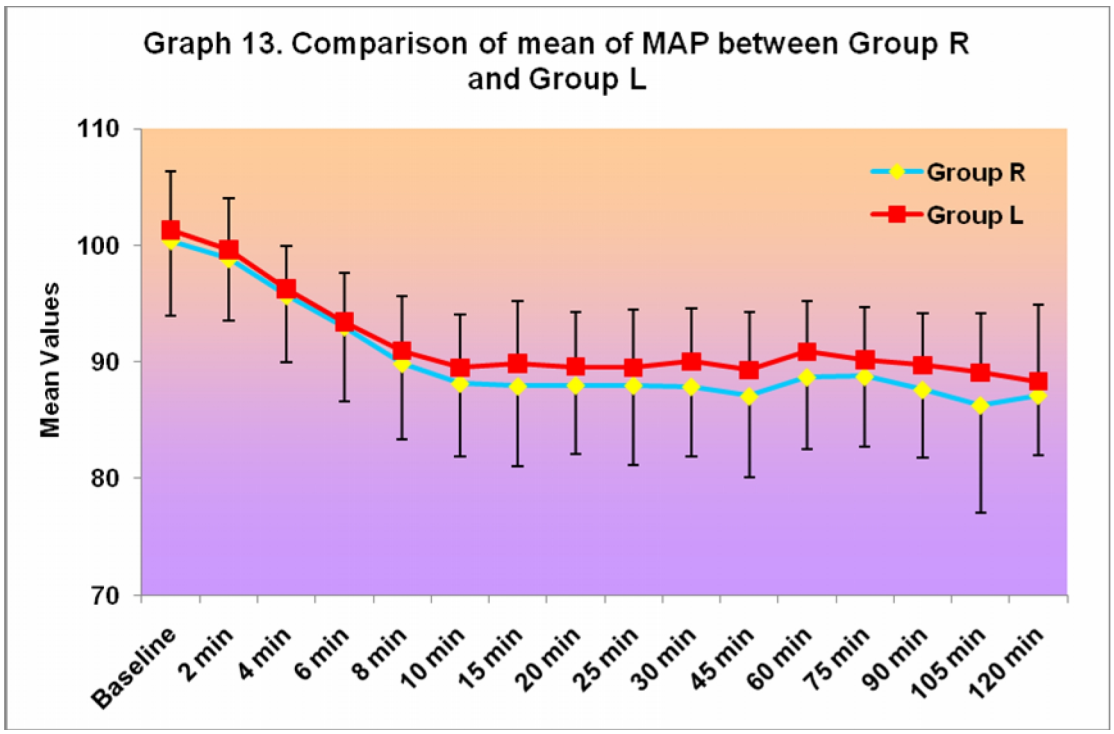
DBP	Group R (n=45)	Group L (n=45)	P Value
	Mean ± SD	Mean ± SD	
Baseline	85.04 ± 6.67	86.73 ± 4.65	0.167
2 min	83.16 ± 6.07	85.11 ± 4.44	0.085
4 min	80.09 ± 6.37	81.78 ± 5.05	0.167
6 min	77.69 ± 7.07	79.02 ± 5.70	0.327
8 min	74.62 ± 7.04	76.58 ± 6.64	0.179
10 min	73.29 ± 7.02	75.11 ± 6.38	0.201
15 min	73.20 ± 7.37	75.24 ± 7.10	0.184
20 min	73.11 ± 6.59	74.58 ± 6.74	0.299
25 min	73.02 ± 7.16	74.44 ± 6.66	0.332
30 min	72.71 ± 6.76	75.02 ± 6.49	0.102
45 min	72.09 ± 7.40	73.87 ± 7.35	0.256
60 min	73.51 ± 6.94	75.56 ± 6.56	0.155
75 min	73.64 ± 6.89	75.11 ± 6.46	0.301
90 min	72.71 ± 6.54	74.84 ± 6.32	0.119
105 min	72.39 ± 6.78	73.83 ± 6.76	0.368
120 min	72.11 ± 5.29	72.82 ± 8.37	0.764



In the present study, the mean diastolic blood pressure between the two groups at different time intervals was comparable with no statistical difference noted. ($p > 0.05$).

Table 13. Comparison of mean of MAP at different intervals (mm of Hg)

MAP	Group R (n=45)	Group L (n=45)	P Value
	Mean ± SD	Mean ± SD	
Baseline	100.40 ± 101.30	101.30 ± 5.05	0.463
2 min	98.84 ± 5.31	99.63 ± 4.35	0.439
4 min	95.68 ± 5.71	96.26 ± 3.67	0.569
6 min	93.02 ± 6.45	93.42 ± 4.15	0.726
8 min	89.88 ± 6.49	90.94 ± 4.72	0.376
10 min	88.17 ± 6.33	89.50 ± 4.59	0.255
15 min	87.93 ± 6.85	89.84 ± 5.40	0.217
20 min	88.01 ± 5.92	89.59 ± 4.72	0.166
25 min	88.00 ± 6.81	89.51 ± 5.00	0.233
30 min	87.90 ± 6.07	90.03 ± 4.51	0.062
45 min	87.08 ± 7.00	89.28 ± 4.93	0.090
60 min	88.71 ± 6.15	90.86 ± 4.33	0.059
75 min	88.76 ± 6.04	90.20 ± 4.45	0.202
90 min	87.63 ± 5.83	89.72 ± 4.39	0.058
105 min	86.31 ± 9.30	89.08 ± 5.05	0.120
120 min	87.15 ± 5.18	88.32 ± 6.54	0.561



In this study, the mean of MAP between the two groups at different time intervals was comparable with no statistical difference noted. ($p > 0.05$)

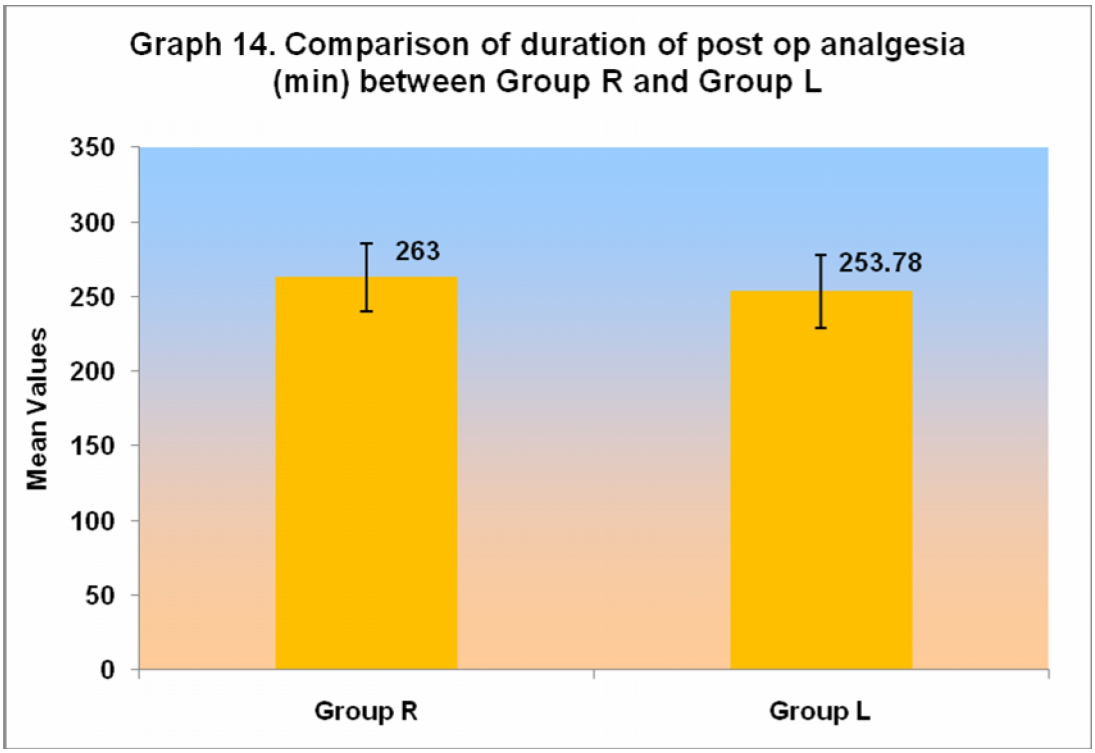
Table 14. Mean duration of surgery

	Group R	**Group L**	**P Value**
	Mean ± SD	**Mean ± SD**	
Mean duration of surgery(min)	**74 ± 10**	**82 ± 12**	**0.095**

The mean duration of surgery was comparable in both group R and group L.($p>0.05$)

Table 15. Comparison of duration of post operative analgesia

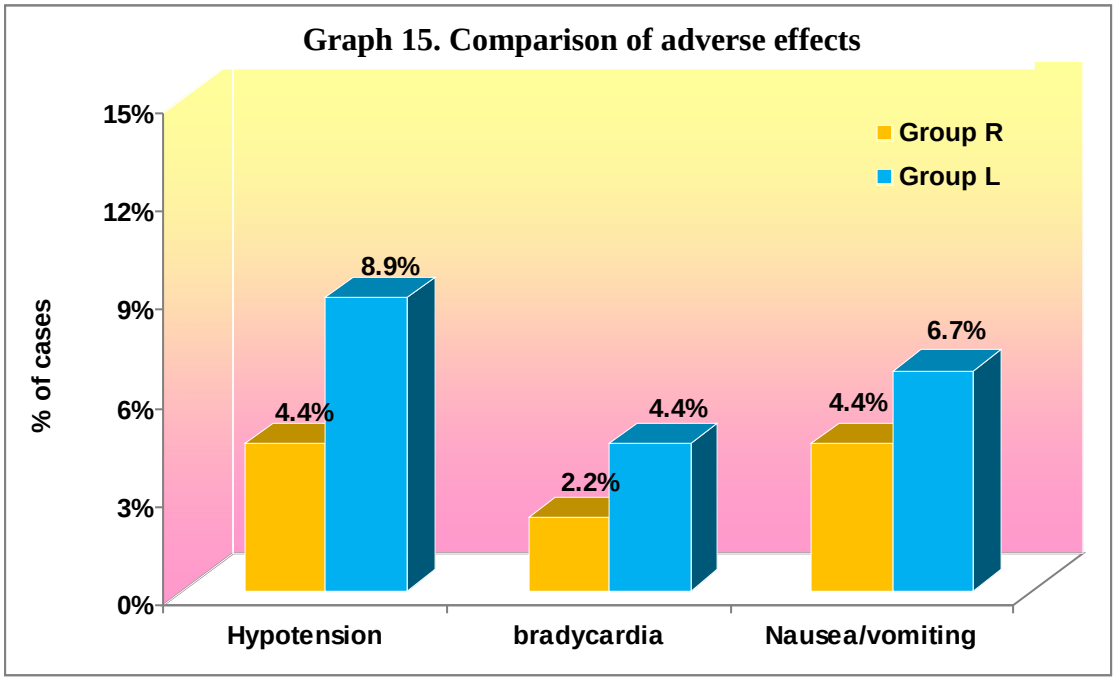
	Group R	**Group L**	**P Value**
	Mean ± SD	**Mean ± SD**	
Duration of post op analgesis (min)	263.0 ± 22.77	253.78 ± 24.43	**0.067**



In this study the comparison of time to request for first post operative rescue analgesia was 263.0 ± 22.77 minutes in group R compared to 253.78 ± 24.43 minutes in group L, though the difference remained statistically insignificant. (p = 0.067).

Table 16. Comparison of adverse effects

	Group R		Group L		P Value
	Frequency	%	Frequency	%	
Hypotension	2	4.4%	4	8.9%	0.677
Bradycardia	1	2.2%	2	4.4%	1.000
Nausea/vomiting	2	4.4%	3	6.7%	1.000



The incidence of adverse events were comparable in both group R and group L. ($p > 0.05$)

Chapter 6

Discussion

DISCUSSION

Neuraxial anaesthesia especially epidural anaesthesia greatly expands the anaesthetic armamentarium and provides better alternate to general anaesthesia when appropriate and can be provided as a single injection or with a catheter to allow intermittent boluses or continuous infusion. Epidural anaesthesia is widely being used especially in patients undergoing lower limb and lower abdominal surgeries where there is a need for desirable properties like longer duration of analgesia and shorter duration of motor blockade.

Local anaesthetics act by interaction with the voltage-gated sodium-ion channels (Na+-ion channels).They reduce the peak permeability for sodium-ions of the axonal membrane, impeding the generation and propagation of action potentials in nerve fibres. Following an epidural injection, local anesthetics may diffuse into the paravertebral area through the intervertebral foramina and block nerves distal to their dural sheaths, resulting in multiple paravertebral blocks. They may alsodiffuse across the dura into the subarachnoid space, where theyact on nerve roots. Finally, after diffusion across the dura, local anesthetics may act directly on the spinal cord.

Recently a number of newer drugs have been introduced namely Ropivacaine and Levobupivacaine which are known to have a better safety profile with more specific action as regards pain relief and early ambulation.

The present one year randomized clinical study was conducted on 90, ASA grade I and II patients of either gender, aged between 20 to 60 years who were allocated to receive either 15ml of 0.75% plain ropivacaine(Group R) or 15 ml of 0.5% plain levobupivacaine(Group L) epidurally for elective lower abdominal

surgeriesat KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

The aim of our present study was to compare the effect of epidural 0.75% ropivacaineand 0.5% levobupivacaine for time of onset, highest level, duration of sensory block and onset and duration of motor block in patients posted for lower abdominal surgeries.

In the present study no statistically significant difference was observed between group R and group L with regard to distribution of sex; M:F ratio was 1:2.21 for group R and 1:1.81 for group L. The mean age for group R and group L was 34.76 ± 11.71 and 33.60 ± 10.61 years respectively ($p > 0.05$).

The mean weight in group R and group L was 65.89 ± 3.94 and 66.36 ± 2.70 Kgs respectively and mean height in group R and group L was 161.51 ± 2.86 and 162.18 ± 2.99cms respectively suggesting that the demographic and pre anaesthetic characteristics in group R and L were comparable ($p > 0.05$). The mean duration of surgery too was comparable in both group R(74 ± 10min) and group L(82 ± 12min).

In the present study, the perioperative hemodynamic parameters i.e, mean heart rate, mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure were comparable in Group R and L. ($P > 0.05$).

In our study it was observed that the mean times for onset of sensory block ingroup R and in group Lwere17.93 ± 2.98 min and 18.62 ± 3.09 min respectively which was similar to the results noted in a study conducted by **Yang et al**[39], which compared 20 ml of 0.5% ropivacaine (11.8 ± 8.6 min)and 20 ml of 0.5% levobupivacaine (15.5 ±9.7 min) for caesarean sections.

Two patients in group R and three patients in group L developed a sensory block level upto T6 dermatomal level.The mean duration of sensory block in group R(196.78 ± 20.31 min)was longer than that in group L(189.56 ± 19.53 min) although the difference was statistically insignificant(p=0.067). The mean duration of post operative analgesia in our study was observed to be longer with ropivacaine than levobupivacaine (263.0 ± 22.77 vs 253.78 ± 24.43 minutes).

This was similar to the results observed by **peduto et al**[38] where, ropivacaine was observed to have a longer duration of sensory block (201 ± 75 min) than levobupivacaine (185 ± 77 min; P = 0.46).

A solution of racemic bupivacaine contains equal amounts R- and S-enantiomers which have been demonstrated to have a different affinity for sodium, potassium, and calciumion channels.[7]Levobupivacaine, the S- enantiomerwhich reversibly blocks the transmission of action potential in sensory, motor and sympathetic nervous fibers by inhibiting the passage of sodium through voltage-sensitive ion channels in the neuronal membrane, demonstrates increased cardiovascular and central nervous system safety and is considered a better alternative to bupivacaine [8,55]

Ropivacaine acts by reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibres. This action is potentiated by dose-dependent inhibition of potassium channels.

In our study, the mean times for onset of motor blockadein group R and in group L were24.09 ± 3.07 min and 25.47 ± 4.13 min respectively (p=0.076),which was similar to the results noted in a study conducted by **Yang et al**[39]where mean

times for onset of motor blockade were(24.9 ± 13.3 min vs 31.0 ± 14.4 min) in Group R and Group L respectively.

The mean duration of motor blockade in our study, was observed to be lesser in group R (111.53 ± 16.70min) as compared togroup L (118.53 ± 18.14 min) though it was statistically insignificant (p=0.056). The results of a similar study by **Peduto et al**,[38] comparing epidural 0.5% levobupivacaine and 0.75% ropivacaine for lower limb surgery, found a duration of motor block similar to results of our study which was much lesser with ropivacaine than with levobupivacaine (95 ± 48 min v/s 105 ± 63 min; P = 0.86).

Ropivacainebeing less lipophilic than bupivacaine is less likely to penetrate large myelinated motor fibres; therefore leading to a selective action on the pain-transmitting Aδ and C nerves rather than Aβ fibres, which are involved in motor function.[7]Several studies have demonstrated that the quality of motor blockade follows the rank of order bupivacaine >levobupivacaine>ropivacaine.[8,9]

In our study, incidence of side effects were minimal in both groups. All patients were haemodynamically stablethroughout the procedure. Patients were comfortable throughout the procedure and did not require any further medication in either of the groups.

LIMITATIONS OF THE STUDY

Since the present study included epidural anaesthesia by single shot approach, the provision of continuous postoperative analgesia through an epidural catheter could not be studied.

FUTURE SCOPE OF STUDY

Since the surgeries in the present study were infraumbilical and of short duration, the adequacy of motor blockade could not be acertained. The advantage of differential blockade seen with both ropivacaine and levobupivacaine for specific provision of analgesia with early ambulation can be studied in future studies by having a continuous catheter technique.

Chapter 7

Conclusion

Conclusion

Based on the results of the present study it can be concluded that both 0.75% ropivacaine(15ml) and 0.5% Levobupivacaine(15ml) when administered epidurally for elective lower abdominal surgeries, provide adequate and comparable sensory and motor blockade with minimal haemodynamic disturbances. Ropivacaine results in a shorter duration of motor blockade and provides a longer duration of sensory blockade and post operative analgesia.

Chapter 8

Summary

SUMMARY

The present one year randomized clinical study was conducted on 90,ASA grade I and IIpatients of either gender, aged between 20 to 60 years who were allocated to receive either 15ml of 0.75% plain ropivacaine (group R) or 15 ml of 0.5% plain levobupivacaine (group L)epidurally for elective lower abdominal surgeries.

The groups were statistically similar as regards demographic data and pre anaesthetic characteristics.

The mean timesfor onset of sensory block inGroup R(17.93 ± 2.98 min) and Group L(18.62 ± 3.09 min) werecomparable.The mean duration of sensory block in group R(189.56 ± 19.53 min)was more than that in group L(189.56 ± 19.53 min) although the difference was statistically insignificant.(p=0.067). Two patients in group R and three patients in group Ldeveloped ahighest sensory block level upto T6 dermatomal level.

The mean time for onset of motor block in group R was similar to that in group L (24.09 ± 3.07 v/s 25.47 ± 4.13; p=0.076) while duration of motor blockade was observed to be lesser in ropivacaine (111.53 ± 16.70min) as compared with levobupivacaine (118.53 ± 18.14 min) though it was statistically insignificant (p=0.056).

It was also observed that ropivacaineprovided a longer duration of post operative analgesia than levobupivacaine (263.0 ± 22.77 vs 253.78 ± 24.43 minutes) although the difference remained statistically insignificant.

Chapter 9

Bibliography

BIBLIOGRAPHY

1. Miller's anaesthesia – 7th edition.
2. George. A. Albright. Cardiac arrest following regional anaesthesia with etidocaine & bupivacaine – editorial views. The journal of anaesthesiology. 1979; 51: 285 – 287.
3. Moller. R, cavoni B. Cardiac electrophysiologic effects of lidocaine & bupivacaine. Anaesthesia analgesia. 1988; 67: 107 – 109.
4. Mc Clure. J. H. Review article – ropivacaine. British journal of anaesthesia. 1996; 76: 300 – 307.
5. J. B Whiteside, J. A. Wildsmith. Developments in local anaesthetic drugs. British journal of anaesthesia. 2001;87(1): 27 – 35.
6. Arthur GR, Feldman HS, Covino BG. Comparative pharmacokinetics of bupivacaine and ropivacaine, a new amide local anesthetic. Anesthesia and Analgesia 1988; 67: 1053–1058.
7. Kuthiala G, Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use. Indian J Anaesth 2011; (55):104-10.
8. Burlacu CL, Buggy DJ. Update on local anesthetics: Focus on levobupivacaine. Ther Clin Risk Manag. 2008; 4: 381–92
9. Foster RH, Markham A. Levobupivacaine. A review of its pharmacology and use as a local anaesthetic. Drugs 2000; 59: 551-579.
10. Aberg G. Toxicological and local anesthetic effects of optically active isomers of two local anesthetic compounds. Acta Pharmacol Toxicol Scand 1972; 31: 273-86.

11. The History of Epidural Anesthesia: Pages, Dogliotti, Guiterrez, Ruiz, Mark G. Mandabach. Department of Anesthesiology, The University of Alabama at Birmingham, Birmingham, United States.
12. Cousins M, Bridenbaugh P. Cousins and Bridenbaugh's neural blockade in clinical anesthesia and pain medicine. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2009.
13. Ruetsch YA, Boni T, Borgeat A. From cocaine to ropivacaine: the history of local anaesthetics. Current topics in medicinal chemistry. 2001;1(3);175-82
14. Schneider M, Ettlin T, Kaufmann M, Schumacher P, Urwyler A, Hampl K, et al. Transient neurologic toxicity after hyperbaric subarachnoid anesthesia with 5% lidocaine. Anesthesia and Analgesia 1993; 76(5):1154–7.
15. Rigler ML, Drasner K, Krejcie TC, Yelich SJ, Scholnick FT, DeFontes J, et al. Cauda equina syndrome after continuous spinal anesthesia. Anesthesia and Analgesia 1991;72(3): 275–81.
16. Chiang YY, Tseng KF, Lih YW, Tsai TC, Liu CT, Leung HK. Lidocaine-induced CNS toxicity--a case report. Acta Anaesthesiol Sin. 1996 Dec;34(4):243-6
17. Morton C. Newer Drugs: Ropivacaine. United Kingdom: Royal Infirmary of Edinburgh. 1997
18. Friedman G. A, Rowlingson J. C, DiFazio C. A, Donegan M. F. Evaluation of the analgesic effect & urinary excretion of systemic Bupivacaine in man. Anaesthesia analgesia.1982: 61:23 – 27.
19. Yamashino. H, Yokihitho. C: Bupivacaine – induced seizure after accidental intravenous injection a complication of epidural anaesthesia. Anaesthesiology. 1977; (47): 472 – 473.

20. Clrkson. C.W, Hondeghem. C. M: Mechanism for bupivacaine depression of cardiovascular conduction: fast block of sodium channels during the action potential with slow recovery from block during diastole. Anaesthesiology. 1985; 62: 396 – 405.

21. Andrea carati, Marco Baciarella. Enachiomeric local anaesthetics : can ropivacaine & levobupivacaine improve our practice : current drugs through : 2006 ; 1: 85 – 89.

22. Anathony M Arkham, Diana Faulds: Ropivacaine. Review of its pharmacology & therapeutics use in regional anaesthesia. Drugs. 1996;52(3):429 – 449.

23. Gissen AJ, Covino BG, Gregus J. Differential sensitivities of mammalian nerve fibers to local anesthetic agents. Anesthesiology. 1980 53:467-474

24. Moller. R, Cavino. B. G. Effects of progesterone on the cardiac electrophysiologic alterations produced by ropivacaine & bupivacaine. Anaesthesiology. 1992; (77):735 – 741.

25. Scott. D. B, Lee. A, Fagan. D, Bowler. G. M. R. Bloom field. P, Lundh. R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anaesthesia & analgesia. 1989; 69: 563 – 569.

26. Vanhouette F, Vereecke J, Verbeke N. Stereoselctive effects of the enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle. Br J Pharmacol 1991; 103:1275–81.

27. Marganella C, Bruno V, Matrisciano F, Reale C, Nicoletti F, Melchiorri D. Comparative effects of levobupivacaine and racemic bupivacaine on excitotoxic neuronal death in culture and N-methyl-D-aspartate-induced seizures in mice. Eur J Pharmacol 2005; 518: 111-5.

28. Huang YF, Pryor ME, Mather LE. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. Anesth Analg.1998; (86):797–804.

29. Bardsley H, Gristwood R, Baker H. A comparison of the cardiovascular effects of levobupivacaine and racemic bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998; 46:245–9.

30. Crosby E, Saudler A, Finucane B, Writer D, Reid D, McKenna J, et al. Comparison of epidural anaesthesia with ropivacaine 0.5% & bupivacaine 0.5% for caesarean section. Canadian journal of anaesthesia. 1998; 45 (11): 1066-1071.

31. Wolff A. P, Hassoltrom L, Kerkkup H. E, Gielen M. J. Extradural ropivacaine & bupivacaine in hipsurgery. British journal of anaesthesia. 1995; 74: 458 – 460.

32. Guler. G, Aksu R, Dogru K, Sofikerim M, Tosun Z, Boyaci A. Comparison of 3 doses of ropivacaine for epidural anaesthesia in transurethral surgery. Saudi medical Journal 2009;30(1):67-71.

33. Korula S, George GM, Ipe S, Abraham SP. Comparison of equipotent doses of ropivacaine and bupivacaine. Saudi J Anaesth 2011;5:277-81

34. Cox CR, Faccenda KA, Gilhooly C. Extradural S(–)-bupivacaine: comparison with racemic RS-bupivacaine. Br J Anaesth, 1998; 80:289–93.

35. Faccenda KA, Simpson AM, Henderson DJ, Smith D, McGrady EM, Morrison LM. Regional Anesthesia and Pain Medicine. 2003 ;28(5): 394 –400

36. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg. 2000;90:642–8.

37. Casati A, Santorsola R, Aldegheri G. Intraoperative epidural anesthesia and postoperative analgesia with levobupivacaine for major orthopedic surgery: a double-blind, randomized comparison of racemic bupivacaine and ropivacaine. J Clin Anesth. 2003; (15) :126–31

38. Peduto VA, Baroncini S, Montanini S. A prospective, randomized, double-blind comparison of epidural levobupivacaine 0.5% with epidural ropivacaine 0.75% for lower limb procedures. Eur J Anaesthesiol. 2003; 20:979–83

39. Yang C.W, Jung S.M, Kwon H.U, Soon P, Ryu S.H. Comparison of Epidural Anaesthesia with 0.5% Levobupivacaine and 0.5% Ropivacaine for cesarean section. Korean J Anaesthesiol 2007;52: 284-90

40. Santorsola R, Casati A, Cerchierini E, Moizo E, Fanelli G. Levobupivacaine for peripheral blocks of the lower limb: a clinical comparison with bupivacaine and ropivacaine. Minerva Anestesiol 2001;67: 33-36

41. Atkinson RS, Rushman GB, Davies NJH. Spinal analgesia: Intradural and Extradural. Lee`s Synopsis of Anesthesia, 11th ed; 1993; 691-745.

42. Williams PL, Warwick R, Dyson M, Bannister LH. Gray's anatomy. 37th Ed. New York: Chruchill Livingstone; 1989.

43. Healy TEJ, Knight PR. Wylie and Churchill-Davidson's A Practice of Anaesthesia. 7thed; 2003.

44. Ellis H, Feldman S. Anatomy for Anaesthetists. 5th ed., Oxford: Blackwell Scientific Publications Ltd; 1988.

45. Hamid M, Fallet-Bianco C, Delmas V & Plaisant O. The human lumbar anterior epidural space: morphological comparison in adult and fetal specimens. Surg Radiol Anat 2002; 24:194-200

46. Reina MA, Franco CD, Lopez A, De Andres JA & van Zundert A.. Clinical implications of epidural fat in the spinal canal. A scanning electron microscopic study. Acta Anesthesiol Belg, 2009;60: 7-17

47. Dommisse G. The arteries and veins of the human spinal cord from birth. 1st ed. Edinburgh: Churchill Livingstone; 1975.

48. Brockstein B, Johns L & Gewertz BL. Blood supply to the spinal cord: anatomic and physiologic correlations. Ann Vasc Surg, 1994; (8):394 –399

49. Bernards CM, Shen DD, Sterling ES, Adkins JE, Risler L, Philips B, et al. Epidural, Cerebrospinal Fluid and Plasma Pharmacokinetics of Epidural Opioids (Part1). Anesthesiology 2003; 99:455-65.

50. Ekenstam B, Egner B, Petterson G. Local anaesthetic I.N-alkyl pyrrolidine and N-alkyl piperidine carboxylic acid amides. Acta Chem Scand. 1957;11(7):1183-90

51. Leone S, Di Cianni S, Casati A, Fanelli G. Pharmacology, toxicology, and clinical use of new long acting local anaesthetics, ropivacaine and levobupivacaine. Acta Biomed. 2008;79:92-105

52. Polley LS, Columb M, Naughton N, Wagner D. Relative analgesic potencies of ropivacaine and bupivacaine for epidural analgesia in labor: implications for therapeutic indexes. Anesthesiology. 1999;90 (4):944-50.

53. Capogna G, Celleno D, Fusco P, Lyons G, Columb M. Relative potencies of bupivacaine and ropivacaine for analgesia in labour. Br J Anaesth. 1999;82(3):371-3.

54. Casati A, Fanelli G, Magistris L, Beccarla P, Berti M, Torri G. Minimum local anaesthetic volume blocking the femoral nerve in 50% of cases. A double-

blinded comparison between 0.5% ropivacaine and 0.5% bupivacaine. Anesth Analg. 2001;92(1):205-8.

55. Sukhminder Jit Singh Bajwa and Jasleen Kaur clinical profile of levobupivacaine in regional anaesthesia: a systematic review J Anaesthesiol Clin Pharmacol. 2013 Oct-Dec; 29(4): 530-539

Annexures

Annexure II

ANNEXURE II – PROFORMA

STUDY: "COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE BETWEEN EQUIPOTENT DOSES OF 0.75% PLAIN ROPIVACAINE AND 0.5% PLAIN LEVOBUPIVACAINE IN LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA- A ONE YEAR RANDOMIZED CLINICAL STUDY".

Patient Name: **IP No.:**

Age: **Weight:**

Height: **Gender:**

Date of Operation: **Occupation:**

Address: **Anaesthesiologist:**

Preanesthetic Evaluation:

Chief Complaints:

Past History:

a. HTN / DM / Asthma / Epilepsy / Rx allergy
b. Drug therapy
c. Previous exposure to Anesthesia

Family history

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Koylonychia / Lymphadenopathy / Edema

PR : BP :

RR : Temp :

Musculoskeletal disorders

Jaw movements : Teeth :

Airway assessment : Spine :

Systemic Examination

RS : CNS :

CVS : GIT :

Investigations

Hb : Total Count :

DC : BT :

Urine routine : CT :

Preoperative physical status: ASA Grade I, II, III, IV, V

Diagnosis

Proposed Surgery

Preoperative baseline values

HR: BP:

Monitors attached

Pulse oxymetry : NIBP :

ECG :

I. Group:

II. Vital parameters :

Time	HR	Blood pressure			$Sp0_2$
		SBP	DBP	MAP	
2 min					
4 min					
6 min					
8 min					
10 min					
1 5 min					
20 min					
25 mm					
30 min					
45 min					
60 min					
75 min					
90 min					
105min					
120min					

III. Sensory Block

a)	Onset at T_{10} (mins)	
b)	Duration of sensory block	
c)	Highest Level of sensory block	

IV. Duration of surgery(min)

Duration of surgery (min)	

V. Motor Block

a)	Onset (mins)	
b)	Grade 3 Motor Block (mins)	
c)	Total duration of motor block	

VI. Side Effects

Side effects	

VII. Post operative analgesia

Time to request for first post operative rescue analgesic (mins)	

Annexures

Annexure IV

ANNEXURE IV – KEY TO MASTER CHART

ABH	-	Abdominal hysterectomy
ASA	-	American Society of Anaesthesiologists
Bpm	-	Beats per minute
Cms	-	Centimeters
F	-	Female
HR	-	Hernia repair
Kgs	-	Kilograms
Mins	-	Minutes
mm Hg	-	Millimeters of mercury
M	-	Male
OA	-	Open appendicectomy
SPO2	-	Oxygen saturation

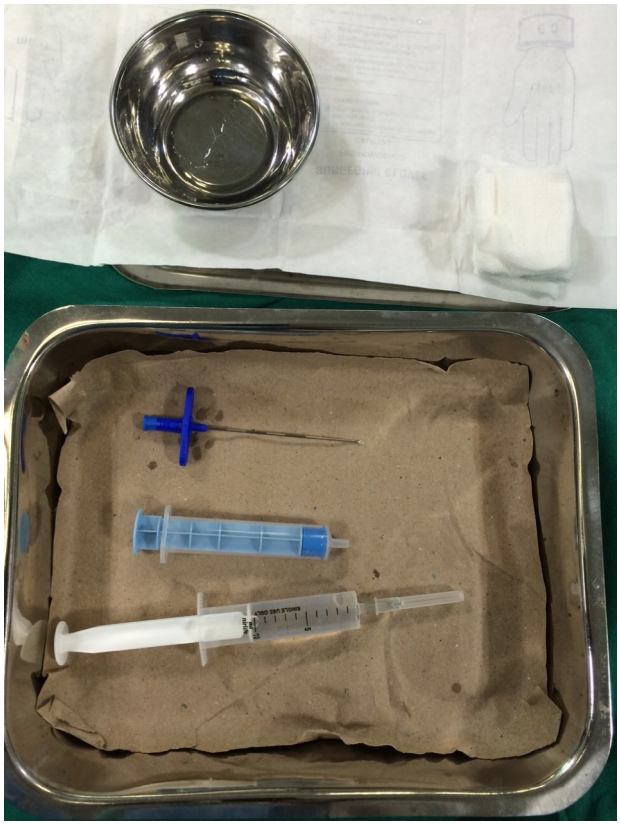
Annexures

Annexure III

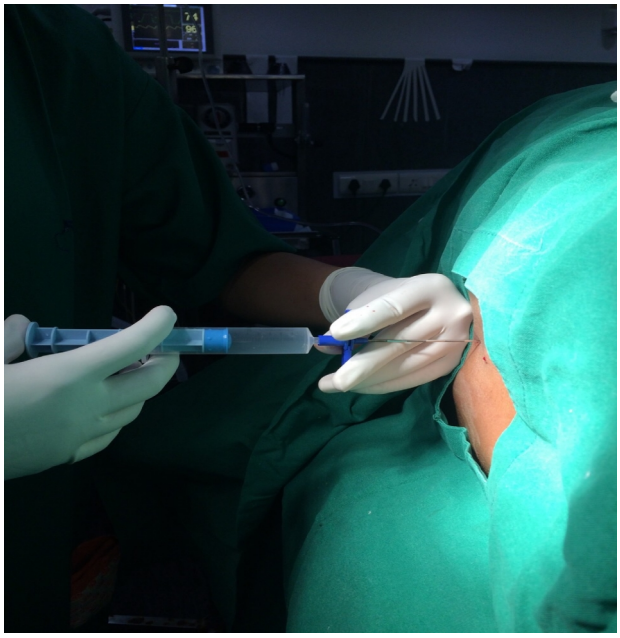
ANNEXURE III – PHOTOGRAPHS

Photograph 1. Isobaric Ropivacaine (0.75%)

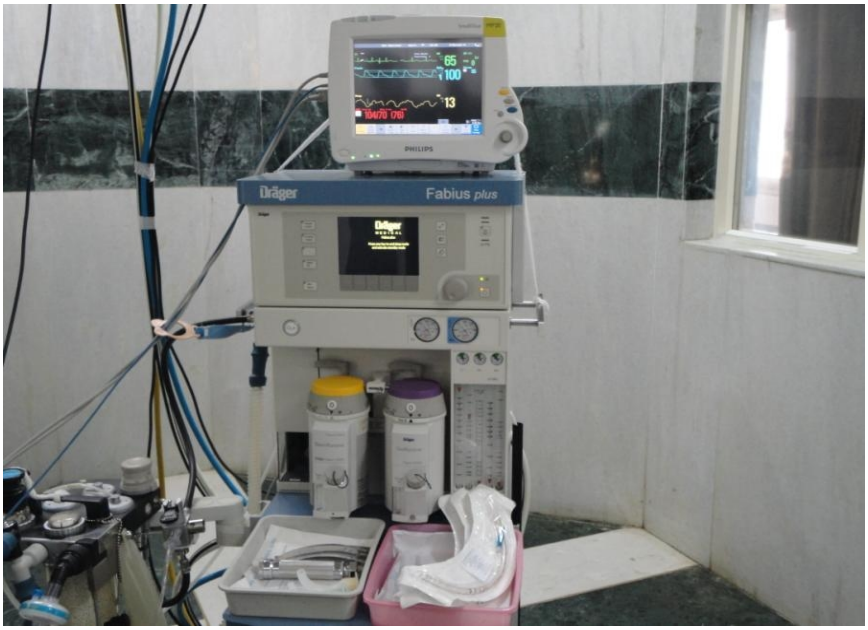
Photograph 2. Isobaric Levobupivacaine (0.5%)



Photograph 3. Spinal tray



Photograph 4. Procedure of epidural anaesthesia



Photograph 5. Monitoring

Annexures

Annexure I

ANNEXURE I – CONSENT FORM

A study, **"COMPARISON OF ONSET AND DURATION OF SENSORY AND MOTOR BLOCKADE BETWEEN EQUIPOTENT DOSES OF 0.75% PLAIN ROPIVACAINE AND 0.5% PLAIN LEVOBUPIVACAINE IN LOWER ABDOMINAL SURGERIES UNDER EPIDURAL ANAESTHESIA- A ONE YEAR RANDOMIZED CLINICAL STUDY"** is being conducted by ----------, Post Graduate in Anaesthesiology at Jawahar Lal Nehru Medical College Belgaum, Karnataka. Under guidance of ---------- Professor, Department of Anaesthesiology, Jawahar Lal Nehru Medical College, Belgaum, under KLE University, Belgaum.

Respected _____ we request you to participate in our study as you are eligible to be included. During the study you will be asked questions regarding your present and past medical history and you are supposed to answer to the best of your knowledge.

Your participation in this study is voluntary. Your decision whether or, not to participate in the study will not affect your relationship with Jawahar Lal Nehru Medical College Belgaum, Karnataka. If you decide to participate you are free to withdraw at any point of time. The purpose of the study is to compare between equipotent doses of Ropivacaine and Levobupivacaine with respect to onset and duration of motor block, onset, duration and level of sensory block and time to request for first post operative rescue analgesia in elective lower abdominal surgeries under epidural anaesthesia.

Objective of the study

Objective of my study is to assess the effect of 15ml of 0.75% Ropivacaine (Plain) and 15ml of 0.5% Levobupivacaine (plain) on onset and duration of motor block, onset, duration and level of sensory block, duration of post operative analgesia in elective lower abdominal surgeries under epidural anaesthesia.

Procedure involved

If you agree to enrol yourself in my study, you will be interviewed regarding your present, past and family history, then you will be clinically examined in detail and investigated accordingly. You will receive either 15ml of 0.75% Ropivacaine (Plain) or 15ml of 0.5% Levobupivacaine (Plain).

Benefits and Risks

The benefits of taking part in this research are that we can avoid G.A with good quality of Analgesia and early ambulation. The risks are minimal which include, hypotension, bradycardia, headache, backache, syncope, paraesthesia.

Voluntary participation / Withdrawal

Taking part in the study is voluntary; you may choose not to enrol in this study. Your decision will not change present or future health care services offered to you at KLE'S Dr. Prabhakar Kore Hospital and Medical Research center, Belgaum.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Confidentiality

All information collected about me during the course of the study will be kept confidential to the extent permitted by law. The code numbers will identify you in this study records and the information from this study may be published but your identity will be confidential in any publication.

Financial Incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation

In the event of injury, related to the study, treatment will be made available at KLE'S Dr. Prabhakar Kore Hospital and Medical Research center, Belgaum. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

If you have any queries, in future or in case of study related injury or illness, you may contact ----------, at Department of Anesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Center or by Phone Number-

---------- or Mobile Number - ----------. If you are injured, you may contact - ---------- Mobile Number - ----------, at Department of Anesthesiology, KLE'S Dr. Prabhakar Kore Hospital and Medical Research Center, or ----------– Mobile Number - ----------. If you have any queries about your rights as a study subject, you may call ----------, Chairperson, J.N. Medical College, Institutional Ethical Committee for Human Subjects Research, Ph. ---------, Mobile : ---------- at J.N. Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

I, Mr./Mrs. _____

voluntarily agree to take part in this study, by signing this consent form I am not giving up my legal rights. I may withdraw at any time. I am signing after having read, or been read to me in the vernacular language including risks and the benefits and having all queries cleared.

Signature of the participant: _____

Witness name: _____

Signature of the participant: _____

Date: _____

Place: _____

Signature of Investigator: _____

GROUP R

surgery	HighestlevelofSensoryBlockachieved	onsentofsensoryblockmin	onsetofmotorblockmin	durationofsensoryblockmin	durationofmotorblockmin	durationofpostopanalgesiamin
HR	T8	16	25	190	129	250
OA	T7	15	20	180	134	300
ABH	T8	15	22	190	125	270
HR	T8	25	28	200	110	230
OA	T6	15	25	240	124	310
HR	T7	17	25	180	80	260
HR	T8	18	27	190	120	300
HR	T8	18	24	220	110	280
ABH	T8	15	23	210	110	250
OA	T7	15	20	190	75	270
OA	T9	19	26	160	110	290
ABH	T8	16	20	210	128	240
OA	T8	17	22	220	130	260
HR	T8	17	23	220	125	275
OA	T7	18	25	170	98	290
OA	T7	17	22	180	84	270
OA	T8	17	24	190	130	240
OA	T8	15	23	190	124	240
HR	T7	17	24	200	90	260
ABH	T8	23	30	220	110	280
HR	T6	17	18	240	145	320
ABH	T8	20	27	180	129	270
OA	T7	23	26	220	95	260
OA	T8	23	30	220	100	240
OA	T8	17	24	190	115	260
HR	T9	19	25	180	110	290
OA	T8	23	25	220	104	270
HR	T8	15	20	190	123	260
OA	T7	24	27	170	100	250
OA	T8	18	23	190	120	260
HR	T7	17	25	210	89	270
HR	T8	19	24	140	128	240
HR	T8	15	23	210	110	300
OA	T8	25	30	200	124	250
OA	T7	15	21	200	80	270
OA	T8	16	21	190	115	240
OA	T7	15	21	190	80	270
OA	T8	18	23	210	124	220
OA	T8	18	24	220	110	250
OA	T7	19	25	180	97	250
HR	T8	15	22	175	120	270
HR	T7	15	20	180	100	230
OA	T8	16	28	210	115	240
OA	T8	18	22	190	127	260
OA	T8	22	32	200	108	230

GROUP L

SNO	In patient number	surgery	HighestlevelofSensoryBlockachieved	onsentofsensoryblockmin	onsetofmotorblockmin	durationofsensoryblockmin	durationofmotorblockmin	durationofpostopanalgesiamin
1	505428	OA	T8	15	24	190	120	220
2	505814	OA	T7	20	32	200	105	250
3	506649	OA	T8	16	25	220	120	270
4	506997	HR	T6	18	27	250	135	310
5	506487	HR	T8	15	22	200	114	260
6	508581	OA	T8	15	17	210	110	230
7	508035	HR	T7	21	30	190	88	250
8	508678	HR	T8	16	22	180	130	270
9	507559	OA	T8	15	23	200	130	240
10	558853	HR	T7	25	27	180	100	230
11	516331	HR	T8	19	29	200	120	210
12	509232	OA	T8	19	28	210	110	250
13	509451	OA	T8	17	23	190	158	260
14	559428	HR	T6	15	22	220	140	330
15	530170	OA	T8	20	21	170	120	250
16	510437	HR	T7	17	27	180	74	230
17	517819	OA	T8	16	20	200	120	230
18	530515	OA	T8	21	29	160	122	250
19	520846	OA	T8	21	26	170	130	250
20	500214	HR	T9	25	31	180	124	270
21	501709	HR	T8	25	32	170	130	240
22	501426	HR	T7	16	23	180	92	200
23	501538	OA	T8	17	22	200	114	240
24	501811	OA	T8	15	19	180	120	260
25	502145	OA	T8	19	29	170	128	270
26	502201	OA	T8	22	30	190	130	240
27	505689	HR	T7	18	29	190	109	250
28	506291	ABH	T8	15	21	180	124	270
29	505297	HR	T8	19	29	190	110	230
30	510531	HR	T8	22	28	200	117	240
31	521658	HR	T7	15	17	180	100	250
32	530951	OA	T8	18	28	170	114	250
33	531513	HR	T6	15	20	230	150	300
34	509691	ABH	T7	23	29	180	80	230
35	523129	HR	T8	20	32	160	120	250
36	522863	HR	T8	18	24	190	140	270
37	525607	HR	T7	18	27	190	115	270
38	517234	HR	T8	19	27	200	129	270
39	514624	HR	T8	17	19	170	125	270
40	550534	OA	T8	23	25	165	120	280
41	541658	HR	T7	17	21	210	124	250
42	510951	HR	T8	17	25	190	160	270
43	534543	OA	T8	24	29	170	108	230
44	523691	OA	T7	17	27	200	125	250
45	520511	HR	T8	23	29	150	80	280