"TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA – ONE YEAR RANDOMISED CLINICAL TRIAL"

By

(REG NO: BA0120011)

DISSERTATION

SUBMITTED TO THE
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KLE Academy of Higher Education & Research(Deemed-to-be-University), Belagavi, Karnataka

ENDORSEMENT

This is to certify that the dissertation entitled **"TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA: A ONE YEAR RANDOMISED CINICAL TRIAL"** is a bonafide research work done by **REG NO: BA0120011** Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi – 590 010.

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ACCEPTANCE LETTER

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA- ONE YEAR RANDOMISED CLINICAL TRIAL",** is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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ABSTRACT

TITLE:

TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA: A ONE-YEAR RANDOMISED CLINICAL TRIAL.

CONTEXT:

Epidural anaesthesia is the most popular method for providing peri-operative anaesthesia and postoperative analgesia for lower abdomen and limb surgeries. There are fewer direct studies contrasting ropivacaine and levobupivacaine with buprenorphine adjuvant, hence we took this study.

AIMS:

Comparison of onset of action of sensory and motor block and the duration of action of buprenorphine with levobupivacaine and buprenorphine with ropivacaine and to compare hemodynamic effects of drugs.

SETTING AND DESIGN: A ONE-YEAR RANDOMISED CLINICAL TRIAL.

MATERIALS AND METHODS:

A total of 70 adult patients of either sex, ASA grade I - II, scheduled for lower abdominal surgery were enrolled in the study and randomized into two groups. Group LB received 14.5ml

of 0.5% Levobupivacaine + Inj Buprenorphine 150mcg (0.5ml) making volume 15ml. Group RB received 14.5ml of 0.75% plain Ropivacaine + Buprenorphine 150 mics (0.5ml) making volume 15ml. The onset and duration of sensory-motor block, hemodynamic variables (HR, SBP, DPB, MAP, RR), and duration of analgesia were recorded.

RESULT:

Sensory and motor blockade onset was earlier in group RB than in group LB. The duration of sensory and motor blockade was earlier in group LB than in group RB. The mean hemodynamic parameters were comparable in both groups.

CONCLUSION:

In adults undergoing lower limb surgery, the LB group produced a longer duration of action with late onset of sensory and motor block than the RB group. Hemodynamic effects were comparable.

KEYWORDS: Epidural anaesthesia, Ropivacaine, levobupivacaine, Buprenorphine, hemodynamic.

LIST OF ABBREVATION

ASA	-	American Society of Anaesthesiologists
HR	-	Heart Rate (bpm)
SBP	-	Systolic Blood Pressure (mm Hg)
DBP	-	Diastolic Blood Pressure (mm Hg)
SpO_2	-	Saturation of peripheral oxygen (%)
L	-	Lumbar sensory dermatomal level
mcg.	-	micrograms
min.	-	minutes
kgs.	-	kilograms
cms.	-	centimeters

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INTRODUCTION

The most popular method for providing both peri-operative anaesthesia and postoperative analgesia for lower abdomen and limb surgeries is epidural anaesthesia.[1]

It offers dynamic analgesia, enabling patients to get back to their regular activities pain-free. In either a single shot or continuous infusion technique, local anaesthetics and opioids continue to be the most frequently used medications in regional anaesthesia.[2]

These epidural practices avoid the disadvantages of general anaesthesia, such as the need for additional intravenous analgesics, the need for airway manipulation, polypharmacy, and other undesirable effects like postoperative nausea and vomiting.

In comparison to SAB, epidural anaesthesia is more versatile and gives the anaesthesiologist more flexibility in managing the case, which SAB does not. Epidural anaesthesia has a longer duration of action, the ability to provide local anaesthetic top-ups if the surgery takes longer than expected, and the ability to provide analgesic top-ups for post-operative pain relief. Because of the segmental nature of the block, it also provides better haemodynamic stability than SAB.[3]

The number of elderly patients scheduled for surgery has increased as a result of longer life expectancies. Epidural anaesthesia has been shown to reduce intraoperative blood loss, perioperative cardiac ischemic events, post-operative hypoxic episodes, and venous thrombosis.[4]

One of the most significant factors of postoperative morbidity is inadequate postoperative analgesia, which is greatly influenced by the type of anaesthesia used during the intraoperative phase.

Additionally, the objective of early rehabilitation is undermined by the occurrence of the motor block following epidural anaesthesia with amide local anaesthetics (LA) and opioids, which is nearly 4-12%.[5]

Bupivacaine is a long-acting local anaesthetic that has been used for obstetric and regional anaesthesia for the past three decades. Epinephrine is not required to prolong the effects of bupivacaine or reduce systemic accumulation because bupivacaine exhibits good motor/sensory segregation. It is not connected to tachyphylaxis, in contrast to lidocaine, which requires steadily higher dosages given more frequently to maintain analgesia.[6]

Bupivacaine's potential for cardiac toxicity exposed the drug's unfavorable properties. The development of local anaesthetic toxicity was thought to involve mild Symptoms, seizures, cardiovascular instability, and sudden cardiac death.[7]

Unexpected heart attacks without the emergence of nervous system manifestations, difficult resuscitations, and increased rates of maternal deaths (76 percent of recorded fatalities) have all been shown to be worrying results.[8]

These techniques, however, were inadequate for ensuring the safety of patients in the situation of accidental intravascular injection. Toxic side effects were eventually curbed by changes to anaesthesia procedures like slow incremental dosing and the usage of test doses. A significant research effort was made to comprehend and circumvent the fundamental processes of

bupivacaine toxicity as a result of an awareness of the clinical advantages of bupivacaine and the development of its isomer levobupivacaine.

In clinical settings, levobupivacaine has not completely taken the role of bupivacaine. Levobupivacaine is equally as potent as bupivacaine. In contrast, levobupivacaine caused fewer CVS and Central nervous system harm in animal studies than bupivacaine. Levobupivacaine produced less QTc interval prolongation than bupivacaine at i.v doses greater than 75mg in healthy subjects and had a less detrimental inotropic effect. With levobupivacaine, there were fewer EEG abnormalities that indicated CNS depression.

There's some difference in efficacy findings among clinical groups, although its clinical effects in comparative trials were not substantially distinct from those of bupivacaine.

Ropivacaine recently developed as an amide local anaesthetic. It’s advertised as the parent chemical ropivacaine's pure S(-) enantiomer. Its obvious advantages over Bupivacaine include lower cardiotoxicity and neurotoxicity, as well as a more targeted action on sensory rather than motor fibres. It is due to Ropivacaine's lower lipophilicity and enantiomer properties.[9]

The introduction of adjuvants, which favorably alter the block properties of local anaesthetics and hence reduce the required dose, can help achieve this delicate balance between safety and efficacy.

The most popular epidural opioid analgesic for surgeries is buprenorphine. It is an agonist-antagonist with approximately five times the lipid solubility of morphine and is 30 times more

effective. It has been applied epidurally for post-surgical analgesia. Because there is no rostral spread, it has been linked to a lower incidence of delayed respiratory depression. It has low abuse potential. It is widely available without the need for a narcotics licence.[10]

We are using the epidural route because no studies had compared these medications using the epidural route alone. In this study, we are examining the effectiveness of buprenorphine in combination with the local anaesthetics ropivacaine and levobupivacaine, both of which have low levels of toxicity for the cardiovascular and nervous systems and have a lower tendency to cause motor block during postoperative epidural analgesia.

Numerous studies have compared different doses of ropivacaine and levobupivacaine with other amide local anaesthetics as well as with different adjuvants in epidural anaesthesia. However, there are less direct studies contrasting ropivacaine and levobupivacaine with buprenorphine adjuvant, hence we **STUDIED THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA.**

OBJECTIVE:

The objectives of the present study are:

PRIMARY OBJECTIVE:

Comparison of onset of action of sensory and motor block and the duration of action of buprenorphine with levobupivacaine and buprenorphine with ropivacaine.

The onset of action i,e time taken to achieve both motor and sensory block up to T-10 level from the time of injection of an epidural drug

in minutes

Duration of action is the time from once the patient feels pain from the time of onset of action or two-segment regression of sensory block.

SECONDARY OBJECTIVE:

Comparison of hemodynamic effects during levobupivacaine 0.5% with buprenorphine 150 microgram and ropivacaine 0.75% with buprenorphine 150 microgram. Various haemodynamic parameters studied are:

Blood pressure,

Heart rate,

Oxygen saturation.

REVIEW OF LITERATURE

The origins of epidural anaesthesia can be traced back to 1901, when two French clinicians, Jean. E. Sicard and Fernand Cathelin, independently injected cocaine through the sacral hiatus, thereby pioneering caudal epidural block.[1]

The caudal block so administered was proven to be adequate for perineal surgery, but clinicians quickly understood that techniques for placing epidural needles in lumbar or even thoracic locations should be devised if surgeries on the belly and thorax were to be conducted under regional anaesthetic.

Various methods were tested for over two decades but none were proven to be satisfactory in detecting the epidural space at higher levels.

Finally, in 1921, Fidel Pages, a Spanish military physician, wrote a groundbreaking essay outlining a tactile approach to identify epidural space at all levels. He inserted a blunt needle into the ligamentum flavum, and to confirm the needle's position in the epidural space, he "felt" and "heard" the entry of the needle.[11]

Following are the review articles and need of study:

Deepa Bulchandani conducted a study in 2017, in 60 adult patients of either sex who were scheduled for total knee replacement surgery and had an ASA grade of I to II were enrolled in the trial and randomly assigned to one of two groups. Group R received 15ml total of 14.5ml of

0.75% plain ropivacaine and 0.5ml of normal saline (NS). Group RB received 14.5ml of 0.75% plain ropivacaine plus 150 mics (0.5ml) of buprenorphine, for a total volume of 15ml. The onset of sensory-motor block, as well as hemodynamic factors (HR, SBP, DPB, MAP, RR). The findings indicated that group R experienced sensory blockage earlier than group RB. In both groups, the motor onset time was comparable. In both groups, the average hemodynamic parameters were similar. We compared the results of this trial's ropivacaine and buprenorphine to those of our study drug, levobupivacaine plus buprenorphine.[12]

In another study published in the IOSR Journal Of Dental and Medical Sciences in 2014, Kulkarni and colleagues evaluated the effectiveness of 15 ml of 0.5% ropivacaine to 15 ml of 0.5% bupivacaine in elderly patients undergoing lower limb surgeries under epidural anaesthesia. They examined changes in pulse rate and systolic blood pressure in both groups, as well as the onset of sensory block, the severity of motor blockade, the highest level of anaesthesia attained, the time needed for two-segment regression, and other factors. They concluded that sensory blocking in the Ropivacaine and Bupivacaine groups is equivalent. When taken in a concentration of 0.5%, ropivacaine offers a less strong motor block with higher cardiac stability. This research was conducted to assess the cardiostable qualities of ropivacaine. It enabled us to use a higher drug concentration to approach the motor block.[13]

International Journal of Pharmaceutical Sciences In a similar trial, performed in 2014 by Thimappa and colleagues, patients undergoing lower abdomen and lower limb procedures were given ropivacaine (R) alone, ropivacaine clonidine (RC), and ropivacaine dexmedetomidine

(RD) combinations. Patients were separated into three groups and given 19ml of 0.75% ropivacaine with 1ml of normal saline, 19ml of 0.75% ropivacaine with 1ml (75 mcg) clonidine, and 19ml of 0.75% ropivacaine with 1ml (75 mcg) dexmedetomidine for group R, group RC, and group RD, respectively. Block characteristics such as analgesia onset, the maximum level of sensory blockade, total motor blockade, hemodynamics, time to two-segment regression, time for rescue analgesia, time to complete motor recovery, and side effects were investigated. The results demonstrated that the addition of additives like clonidine and dexmedetomidine hastened the onset of blockage. In the non-additive Group, the time for two-segment regression was 30-35 minutes earlier. This study aided in choosing additives to extend the block time.[14]

In Saudi J Anesthesiology 2011, Bajwa and colleagues evaluated the effects of fentanyl with dexmedetomidine combined with ropivacaine for epidural anaesthesia in patients having lower limb orthopaedic procedures. 15ml of 0.75% ropivacaine and 1 mcg/kg of fentanyl were administered to group RF, whereas 15ml of 0.75% ropivacaine and 1 mcg/kg of dexmedetomidine were administered through the epidural route to group RD. They concluded that Dexmedetomidine appears to be a better option than fentanyl as an epidural adjuvant since it offers equivalent stable hemodynamics, early onset and establishment of sensory anaesthesia, longer post-op analgesia, lower consumption of post-op LA for epidural analgesia, and considerably superior sedation levels. This study explains the superiority of alpha 2 agonists vs opioids.[15]

Bajwa et al. in Saudi J Anesthesiology 2010 May-Aug compared the effects of epidural ropivacaine (Group R) and the combination of epidural ropivacaine and clonidine (Group RC) in

patients undergoing elective caesarean sections. 20 ml of 0.75% ropivacaine was given to group R, whereas 75 mcg of clonidine, a -2 agonist, was given to group RC. In the RC group, analgesia began much more quickly and lasted longer overall. It was statistically significant that there was a higher incidence of bradycardia and hypotension in the RC group as compared to the R group. The dose needed to relieve postoperative pain was noticeably lower in the RC group. they concluded that compared to using plain ropivacaine for caesarean birth, adding 75 g of clonidine to isobaric epidural ropivacaine leads to longer, more complete, and effective analgesia with similar block qualities.[16]

In a 2009 study by Guler G et al. that was published in the Saudi Medical Journal, 81 males in ASA I-II who were undergoing transurethral resection of the prostate were divided into three groups and given epidural ropivacaine at different concentrations: Group I received 15 ml of a 0.75% solution, Group II received 10 ml of a 0.75% solution, and Group III received 10 ml of a 0.5% solution. The hemodynamic alterations and block quality were evaluated. Group III experienced much less motor block than groups I and II. In 55% of patients in group I, 35% in group II, and 21% in group III, the sensory block level was T6 or higher. In group III, the sensory block lasted a shorter time and it took longer to reach the T10 threshold. In group I, bradycardia and hypotension was more common. Low dosage ropivacaine provided effective anaesthesia with minor side effects. This study assisted us in selecting a larger volume and concentration of ropivacaine as the study drug.[17]

V. A. Peduto published research in the European Journal of Anaesthesia in 2003. Adult patients in the ASA I–III range undergoing elective lower limb surgeries were randomly assigned to

receive either 15 mL of epidural ropivacaine (n=35) or 15 mL of epidural levobupivacaine (n=30). When a motor and sensory block's onset time and regression were measured by a blinded observer, The onset time for ropivacaine was 25±22 min. and for levobupivacaine, it was 29±24 min (p-0.41). Levobupivacaine took 105 minutes and 63 seconds to completely resolve the motor block, while ropivacaine took 95 minutes and 48 seconds (p-0.86). Levobupivacaine took 185 and 77 minutes for the sensory block to regress to T12, while ropivacaine took 201 and 75 minutes (p-0.46). they concluded. Levobupivacaine 0.5% 15 mL causes an epidural block with the same clinical profile as ropivacaine 0.75% 15 mL in people having lower limb surgery. This study served as our reference.[18]

In a research published in the Canadian Journal of anaesthesia in 1998, 60 patients scheduled for caesarean section were separated into two groups, one receiving 22 ml of 0.5% bupivacaine via an epidural channel and the other receiving 22 ml of 0.5% ropivacaine via the epidural route. In surgically important dermatomes (T6 - S3), the median onset for the time of sensory block ranged from 7.5 to 25 minutes in the ropivacaine group and from 5 to 17.5 minutes in the bupivacaine group. In the ropivacaine group, the median length of the sensory block ranged from 1.7 to 4.2 hours, while in the bupivacaine group, it ranged from 1.8 to 4.4 hours. For ropivacaine and bupivacaine, the median time for the onset of motor blockade was 15 minutes and 12.5 minutes, respectively. For ropivacaine and bupivacaine, the median time of motor blockage was 2.1 hours and 2.4 hours, respectively. They concluded. Bupivacaine produced sensory and motor blocks that began and persisted earlier and longer than ropivacaine. Only surgical procedures involving the lower abdomen and lower limbs from our study were contrasted with 15 ml of ropivacaine and levobupivacaine. Using ropivacaine for obstetric procedures was facilitated by this study.[19]

In a comparable study published in the Anaesthesia and Intensive Care journal in 1997, McGlade D.P. and colleagues evaluated the block characteristics of 20 ml ropivacaine 0.5% and 20 ml bupivacaine 0.5% given epidurally in patients having lower limb orthopaedic surgeries. The median and interquartile range for the onset and duration of analgesia at the T10 dermatome for ropivacaine and bupivacaine, respectively, were 10 (5–15) minutes and 3.5–4.3 hours and 10 (6–15) minutes and 3.4–3.8 hours, respectively.T6 was the highest block height allowed in both categories. Grade III motor blockage occurred in only 4/27 patients treated with ropivacaine and 6/34 patients treated with bupivacaine, with no statistically significant difference between the two groups. In the ropivacaine group, 78% of patients had a sufficient level of sensory and motor block, compared to 62% and 71% in the bupivacaine group. Similar cardiovascular alterations occurred in both groups. As a result, neither 0.5% ropivacaine nor 0.5% bupivacaine showed any statistically significant difference in any of the research parameters. This study was useful in choosing the dosage of ropivacaine.[20]

In a 1990 study by Jeffrey A. Katz that was published in the American Society of Regional Anesthesia, 44 patients between the ages of 18 and 70 who were undergoing lower orthopaedic procedures were examined. Of these patients, 21 received 20 ml of 0.5% Bupivacaine and 23 received 20 ml of 0.75% ropivacaine. The onset of sensory block occurred at T12 for ropivacaine after 9±10 minutes and 6±4 for bupivacaine. In total, the sensory regression to T12 lasted 6.6 hours with ropivacaine and 6.5 hours with Bupivacaine. The time is taken for the onset of maximum motor block ropivacaine after 47±29 minutes and 32±17 for bupivacaine. This study assisted us in deciding the concentration of ropivacaine. [21]

BASIC SCIENCES

Applied Anatomy

An anaesthesiologist requires to have an accurate and in depth knowledge of the anatomy of vertebral column and its contents for a 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

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

Curves of spine

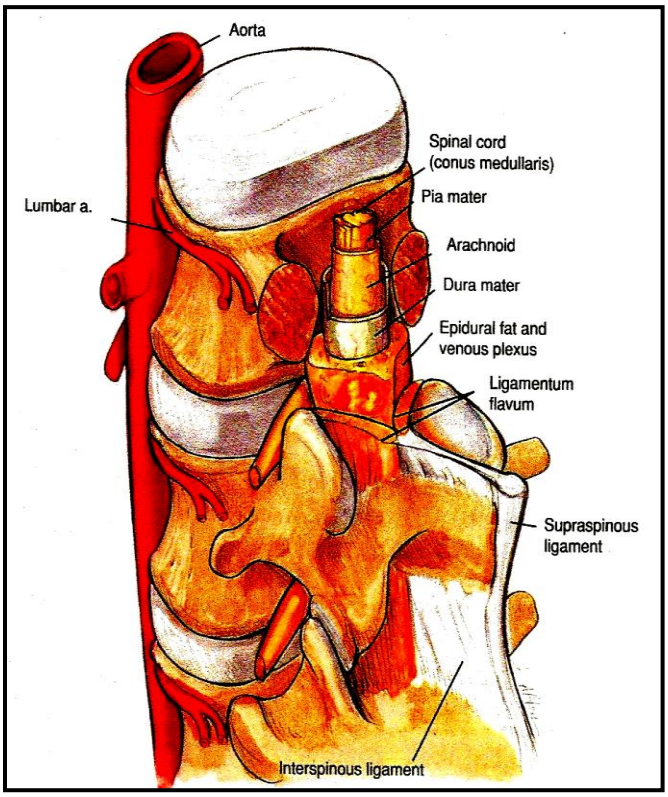
In adults, curves of vertebral column have significant effect on spread of drugs in subarachnoid space and these curves are:[22]

- 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.[22]

Figure 1: Vertebral Column



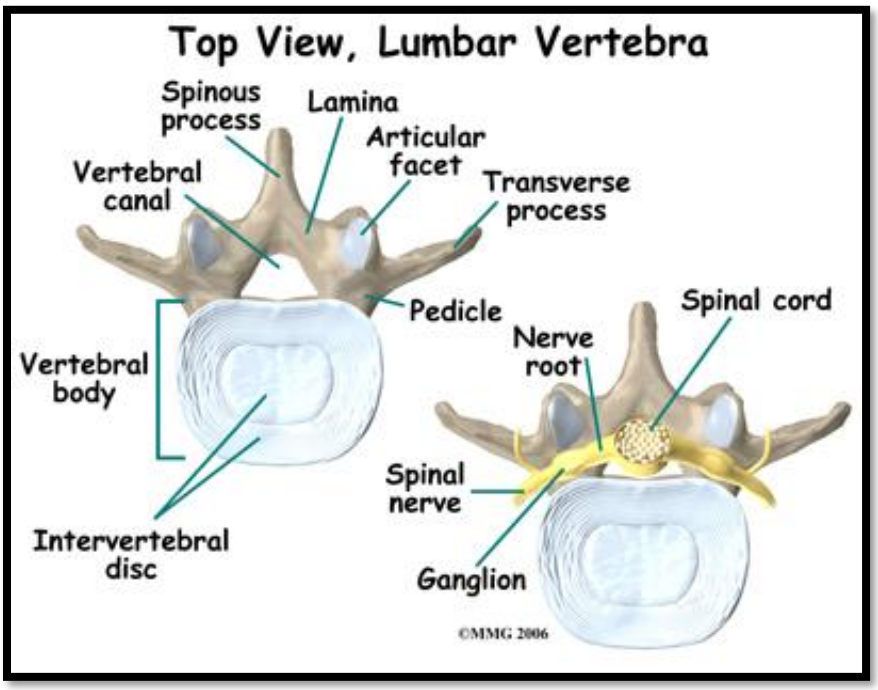
Lumbar vertebrae

A typical lumbar vertebra consists of:

- 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.
- Thick, broad and quadrilateral spinous processes.
- Two upper and lower articular processes which prevent rotation but allow limited flexion and extension between contiguous vertebrae.

Figure 2: Typical lumbar vertebra



Thoracic vertebrae :

- A heart shaped body
- A small costal demi facet on superior border of lateral side of body and a larger demi facet on the inferior surface
- Shallow superior vertebral notches and deeper inferior vertebral notches

- Transverse processes are directed backwards and laterally , carrying a costal facet for articulation with ribs.

Vertebral ligaments

The following overlapping ligaments provide stability to the vertebral column and protect the spinal cord :

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from sacrum to C_5 where it is continued as the ligamentum nuchae . The width depends upon the width of the spinous process – in lumbar region it might be upto 1 cm wide. In elderly people and manual labourers this ligament calcifies thus making the midline approach difficult.

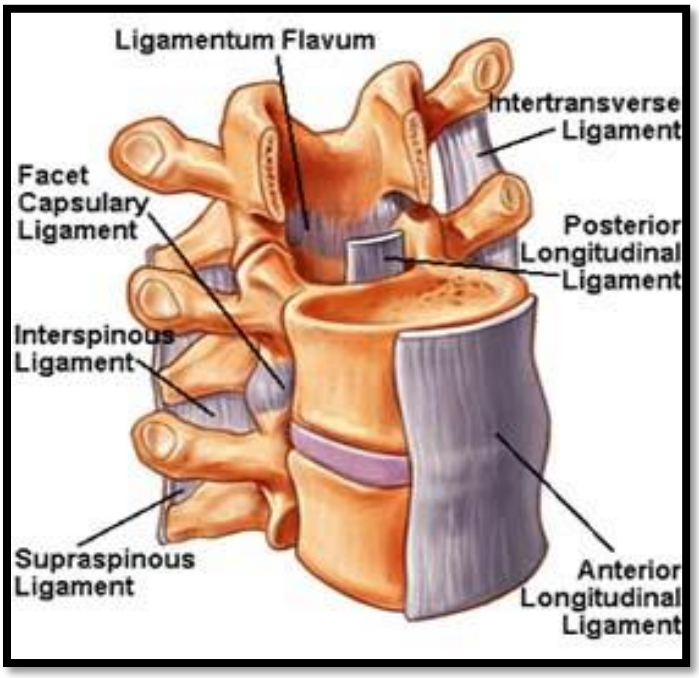
Interspinous ligament: This is a thin membranous ligament running obliquely and connecting spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament. In the lumbar region, this ligament is rectangular in shape leading to the characteristic and identifiable “loss of resistance” feel to air or saline.

Ligamentum flavum: This ligament comprises of 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. It provides the classic springy resistance in the lumbar region.

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

For epidural anaesthesia, needle pierces the first three ligaments when midline approach is used, in para median approach only the ligamentum flavum is encountered.

Figure 3 :Vertebral ligaments



Intervertebral Discs[23]

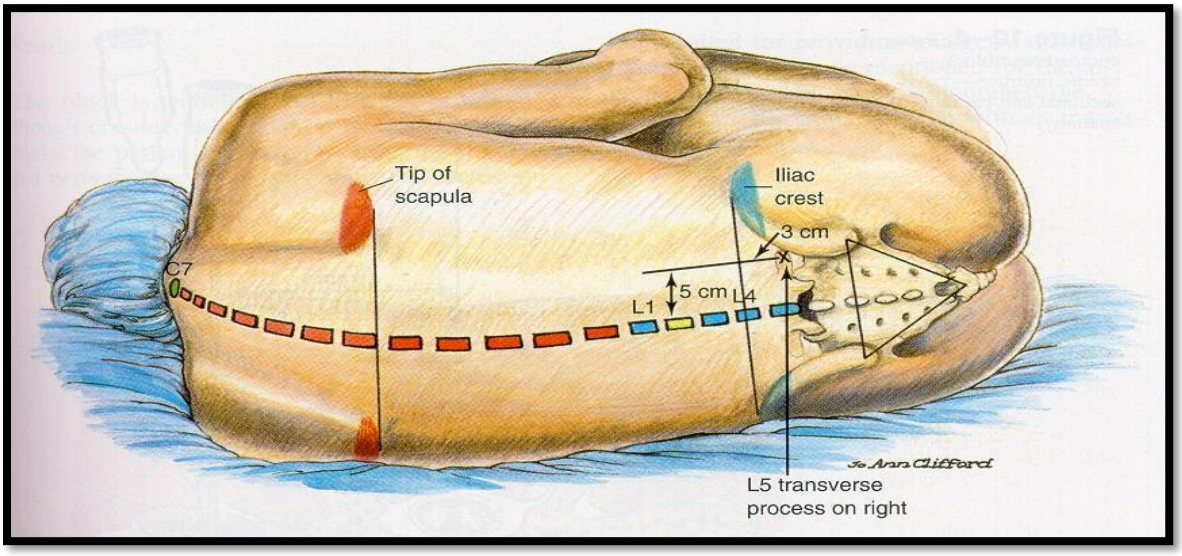
These are principle connecting link between vertebral bodies. They form about 25% of the length of the spine. They consist of two parts - The outer fibrous part called the *annulus fibrosus* (made up of fibrous tissue), while the *nucleus pulposus* is the softer core. The discs serve as shock absorbers and lend flexibility to the vertebral column.

Topographical Line of Tuffier

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: Topographical line of Tuffier



Vertebral canal:

The vertebral canal is bound by the vertebral bodies and intervertebral discs anteriorly , the laminae , ligamentum flavum and laterally by pedicles and laminae.

The contents of vertebral canal are as follows :

- Spinal cord
- Spinal nerve roots
- Meninges
- Cerebrospinal fluid
- Vessels
- Fat

- Loose areolar tissue

Spinal cord

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.

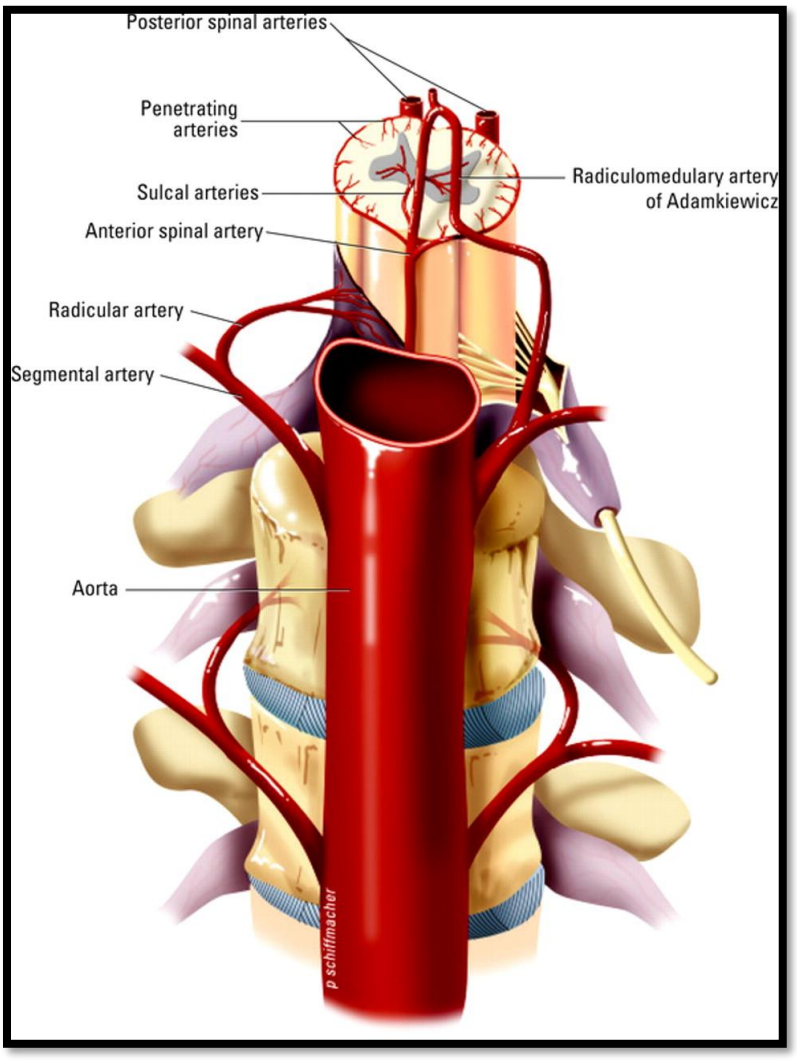
At birth, Spinal cord ends at the level of lower border of lumbar (L) three vertebra and in adults, it is as follows;

- 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, each 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:

The spinal cord receives its blood supply from 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

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

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.

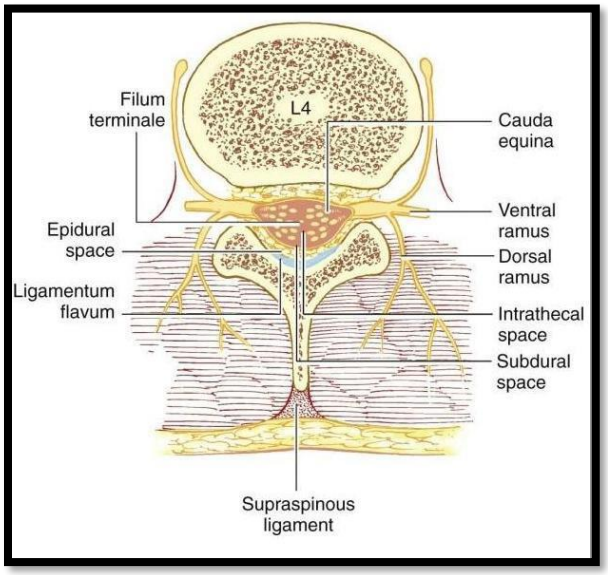
Arachnoid Mater

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

Below this the dura continues as the filum terminale. The subarachnoid space is the space between the arachnoid and pia mater. This space is occupied 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 in shape.

EPIDURAL SPACE[24]

Figure 6 : Epidural Space



Boundaries of the epidural space

The epidural space is bounded

Superior: by foramen magnum , where periosteal and spinal layers of duramater fuse.

Inferior: by sacroccygeal membrane and sacral hiatus .

Anterior : by the posterior longitudinal ligament, vertebral bodies and discs

Posterior : by ligamentum flavum , periosteum of anterior surface of laminae and connecting ligaments.

Lateral : by periosteum of pedicles and intervertebral foramina.

Rarely, a fold of duramater divides the space into ventral and dorso – medial compartments leading to patchy or unilateral analgesia or missed segments.

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.

Cervical : 1.5 mm

Upper thoracic : 2.5 – 3 mm

Lower thoracic : 4-5 mm

Lumbar : 5-6 mm

Types of epidural space

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 C_7 to the upper margin of L_1, the lumbar epidural space is formed by the lower margin of L_1 vertebra to the upper margin of S_1 vertebra. The sacral epidural space is formed by the upper margin of S_1 to sacrococcygeal membrane and sacral hiatus.

Contents of the epidural space :

Contains semi liquid fat , lymphatics , arteries , loose areolar tissue spinal nerve roots and a very rich plexus of veins.

Fat

The epidural space is filled with semi fluid , lobulated fat tissue. 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 areolar tissue of this space has a very rich blood supply with small capillaries forming a network in its substance . 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 maximum amount of fat is present posteriorly, where it assumes triangular capsular shapes and is linked to the midline of the ligamentum flavum by a vascular pedicle. Drugs with high lipid solubility like bupivacaine have a high affinity for fatty tissue and thus remain in epidural fat for a longer time thus leaving a small quantity of the drug to interact with nerve roots at any time. Uptake of local anaesthetic by fat competes with it's vascular and neural uptake .

Lymphatics

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

Vertebral venous plexus

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, azygous 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, tumours etc.) 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 sinus, basilar venous sinus, 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 venous plexus is also connected to the iliac veins through the sacral venous plexus. Obstruction of the inferior vena cava, advanced pregnancy or intra abdominaltumors 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. These veins are more prominent along the lateral wall of the vertebral canal usually they are out of reach of a correctly placed needle by midline approach. The dose and rate of local anaesthetic should also be reduced in any case of increased intraabdominal pressure / inferior vena cava obstruction as the resultant engorgement of the venous plexus would reduce the effective volume of the epidural space. The injected drug may therefore spread rapidly upwards or downwards along the epidural space.

Epidural arteries

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 accidental puncture is uncommon by midline approach.

Spinal arteries:

As already discussed, the spinal cord is supplied by one anterior spinal and two posterior spinal arteries. The spinal branches of the subclavian, aortic and iliac arteries cross the epidural space on the way to sub arachnoid space. The largest of them, the artery of Adamkiewicz supplies the anterior spinal artery at the lumbar level. This artery enters the epidural space between $T_8 – L_3$ levels and any damage to itwoul cause ischaemia of entire lumbar region of the cord. In general, anterior spinal artery is more susceptible due to it being unpaired.

Pharmacokinetics Of Epidural Blockade

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

Specifically, drugs may

1) exit the intervertebral foramina to reach the paraspinous muscle space,
2) drugs may diffuse into epidural fat,
3) drugs may diffuse into ligaments and finally,
4) 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.

Lipid soluble drugs have a tendency to get sequestrated into epidural fatty tissue. The dura mater is an important site of drug clearance especially in humans where dura mater is a highly vascular structure. As lipid soluble molecules traverse capillaries more readily than do more hydrophilic molecules, 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 anaesthetics 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 this happens only when the drug concentration in the epidural space falls below that in the CSF. Diffusion is dependent mainly on the drug's physicochemical properties, particularly, lipid solubility.

Physiological Effects Of Epidural Blockade

The physiological responses to epidural anaesthesia are mainly due to sympathetic blockade accompanied by sensory and motor blockade to various degrees. 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 T_4) and/or of cardiac sympathetic fibres. Major sympathetic blockade can be avoided by trying to keep the block level around or below T_{10}. Lower abdominal, urologic, gynaecological and lower limb surgeries can be carried out satisfactorily with acceptable sympathetic blockade.

Zone of differential blockade:

Erlanger and Gasser showed that action of local anaesthetics on nerve fibres is by "differential conduction blockade". The nerve fibres are of three types viz A, B , C

A minimum length of myelinated nerve fibres should come in contact with local anaesthetic for conduction blockade. In myelinated fibres, the blockade occurs at nodes of Ranvier and three consecutive nodes need to be blocked for impulse conduction to be completely interrupted.

All types of nerve fibres are affected by local anaesthetics. but within any one fibre type, there is tendency for small, slower conducting fibers to be more readily blocked than large, fast conducting fibres. Between fibre types however, these rules do not hold good. Myelinated preganglionic B fibres 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 $A\alpha$ fibres appear to be more sensitive to blockade than motor $A\beta$ fibres, although of the same conduction velocity, this may be because sensory fibres conduct at a higher frequency. It has been suggested that this selectivity for sensory fibres exhibited by Bupivacaine and Ropivacaine is a function of frequency dependent block.

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.

Factors Influencing Height And Distribution Of Local Anaesthetic:

Patient characteristics:

- Age: Study done by Bromage shows a correlation between age and dose, an increase in dose from age 4-18 years followed by a gradual decrease from 19 year onwards.
- Height: A simple thumb rule is to use 1ml per segment for height of 150 cm and then add 0.1 ml per segment for each 5 cm over 150 cm.
- Weight: Under normal circumstances, there is not much correlation between spread of analgesia and the weight. However in morbidly obese patients a given dose of local anaesthetics can cause a higher than normal block due to compression of epidural space due to increased intra-abdominal pressure.

- Intra-abdominal pressure: epidural venous engorgement in pregnancy, obesity, tumours can cause a higher blockade with a given dose due to narrower epidural space
- Posture: In sitting position there is slight propensity of the drug to spread caudally and higher doses may be required.
- Gender

Technique of injection:

- Site of injection: Rapid onset and denser blockade is seen when the point of injection was nearer to nerve roots. Lumbar epidural injection has a better cephalad spread than caudal epidurals.
- Direction of bevel
- Rate of injection: A rapid injection of local anaesthetic produces a rapid but incomplete and more extensive block. Injection rate of 0.3 – 0.75 ml/sec results in most reliable block.

Characteristics Of Anaesthetic Solution:

- Amount: Earlier epidural anaesthesia was considered to be equivalent to multiple paravertebral blocks and the tendency was to give a large volume of diluted drug. However studies by Bromage showed that increasing dosage linearly increases the degree of sensory blockade.
- Concentration: An increase in the drug concentration increases the density of motor blockade.
- Density

- Temperature
- Use of adjuvants

Effects Of Epidural Anaesthesia On Various Organ Systems:

Cardiovascular System:

The action of epidural anaesthesia on cardiovascular system depends on the level of block:

1. If the level of block is below T_4 there is dilation of resistance and capacitance vessels due to loss of sympathetic tone. This causes a fall in BP. However if there is a blockade of cardiac efferent sympathetic fibres from T_1 to T_4 there is a loss of chronotropic and inotropic drive resulting in a fall in cardiac output.
2. The activation arterial or Bainbridge reflex causing bradycardia -The lowering of blood pressure in the right atrium consequent to diminished venous return [Bainbridge (1874-1921) effect]
3. The operation of Mary's law causing tachycardia.
4. Depression of vascular smooth muscle and β adrenergic blockade of myocardium with fall in cardiac output.

Block not extending above T4 is not always associated with fall of blood pressure in fit young adults. However, 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 fibres are blocked (T_1– T_4). Activation of Bainbridge reflex may further contribute to bradycardia which is more frequent than tachycardia.

Theories of causation of fall in blood pressure

1. Diminished cardiac output consequent on reduction of venous return to heart due to failure of peripheral pump – calf muscles.
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 fibres including those to arm (T2-T10), are paralyzed, hence low blood pressure.
3. Paralysis of sympathetic nerve supply to heart T_1-T_4. 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. Seen more commonly with epidural blockade due to the larger volume of drug used.
6. Pre-existent hypovolemia, if present, may cause precipitous hypotension after central neuraxial blockade. 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 C_3, C_4, C_5 and should not be encroached upon during neuraxial blockade. Lumbar and even mid thoracic epidurals usually do not cause much effects on respiratory system. 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.

The ventilation perfusion during extradural block is not greatly altered and effects on respiratory functions are relatively small with no effect on FRC or V/Q ratio. The lung volumes and capacities (tidal volume, vital capacity) are basically unchanged during epidural anaesthesia. Abdominal muscle and intercostals muscle paralysis is compensated by diaphragm moving down. The pulmonary gas exchange is preserved.

The patient may stop breathing so that respiratory support by IPPV and, if necessary, the tracheal intubation maybe 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 fibres 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 in up to 20% of patients and usually come on in waves-lasting a minute or so and then passing away spontaneously. Stimuli arising in the upper abdomen might not be blocked causing discomfort. Colonic blood supply and oxygen availability are increased, perhaps an important factor in the prevention of anastomotic breakdown following gut resection.

1. Theories of causation of nausea and vomiting:
    a. Hypotension: corrected using fluid boluses and vasopressor drugs
    b. Increased peristalsis
    c. Traction on nerve endings and plexuses, especially via vagus (usually upper abdomen)
    d. Presence of bile in stomach due to relaxation of pyloric and bile-duct sphincters
    e. Narcotic analgesics (premedication)
    f. Psychological factors
    g. Hypoxia

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

Surgical stress produces a variety of changes in endocrine system and metabolic function. There is an increased catabolism of proteins and oxygen consumption. Increased plasma concentrations of catecholamines, vasopressin, growth hormones, renin, angiotensin, glucose, Anti diuretic hormone (ADH) and Thyroid Stimulating Hormone (TSH) are noted and this is referred to as surgical stress response.

Neuraxial blocks in general suppress the increase of ADH.It also 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.

Epidural block prevents lymphopenia and granulocytosis after operation, thus inhibiting the metabolic endocrine response to surgery and preventing immune depression.

Genito Urinary System

Sympathetic supply of kidney is from T_{11} to L_1 via the lowest splanchnic nerves. As renal blood flow is maintained by autoregulation, epidural anaesthesia has very little effect on renal function. Any effects on renal function if seen is due to severe and intractable 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. In fact there is urinary retention till block wears off and catheterizing the patient should be considered. Retention of urine may be moderately prolonged as L_2 and L_3 contain small autonomic fibres and their paralysis lasts longer than of the larger sensory and motor fibres. The penis is often engorged and flaccid due to paralysis of the *nervi erigentes* (S_2 and S_3). This is a useful positive sign of successful block.

Body Temperature

Vasodilatation favors heat loss. Absence of sweating favours 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

ROPIVACAINE

Introduction

Ropivacaine is a newer, longer acting local anaesthetic agent which belongs to the amino amide group. It was first synthesized by Ekenstam in 1957; however it was first introduced for clinical practice only since 1996. Chemically it belongs to the same group as bupivacaine and mepivacaine (epipecoloxylidide local anaesthetic).

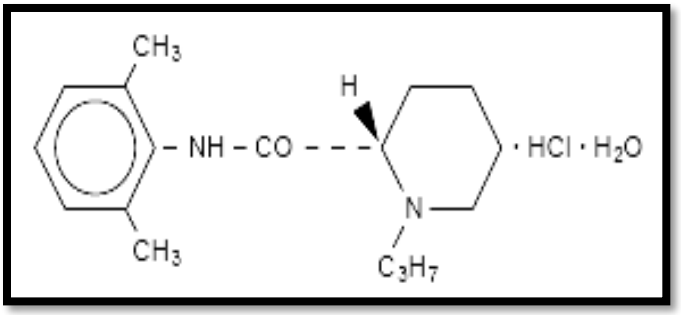
It was found that butyl derivatives of pipecoloxylidides (example bupivacaine) were more cardiotoxic than propyl derivatives, causing a significant number of cardiac arrests.[25]

Thus ropivacaine was developed as a pure S – enantiomeric form of pipecoloxylidides. Though ropivacaine has been available internationally for over three decades, it is a relative new entrant in the Indian market.

It is becoming increasingly popular among anaesthesiologists and has been used extensively in almost all modes of regional anaesthesia: infiltration, peripheral nerve blocks, spinal anaesthesia, epidural anaesthesia as well as caudal epidural blocks in paediatric patients.

Chemical Structure

Figure 7: Chemical structure of ropivacaine



Ropivacaine is an amino amide local anaesthetic agent, 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. It's molecular formula is $C_{17}H_{26}N_2O•HCl•H_2O$ and it has a molecular weight of 328.89.

Ropivacaine is a white crystalline powder. At 25℃ ropivacaine hydrochloride has a solubility of 53.8 mg/mL in water and a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1. The pKa of ropivacaine is 8.07 which is very similar to that of bupivacaine (8.1) .

However, ropivacaine has a much lesser lipid solubility as compared to bupivacaine and mepivacaine. This can be explained on the basis of presence of a propyl (3 Carbon) side chain in ropivacaine as compared to a butyl (4 Carbon) side chain in the other two local anaesthetics. This lower lipid solubility ***Physical Properties***

of ropivacaine has a significant effect on the block characteristics of ropivacaine as discussed ahead.[26]

Mechanism Of Action And Corelation With Structure

Ropivacaine reversibly inhibits the voltage gated sodium channels present on the nerve cell membranes thus preventing the influx of sodium ions into the cells. This:

I. Blocks generation and conductance of nerve impulses.
II. Slows propagation of nerve impulses
III. Reduces the rate of rise of action potential

Almost all local anaesthetic agents block the unmyelinated C and myelinated Aδfibres, which transmit pain impulses, at the same rate.

The rate of blockade of motor fibres (Aα and Aβ), however depends upon the physio chemical properties like pKa and lipid solubility of the individual drug. As ropivacaine is less lipid soluble than bupivacaine, the Aα and Aβ blockade is slower and hence motor blockade is less potent. Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block but the motor block produced by ropivacaine is slower in onset, lesser in intensity and shorter in duration.

Clinically the order of blockade of nerve fibres is autonomic, sensory and motor, while the regression of the block occurs in reverse order.

The nerve impulse transmission is lost in the following order:

The order of the loss of nerve function is

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

Pharmacokinetics

Absorption :

The systemic concentration of ropivacaine depends on the total dose and concentration of drug given, the route of administration, the patient's haemodynamic state and the vascularity of the site of administration. When administered in the epidural space, ropivacaine has a biphasic absorption. The half-lives of the two phases (mean± SD) are 14±7 minutes and 4.2 ±0.9 hours respectively.

Distribution :

After intravascular infusion, ropivacaine has a steady state of distribution of 41 ± 7 litres. It is 94% protein bound, mainly to α_1-acid glycoprotein. In case of continuous epidural infusion of ropivacaine the plasma concentration can rise due to increased protein binding and reduced clearance. Ropivacaine can easily cross the placenta.

Metabolism and excretion :

Ropivacaine is extensively metabolized by the liver, predominantly by the cytochrome P_{4501A} mediated aromatic hydroxylation to produce 3 – hydroxyl 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. An additional unquantified amount of 2 – hydroxyl – methyl ropivacaine has also been identified s a metabolite.

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 IV 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.

Pharmacodynamics

Central Nervous System &CardioVascularSystem :

Ropivacaine has a higher threshold for both cardiac as well as neuro toxicity as compared to bupivacaine due to its lower lipid solubility and stereo - selective properties. This holds good for both isomers of ropivacaine which have been shown to be less cardio depressant than respective bupivacaine isomers in animal studies.

CNS toxicity occurs earlier than cardiac toxicity on iv infusion in healthy volunteers.

Potency :

Lipid solubility of a local anaesthetic correlates well with its potency and toxicity. Compounds which are more lipophilic penetrate the nerve cell membrane more readily. Thus, fewer molecules are required to produce the desired conduction blockade.

Others :

Continuous epidural infusion of 0.375 % and 0.188% ropivacaine has been shown to inhibit platelet aggregation in plasma.

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 0.6 mcg/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 which include wide QRS complexes, increased conduction time and reduced contractility.
c) **Gastrointestinal system toxicity:** Faecal 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

Advantages Over Other Local Anaesthetics

Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and is therefore a better choice for use in labour analgesia and post operative pain relief. When compared to bupivacaine it produces less dense motor blockade of shorter duration and hence permits earlier mobilization and discharge thus reducing both morbidity as well as cost of treatment. It has a lower systemic toxicity than bupivacaine and a better, cardio stable profile. Ropivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine.

LEVOBUPIVACAINE

Introduction

Levobupivacaine is the S(–)-enantiomer of the local anaesthetic bupivacaine. Racemic bupivacaine (herein called bupivacaine) has traditionally been the longest acting local anaesthetic commercially available and is widely used.Its prolonged duration of action reduces the need for repeated administration or top-up doses.Its clinical profile closely resembling that of bupivacaine. However, current preclinical safety and toxicity data show an advantage for levobupivacaine over bupivacaine.[27,28]

Chemical Structure

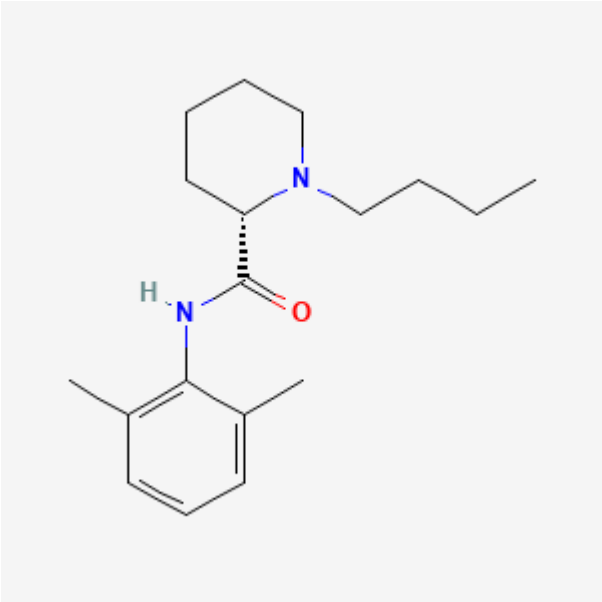


Figure 8: Chemical structure of levobupicaine

Physical Properties

Levobupivacaine is a white solid. Levobupivacaine hydrochloride has a solubility of 0.0267 mg/mL in water. The pKa of Levobupivacaine is 8.0 which is very similar to that of bupivacaine (8.1).

Mechanism Of Action and Corelation with Structure

Levobupivacaine block the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination and conduction velocity of affected nerve fibers. Specifically, the drug binds to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, which prevents depolarization

Pharmacokinetics

Absorption:

The plasma concentration of levobupivacaine following therapeutic administration depends on dose and also on route of administration, because absorption from the site of administration is affected by the vascularity of the tissue. Peak levels in blood were reached approximately 30 minutes after epidural administration, and doses up to 150 mg resulted in mean C_{max} levels of up to 1.2 µg/mL.

Distribution:

After intravenous administration of 40 mg in healthy volunteers, levobupivacaine has a steady state of distribution of 66.91 ±18.23 L. It is 97% protein bound. Its classified as category B drug in pregnancy.

Metabolism and excretion:

Levobupivacaine is extensively metabolized with no unchanged levobupivacaine detected in urine or feces. In vitro studies using [14 C] levobupivacaine showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of levobupivacaine to desbutyl levobupivacaine and 3-hydroxy levobupivacaine, respectively. In vivo, the 3-hydroxy levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates. Metabolic inversion of levobupivacaine to R(+)-bupivacaine was not evident both in vitro and in vivo.

Following intravenous administration, recovery of the radiolabelled dose of levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. After intravenous administration of 40 mg in healthy volunteers clearance 39.06 ±13.29 L/h.The mean half life is 3.3 hours.

Pharmacodynamics

Central Nervous System & Cardiovascular System:

The risk of CNS toxicity was also less with levobupivacaine than bupivacaine in human volunteers. Central or peripheral nervous system disorders were experienced by 36% of levobupivacaine recipients in the study where volunteers received intravenous doses of

levobupivacaine (mean 67.7mg). Similarly, intravenous levobupivacaine produces tinnitus CNS depression on EEG .The magnitude of the effect and the area affected was less with levobupivacaine. For instance, levobupivacaine is associated with a lesser decrease in high alpha power and does not cause the increase in theta power in the parietal, temporal and central regions that occurred with bupivacaine.

Levobupivacaine also showed less depressant effect on the atrioventricular conduction and QRS complex duration, and provoked less impairment of the contractile function of the isolated animal heart. Levobupivacaine is also less potent in blocking cloned human heart sodium and potassium channels.

Potency *:*

The nerve blocking potency of levobupivacaine is similar to that of bupivacaine and the R(+)-enantiomer of bupivacaine (dexbupivacaine) in vitro.In vivo, the comparative effects of levobupivacaine and dexbupivacaine or bupivacaine were affected by the route of administration and concentration.

Adverse Effects

Cardiovascular system toxicity: bradycardia, hypotension, sudden cardiovascular collapse

Gastrointestinal system toxicity: nausea (12%), vomiting (14%), constipation (7%),

Central nervous system toxicity: Headache (7%) disorientation, drowsiness, slurred speech, which may culminate with tonic-clonic seizures

Haematological: Anaemia (12%), increased serum albumin level, leucocytosis and purpura

Advantages Over Other Local Anaesthetics

Levobupivacaine has a lower systemic toxicity than bupivacaine and a better, cardio stable profile. Levobupivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine

OPIOID RECEPTORS

Opioid receptors were classified into three groups, according to the radioligand binding assays in 1973 and were termed μ for the morphine group, κ for the ketocyclazocine group, and σ for the SKF10047 (N-allylnormetazocine) group. δ-receptor were the group of high affinity receptors for enkephalins and was discovered in vas deferens of mouse. Another ε-receptor was thought to be the binding site for β-endorphin which was also found to be present in the vas deferens of the mouse.

Mechanism Of Action Of Opioids

The opioids exert its action at both spinal and supra spinal levels. The majority of the receptors are present at the substantia gelatinosa in the dorsal horn of the spinal cord. The supra spinal actions are mediated through the descending inhibitory pathways. In substantia gelatinosa, the receptors are present mainly on the presynaptic terminals of the primary afferent sensory neurons. Some of the receptors are also present on the post synaptic dendrites of the inter neurons. These neurons regulate the spinothalamic transmissions. The presynaptic neurons hinder the release of various neurotransmitters including substance P, glutamate etc, whereas the post synaptic receptors inhibit the evoked excitatory post synaptic potential also known as EPSP. The μ and Δ receptors act on the potassium channels and facilitates the opening of the receptors, which further leads to the hyperpolarisation. It also leads to the reduced neuronal firing. It reduces the action potential plateau and thereby reducing the calcium influx and the neurotransmitter release. Contrary to the above-mentioned receptors, κ receptors, shuts the calcium channels

BUPRENORPHINE

Introduction

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occurring alkaloid of the opium poppy, Papaver somniferum. The pharmacology of buprenorphine is unique in that it is a partial agonist at the opioid mu receptor,highly lipid-soluble μ analgesic that is 25 times more potent than morphine but with lower intrinsic activity and ceiling effect.

Chemical Structure

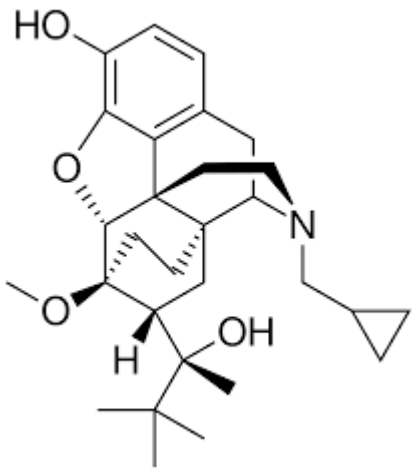


Figure 9: Chemical structure of Buprenorphine

Molecular weight of Buprenorphine is 467.6 g/mol)

Buprenorphine is a derivative of thebaine, an alkaloid found in opium poppies (Papaver somniferum).

Buprenorphine also has the following characteristics:

• Classified as a partial mu agonist, kappa antagonist, nociceptin agonist. As a partial agonist, its effects increase only to a certain point with increased dose, and level off at moderate doses, thus contributing to its being abused less than full agonists.

• A potent analgesic, used in low doses to avoid side effects. Formulations include intravenous or intramuscular (Buprenex) and transdermal (Butrans®).

• Mildly reinforcing, which improves treatment adherence and, therefore, clinical effectiveness compared with antagonist treatment

• Limit on the maximum effect that can be achieved. However, the ceiling effect may not apply to the analgesic effect.

Physical Properties

Mechanism Of Action and Corelation with Structure

Buprenorphine is a partial agonist at the mu receptor, meaning that it only partially receptor agonist. It is a potent analgesic that acts on the central nervous system (CNS). The partial agonism at the mu receptor is a unique quality to buprenorphine. The feature gives its many unique properties, specifically that its analgesic effects plateau at higher doses, and then its effects become antagonistic.[29] Buprenorphine exhibits ceiling effects on respiratory depression, which means that it is safer than methadone for agonist substitution treatment in addiction.[30,31]

Buprenorphine has high-affinity binding to the mu-opioid receptors and slow-dissociation kinetics. In this way, it differs from other full-opioid agonists like morphine and fentanyl, allowing withdrawal symptoms to be milder and less uncomfortable for the patient.

Pharmacokinetics

Absorption:

Bioavailablity of buprenorphine is very high following intravenous or subcutaneous administration, lower by the sublingual or buccal route, and very low when administered by the oral route. It is therefore provided as a sublingual tablet that is absorbed from the oral mucosa directly into systemic circulation.

Clinical pharmacokinetic studies found that there was wide inter-patient variability in the sublingual absorption of buprenorphine, but within subjects the variability was low. Both Cmax and AUC of buprenorphine increased in a linear fashion with the increase in dose (in the range of 4 to 16 mg), although the increase was not directly dose-proportional. Buprenorphine combination with naloxone (2mg/0.5mg) provided in sublingual tablets demonstrated a Cmax of 0.780 ng/mL with a Tmax of 1.50 hr and AUC of 7.651 ng.hr/mL.

Coadministration with naloxone does not affect the pharmacokinetics of buprenorphine.

Distribution:

Buprenorphine is highly lipophilic, and therefore extensively distributed, with rapid penetration through the blood-brain barrier. The estimated volume of distribution is 188 - 335 L when given intravenously. It is able to cross into the placenta and breast milk. Buprenorphine is approximately 96% protein-bound, primarily to alpha- and beta-globulin.

Metabolism and excretion :

Buprenorphine is metabolized to norbuprenorphine via Cytochrome P450 3A4/3A5-mediated N-dealkylation. Buprenorphine and norbuprenorphine both also undergo glucuronidation to the inactive metabolites buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, respectively.

While norbuprenorphine has been found to bind to opioid receptors in-vitro, brain concentrations are very low which suggests that it does not contribute to the clinical effects of buprenorphine.

- Buprenorphine
  - Norbuprenorphine
    - Hydroxynorbuprenorphine
  - Hydroxybuprenorphine
    - Hydroxynorbuprenorphine
  - Buprenorphine glucuronide

Buprenorphine, like morphine and other phenolic opioid analgesics, is metabolized by the liver and its clearance is related to hepatic blood flow. It is primarily eliminated via feces (as free forms of buprenorphine and norbuprenorphine) while 10 - 30% of the dose is excreted in urine (as conjugated forms of buprenorphine and norbuprenorphine).

The overall mean elimination half-life of buprenorphine in plasma ranges from 31 to 42 hours, although the levels are very low 10 hours after dosing (majority of AUC of buprenorphine is captured within 10 hours), indicating that the effective half-life may be shorter

Buprenorphine demonstrates slow dissociation kinetics (~166 min), which contributes to its long duration of action and allows for once-daily or even every-second-day dosing.In clinical trial studies, the half-life of sublingually administered buprenorphine/naloxone 2mg/0.5mg was found to be 30.75 hours.

Clearance may be higher in children than in adults. Plasma clearance rate, IV administration, anaesthetized patients = 901.2 ± 39.7 mL/min; Plasma clearance rate, IV administration, healthy subjects = 1042 - 1280 mL/min

Pharmacodynamics

Buprenorphine interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, buprenorphine exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. In addition to analgesia,

alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Buprenorphine depresses the respiratory centers, depresses the cough reflex, and constricts the pupils.

Dependence

Buprenorphine is a partial agonist at the mu-opioid receptor and chronic administration produces physical dependence of the opioid type, characterized by withdrawal signs and symptoms upon abrupt discontinuation or rapid taper. The withdrawal syndrome is typically milder than seen with full agonists and may be delayed in onset. Buprenorphine can be abused in a manner similar to other opioids. This should be considered when prescribing or dispensing buprenorphine in situations when the clinician is concerned about an increased risk of misuse, abuse, or diversion.

Withdrawal

Abrupt discontinuation of treatment is not recommended as it may result in an opioid withdrawal syndrome that may be delayed in onset. Signs and symptoms may include body aches, diarrhea, gooseflesh, loss of appetite, nausea, nervousness or restlessness, anxiety, runny nose, sneezing, tremors or shivering, stomach cramps, tachycardia, trouble with sleeping, unusual increase in sweating, palpitations, unexplained fever, weakness and yawning.

Precipitation of Opioid Withdrawal Signs and Symptoms

If buprenorphine is started in opioid-dependent individuals, it will displace the other opioids and cause a phenomenon known as "precipitated withdrawal" which is characterized by a rapid and intense onset of withdrawal symptoms. Individuals must therefore be in a state of mild to moderate withdrawal before starting therapy with buprenorphine.

Because it contains naloxone, buprenorphine and naloxone sublingual tablets are also highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone.

Gastrointestinal Effects

Buprenorphine and other morphine-like opioids have been shown to decrease bowel motility and cause constipation.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in

the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific symptoms and signs including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

Orthostatic Hypotension

Like other opioids, buprenorphine sublingual tablets may produce orthostatic hypotension in ambulatory patients.

Elevation of Cerebrospinal Fluid Pressure

Buprenorphine, like other opioids, may elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions, and other circumstances when cerebrospinal pressure may be increased. Buprenorphine can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Elevation of Intracholedochal Pressure

Buprenorphine has been shown to increase intracholedochal pressure, as do other opioids, and thus should be administered with caution to patients with dysfunction of the biliary tract.

Adverse Effects

- **Cardiovascular system toxicity:** hypertension and peripheral oedema
- **Gastrointestinal system toxicity:** nausea, constipation, diarrhoea
- **Central nervous system toxicity:** fatigue, headache, dizziness, drowsiness, anxiety, opioid withdrawal syndrome
- **Hematologic:** Anaemia and bruise
- **Metabolic disorders:** Hot flush

MATERIALS AND METHODS

Type of Study: Randomized clinical trial.

Duration of study and study population:

Patients aged 20-45 years referring to American Society of Anaesthesiologists I, American Society of Anaesthesiologists II Undergoing lower abdominal surgery under epidural anaesthesia are divided into two groups at "KLE's Dr Prabhakar Kore Charitable Hospital And Medical Research Centre, Nehru Nagar, Belagavi during the period from January 2021 to December 2021".

(Data Collection-12 Months)

Inclusion Criteria:

- Written Informed Consent
- American Society of Anaesthesiologists physical status I and II.
- Age between 20-45 years.

Exclusion Criteria:

- Hypersensitivity to amide local anaesthetic drugs
- Neurological disorders, Cardiac disease, pre-existing bleeding disorder.
- Local infections at the site
- Patients who do not fulfill inclusion criteria.

Sample Size Calculation

The prevalence rate-based formula for the required sample size is

The total sample size is 70

where P is the percentage of prevalence and d is the percentage likely difference in the prevalence.

zα is linked with the level of significance. For a 5% level of significance zα = 1.96. P value of 0.05 is considered significant.

n=500,

confidence level 95%

margin of error 10%

Population proportion 70% Population size=500

With P = 59.8% and d = 20% of P, the sample size is 70

Sampling procedure:

A one-year randomized clinical trial.

METHODOLOGY:

A total of 70 patients who met the inclusion criteria were included in the study after receiving ethical committee approval and written informed consent.

Those who met the inclusion criteria were thoroughly evaluated prior to anaesthesia and then randomly divided into two groups using the envelope method of randomization.

Group A: Patients receive 14.5ml of 0.5% Levobupivacaine ± Inj Buprenorphine 150mcg (0.5ml)

Group B: Patients receive 14.5ml of 0.75% Ropivacaine ± Inj Buprenorphine 150mcg (0.5ml)

In the preoperative holding area, an 18G IV cannula was used to secure intravenous access.

All standard monitors, such as an ECG, noninvasive blood pressure cuff, and SpO2 monitors, were attached after bringing the patients into the operating room. SpO2, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and perfusion index were all recorded three times in five-minute intervals, and Pre-loading the patient with Ringer's lactate fluid (10-15ml/kg BW).

The patient in a sitting position and under strict aseptic precautions, a skin wheal was raised at the Lumbar 3-Lumbar 4 interspace using 2 ml of 2 % lidocaine. Using an 18 G Touhy needle and 20 G catheter in the midline and the loss of resistance to air technique, the epidural space was identified.

14.5 millilitre of 0.5% levobupivacaine ± Inj Buprenorphine 150 microgram (0.5 milliliters) increasing volume to 15 milliliters in (Group A)

Or 14.5 milliliter of

0.75% ropivacaine ± Inj Buprenorphine 150 microgram (0.5 milliliters) increasing volume to 15 milliliters in (Group B)

Five-minute intervals of 5 ml to 15 ml of the drug were administered, To prevent sudden hypotension.

An anaesthetist prepared the study drug solutions following written instructions and without being aware of the study's design.

Every 2.5 minutes for the next 10 minutes, until two consecutive readings of the same value are obtained. The pin-prick method was used to assess the sensory block.

“Motor block was assessed by Modified Bromage scale,

- 0 = no paralysis, able to flex hips/knees/ankles;
- 1 = able to move knees, unable to raise extended legs;
- 2 = able to flex ankles, unable to flex knees; and
- 3 = unable to move any part of the lower limb).”

After the epidural injection, every five minutes for 30 minutes, or until two consecutively identical readings were obtained. Overall duration and maximum motor block time (from drug administration via epidural injection to motor recovery).

For the first 30 minutes, measurements of heart rate, blood pressure, oxygen saturation, and respiratory rate were taken every 5 minutes; thereafter, they were taken every 15 minutes until the surgery was complete.

During surgery, every patient received oxygen at a rate of 5L/min via a cannula Anaesthesiologist. The patients were observed for hypotension, nausea, vomiting, respiratory depression, and pruritis. Mephentermine 6 mg was used to treat hypotension, along with fluids. Ondansetron injection, 4 mg, was used to treat nausea and vomiting, while chlorpheniramine, 10 mg, was administered intravenously to treat pruritis. Patients who felt uneasy or anxious at any

point during surgery received additional sedation in the form of IV boluses of midazolam 0.03–0.05 mg/kg.

Top-up dosage was given based on two groups, 1.5–3 ml per segment if the patient complained of any pain in the lower limbs (below the region of the segmental blockade) as a result of regression of motor and sensory blockade.

After 72 hours, the epidural catheter was removed.

Statistical Analysis:

The study compared two groups that were randomly assigned using the ENVELOPE method. We computed the mean and standard deviation for the continuous quantitative data. Suitable statistical procedures, such as one-group ANOVA, were used to compare the continuous variables between groups. The student's paired t-test was used to compare the two groups' quantitative variables.

Rates, ratios, and percentages were used to express the categorical data. Using the Chi-square test or Fisher's exact test, the relationship between the result, clinical, and demographic factors were examined.

The Median was used to represent discrete variables. Discrete variable comparisons were made using nonparametric testing.

The comparison will be shown using the appropriate graphs. The value of p less than 5% (0.05) was regarded as significant for all tests.

RESULTS

This randomised clinical trial lasted for a year in the “Department of Anaesthesiology at KLES Dr Prabhakar Kore Charitable Hospital, Belagavi, which is affiliated with Jawaharlal Nehru Medical College, Belagavi, from January 2021 to December 2021”.

Seventy patients undergoing lower abdomen operations under epidural anaesthesia were split into one of the two different groups using the envelope method of randomization.

Group LB: Patients receive 14.5ml of 0.5% Levobupivacaine ± Inj Buprenorphine 150mcg (0.5ml)

Group RB: Patients receive 14.5ml of 0.75% Ropivacaine ± Inj Buprenorphine 150mcg (0.5ml)

The collected data were coded and analysed as following.

TABLE 1: GENDER DISTRIBUTION OF THE PATIENTS IN THE STUDY

GENDER	GROUP LB		GROUP RB	
	No	**%**	**No.**	**%**
MALE	22	63	20	57
FEMALE	13	37	15	43
TOTAL	35	100	35	100

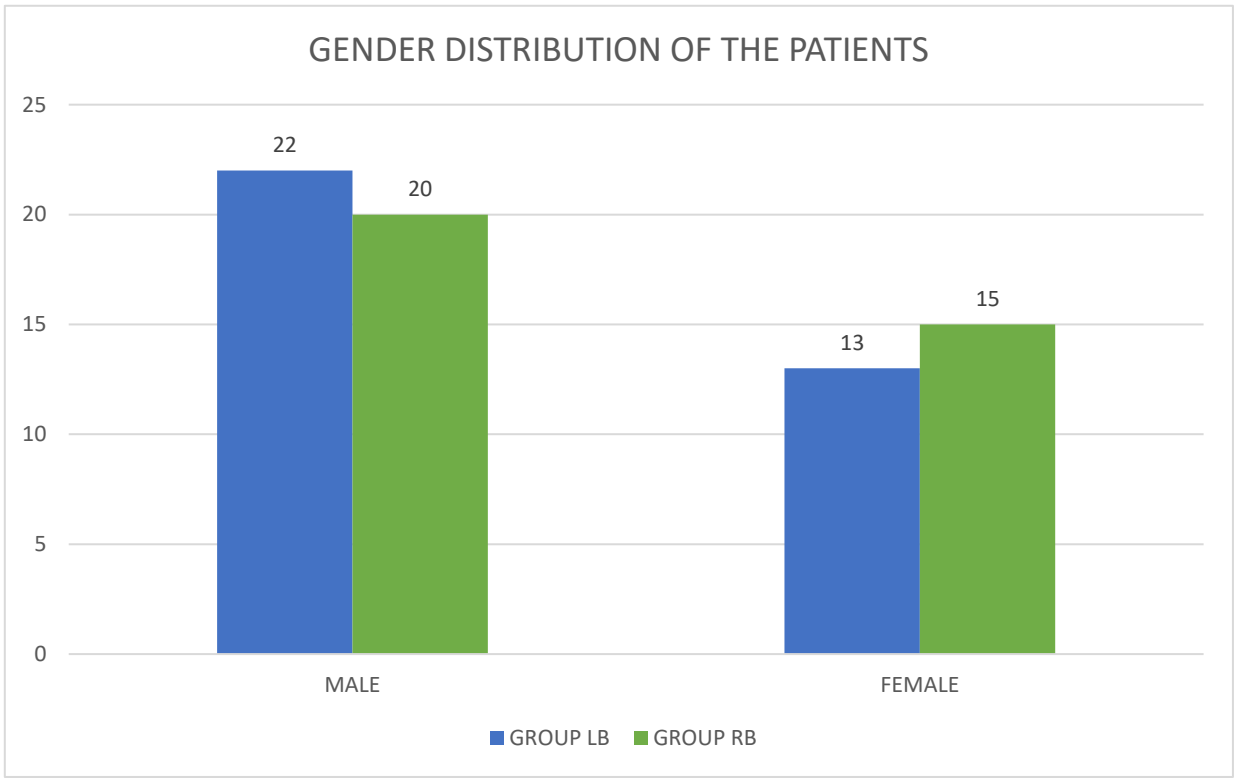


Table 2. Age distribution in the two study groups

Age	Group LB		Group RB	
	No.	%	No.	%
20-25 years	5	14.3	5	14.3
26-35 years	11	31.4	8	22.8
36-45 years	19	54.3	22	62.9
Total	35	100.0	35	100.0

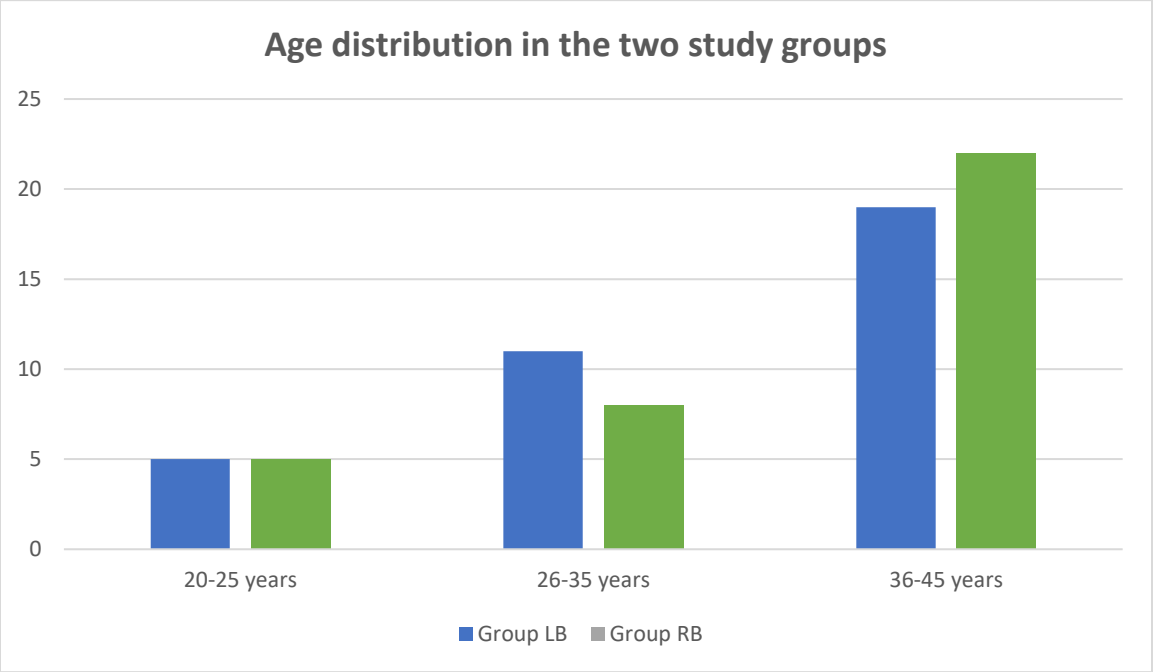


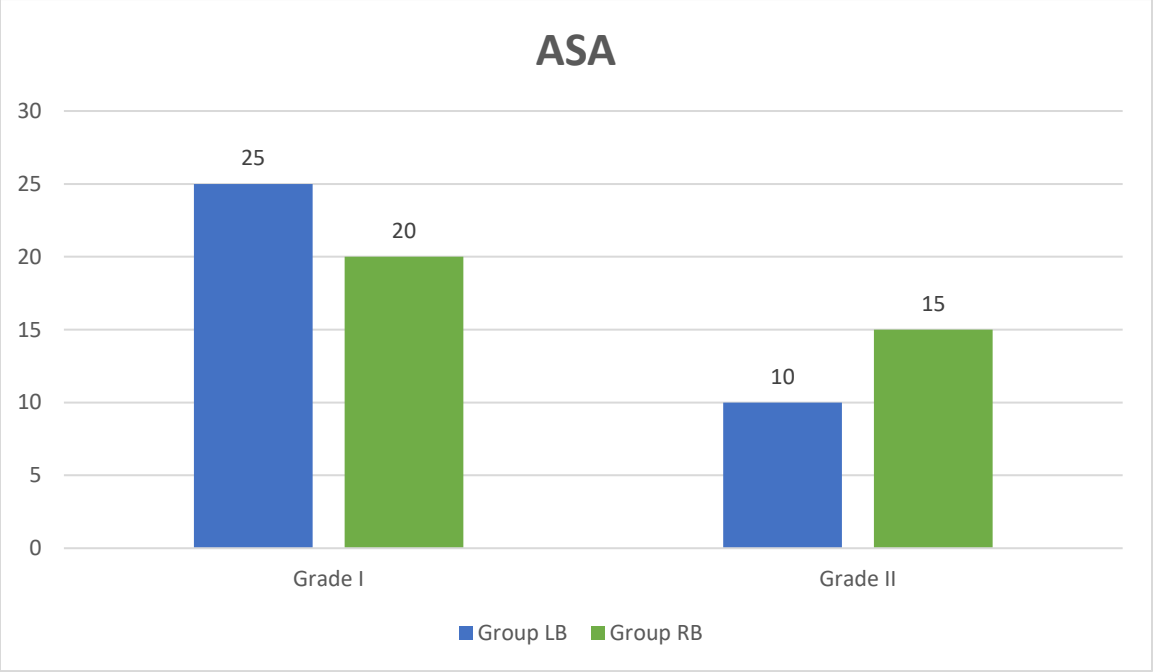
Table 3. Age and weight distribution in the two study group

	MEAN	SD	MIN	MAX	P-value
AGE (years)	35.40	8.54	20	45	0.3045
	36.51	7.44	20	45	
Weight (Kgs.)	70.2	9.10	55	86	0.2463
	68.57	10.03	52	90	

Regarding mean age (35.4 ± 8.54 and 36.51 ± 7.44 years, respectively; p =0.3045) and mean weight (70.2 ± 9.10 and 68.57 ± 10.03 kgs, respectively; p =0.2463), In the current study, there was no statistically significant difference between groups LB and RB.

Table 4. ASA in the two study group

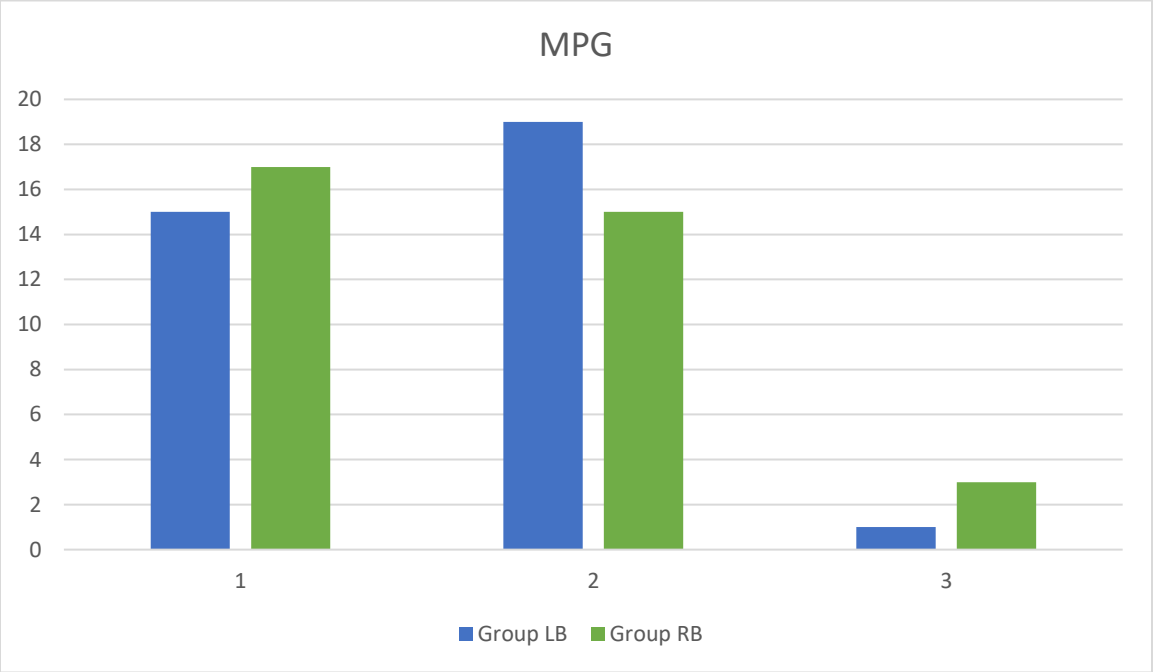
ASA	Group LB		Group RB	
	Frequency	%	Frequency	%
Grade I	25	71.4	20	57.1
Grade II	10	28.6	15	42.9



In group LB 71.4 % patients were ASA grade I and 28.6 % were ASA grade II. In group RB 57.1% patients were ASA grade I while 42.9 % were ASA grade II.There was no statistically significant difference between groups LB and RB.

Table 5. MPG in the two study group.

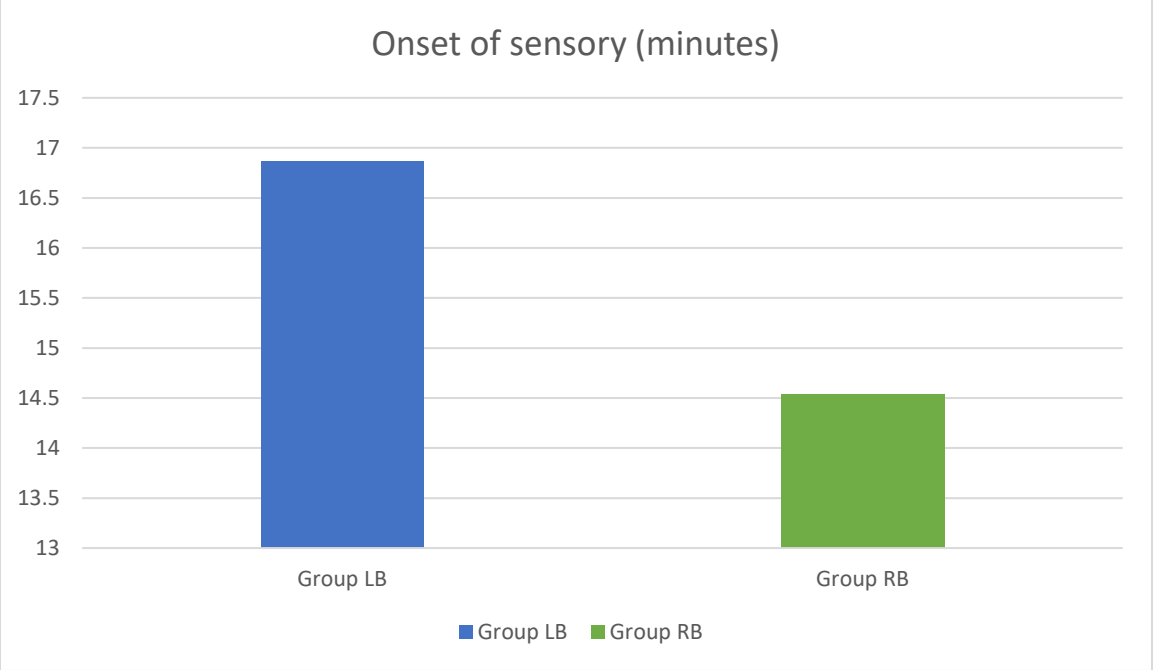
MPG	Group LB		Group RB	
	Frequency	%	Frequency	%
1	15	42.9	17	48.6
2	19	54.3	15	42.9
3	1	2.9	3	8.6



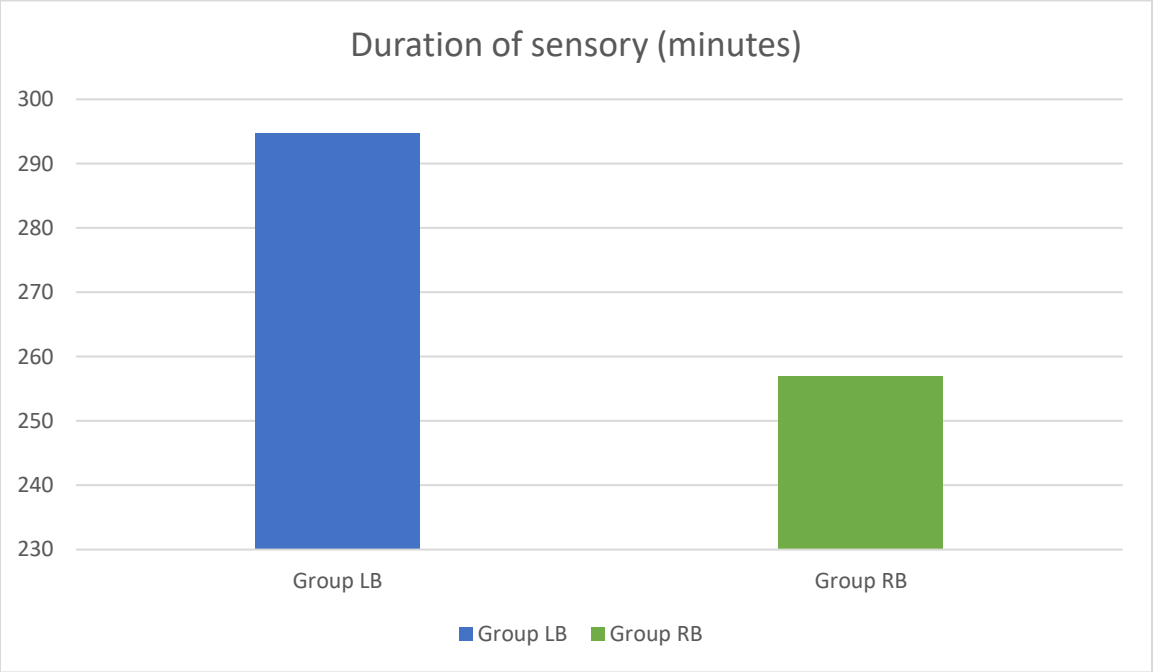
Sensory Block

Table 6: Onset and duration of sensory block

	Onset(minutes)		Duration(minutes)	
	Mean	Standard Deviation	Mean	Standard Deviation
Group LB	16.86	0.85	294.80	8.12
Group RB	14.54	0.78	256.97	6.47
p-value	p=0.00001		p=0.0001	



In our study, group RB experienced sensory blockade on average more quickly than group LB (14.54 ± 0.78 minutes vs 6.86 ± 0.85 minutes.), and this difference was statistically significant (p= 0.00001).

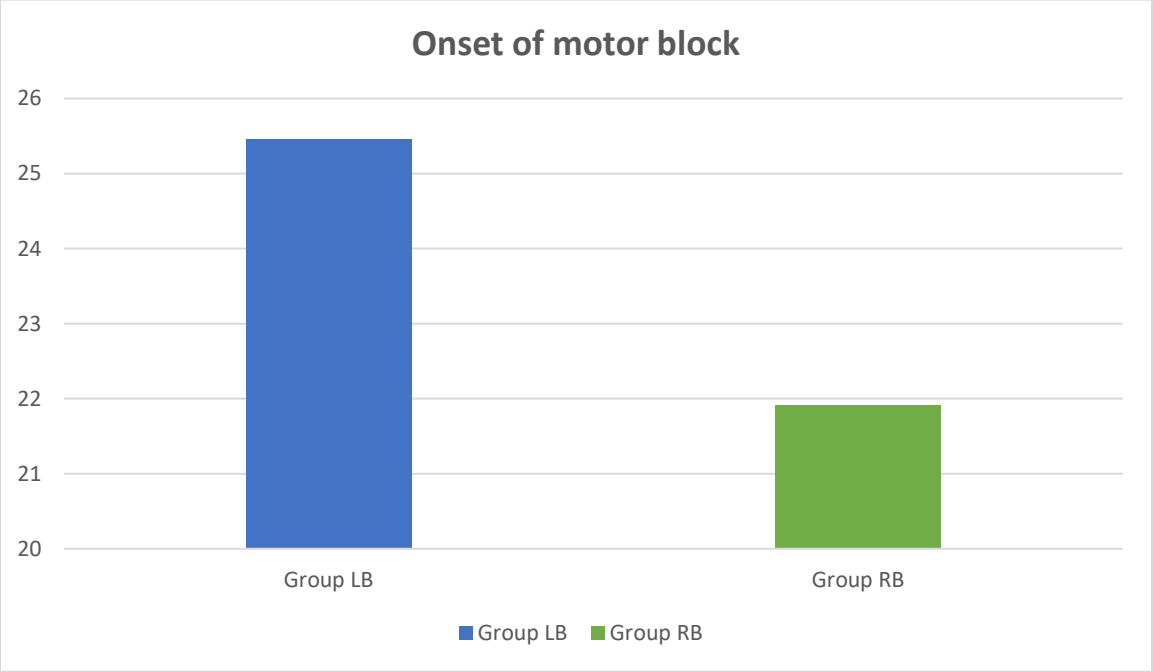


The mean time of sensory blockade in group LB was longer than in group RB (294.80 ± 8.12 vs 256± 6.47 min) and it showed statistical significance. (p=0.0001).

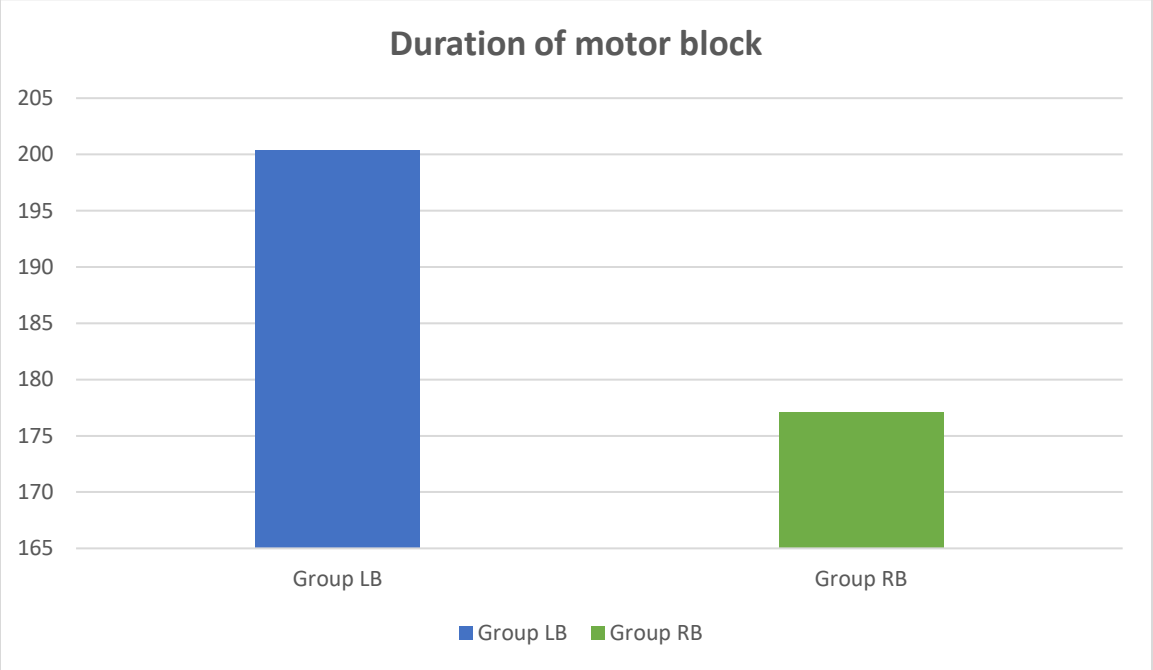
Motor Block

Table 7 : ONSET AND DURATION OF MOTOR BLOCK

MOTOR	Onset (minutes)		Duration (minutes)	
	Mean	Standard Deviation	Mean	Standard Deviation
Group LB	25.46	1.84	200.40	3.73
Group RB	21.91	1.07	177.09	7.96
p-value	0.00001		0.00001	



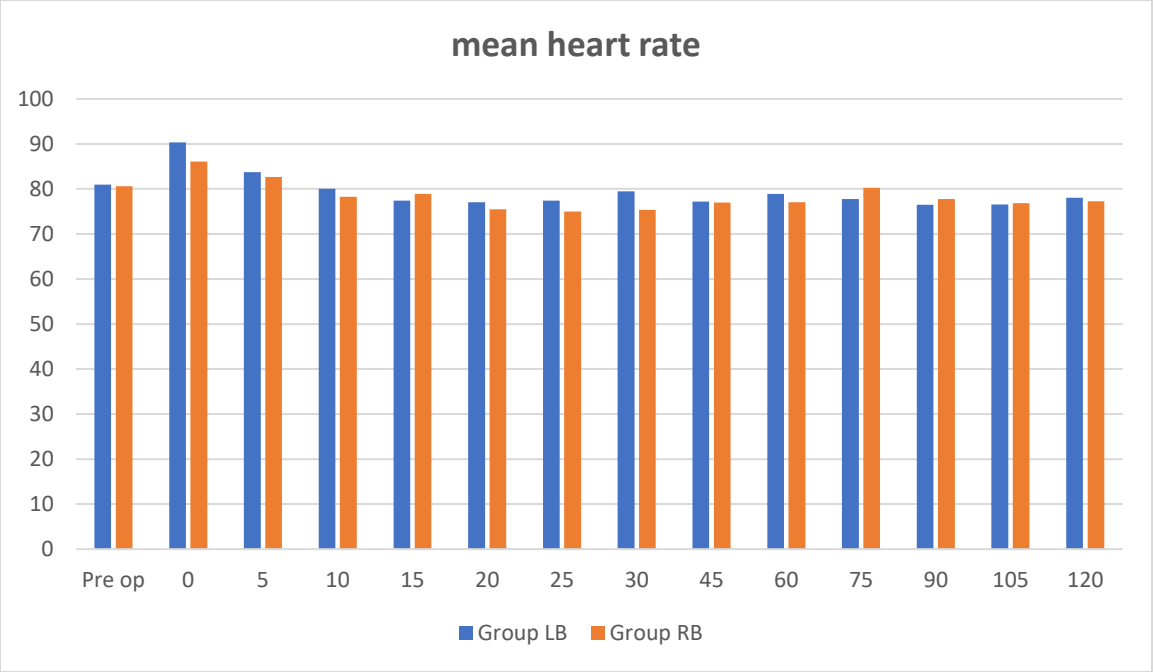
In the ongoing study, the mean time for the start of motor block was faster in group RB (21.91 ±1.07 min) than group LB (25.46 ± 1.84 min) and was statistically significant (p< 0.00001).



In group LB, the mean motor block lasted longer (200.40 ± 3.73 min) than in group RB (177.09 ± 7.96 min), and this difference exhibited statistical significance (p 0.00001).

Table 8: Comparison of mean heart rate at different time intervals (bpm)

Intervals(min)	Group LB		Group RB		p value
	Mean	SD	Mean	SD	
Pre op	80.94	11.27	80.63	12.11	0.453
0	90.31	15.41	86.09	16.23	0.089
5	83.71	12.91	82.66	13.66	0.343
10	80.06	14.91	78.26	11.94	0.266
15	77.40	13.68	78.89	13.73	0.322
20	77.06	13.90	75.46	12.71	0.313
25	77.40	12.95	74.97	12.66	0.203
30	79.46	12.33	75.37	13.48	0.075
45	77.20	11.78	77.00	14.20	0.473
60	78.89	14.13	77.03	12.90	0.229
75	77.77	11.47	80.26	12.84	0.215
90	76.51	12.91	77.74	12.73	0.355
105	76.54	12.02	76.82	10.33	0.50
120	78.03	12.78	77.24	10.78	0.348



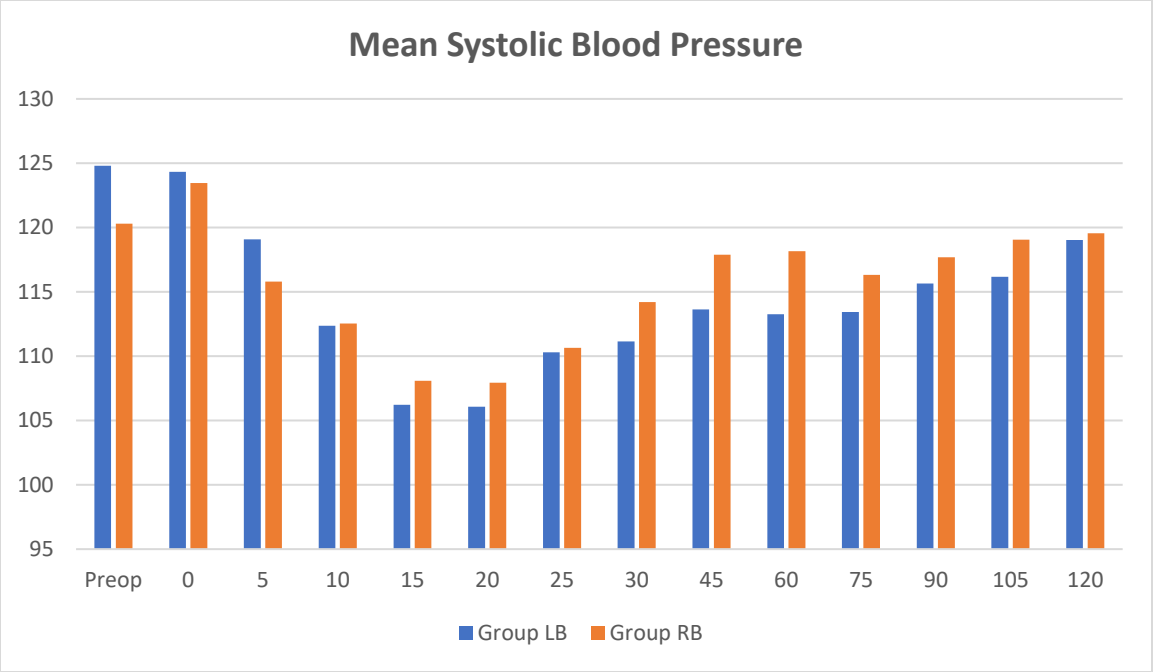
The preoperative mean heart rates in this study were 80.94 ± 11.27 bpm in group LB and 80.63 ± 12.11 bpm in group RB, and they were comparable (p = 0.453).

In group LB, the heart rate dropped to 77.06 ± 13.90 bpm at 20 minutes and 77.40 ± 12.95 bpm at 25 minutes, while in group RB, the heart rate dropped to 75.46 ± 12.71 bpm at 20 minutes and 74.97 ± 12.66 bpm at 25 minutes.

The heart rate was not statistically significantly in both the groups RB and group LB at 20,25, and 30minutes (p values 0.313, 0.203,0.075, respectively).

Table 9: Systolic Blood Pressure : Comparison of Group LB and Group RB mean values

Intervals(min)	Group LB		Group RB		p value
	Mean	SD	Mean	SD	
Preop	124.80	11.27	120.31	12.11	0.1474
0	124.34	10.30	123.46	11.38	0.3764
5	119.09	11.13	115.80	9.81	0.0999
10	112.37	10.11	112.54	10.93	0.4748
15	106.23	10.47	108.09	10.64	0.2655
20	106.06	10.51	107.94	11.97	0.2559
25	110.29	10.39	110.66	10.17	0.4471
30	111.14	11.47	114.20	11.11	0.1498
45	113.63	10.93	117.89	10.84	0.0483
60	113.26	10.93	118.15	10.74	0.0426
75	113.43	10.02	116.32	10.04	0.1597
90	115.66	11.06	117.68	10.65	0.2383
105	116.17	9.51	119.06	9.37	0.1192
120	119.03	11.01	119.56	10.85	0.4467



The mean systolic blood pressure in this study's preoperative phase was 124.80 mm Hg in group LB and 120.31 mm Hg in group RB, and both values were comparable (p = 0.1474).

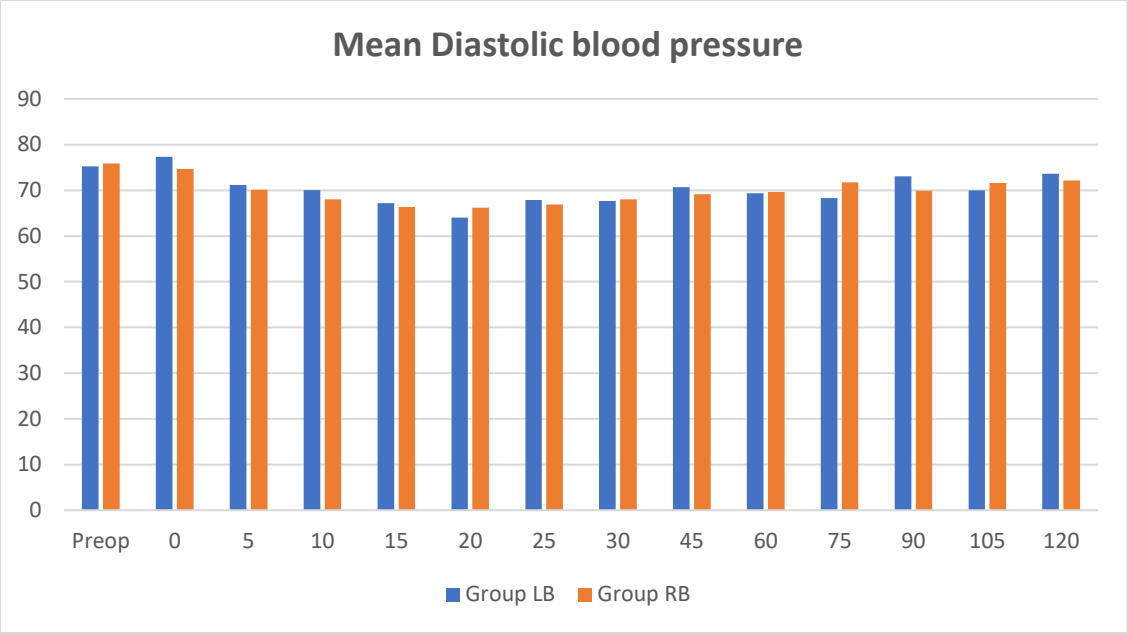
Systolic blood pressure in group LB decreased to 106.23 ± 10.47 mm Hg at 15 minutes and 106.06 ± 10.51 mm Hg at 20 minutes, while it decreased to 108.09 ± 10.64 mm Hg at 15 minutes and 107.94 ± 11.97 mm Hg at 20 minutes in group RB.

Systolic blood pressure in group LB decreased to 113.63± 10.93 mm Hg at 45 minutes and 113.26± 10.93 mm Hg at 60 minutes, while it decreased to 117.89± 10.84mm Hg at 45 minutes and 118.15± 10.74 mm Hg at 60 minutes in group RB

Systolic blood pressure fell similarly in group LB at 15, 20, 25, 30, 45, and 60 minutes compared to group RB and statistical significance was seen at 45 and 60 minutes.

Table 10: Comparison of diastolic blood pressure at different time intervals (mm of Hg)

Intervals(min)	Group LB		Group RB		p value
DBP	Mean	SD	Mean	SD	
Preop	75.26	7.56	75.86	5.47	0.3375
0	77.34	9.34	74.69	8.07	0.1389
5	71.14	10.10	70.11	8.40	0.3267
10	70.06	10.19	68.00	8.36	0.1891
15	67.20	10.73	66.34	10.59	0.3811
20	64.06	10.51	66.23	8.56	0.1000
25	67.91	7.59	66.91	7.87	0.3095
30	67.69	9.36	68.00	11.38	0.4460
45	70.69	10.35	69.14	10.80	0.2596
60	69.34	9.20	69.62	9.52	0.4766
75	68.29	9.72	71.71	11.10	0.1110
90	73.06	11.22	69.88	8.97	0.1006
105	69.97	9.10	71.59	9.29	0.2652
120	73.60	9.33	72.18	9.44	0.2148



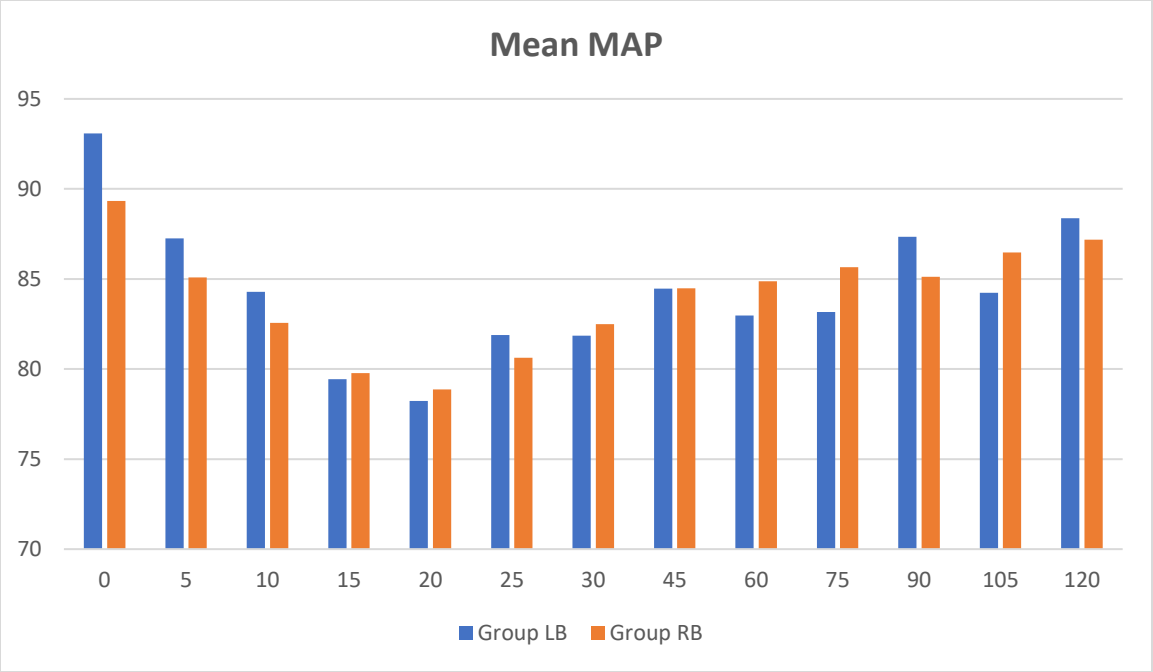
The mean diastolic blood pressure in this study's pre-operative phase was 75.26 7.56 mm Hg in the LB group and 75.86 ± 5.47 in the RB group, and both values were comparable (p = 0.3375).

In group LB, the diastolic blood pressure decreased to 67.20 ± 10.73 mm of Hg at 15 minutes and 64.06 ± 10.51 mm of Hg at 20 minutes; in group RB, the diastolic blood pressure decreased to 66.34 ± 10.59 mm of Hg at 15 minutes and 66.23 ±8.56 mm of Hg at 20 minutes.

Comparable to group RB, the diastolic BP fell in group LB at 15, 20, 25, 30, 45, and 60 minutes and were not statistically significant.

Table 11: Comparison of MAP at different time intervals (%)

MAP	Group LB		Group RB		p-value
	Mean	SD	Mean	SD	
0	93.09	8.62	89.34	9.78	0.0684
5	87.26	9.30	85.09	8.52	0.1610
10	84.29	8.90	82.57	8.85	0.2336
15	79.43	10.20	79.77	10.03	0.4497
20	78.23	8.52	78.86	10.06	0.4016
25	81.89	7.09	80.63	8.69	0.2780
30	81.86	9.70	82.49	10.99	0.4020
45	84.46	9.42	84.49	10.76	0.4952
60	82.97	8.95	84.88	8.79	0.1992
75	83.17	8.61	85.65	10.04	0.1659
90	87.34	9.88	85.12	8.86	0.1514
105	84.23	8.55	86.47	8.94	0.1762
120	88.37	9.25	87.18	9.11	0.2521



In group LB, the MAP decreased to 79.43 ± 10.20 mm of Hg at 15 minutes and 78.23 ± 8.52 mm of Hg at 20 minutes, whereas in group RB, the MAP decreased to 79.77 ± 10.03 mm of Hg at 15 minutes and 78.86 ±10.06 mm of Hg at 20 minutes.

Comparable to group RB, the MAP fall occurred in group LB at 15, 20, 25, 30, 45, and 60 minutes and were not statistically significant.

Table 12: Comparison of SpO_2 at different time intervals (%)

SpO2	Group LB	Group RB
0	100	100
5	100	100
10	100	100
15	100	100
20	100	100
25	100	100
30	100	100
45	100	100
60	100	100
75	100	100
90	100	100
105	100	100
120	100	100

The preoperative SpO2 in this study was 100 ± 0% in both group LB and group RB, making them identical. There was no statistically significant difference in intra-op oxygen saturation in two groups.

DISCUSSION

Neuraxial blockade has long been the primary anaesthetic strategy for lower abdomen and lower leg procedures. Subarachnoid block has been the conventional neuraxial block approach for these patients, however in recent years epidural anaesthesia has been used more frequently for such procedures.

The most significant benefits of epidural anaesthesia over sub arachnoid block are the capacity to titrate the dose of local anaesthetic to the desired degree and duration of block and the provision of post-operative analgesia. Epidural anaesthesia, particularly when an epidural catheter is placed, has certain specific advantages over sub arachnoid block. Because of the segmental form of the block, it also provides superior haemodynamic stability.

Historically, the preferred medication for epidural anaesthesia has been bupivacaine. The potential cardiac toxicity of bupivacaine was exposed as its negative aspect. Mild symptoms, seizures, cardiovascular instability, and sudden cardiac death were long thought to be all indicators of local anaesthetic overdose.

In clinical settings, levobupivacaine has not completely taken the role of bupivacaine. Levobupivacaine is equally as potent as bupivacaine. In contrast, levobupivacaine caused less cvs and Central nervous system harm in animal studies than bupivacaine. Levobupivacaine produced less QTc interval prolongation than bupivacaine at i.v doses greater than 75mg in healthy subjects and had a less detrimental inotropic effect. With levobupivacaine, there were less EEG abnormalities that indicated CNS depression.

Ropivacaine is a recently developed long-acting amide local anaesthetic. It is advertised as the parent chemical ropivacaine's pure S(-) enantiomer. Its obvious advantages over Bupivacaine

include lower cardiotoxicity and neurotoxicity, as well as a more targeted action on sensory rather than motor fibres. It is due to Ropivacaine's lower lipophilicity and enantiomer properties.[9]

The current randomised clinical trial lasted one year, from January 2021 to December 2021, at the KLES Dr. Prabhakar Kore Charitable Hospital in Belagavi's Department of Anaesthesiology. Using the envelope method of randomization, 70 patients undergoing lower abdominal surgeries under epidural anaesthesia were divided randomly into two groups.

Group LB: Patients receive 14.5 ml of 0.5 % Levobupivacaine ± Inj Buprenorphine 150 mcg (0.5 ml)

Group RB: Patients receive 14.5 ml of 0.75 % Ropivacaine ± Inj Buprenorphine 150 mcg (0.5 ml)

With regard to mean age (35.40 and 36.51 years, respectively; p value = 0.3045) and mean weight (70.2 kg and 68.57 kg, respectively; p value = 0.2463), In our study, we did not discover any statistically significant differences between groups LB and RB.

The time it took to onset sensory block at the T10 dermatomal level was used to define the onset of sensory block in our analysis. In this study, Group LB experienced sensory block on average (16.86 ± 0.85 min) versus group RB's (14.54 ± 0.78 min). A statistically significant difference existed between the groups (p-value 0.00001).

Deepa Bulchandani et al observed[12], Group RB took longer (20.25±2.31 minutes) than group R (17.67±2.00 minutes) to reach sensory block at the T12 level. This study was comparable and Ropivacaine with buprenorphine took longer time when compared to our study.

In V. A. Peduto[18], onset time of sensory block was 29±24 min, with ropivacaine it was (25 ± 22 min) (P-0.41). When compared to our study, the onset of sensory block took longer in both the groups and no adjuvants was used.

The time it took for the total sensory block to regress was used in our study to define the duration of the sensory block. In this study, the mean time of sensory block was (294.80 ± 8.12) min for group LB and (256 ± 6.47) min for group RB. A statistically significant difference existed between the groups (p-value 0.0001).

In Deepa Bulchandani et al[12].found that when ropivacaine was compared to its combination with buprenorphine, the duration of sensory block, i.e. The average post-operative analgesic duration was statistically significantly longer in group RB (297.33±12.08 minutes) than in group R (259.3±12.08 minutes). The findings agreed with those of our study.

In the aforementioned study by V. A. Peduto[18], Levobupivacaine took (185 min and 77 seconds) to cause the sensory block to regress to T12, while ropivacaine took (201 min and 75 seconds) (P=0.46).when compared to our duration of block was longer with the use adjuvants buprenorphine(150mg).

In our study, the period of time required to reach modified bromage grade 3 served as a marker for of motor block. For group LB and group RB, the mean time for the onset of motor block in this study was 25.46 ±1.84 min and 21.91 ±1.07 min, respectively. Between the groups, a statistically significant difference was present (p-value 0.00001).

In Deepa Bulchandani et al[12] ,Complete motor block was achieved in (25.95 ±1.23 minutes) in group R and (26.58 ±1.55 minutes) in group RB (p = 0.086). The findings were similar with those of our study.

The time it took for modified bromage 0 to return was used in our study to define the duration of the motor block. In our study, the mean motor block time was (200.40±3.73 min) for group LB and (177.09±7.96 min) for group RB. A statistically significant difference existed between the groups (p-value 0.00001).

Complete resolution of the motor block required in the aforementioned study by V. A. Peduto[18] took (105 ± 63 min) with levobupivacaine and (95± 48 min) with ropivacaine (P= 0.86).Buprenorphine was used as an adjuvant in our study, prolonging the duration of the motor block.

Heart rate, systolic and diastolic blood pressure, mean arterial pressure, and SpO2 were the baseline vital signs compared between the two groups in the current study.

The preoperative mean heart rates in this study were (80.94 ±11.27 bpm) in group LB and (80.63 ±12.11 bpm) in group RB, and they were comparable (p = 0.453).

In group LB, the heart rate rate decreased to (77.06 ±13.90 bpm) at 20 minutes and (77.40 ±12.95 bpm) at 25 minutes, whereas in group RB, the heart rate decreased to (75.46 ±12.71 bpm) at 20 minutes and 74.97±12.66 bpm at 25 minutes. At 20, 25, and 30 minutes, the heart rate in group RB was lower than that in group LB (p values of 0.313, 0.203, and 0.075, respectively).

The mean systolic blood pressure in this study's pre-operative phase was (120.31±12.11) mm Hg in group RB and (124.80 ± 11.27) mm Hg in group LB, and both values were comparable (p = 0.1474). Systolic blood pressure in group LB decreased to (106.23±10.47) mm of Hg at 15 minutes and (106.06±10.51) mm of Hg at 20 minutes, while it decreased to (108.09±10.64) mm of Hg at 15 minutes and (107.94±11.97) mm of Hg at 20 minutes in group RB. Systolic blood pressure fell similarly in group LB at 15, 20, 25, 30, 45, and 60 minutes compared to group RB.

The mean diastolic blood pressure in this study was 75.26± 7.56 mm Hg in group LB and 75.86 ± 5.47 in group RB, and both values were comparable (p = 0.3375). In group LB, the diastolic blood pressure dropped to 67.20 ± 10.73 mm of Hg at 15 minutes and 64.06 ± 10.51 mm of Hg at 20 minutes, while in group RB, it dropped to 66.34 ± 10.59 mm of Hg at 15 minutes and 66.23 ±8.56mm of Hg at 20 minutes. In comparison to group RB, the diastolic BP fell in group LB at 15, 20, 25, 30, 45, and 60 minutes (p values 0.05).

The MAP decreased in group LB to 79.43±10.20 mm of Hg at 15 minutes and to 78.23±8.52 mm of Hg at 20 minutes, while it decreased in group RB to 79.77±10.03 mm of Hg at 15 minutes and to 78.86±10.06 mm of Hg at 20 minutes. Comparable to group RB, the MAP fall occurred in group LB at 15, 20, 25, 30, 45, and 60 minutes.

Throughout the procedure, heart rate, systolic and diastolic blood pressure, mean arterial pressure values between group LB and group B were comparable. There was no statically significance between the group.

Throughout the procedure, SpO2 values between group LB and group B were comparable. To manage the decline in vital parameters, neither patient in either group needed any intervention.

CONCLUSION

Our study showed that 0.5% levobupivacaine with buprenorphine is significantly more potent than 0.75% ropivacaine with buprenorphine in terms of duration of sensory and motor block in patients undergoing lower abdominal surgery under epidural anaesthesia. While the onset of sensory and motor blockade is earlier in 0.75% ropivacaine compared to 0.5% levobupivacaine with the buprenorphine group.

The haemodynamic parameters including HR, SBP and DBP are stable and comparable and have no static significance in 0.75% ropivacaine with buprenorphine group and 0.5% levobupivacaine with buprenorphine group.

SCOPE AND LIMITATIONS

- This study is done only in ASA grades I and II, further study can be done in ASA III and IV.
- A newer drug like α2 agonist like dexmedetomidine, can be studied with levobupivacaine and ropivacaine.

SUMMARY

Epidural anaesthesia is fast emerging as the preferred neuraxial block technique for lower abdominal and lower limb surgeries. Epidural anaesthesia allows the anaesthesiologist to titrate the dose of drugs to the level of desired block and duration of surgery, maintain better haemodynamic stability and provide post-operative analgesia to the patients. The newer local anaesthetics ropivacaine and levobupivacaine are fast gaining popularity in regional anaesthesia due to their more cardiostable profile and dense sensory block. Various adjuncts along with local anaesthetics have been tried via the epidural route to hasten the onset and prolong the duration of the block. Opioids have been shown to have a synergistic effect along with local anaesthetics. Buprenorphine is one of the most commonly used adjuvants in epidural anaesthesia.

This one-year randomised controlled trial was conducted in the Department of Anaesthesiology, KLES Dr Prabhakar Kore Charitable Hospital Belagavi, from January 2021 to December 2021. Total of 70

patients undergoing lower abdominal surgeries were randomly allocated to two groups namely, Group LB: Patients receive 14.5ml of 0.5% Levobupivacaine + Inj Buprenorphine 150mcg (0.5ml) Group RB: Patients receive 14.5ml of 0.75% Ropivacaine + Inj Buprenorphine 150mcg (0.5ml) through the epidural route. The onset and duration of sensory and motor block and vital parameters were studied. The haemodynamic parameters like heart rate, blood pressure and oxygen saturation were continuously monitored.

Demographic parameters were comparable in both groups. In this study, the onset of sensory block was faster in group RB (14.54 ±0.78 minutes) than in group LB (16.86 $\pm$ 0.85 minutes). The duration of the sensory block was longer in group LB (294.80 $\pm$ 8.12 minutes) than in group RB (256.97 $\pm$ 6.47 minutes). The onset of motor block was faster in group RA (21.91 $\pm$ 1.07

minutes) as compared to group LB (25.46 ± 1.84 minutes). The duration of the motor block was longer in group LA (200.40± 3.73 minutes) as compared to group RB (177.09 ± 7.96 minutes). The pre-operative heart rate, systolic BP, diastolic BP and SpO2 were comparable in both groups. However falls in heart rate, systolic BP and diastolic BP were comparable in both group LA group RB intraoperatively. The side effects were comparable between the two groups.

Overall, based on this study it may be concluded that 0.5% levobupivacaine with buprenorphine is significantly more potent than 0.75% ropivacaine with buprenorphine in terms of duration of sensory and motor block in patients undergoing lower abdominal surgery under epidural anaesthesia. While the onset of sensory and motor blockade is earlier in 0.75% ropivacaine compared to 0.5% levobupivacaine with the buprenorphine group.

BIBLIOGRAPHY

1.Grass JA. The role of epidural anesthesia and analgesia in postoperative outcome. Anesthesiology Clinics of North America. 2000 Jun 1;18(2):407-28.

2. Choi P, Bhandari M, Scott J, Douketis JD. Epidural analgesia for pain relief following hip or knee replacement. Cochrane database of systematic reviews. 2003(3).

3. Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, Young WL. Miller's anesthesia e-book. Elsevier Health Sciences; 2014 Oct 20.

4.Sakura S. Epidural anesthesia and spinal anesthesia in the elderly. Masui. The Japanese Journal of Anesthesiology. 2007 Feb 1;56(2):130-8.

5. Simpson D, Curran MP, Oldfield V, Keating GM. Ropivacaine. Drugs. 2005 Dec;65(18):2675-717.

6. REYNOLDS F, Taylor G. Plasma concentrations of bupivacaine during continuous epidural analgesia in labour: the effect of adrenaline. BJA: British Journal of Anaesthesia. 1971 May 1;43(5):436-40.

7.Covino BG, Vassallo HG. Clinical aspects of local anesthesia. Local Anesthetics: Mechanisms of Action and Clinical Use. New York: Grune and Stratton. 1976:57-94.

8. Rice SA, Fish KJ. Toxicity of Local Anesthetic Agents. Anesthetic Toxicity. 1994 Jun 30:107.

9.Kuthiala G, Chaudhary G. Ropivacaine: A review of its pharmacology and clinical use. Indian journal of anaesthesia. 2011 Mar;55(2):104.

10. Nagesh KS, Sathesha M, Prasad RS. Comparative study between epidural bupivacaine with buprenorphine and epidural bupivacaine for post-operative analgesia in abdominal and lower limb surgery. Journal of Evolution of Medical and Dental Sciences. 2015 Mar 2;4(18):3057-65.

11. Brill S, Gurman GM, Fisher A. A history of neuraxial administration of local analgesics and opioids. European journal of anaesthesiology. 2003 Sep;20(9):682-9.

12. Bulchandani D, Code QR. Comparison of epidural Ropivacaine 0.75% and Ropivacaine 0.75% Plus Buprenorphine (0.5 ml) for total knee replacement surgery.

13. Kulkarni J, Tammewar A, Jewalikar S, Bengali R. Epidural anaesthesia in elderly: A Comparison of Ropivacaine with Bupivacaine. IOSR Journal of Dental and Medical Sciences. 2013;6:3.

14. Thimmappa M, Madhusudhana R, Potli S, Karthick D. A comparative study of epidural ropivacaine 0.75% alone with ropivacaine plus clonidine and ropivacaine plus dexmedetomidine for lower abdominal and lower limb surgeries. World Journal of Pharmacy and Pharmaceutical Sciences. 2014 Feb 15;3(4):1218-30.

15. Bajwa SJ, Arora V, Kaur J, Singh A, Parmar SS. Comparative evaluation of dexmedetomidine and fentanyl for epidural analgesia in lower limb orthopedic surgeries. Saudi journal of anaesthesia. 2011 Oct;5(4):365.

16.Bajwa SJ, Bajwa SK, Kaur J. Comparison of epidural ropivacaine and ropivacaine clonidine combination for elective cesarean sections. Saudi journal of anaesthesia. 2010 May;4(2):47.

17. Guler G, Aksu R, Dogru K, Sofikerim M, Tosun Z, Boyaci A. Comparison of 3 doses of ropivacaine for epidural anesthesia in transurethral surgery. Saudi Med J. 2009 Jan 1;30(1):67-71.

18. Peduto VA, Baroncini S, Montanini S, Proietti R, Rosignoli L, Tufano R, Casati A. A prospective, randomized, double-blind comparison of epidural levobupivacaine 0.5% with epidural ropivacaine 0.75% for lower limb procedures. European journal of anaesthesiology. 2003 Dec;20(12):979-83.

19. Crosby E, Sandler A, Finucane B, Writer D, Reid D, McKenna J, Friedlander M, Miller A, O'Callaghan-Enright S, Muir H, Shukla R. Comparison of epidural anaesthesia with ropivacaine 0.5% and bupivacaine 0.5% for caesarean section. Canadian journal of anaesthesia. 1998 Nov;45(11):1066-71.

20. McGlade DP, Kalpokas MV, Mooney PH, Buckland MR, Vallipuram SK, Hendrata MV, Torda TA. Comparison of 0.5% ropivacaine and 0.5% bupivacaine in lumbar epidural anaesthesia for lower limb orthopaedic surgery. Anaesthesia and intensive care. 1997 Jun;25(3):262-6.

21. Lyons G, Columb M, Wilson RC, Johnson RV. Epidural pain relief in labour: potencies of levobupivacaine and racemic bupivacaine. British journal of anaesthesia. 1998 Dec 1;81(6):899-901.

22. Atkinson RS, Rushman GB, Davies NJ. Spinal analgesia: intradural and extradural. Lee's synopsis of anaesthesia. 11th ed. Edt. Atkinson RS, Oxford: Butterworth heinemanu. 1993:691-745.

23. Williams PL, Warwick R, Dyson M, Bannister LH. Gray's Anatomy. 37th edn, Churchill Livingstone. Edinburgh pp748. 1989;406.

24. Hamid M, Fallet-Bianco C, Delmas V, Plaisant O. The human lumbar anterior epidural space: morphological comparison in adult and fetal specimens. Surgical and Radiologic Anatomy. 2002 Jan;24(3):194-200.

25. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. The Journal of the American Society of Anesthesiologists. 1979 Oct 1;51(4):285-7.

26. Mantouvalou M, Ralli S, Arnaoutoglou H, Tziris G, Papadopoulos G. Spinal anesthesia: comparison of plain ropivacaine, bupivacaine and levobupivacaine for lower abdominal surgery. Acta Anaesthesiologica Belgica. 2008 Jan 1;59(2):65-71.

27. McCaughey W, Mirakhur RK. Drugs in anaesthetic practice and analgesia. Avery's drug treatment. 4th ed. Yardley, PA: Adis International Limited. 1997:451-514.

28. Albaladejo P, Bouaziz H, Benhamou D. Epidural Analgesics. CNS drugs. 1998 Aug;10(2):91-104.

29. Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ. Buprenorphine-induced antinociception is mediated by μ-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. Journal of Neuroscience. 2003 Nov 12;23(32):10331-7.

30. Dahan A. Yas sen A, Bijl H, Rom berg R, Sar ton E, Teppe ma L, Olof sen E, Dan hof M (2005) Com pa ri son of the re spi ra to ry ef fects of in tra ve nous bu p re norphi ne and fen ta nyl in hu mans and rats. Br J Anaest.;94:825-34.

31. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacology & Therapeutics. 1994 May;55(5):569-80.

ANNEXURE I

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr. /Mrs. /Miss. _____ we are requesting you to enroll you in the study titled **"**TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA: A ONE YEAR RANDOMISED CINICAL TRIAL AT DR.PRABHAKAR KORE CHARITABLE HOSPITAL, BELAGAVI conducted by Dr**.** PRUTHVI D HIREMATH Post Graduate in M.D. Anesthesiology under the guidance of Dr.KEDARESHVARA K.S.M.D. ,PDCC, Professor, Department of Anesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.-10

Respected Sir/Madam, we request you to participate in our study as you are eligible for it. During the study you will be asked some questions regarding your medical history and you are supposed to answer to the best of your knowledge.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.Medical College. If you decide to participate you are free to withdraw at any time.

Purpose of the study: To compare onset and duration and hemodynamic effects of study drug

Procedure Involved: If you agree to enroll in my study, I will ask you present and past history medical history and family history, then u will be clinically examined in details. Epidural anaesthesia will be given by senior anaesthesiologist. Each is randomly assigned in to two groups . Group A will be given levobupivacaine with buprenorphine and Group B will be given ropivacaine with buprenorphine for epidural anaesthesia and will be monitored through out the procedure and in post-operative period.

Voluntary Participation/Withdrawal:

Taking part in the study is voluntary. You may choose not to enrol yourself in this study. Your decision will not change any health care services offered to you or your ward at K.L.E. S Hospital & MRC.

Benefits: Efficacy, hemodynamic effects can be studied and in anaesthesiology practice

Risks: opioid over dose should be monitored

Privacy and Confidentiality:

The only people to know that you are as research subject are you and members of the research team. No information provided by you during the research will be disclosed to other without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results:

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

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 through KLES Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If you get injured you may contact Dr. PRUTHVI D HIREMATH at Department of Anesthesiology, J.N. Medical College or by Ph. No:8861226237.

Questions:

In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. PRUTHVI D HIREMATH, Department of Anesthesiology, J.N. Medical College, Belagavi. Phone number: 8861226237 Or Dr. KEDARESHVARA K.S M.D., PDCC, Professor, Dept. Of Anesthesiology, J.N. Medical College, Belagavi. Ph. No:9886375154

If you have any queries about your rights as a study subject, you may call Dr. HARSHA HEGDE M.D Chairperson, J.N. Medical college, IEC & scientist department, ICMR, national institute of traditional medicine, Belagavi - 9480422500.

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH TRIAL

"TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA: A ONE YEAR RANDOMISED CINICAL TRIAL AT DR. PRABHAKAR KORE CHARITABLE HOSPITAL, BELAGAVI"

Mr./Ms./Mrs. _____ voluntarily agree for the participation of as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Signature or the Left Thumb Print of Subject/Guardian: _____

Date:

Witness Name: _____ Signature: _____

Investigators Name: _____ Signature: _____

Date:

Place : _____.

ANNEXURE II

PROFORMA

"TO STUDY THE EFFICACY OF BUPRENORPHINE WITH LEVOBUPIVACAINE AND BUPRENORPHINE WITH ROPIVACAINE IN EPIDURAL ANAESTHESIA: A ONE YEAR RANDOMISED CINICAL TRIAL AT DR. PRABHAKAR KORE CHARITABLE HOSPITAL, BELAGAVI"

Group allotted :

Name	:	Age	:
Gender	:	Weight	:
Height	:	Date of Examination	:
Address	:	Occupation	:

Pre examination evaluation

Past History

- HTN ☐ DM ☐ IHD ☐ Arrhythmia ☐ Valvular heart diseases . ☐

- H/o previous surgery/(s) where airway difficulty will be encountered.

  Yes ☐ No ☐

General physical examination

Weight (Kg)	:	Temperature (^{0}F)	:	Pallor	:
Cyanosis	:	Pedal edema	:	Clubbing	:
PR	:	BP	:	RR	:

Musculoskeletal disorders:

Jaw movements : Teeth:

Airway assessment : Spine:

Investigations

Hb%: TLC: Platelet Count : INR: FBS:

Systemic examination:

RS: CNS:

CVS: GIT:

Preoperative physical status American society of anaesthesiologist I ☐ II ☐

Proposed surgery

Post-operative baseline values

HR : BP: SpO2:

Monitors attached:

Pulse oxymetry: NIBP:

ECG:

Group: A B

Sensory Block:

a)	Onset at T10(min)	
b)	Duration at T10(min)	
c)	Highest level of sensory block	

Motor Block:

a)	Onset (min) Grade 3 motor blockade	
b)	Total duration of Motor blockade	

Vital Parameters

Time	HR	SBP	DBP	MAP	SpO2
0min					
5 min					
10 min					
15 min					
20 min					
25 min					
30 min					
45 min					
60 min					
75 min					
90 min					
105 min					
120 min					

SIGNATURE OF THE ANAESTHESIOLOGIST: _____

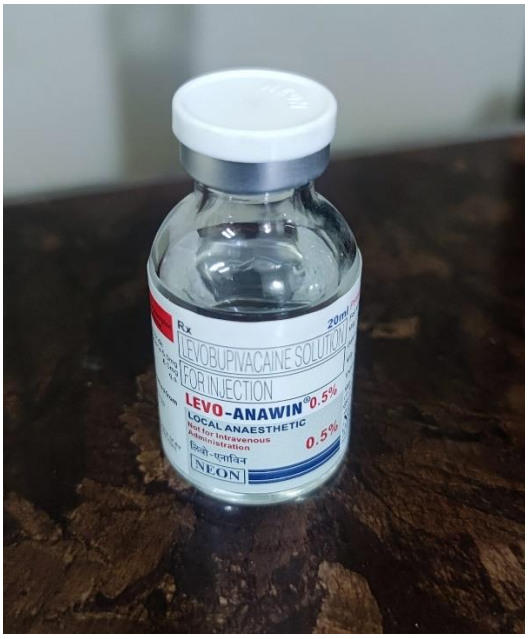
SIGNATURE OF THE WITTNESS - _____

SIGNATURE OF THE PRINCIPAL INVESTIGATOR - _____

ANNEXURE III: PHOTOGRAPHS

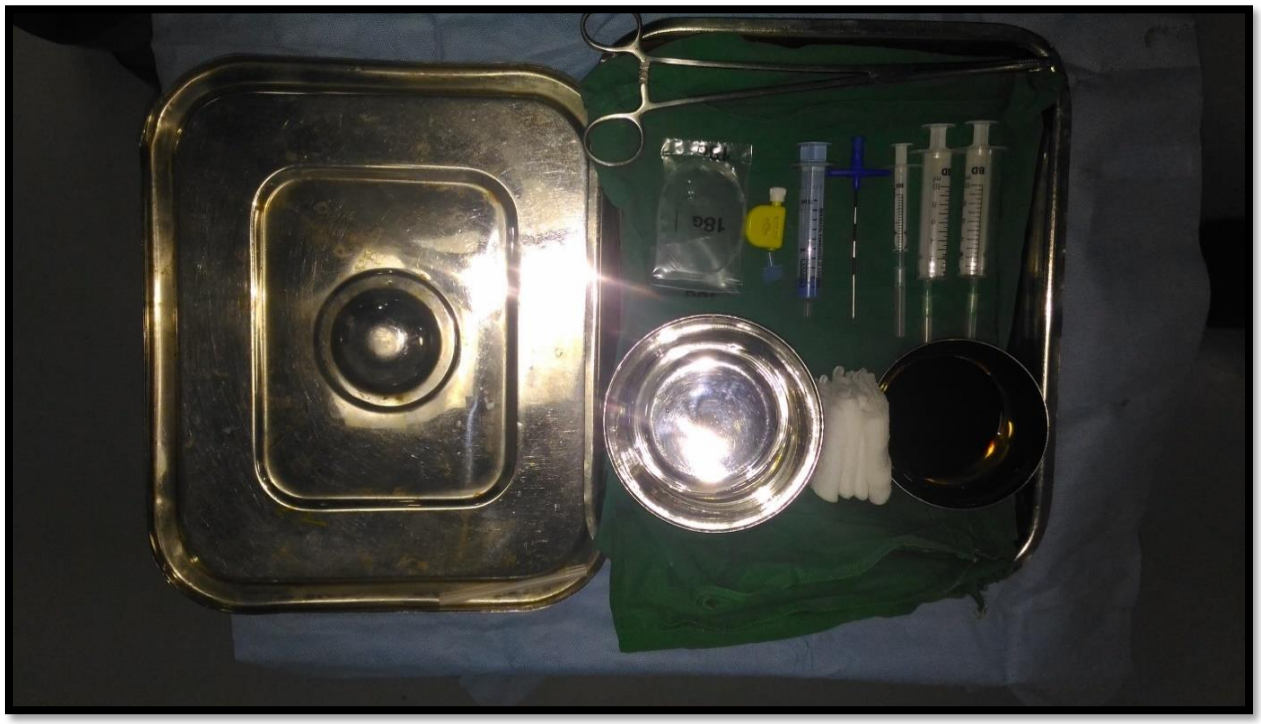
Photograph 1: 0.75% Ropivacaine ampoule

Photograph 2: 0.5% Levobupivacaine ampoule

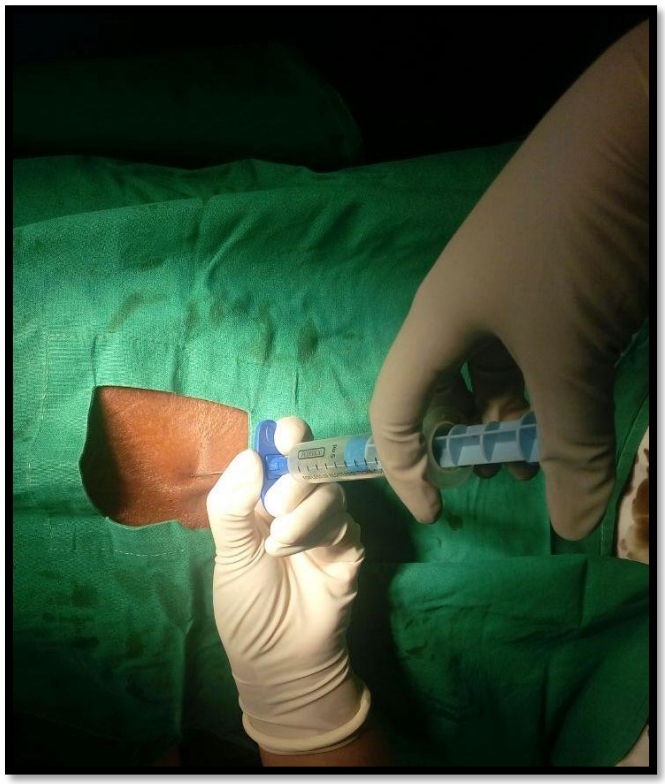


Photograph 3 : Buprenorphine ampoule

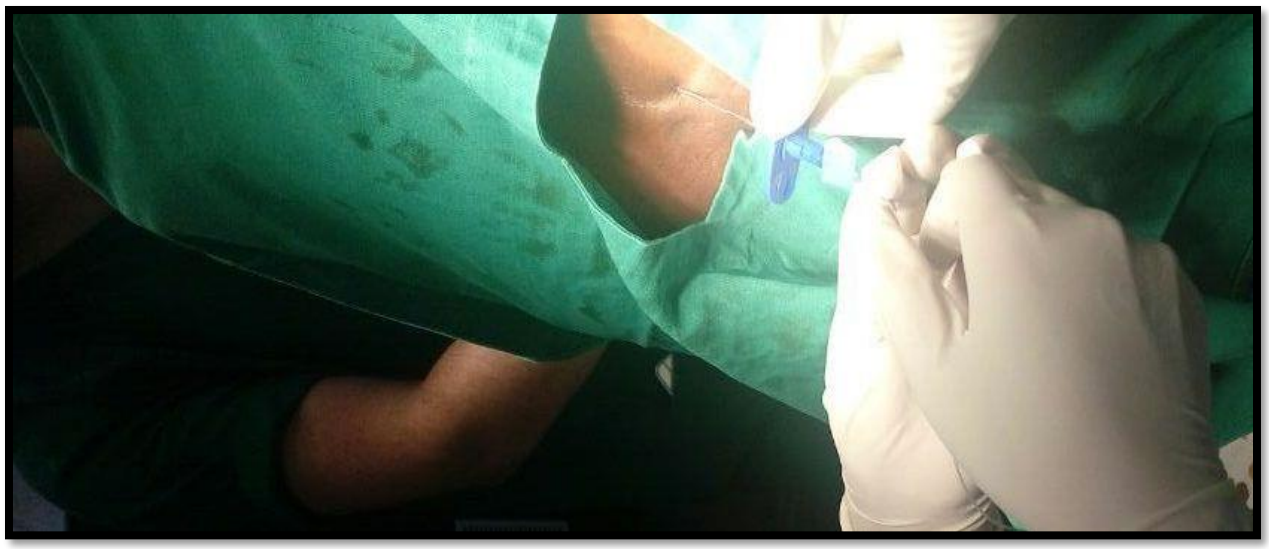
Photograph 4 : Epidural tray



Photograph 5 A : Procedure of epidural (Loss of resistance technique)



Photograph 5 B : Procedure of epidural (Threading the epidural catheter)



Photograph 6 : Monitoring during surgery