"COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUAL DOSES OF ISOBARIC LEVOBUPIVACAINE 0.5% -FENTANYL AND ISOBARIC ROPIVACAINE 0.5%-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL"

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LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologists
C	-	Cervical
T	-	Thoracic
Mcg	-	Microgram
cc	-	Cubic centimeter
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ED	-	Effective dose
FDA	-	Food and Drug Administration
GA	-	General anaesthesia
HCO_3	-	Bicarbonate
HR	-	Heart rate
bpm	-	Beats per minute
IV	-	Intravenous
HCL	-	Hydrochloric Acid
KCl	-	Potassium chloride
kg	-	Kilogram
L	-	Lumbar
m	-	Meters
MAP	-	Mean arterial pressure
mg	-	Milligram
v/s	-	Versus

Mins	-	Minutes
ml	-	Millilitre
NIBP	-	Non invasive blood pressure
O_2	-	Oxygen
$PaCO_2$	-	Partial pressure of carbon dioxide
S	-	Sacral
SAB	-	Subarachnoid block
SBP	-	Systolic blood pressure
SD	-	Standard deviation
Sec	-	Second
SpO_2	-	Peripheral saturation of oxygen
TNS	-	Transient neurological symptoms
α	-	Alpha
β	-	Beta
δ	-	Delta
μ	-	Micro
cm	-	centimeter
G	-	Gauge
mEq	-	milliequivalents
Lt	-	litre
Dl	-	decilitre
V_{max}	-	maximum initial velocity or rate of a reaction.

ABSTRACT

Background and Objective

Spinal anaesthesia is the most convenient anaesthetic technique for lower abdominal surgeries that offers many advantages over general anaesthesia, including reduced stress response and improved post-operative pain relief. Levobupivacaine and ropivacaine have been described as alternatives to bupivacaine for spinal anaesthesia. Fentanyl is a commonly used adjuvant. The present study was done to evaluate onset and duration of sensory and motor block between 3.0 ml of 0.5 % isobaric levobupivacaine + 0.5 ml (25mcg) fentanyl and 3.0 ml of 0.5 % isobaric ropivacaine + 0.5 ml (25 mcg) fentanyl in lower abdominal surgeries.

Methods

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi during the period January 2014 to December 2014. A total of 80 patients undergoing lower abdominal surgeries under spinal anaesthesia were allocated into two groups namely, Group LF (n =40 , Patients received 3.0 ml of 0.5 % isobaric levobupivacaine + 0.5 ml (25mcg) fentanyl intrathecally) or Group RF (n =40 , Patients received 3.0 ml of 0.5 % isobaric ropivacaine + 0.5 ml (25 mcg) fentanyl intrathecally)

Results

In this study demographic parameters were comparable in both the groups. The onset of sensory block was significantly faster in Group RF (5.25 ± 0.74 min) than in Group LF (6.53 ± 0.51 min).The duration of sensory block was significantly longer

in Group LF (169.5 ± 7.15 min) than in Group RF (144.25 ± 5.94 min). The onset of motor block was significantly faster in Group RF (7.25 ± 0.98 min) than in Group LF (11.2 ± 0.61 min). The duration of motor block was significantly longer in Group LF (219.5 ± 6.39 min) than in Group RF (171.25 ± 7.23 min). Hemodynamic parameters were comparable between the two groups with no major side effects / complications observed.

Conclusion and interpretation

Overall, based on the findings of this study it may be concluded that intrathecal 0.5 % isobaric levobupivacaine - fentanyl is more potent than intrathecal 0.5 % isobaric ropivacaine - fentanyl with respect to the duration of sensory and motor block with no significant hemodynamic changes. Both the drugs can be used as alternative to bupivacaine intrathecally with no risk of major side effects / complications.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

Spinal anaesthesia is a commonly performed procedure when the surgical site is located on the lower abdomen, perineum or lower extremities. The advantages are an awake and spontaneously breathing patient, minimal drug costs, reduction of poly-pharmacy and rapid patient turnover. It is a simple, effective and safe technique. Hence it has become the method of choice for such surgeries.

Spinal anaesthesia is performed by injection of a local anaesthetic with or without adjuvant in the sub-arachnoid space producing intense sensory, motor and sympathetic blockade. Anaesthesiologists, all across the world, have been trying to make spinal anaesthesia as safe as possible by providing adequate intra and post-operative analgesia and at the same time promoting early ambulation post– surgery.

Regional anesthesia techniques have seen numerous modifications over the last two decades with the advent of many new and safer local anesthetics. Presently, bupivacaine is the most commonly used drug for administration of spinal anaesthesia.[1] It's levorotatory or S (−) stereoisomer known as levobupivacaine has been available since the late 1990s. Levobupivacaine, the pure S-enantiomer of bupivacaine, has emerged as a safer alternative for regional anaesthesia than its racemic parent. Clinically levobupivacaine is well tolerated in a variety of regional anaesthesia techniques either intrathecally or after bolus administration or continuous post-operative infusion. In clinical anesthesia, levobupivacaine produces comparable surgical sensory and motor block with bupivacaine in spinal anaesthesia.[2]

Ropivacaine was introduced into clinical practice in 1996. It was the first commercially available local anaesthetic in its category as a pure S-enantiomer.

Ropivacaine resembles bupivacaine structurally. It has demonstrated an improved safety profile over bupivacaine, with a reduced central nervous system and cardiotoxicity, together with a wide clinical utility at different doses and for a wide range of indications.[3] Although these concerns are not clinically relevant to spinal anaesthesia because of the smaller doses required, there has, nevertheless, been an increased interest in these agents for intrathecal use.[4]

The aim of using adjuvants with local anaesthetics is to improve analgesic intensity, to increase duration of action, to achieve faster onset and to achieve acceptable, effective prolonged post - operative analgesia with lower drug doses and thus reduced risks of side-effects. Efforts to find an ideal adjuvant in regional anaesthesia have been going on since a long time. Thus opioids (like fentanyl[5], buprenorphine[6]), alpha-2 agonists (like clonidine[6]) have been used intrathecally as adjuvants to the local anaesthetics for improvement in quality and extending the duration of spinal blockade.

Levobupivacaine and ropivacaine have recently become available in India for clinical use. Very few studies have been done comparing these two drugs. Hence by taking this study we make an attempt to compare Levobupivacaine (isobaric)-fentanyl and Ropivacaine (isobaric)-fentanyl with regards to onset and duration of blockade in lower abdominal surgeries in spinal anaesthesia.

OBJECTIVES

The objectives of the present study were:

Primary Objective: To compare the onset, duration of motor and sensory blockade between intrathecal 0.5 % isobaric levobupivacaine + fentanyl and intrathecal 0.5 % isobaric ropivacaine + fentanyl in lower abdominal surgeries.

Secondary objective: To study and evaluate associated complications, if any.

REVIEW OF LITERATURE

Spinal anaesthesia is a form of regional anaesthesia where conduction block of nerve roots is achieved by injecting local anaesthetic solution into the subarachnoid space through a lumbar puncture.

Spinal anaesthesia has come a long way since its discovery and its history is very interesting. In 1885 J. Leonard Corning, a neurologist from New York, was the first to administer spinal anaesthesia, when he accidentally pierced the duramater while experimenting with cocaine on the spinal nerves of a dog. Within a few minutes, the dog developed marked weakness in the hind legs. Corning then went on to inject cocaine into a man at the T_{11}-T_{12} inter-vertebral space into what he thought was subarachnoid space. He repeated the injection when he did not observe any effect. Ten minutes after the second injection, the patient informed of heaviness in his legs, but was able to stand and walk around. In his records, Corning never mentioned of cerebrospinal fluid flow. Therefore most likely he inadvertently gave an epidural rather than a spinal injection to the patient. He later used this technique in various neurological disorders but did not use it for surgeries though he appreciated its potential use.[7]

In 1891 Essex Wynter described dural puncture.[8] Six months later, Quincke demonstrated a safe and predictable method of performing lumbar puncture.[9]

The first planned spinal anaesthesia for surgery in man was performed in 1898 by August Karl Bier in Germany. Bier and his assistant Otto Hildebrandt both administered spinal anaesthesia by injecting cocaine to each other. Bier had to discontinue after experiencing post dural puncture headache (PDPH). Bier attributed

his PDPH to the loss of CSF and felt the use of small-gauge needles would prevent the headache. After injection of cocaine intrathecally into Hildebrandt, he reported minimal to no pain during the experiments. Bier then went on to administer cocaine in the subarachnoid space of six patients undergoing lower limb surgeries.[10]

In 1905, Heinrich Braun reported the use of procaine for administration into subarachnoid space. In 1907, Arthur Baker reported on the advancement of spinal techniques, including the use of a hyperbaric spinal local anaesthetic, emphasis on sterility and ease of midline route over paramedian for dural puncture.[11] In 1923 Gaston Labat popularized spinal anaesthesia in United States and performed studies on the effects of Trendelenburg position on blood pressure after spinal anaesthesia.

Tetracaine was synthesized in 1931 and was introduced into clinical practice by Lincoln Sise in 1935. Spinal anaesthesia became more popular as new developments occurred. In 1946, Adriani and Roman-Vega introduced saddle block. The popularity of spinal anaesthesia reached newer heights in the 1940's. Continuous spinal anesthesia was demonstrated by Lemmon in 1940 and Tuohy in 1945.[12]

The technique of spinal anaesthesia has evolved with time since its inception in the nineteenth century. Usage of a finer bore and dura separating pencil-point needle along with strict asepsis have reduced complications due to the technique.

Spinal anaesthesia has many advantages like ease of administration, rapid onset of action and good muscle relaxation. The major limitations are its limited duration of action hence the paucity of post-operative analgesia and hemodynamic instability.

Spinal anaesthesia is performed by injection of a local anaesthetic with or without adjuvants in the sub-arachnoid space producing intense sensory, motor and sympathetic blockade. The aim of using adjuvants with local anesthetics is to improve the analgesic intensity, to increase the duration of action, to achieve faster onset of action and to achieve acceptable analgesia with lower drug doses and thus reduced risks of side-effects.[13]

The three most important factors determining the spread of local anaesthesia in the subarachnoid space are the baricity of the local anaesthetic solution, position of the patient during and immediately after the injection and dose of the drug injected. Hypobaric drugs are less dense than CSF and tend to rise against gravity. Isobaric drugs are as dense as CSF and tend to remain at the same level as injected. Hyperbaric drugs are denser than CSF and tend to follow gravity after injection. With isobaric drugs, injection can be made in any position and then the patient can be placed into the position required for the surgery. Gravity does not play a role in the spread of isobaric drugs, unlike with hypo or hyperbaric local anaesthetics.[14]

Ever since the development of the technique of spinal anaesthesia various local anaesthetics such as cocaine, procaine, etidocaine, tetracaine, lignocaine and bupivacaine have been tried and studied for their effects. Lignocaine was first used as a spinal anaesthetic in 1945. Earlier lignocaine 5% was commonly used for spinal anaesthesia, but its use has declined because of concerns about cauda equina syndrome and transient neurological symptoms.[15]

Since a few decades lignocaine has been almost replaced with bupivacaine and ropivacaine. Lately levobupivacaine has also been introduced for clinical use. Hence its use mandates for further research and knowledge about the drug.

Guler et al compared 10 mg levobupivacaine with 15 mcg of fentanyl (LF) and 10 mg bupivacaine (hyperbaric) with 15 mcg of fentanyl (BF) in spinal anesthesia for Cesarean sections. It was observed that maximum sensory block level in bupivacaine - fentanyl group (BF) was higher ($T_4 > T_5$) and development of motor block was faster (2.36 min for BF vs 4.1 min for LF) and lasted longer (132.66 min for BF vs 99 min for LF). Since motor block time is shorter, and side effects like hypotension, bradycardia and nausea are less, the combination of levobupivacaine + fentanyl can be a good alternative in Cesarean sections.[16]

Levobupivacaine has been subjected to various other studies in surgeries of the lower abdomen and pelvis. In the following study by Ackaboy et al subjected levobupivacaine to a study in surgeries of the lower abdomen and pelvis. In the study, patients in levobupivacaine group (Group L) received 5 mg levobupivacaine + 25 mcg fentanyl and bupivacaine group (Group B) received 5 mg bupivacaine + 25 mcg fentanyl for transurethral resection of prostate surgeries. Sensory block characteristics were comparable and clinically effective in both groups. Time to achieve sensory block of T_{10} was shorter in Group B (10.98 min vs 11.27 min) than Group L. Time to two segment regression was 67.41 min in Group L and 64.16 min in Group B. At the beginning of operation, 3 patients who received bupivacaine-fentanyl had Bromage score of 3, but none of the patients had Bromage score of 3 in levobupivacaine-fentanyl group. This difference was statistically significant ($p = 0.042$). Bromage scores at the end of the surgery were comparable between the groups. Therefore the study concluded that for transurethral prostate surgery, 5 mg levobupivacaine with 25 mcg fentanyl can provide stable hemodynamics, patient and surgeon satisfaction and effective sensory blockade with less motor blockade in spinal anaesthesia; so it could be used at low doses as a good alternative to bupivacaine.[17]

Intrathecal levobupivacaine has been compared with ropivacaine in several obstetric studies for Caesarean section. When 6.6 mg of levobupivacaine was compared with a purported "equipotent" dose of 10 mg ropivacaine (both with sufentanil at 3.3 mcg), analgesic supplementation was still required with the ropivacaine group.[18] On the other hand, an intrathecal dose of 8 mg levobupivacaine was just as efficacious as 12 mg ropivacaine (both with 2.5 mcg sufentanil added). The differences may be explained by dosing closer to ED_{95} rather than ED_{50}.[19]

With levobupivacaine been tested and compared with bupivacaine and with ropivacaine for cesarean sections, the efficacy of ropivacaine had to be evaluated. A study was undertaken by Varun et al to compare the effect of intrathecal isobaric bupivacaine-fentanyl and isobaric ropivacaine-fentanyl with regards to sensory blockade, motor blockade and quality of analgesia in post-operative period for lower abdomen and lower limb surgeries. It was hypothesized that ropivacaine would provide similar anesthesia with less motor blockade as compared to bupivacaine. Group 1 received 3 ml 0.5% isobaric bupivacaine + 20mcg fentanyl. Group 2 received 3 ml 0.5 % isobaric ropivacaine + 20 mcg fentanyl. The time taken to achieve T_{10} (2. 10 ± 1.11 min in Group 1 and 2.56 ± 1.15 min in Group 2), T_8 and T_6 level of sensory block was significantly more ($p<0.05$) in Group 2 as compared to Group 1, but the sensory block level was comparable ($p=0.981$). Mean time taken to achieve maximum grade of motor blockade was also more Group 2 (4.06±1.62 min) than Group 1(3.00±1.29 min) ($p<0.001$). The sensory block regression to S_2 was faster in Group 2 (198.50±19.07 min) as compared to Group 1(212.90±40.50 min)($p=0.025$). Motor recovery was comparable in two groups (180.20±41.66 min in Group 1 and 173.00±17.76 min in Group 2) ($p=0.264$). The duration of analgesia was prolonged in Group 1 as compared to Group 2($p=0.027$). It was concluded that intrathecal

administration of ropivacaine-fentanyl has faster onset and regression of sensory block, delayed onset but comparable regression of motor block and shortened duration of analgesia as compared to intrathecal bupivacaine-fentanyl.[20]

In conclusion, there exist various studies comparing efficacy of ropivacaine-fentanyl and bupivacaine-fentanyl or studies comparing levobupivacaine-fentanyl with bupivacaine-fentanyl or with levobupivacaine at various doses but there are no studies comparing the efficacy of isobaric levobupivacaine-fentanyl and isobaric ropivacaine-fentanyl in spinal anesthesia.

These two new local anesthetics are being used very commonly with adjuvants in spinal anaesthseia. So there exists a knowledge gap with regards to these two drugs and hence our study is being undertaken to compare the combination of these drugs in spinal anesthesia.

BASIC SCIENCES

Subarachnoid block is the choice of anaesthesia when the surgery is to be performed on the lower extremities, perineum, or lower abdominal wall. Spinal anaesthesia causes motor, sensory and sympathetic blockade.

The main advantages of spinal anaesthesia are avoidance of poly-pharmacy and airway manipulation that accompany general anaesthesia. The other added benefits are reduction of metabolic stress response to surgery, reduction in blood loss, reduced incidence of venous thromboembolism, reduction in pulmonary compromise (particularly in patients with advanced pulmonary disease).

The absolute contraindications to spinal anaesthesia are patient refusal, lack of cooperation by patient, difficulties with positioning, and increased intracranial pressure. Other relative contraindications are spinal abnormalities, hypovolemia, coagulopathies, fixed cardiac output lesions, septicaemia, and local infection at the site of needle insertion. Allergy to local anaesthetics may also be a contraindication, but true allergies are usually found with ester-based local anaesthetics (tetracaine), not the amide-based local anaesthetics (bupivacaine, levobupivacaine and ropivacaine) that are more commonly used now-a-days.

ANATOMY

A detailed knowledge of anatomy of vertebral column, spinal cord and spinal nerves is essential to all the anaesthesiologists for safe and successful administration of spinal anaesthesia.

Vertebral column

The main function of the vertebral column is to protect the spinal cord (Figure 1). The vertebral column comprises of 33 vertebrae and includes[21]

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

Curves of spine

In adult, the vertebral column has four curves [21](Figure2) :

- Cervical and lumbar curve - Convex anterior
- Thoracic and sacral curve - Concave anterior

In adults the curves of the spine are important when patient is supine. The highest point of cervical and lumbar curves in supine position are at cervical (C) five and lumbar (L) five; lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively. The vertebral column curves, dose as well as the baricity of local anaesthetic and patient position determine the spread of local anaesthetic in the subarachnoid space.

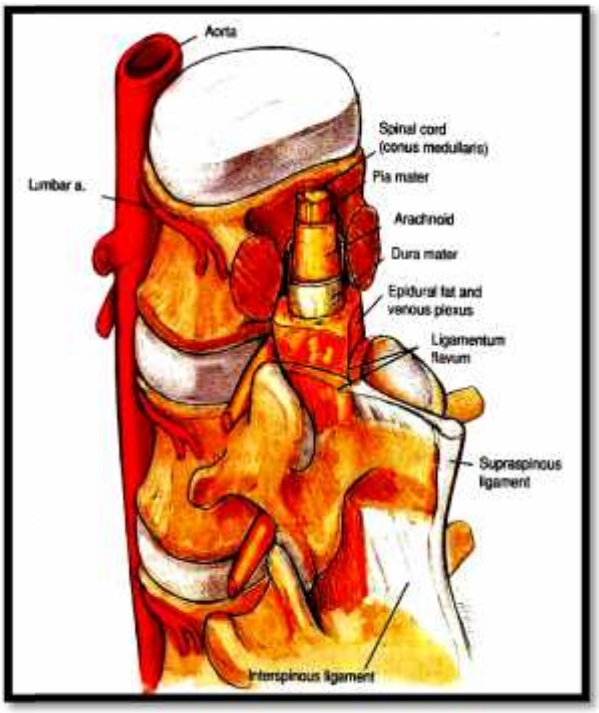


Figure 1: Vertebral Column

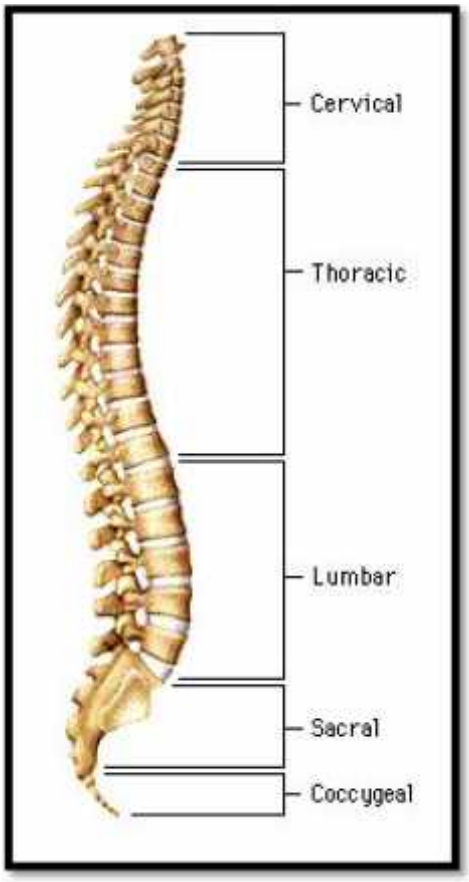


Figure 2 : Curves of the spine

Vertebral ligaments

Vertebral column is bound together by following ligaments which give stability and elasticity.

Supraspinous ligament: This is a strong fibrous cord which connects apices of spinous processes from the seventh cervical vertebra (C_7) to the sacrum. The supraspinous ligament is known as the ligamentum nuchae in the area above C_7

Interspinous ligament: This is a thin membranous ligament which connects spinous processes blending anteriorly with ligamentum flavum and posteriorly with supraspinous ligament (Figure 3).

Ligamentum flavum: This ligament comprises yellow elastic fibres and connects adjacent lamina. Laterally this ligament begins at the root of articular processes and extends posteriorly and medially to the point where laminae join to form spinous process (Figure 3).

Longitudinal ligaments:There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together (Figure 3).

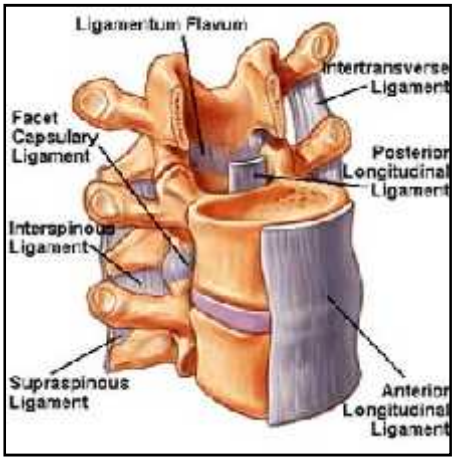


Figure 3: Spinal Ligaments

Lumbar vertebrae

A typical lumbar vertebra consists of (Figure 4);

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

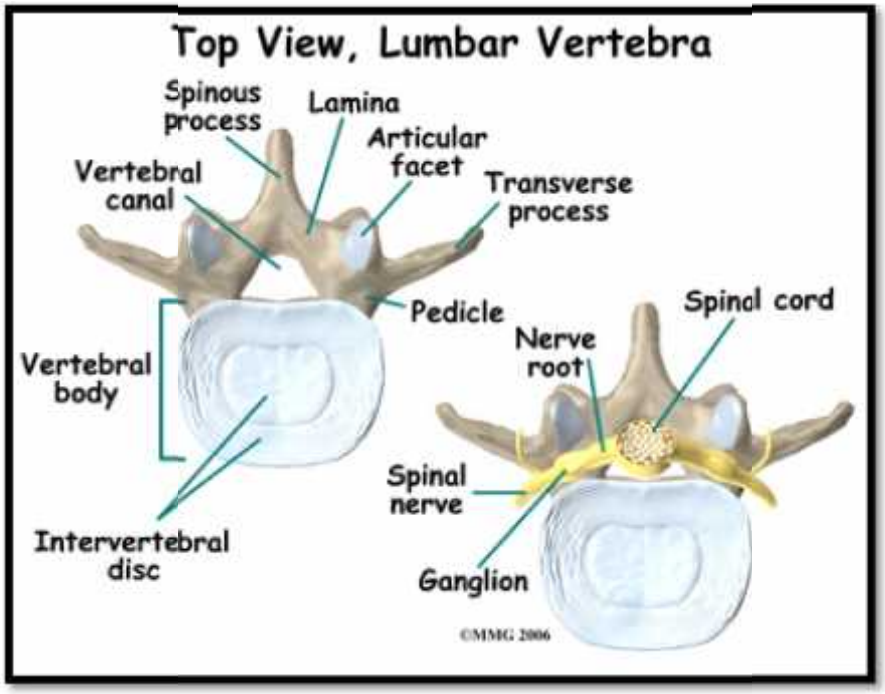


Figure 4 : Typical Lumbar Vertebra

Topographical Line of Tuffier[23]

An imaginary line that passes between the highest points of the iliac crests crossing the spine of the 4th lumbar vertebra in the upright position. In a patient lying

in the lateral position it may also pass through L_4 and L_5 interspaces. The superior iliac crest is used to identify the L_4 and L_5 interspace during spinal anaesthesia (Figure 5).

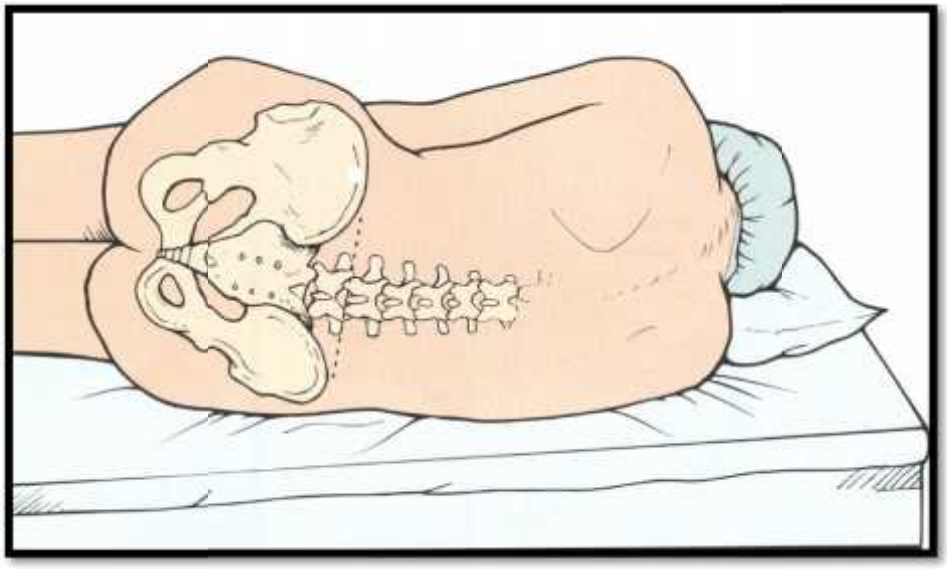


Figure 5: Line of Tuffier

Vertebral canal[7]

Vertebral canal is bound posteriorly by spinous processes and interspinous ligaments, laterally by the pedicles and posterolaterally by the laminae and ligamentum flavum. It terminates superiorly in the foramina magnum and inferiorly in the sacral hiatus. The vertebral canal contains the spinal cord, dorsal root ganglia and ventral rootlets, roots of the spinal nerves, sympathetic trunk, rami communicantes, adipose tissue, blood vessels, CSF and spinal membranes

Spinal cord[21]

The average length of the spinal cord in males is 45 centimeter (cm) and females it is 42 cm (Figure 6).

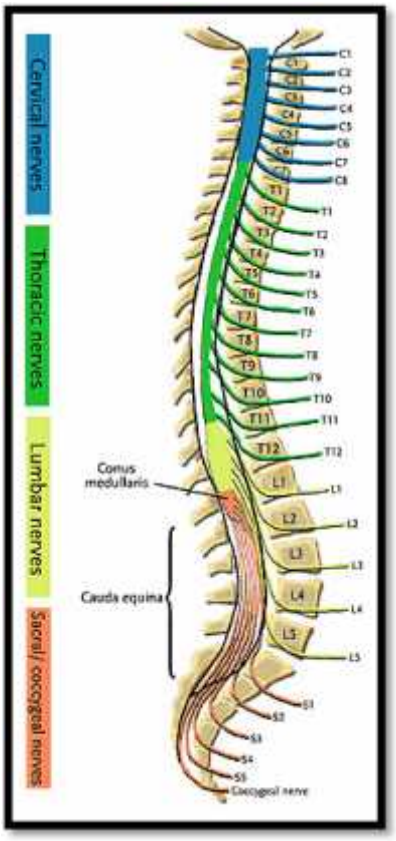


Figure 6: Spinal nerve roots

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. A delicate fibrous filament descends to the back of first segment of coccyx from apex of conus medullaris. This is known as the filum terminale, which is a continuation of the piamater. The length of the spinal cord differs according to age. In the first trimester, the fetal spinal cord extends up till the end of the spinal column. As the fetus grows, the vertebral column lengthens more than the spinal cord. At birth, the spinal cord ends approximately at L_3 space. In an adult it ends approximately at L_1 space.

Blood Supply of Spinal Cord[21]

The spinal cord receives blood supply from three arteries, one anterior and two posterior spinal arteries (Figure 7).

Anterior spinal artery is a single vessel lying in the substance of piamater overlying the anterior median fissure. It supplies the lateral and anterior columns, comprising three quarters of substance of the cord. Thrombosis of this artery causes anterior spinal artery syndrome.

There are two pairs of posterior spinal arteries, one pair on each side arising from posterior inferior cerebellar arteries at the level of foramen magnum. They supply posterior column of the cord.

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.

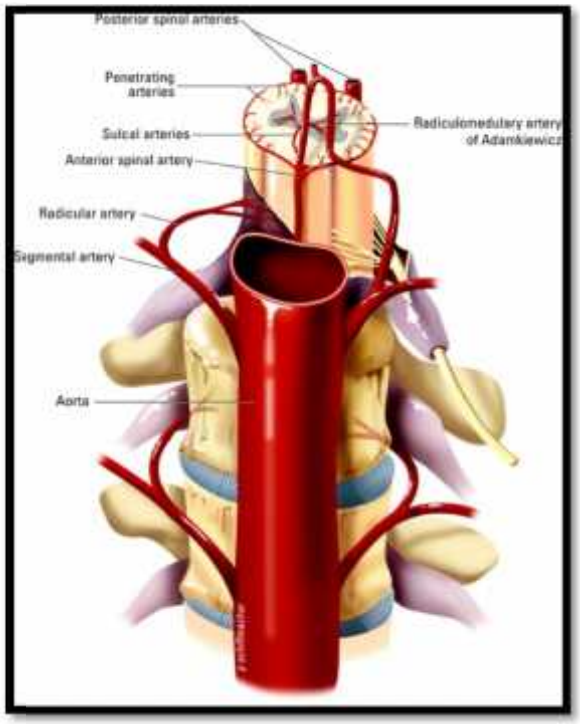


Figure 7: Blood Supply of Spinal Cord

Spinal Meninges[23]

Along with the bony vertebral column spinal cord is also protected with three connective tissue coverings called meninges.

Dura mater[24]

This is a tough outermost fibro-elastic covering consisting of outer endosteal layer and inner meningeal layer. Fibers of duramater run longitudinally, thus it is important to insert the spinal needle in such a way that its fibers are split and not cut. Dural sac ends at lower border of S_2, where it is pierced by filum terminale.

Arachnoid mater[24]

It is a delicate, non-vascular, middle covering and is closely attached to the duramater. There is a capillary interval or potential space between duramater and arachnoid mater called subdural space and contains serous fluid.

Pia mater[24]

The piamater, the innermost membrane is a vascular sheath which closely invests the brain and spinal cord. It continues till the coccyx as filum terminale.

Subarachnoid Space[24]

The space between the arachnoid and pia mater is called the subarachnoid space and is filled with cerebrospinal fluid and contains numerous arachnoid trabeculae which form delicate sponge like mass. This space has three divisions which are in free communication with each other: cranial (surrounding the brain), spinal (surrounding the spinal cord) and root (surrounding the dorsal and ventral nerve

roots). In the spinal cord these nerve roots are covered only by pia mater and bathed in CSF. As these spinal nerve roots pass beyond the spinal dura and traverse the epidural space, they carry with them all the three meningeal layers and have a distinct epidural, subdural, subarachnoid and sub pial spaces. The subarachnoid space extends separately along both the dorsal and ventral roots to the level of dorsal root ganglion, where arachnoid and pia continue as perineural epithelium of peripheral nerve.

Cerebrospinal Fluid[24]

It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles. CSF is mainly formed by either secretion or ultrafiltration from the choroidal plexus of lateral ventricles. CSF flows from the lateral ventricles into the third ventricle through the foramina of Monro into the fourth ventricle through the Aqueduct of Sylvius into the cerebro-medullary cisterna (cisterna magna) through foramen of Magendie and foramina of Luschka. From the cisterna magna, CSF enters subarachnoid space circulating around brain and spinal cord before being absorbed into the arachnoid granulations over the cerebral hemispheres.

Composition of cerebrospinal fluid

- Specific gravity : 1.003 to 1.009 at 37^0C.
- Volume : 120 ml to 150 ml (25 ml to 35ml in spinal space).
- CSF pressure : 60 to 80 mm Hg in lumbar space.
- pH : 7.27 to 7.37
- PCO_2 : 48 mm Hg
- HCO_3 : 23 mEq/Lt
- Sodium : 135 to 145 mEq/Lt
- Calcium : 2 to 3 mEq/Lt

- Phosphorous : 1.6 mg/dl
- Magnesium : 2 to 2.5 mEq/L
- Chloride : 15 to 20 mEq/L
- Proteins : 23 to 38 mg/dl

PHYSIOLOGY OF SUB ARACHNOID BLOCK

The various factors, which control the different effects of a spinal anaesthetic technique, are: [25]

- Amount and type of drug
- Volume of solution
- Site of injection
- Rate of injection
- Specific gravity of solution – density and baricity
- Barbotage

The various factors which affect the spread of local anaesthetics include: [26,27]

1) Patient factors:

- Age
- Height
- Position
- Spinal column configuration
- Cerebrospinal fluid volume

2) Technical factors

- Site of injection
- Direction of needle
- Local anaesthetic dose

- Local anaesthetic baricity
- Local anaesthetic volume

The nerve roots as well as spinal cord take up local anaesthetics after injection into the subarachnoid space. More the surface area of exposure of the nerve root, greater is the uptake. There are two mechanisms for uptake of local anaesthetics. The first mechanism is by diffusion from CSF to the pia mater and into the spinal cord. This is a slow process and only the most superficial portion of spinal cord is affected by it. The second method of local anaesthesic uptake is by extension into the spaces of Virchow- Robin, which are areas of pia mater that surround the blood vessels that penetrate the CNS. These spaces connect with perineuronal clefts that surround the nerve cell bodies in the spinal cord. The site of action is on both anterior and posterior nerve roots, affecting smaller nerve fibers first, and thick large motor fibers last. Generally, the sympathetic paralysis is more diffuse and will extend to two to four segments above motor block. The sympathetic fibers are affected first and are last to recover. On the other hand, motor nerve blockade is usually last to be affected and first to recover. [28]

Sequence of spinal anaesthesia (SA) [29]

- Vasomotor block: Dilatation of skin vessels and increase cutaneous blood flow
- Temperature fibers: Cold first and then warmth
- Loss of temperature discrimination
- Pain – pin prick fibers first
- Loss of tactile sensation
- Motor paralysis
- Pressure sensation
- Proprioception and vibratory sensation.

Sympathetic blockade is the major determinant of physiologic response to spinal anaesthesia.

Sympathetic blockade

Since the level of sympathetic denervation determines the magnitude of cardiovascular responses to subarachnoid block, it might be anticipated that the higher the level of neural blockade, the greater would be the change in the cardio-circulatory parameters. Sympathetic fibers are blocked usually two to three segments higher than sensory fibers and sensory block is two segments higher than motor block

Cardiovascular effects of spinal anaesthesia[27]

The autonomic denervation accompanying spinal block influences cardiovascular system in the following ways:

a. Vasodilatation of resistance and capacitance vessels.
b. Block of cardiac efferent sympathetic fibers from T_1-T_4 resulting in loss of chronotropic and inotropic drive and fall in cardiac output.
c. Bainbridge reflex causing bradycardia.
d. Depression of vascular smooth muscle and beta adrenergic blockade of myocardium with fall in cardiac output following systemic absorption of local anaesthetic drug.

Block extending above T_4 is associated with fall in BP. Slowing of HR is caused if any of anterior roots carrying sympathetic cardiac accelerator fibers are blocked as may happen in high spinals above T_4-T_5. Bradycardia may also be due to lowering of BP in the right atrium consequent to diminished venous return.

Theories of causation of hypotension.

a. Diminished cardiac output due to reduction of venous return

b. Dilatation of post arteriolar capillaries and small venules

c. Paralysis of sympathetic nerve supply to heart.

d. Paralysis of sympathetic nerve supply to adrenal glands with consequent catacholamines depletion.

Cerebral Blood Flow

Cerebrovascular autoregulatory mechanisms maintain cerebral blood flow in humans at constant levels.

Respiratory System

During spinal anaesthesia breathing becomes quiet and tranquil. This is not only due to motor blockade but also due to differentiation with reduction of sensory input to the respiratory center. The pulmonary gas-exchange is preserved. Intercostal paralysis is compensated for by increased descent of the diaphragm, which is made easier by a lax abdomen.

Gastrointestinal System

Pre-ganglionic sympathetic fibers from T_5-L_l are inhibitory to the gut. There is no effect on oesophagus, the innervation of which is vagal. The small gut is contracted as sympathetic inhibitory impulses are removed, the vagus being dominant. Pressure within the bowel lumen is increased. Nausea and vomiting occur due to hypotension. Relaxation of sphincters also occurs.

Causes of Nausea and Vomiting

- Hypotension
- Hypoxia
- Increased peristalsis
- Traction on nerve endings, especially vagus
- Presence of bile in stomach due to relaxation of pyloric sphincters
- Narcotic analgesics used in pre medication
- Psychological effects

Genitourinary System

Renal blood flow due to hypotension is decreased but does not cease until blood pressure has fallen to about 80 mm Hg. These changes are transient. The penis becomes engorged and flaccid due to paralysis of nervi erigenti (S_2 to S_3). Post spinal retention of urine may be moderately prolonged as S_2 to S_3 contain small autonomic fibers and their paralysis lasts longer that of larger sensory and motor fibers.

Uterus

The tone of uterus is not greatly altered after spinal analgesia in pregnancy..

Body Temperature

Vasodilatation favours heat loss, absence of sweating favours hyperpyrexia in hot environment, catacholamine secretion is depressed hence heat loss is prevented by metabolism. Spinal anaesthesia also reduces the threshold for shivering.

PHARMACOLOGY

Local anaesthetics are drugs that produce reversible blockade of conduction of nerve impulses.

The primary desirable properties of an ideal local anaesthetic agent are:

1. Short latency
2. High potency or anaesthetic activity
3. High diffusion
4. Low toxicity
5. Complete reversibility of action
6. Prolonged duration of action
7. No tachyphylaxis
8. Stability and ability to withstand heat sterilization

Classification:

Clinically useful agents can be classified into two groups depending on the link between the aromatic portion and the intermediate chain. The aminoester groups have an ester link and include procaine, chloroprocaine and amethocaine. The amino amides have an amide link between the aromatic head and the intermediate chain and include lignocaine, bupivacaine, levobupivacaine, mepivacaine, prilocaine, etidocaine and ropivacaine.

Levobupivacaine:[30]

Levobupivacaine hydrochloride is 2-piperidine carboxamide, 1 butyl N-2, 6 dimethyl phenyl, monohydrochloride, monohydrate. Levobupivacaine molecule is a tertiary amine separated from an aromatic ring system that is a benzene ring by an intermediate chain. The tertiary amine is a base that is a proton acceptor. The chain contains an amide linkage (-NHCO-) therefore; it is classified as an aminoamide compound. This amide linkage contributes to the anaesthetic potency.

The aromatic ring system gives a lipophilic character to its portion of molecule whereas; the tertiary amine end is relatively hydrophilic.

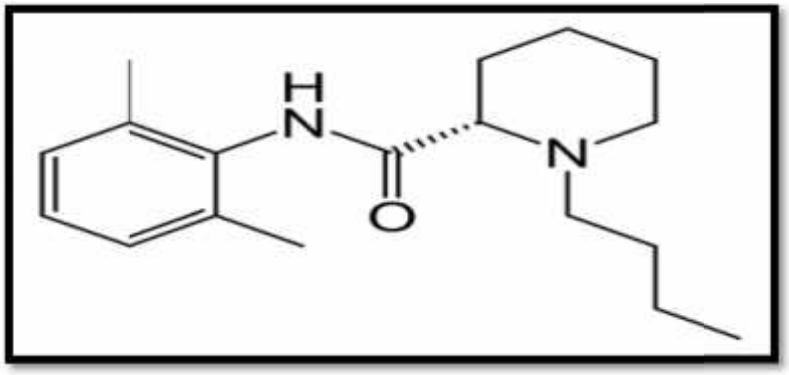


Figure 8: Chemical structure of levobupivacaine

Structure – Activity relationship

Levobupivacaine, being more lipophilic (because of butyl group), is very potent and produces longer lasting blocks. pKa of Levobupivacaine hydrochloride is 8.1 at 36ºC.

Anesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency and Levobupivacaine is highly hydrophobic, hence is very potent.

Onset of Action

The onset of conduction blockade is dependent on the dose or concentration of the local anesthetic

Differential Sensory Motor Blockade

Levobupivacaine in low concentration (0.125%) produces acceptable analgesia with only mild muscular weakness.

Pharmacokinetics[31]

The concentration of Levobupivacaine in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of absorption from the site of injection, the rate of tissue distribution and the rate of biotransformation and excretion of Levobupivacaine. Various studies have demonstrated that although the volume of distribution of levobupivacaine at steady state was significantly lower than that of dextrobupivacaine, its decreased toxicity was likely attributed to its increased protein-binding affinity, resulting in a smaller fraction of unbound drug, which causes a higher clearance and shorter elimination half-life. Levobupivacaine has a non-linear binding pattern, binding to both albumin (a low-affinity, high-capacity binding site) and α_1-acid glycoprotein (a high-affinity, low-capacity binding site) in plasma. At lower concentrations it is mainly bound to albumin; however, in higher concentrations there is a much greater affinity for α_1-acid glycoprotein.

Absorption

The site of injection, dose and addition of a vasoconstrictor determine the systemic absorption. The maximum blood level of Levobupivacaine is related to the total dose of drug administered from any particular site. Absorption is faster in areas of high vascularity.

Distribution

The two-compartment model can be used to describe distribution of the drug. The rapid distribution phase α is believed to be related to uptake by rapid equilibrating tissue i.e., tissues that have high vascular perfusion. The slow distribution phase β is mainly a function of distribution to slowly equilibrating tissue, biotransformation and excretion of the compound.

More highly perfused organs show higher concentrations of the drug. Though skeletal muscle does not show any particular affinity for Levobupivacaine it is the largest reservoir of the drug.

Clinical Pharmacology

1. Anaesthetic potency: Hydrophobicity is a major determinant of intrinsic anaesthetic potency and Levobupivacaine being highly hydrophobic, is very potent.
2. Onset of action: It depends on the pH of the drug and its concentration.
3. Differential sensory/motor blockade:

Factors influencing anaesthetic activity

1. ***Dosage of Levobupivacaine:*** As the dosage of Levobupivacaine is increased, the probability and duration of satisfactory anaesthesia increases and the onset of block is faster.

2. ***Addition of vasoconstrictors:*** Addition of adrenaline does not significantly increase the duration of action of Levobupivacaine.

3. ***Site of action:*** The latency and duration are prolonged when given for brachial block, epidural block and subarachnoid block.

4. ***Carbonation and pH adjustment:*** The success of any local anaesthetic depends upon the quantity of drug that can be absorbed on to the axon membrane of the target nerves. This in turn depends upon the ability of the drug to penetrate tissue barrier around the nerve. Alkalinisation of local anaesthetic solution improves the penetration and increases the availability of diffusible base of the local anaesthetic. When pH of the solution is equal to

pKa of local anaesthetic solution, one half of the drug is present as ionized water-soluble cation and the remaining half as lipid soluble unionized base This non-ionised soluble form is permeable to nerve cell membrane and it has a major role in diffusion.

Alkalinisation of local anaesthetic solution acts by

- A direct depressant effect of CO_2 on the axon.
    - Increased concentration of local anaesthetic inside the nerve trunk (diffusion trapping).
    - Converting local anaesthetic to the active cation through its effects on pH at the site of action inside the nerve.

The addition of sodium bicarbonate to levobupivacaine increases the pH of the solution without affecting its chemical stability.

Actions

Central Nervous System

Levobupivacaine readily crosses the blood brain barrier causing CNS depression following higher doses. The initial symptoms involve feeling of light-headedness, paraesthesia and dizziness followed by visual and auditory disturbances. Objective signs are usually excitatory in nature, which includes shivering, muscular twitches and tremors, initially involving muscles of the face (perioral numbness) and part of extremities. At higher doses cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from levobupivacaine, since an elevation

of $PaCO_2$ enhances cerebral blood flow, so that more anesthetic is delivered rapidly to the brain

Autonomic nervous system

Levobupivacaine does not inhibit Nor Adrenaline uptake and hence does not potentiate sympathetic effect. Myelinated preganglionic B fibers have a faster conduction and are more sensitive to action of Levobupivacaine. When used for conduction blockade, all local anesthetics, particularly Levobupivacaine produces higher incidence of sensory than motor fibers.

Cardiovascular System

The cardiovascular effects include negative inotropy, conduction disturbance (QRS complex widening and dysrhythmias), and death caused by pump failure and/or malignant dysrhythmias. It is thought that the cardiotoxic effects of bupivacaine arise as a result of blocking of sodium and potassium channels. In studying the toxicity of bupivacaine,the significance of chirality became evident. An isolated heart model showed that the two pure enantiomers (ropivacaine and levobupivacaine) have less myocardial depressant properties than racemic bupivacaine, with the pure R(+) bupivacaine enantiomer being the most cardiotoxic.

Respiratory System

Respiratory depression may be caused if excessive plasma level is reached which in turn results in depression of medullary receptor center. Respiratory depression may also be caused by paralysis of respiratory muscles of diaphragm as may occur in high spinal or total spinal anesthesia.

Biotransformation and Excretion

Levobupivacaine undergoes enzymatic degradation primarily in the liver. The excretion occurs primarily via the kidney. Renal perfusion and factors affecting urinary pH affect urinary excretion. Less than 5% of Levobupivacaine is excreted via the kidney unchanged through urine. The major portion of injected agent appears in urine in the form of 2, 6 pipecolyoxylidine which is a de-alkylated metabolite of Levobupivacaine. Renal clearance of the drug is related inversely to its protein binding capacity and pH of urine.

Adverse effects are encountered in clinical practice mostly due to overdose, inadvertent intravascular injection or slow metabolic degradation.

Adverse Effects

Central Nervous System: Nervousness, dizziness, blurring of vision or tremors, drowsiness, convulsions and respiratory arrest.

Cardiovascular System: Myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, SA node depression and cardiac arrest.

Allergic reactions: Urticaria, bronchospasm, hypotension.

Other: Constriction of pupil and tinnitus.

ROPIVACAINE[32]

Introduction

Ropivacaine is a new long acting local anaesthetic drug belonging to the amino amide group. Though it was synthesized by Ekenstam[36] in 1957 and belongs to

the pipecoloxylidides group of local anaesthetics. It was introduced to clinical practice in 1996.

It was found that "propyl derivatives" of pipecoloxylidides were less toxic than 'butyl derivatives' (bupivacaine). Despite being in the market for close to three decades internationally; it was only introduced into the Indian market very recently.

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

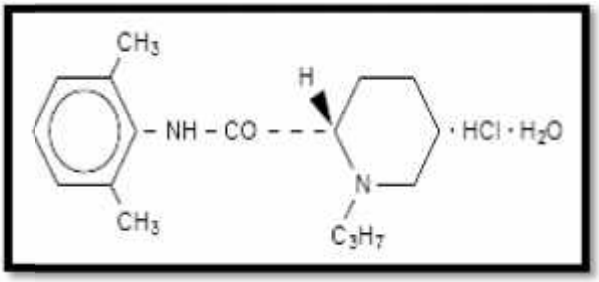


Figure 9 : Chemical structure of ropivacaine

Structure – Activity relationship

The pKa of ropivacaine is 8.07 which is approximately the same as bupivacaine (8.1). However, ropivacaine has a lower lipid solubility (substitution of pipecoloxylidine with a 3-carbon side chain instead of a 4–carbon side chain)[38] compared to bupivacaine and mepivacaine.

Most local anaesthetics block the unmyelinated C and myelinated Aδ fibers that transmit pain impulses at the same rate. However the rate of blockade of Aα and Aβ (that carry motor impulses) depends on the physiochemical properties, pKa and lipid solubility of the individual local anaesthetic drugs. As ropivacaine is less lipid

soluble when compared to bupivacaine , the blockade of Aα and Aβ is slow and hence produce less motor blockade than bupivacaine.

Pharmacokinetics [33]

Absorption

The systemic concentration of ropivacaine is dependent on the total dose, concentration of drug, the route of administration, the patient's hemodynamic condition and the vascularity of the site of administration

Distribution

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

Metabolism

Ropivacaine is extensively metabolized in the liver, predominantly by aromatic hydroxylation mediated by cytochrome $P450_{1A}$ to 3-hydroxy ropivacaine. After a single IV dose, approximately 37% of the total dose is excreted in the urine as both free and conjugated 3-hydroxy ropivacaine. Low concentration of 3-hydroxy ropivacaine has been found in the plasma. An additional metabolite, 2-hydroxy-methyl-ropivacaine has been identified but not quantified. N-de-alkylated metabolite of ropivacaine and 3OH-ropivacaine are the major metabolites excreted in urine during epidural infusion.

Elimination

Ropivacaine metabolites are mainly excreted via kidney. After i/v administration 86% of the dose is excreted in urine of which only 1% is in unchanged

form. Following i/v administration ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ± 1.6 L/min and a renal clearance of 1 mL/min. The mean ± SD terminal half-life is 1.8 ± 0.7 h and 4.2 ±1.0 h after i/v and epidural administration respectively.

Potency

Lipid solubility appears to be the primary determinant of intrinsic anaesthetic potency. Chemical compounds which are highly lipophilic tend to penetrate the nerve membrane more easily, so that fewer molecules are required for conduction blockade resulting in enhanced potency. Therefore a strict correlation exists between the lipid solubility of the local anaesthetic and its potency and toxicity.

Adverse effects

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

a. Cardiovascular system toxicity: Vasovagal reaction, syncope, postural hypotension, non-specific ECG abnormalities.

b. Central nervous system toxicity: Tremor, Horner's syndrome, dyskinesia, neuropathy, vertigo, convulsion and coma. Due to the depressant effect of ropivacaine on medulla, excitatory stage of CNS might not occur.

c. Liver and Biliary system toxicity: Jaundice

d. Metabolic disorders: Hypomagnesemia

e. Gastrointestinal system toxicity: Fecal incontinence, tenesmus, nausea, vomiting.

Advantages over other local anaesthetics

Ropivacaine produces a more differential blockade allowing better separation between sensory and motor block and hence a better choice for use in labour analgesia and post operative pain relief. When compared to bupivacaine it produces less motor blockade of shorter duration and hence permitting earlier mobilization and discharge. It has a low systemic toxicity than bupivacaine and a better cardiotoxic profile. Ropivacaine has been developed to offer a safer alternative to bupivacaine while retaining the desirable blocking properties of racemic bupivacaine.

FENTANYL[34]

Fentanyl was synthesized by Janssen Pharmaceutica in the year 1960 with the emphasis on potency and safety.

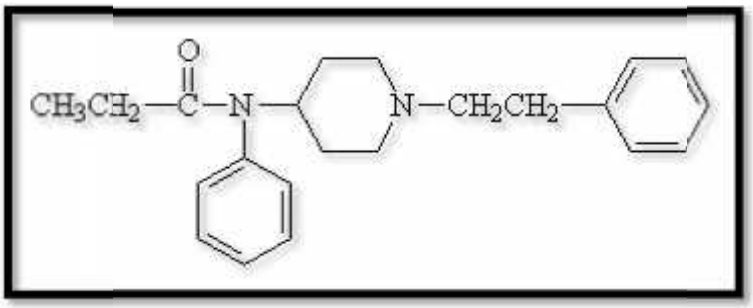


Figure 10: Chemical Structure of Fentanyl

Fentanyl citrate is a synthetic phenyl piperidine opioid analgesic and a chemical congener of the reversed ester of Pethidine (Meperidine)

Physiochemical properties

It occurs as a white crystalline powder. It is highly lipid soluble and sparingly soluble in water. The commercially available injections have a pH of 7 to 7.5. pKa value of 8.4. At physiologic pH of 7.4 less than 10% is unionized. Its plasma protein binding is 84%. It is 50 to 100 times more potent than Morphine. Injection should be protected from light and stored at 15 to 30° C. It is also available as intrabuccal, transdermal and aerosolized preparations.

Mechanism of action

Fentanyl is primarily a mu receptor agonist and these mu receptors are present in the brain (periaqueductal gray matter of brain stem, amygdala, corpus striatum and hypothalamus), spinal cord (substantia gelatinosa) and peripheral nerves. These receptors are involved with pain perception, integration of pain impulses and responses to pain.

Opioids act as agonists at stereospecific opioid receptors at pre-synaptic and post-synaptic sites. The most likely mechanism of these peripheral actions appears to be activation of opioid receptors on primary afferent neurons; Fentanyl mimics the actions of endogenous ligands by binding to receptors resulting in activation of pain modulating system. Opioid receptor activation leads to decrease in neurotransmission. This decrease occurs largely by presynaptic inhibition of neurotransmitter (acetylcholine, dopamine, norepinephrine, substance P) release.

Biochemical events on activation are increased potassium conductance leading to hyperpolarization and calcium channel inactivation or both. Fentanyl also binds to Kappa receptors to a lesser extent in the spinal cord and mediates sedation and miosis.

Pharmacokineties

Absorption

After I.V administration the onset of action is rapid with short duration of action. The effect site equilibration time between blood and the brain is 6.4 minutes.

Distribution

Fentanyl has high lipid solubility, so distributes widely throughout the body to inactive sites. Initially it distributes to vascular organs such as heart, lungs and brain, then to skeletal muscles and fat. Lungs also serve as inactive storage site with estimated 75% of initial dose undergoing first pass pulmonary uptake. Volume of distribution for Fentanyl after administration is 4 ± 0.4 Liters kg^{-1}.

Metabolism

- Fentanyl is extensively metabolized by N-demethylation producing Norfentanyl in the liver and hydrolysed to 4-N amilinopiperidine and proprionic acid.
- Lungs exert significant first pass effect and transiently take up 75% of injected dose of Fentanyl, 80% of Fentanyl is bound to plasma proteins, approximately 50% to α – acid glycoprotein.

Elimination

Fentanyl is excreted mainly in the urine as metabolite and less than 8% is excreted as unchanged drug. The mean clearance after i/v administration is between the range of 34-53 liters $hour^{-1}$ or approximately 13 ml min^{-1} kg^{-1}. Mean terminal half lives are between 2.5 and 8 hours. Context sensitive half life (After continuous infusion for 4 hours) is 260 minutes and this reflects saturation of inactive tissues during infusion and

Adverse Reactions

Cardiovascular system: Hypotension, orthostatic hypotension, syncope and drug induced bradycardia.

Respiratory System: Dose dependent depression of ventilation which is characterized by reduced response of ventilator centres to carbon dioxide.

Central nervous system: In the absence of hypoventilation, fentanyl decreases cerebral blood flow and in turn decreases intracranial pressure. Myoclonus during administration may resemble generalized tonic clonic seizures. It can produce thoracic and abdominal skeletal muscle rigidity. Miosis may occur as most of mu and kappa agonists cause constriction of pupil by an excitatory action on the parasympathetic nerve innervating the pupils.

It causes pruritus when administered for central neuraxial blockade. . Pruritus produced by neuraxial opioids is likely due to cephalad migration of opioids in cerebrospinal fluid and subsequent interaction with opioid receptors in trigeminal nucleus. Pruritus is more likely to be localized to face, neck and upper thorax.

Biliary system

It produces increase in biliary duct pressure and sphincter of oddi tone which are dose dependent.

Gastrointestinal system

It delays gastric emptying time and it can also produce nausea and vomiting by directly stimulating chemoreceptor trigger zone.

Immune system

The overall effect appears to be suppressive leading to increased susceptibility to infection.

Allergic reactions

True allergic and anaphylactoid reactions are rare. More commonly local reactions may occur due to preservatives or histamine release

Tolerance and physical dependence

Tolerance can occur without physical dependence but the reverse does not seem to occur. Cross tolerance develops between all the opioids.

METHODOLOGY

Study design

A one year hospital based randomized controlled clinical trial.

Study Period

One year from January 2014 to December 2014.

Place

The present study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, attached to Jawaharlal Nehru Medical College, Belagavi.

Source of Data

Patients aged between 18 to 65 years of either gender, belonging to ASA Grade I and II, scheduled for elective lower abdominal surgeries under spinal anaesthesia were studied.

Sampling procedure

Based on the results of previous studies considering onset of motor blockade 223 ± 86 minutes for Levobupivacaine and 173 ± 18 minutes for Ropivacaine-fentanyl and based on the statistical formula the sample size was calculated as below.

$$\text{Sample Size (n)} = \frac{2 \text{ X } (Z\alpha + Z\beta)^2 \text{ X } (S_1^2 + S_2^2)}{(\overline{X_1} - \overline{X_2})^2}$$

Taking the level of significance at 5 %(α=0.05), power of the test as 80%(β=0.2), and using one sided test we get Zα=1.65 and Zβ=0.84

S1 is S.D of Levobupivacaine[35]

S2 is S.D of Ropivacaine-Fentanyl[20]

X1 is duration of motor block in Levobupivacaine[35]

X2 is duration of motor block in Ropivacaine -Fentanyl group[20]

Hence, $Z\alpha = 1.65$

$Z\beta = 0.84$

$S_1 = 86$

$S_2 = 18$

$X_1 = 223$

$X_2 = 173$

With these values, the minimum sample size was obtained as 38.29 for each group. Hence the sample size was considered as 40 in each group.

Sample size :

Total sample size= 80 patients

- Levobupivacaine-fentanyl Group – 40
- Ropivacaine-fentanyl Group – 40

Randomization was achieved by computer generated randomization chart.

Selection criteria

Inclusion:

- Patients who underwent lower abdominal surgeries lasting for 60 to 120 min.
- Age: 18 to 65 years group
- ASA Grade I and Grade II patients
- Patients provided consent

Exclusion:

- Contraindications to sub-arachnoid block.
- Pre-existing neurological deficits in the lower extremities, and co-existing cardiovascular, respiratory, neurological, psychological, hepatic, or renal disease.

Ethical clearance

Prior to the commencement, the ethical clearance was obtained from Institutional Ethics Committee, Jawaharlal Nehru Medical College, Belagavi.

Informed Consent

The patients fulfilling selection criteria were briefed about the nature of the study and interventions and a written informed consent was obtained (Annexure I).

Data collection

Demographic data of the patients like name, age, sex and history was obtained through an interview. The physical and medical examination conducted. These findings were recorded on predesigned and pretested proforma (Annexure-II).

Procedure

Pre-anaesthetic Examination and Preparation

Overnight fasting status was confirmed. Anaesthetic techniques were standardized for all patients. Pre anaesthetic checkup was done one day prior to the surgery. Routine investigations such as Complete Blood Picture, Random Blood Sugar, Serum Creatinine, Blood Grouping and Typing, Chest X-ray, Electrocardiography were carried out.

Preparation of operation room

Anaesthesia machine was checked. Appropriate size endotracheal tubes, working laryngoscope with medium and large size blades, stylet and working suction apparatus were kept ready before the procedure.

Intervention

Group LF: Under strict aseptic precautions, patient in lateral decubitus position, L_{3-4} inter-spinous space was identified and a 23G Quincke's spinal needle was inserted into L_{3-4} Sub-arachnoid space (SAS). After confirming free flow of clear CSF, 3.0 ml (15.0 mg) of 0.5 % isobaric Levobupivacaine + 0.5 ml (25 mcg) fentanyl was injected.

Group RF: Under strict aseptic precautions, patient in lateral decubitus position, L_{3-4} inter-spinous space was identified and a 23G Quincke's spinal needle was inserted into L_{3-4} SAS. After confirming free flow of clear CSF, 3.0 ml (15.0 mg) of 0.5% isobaric Ropivacaine + 0.5 ml (25 mcg) fentanyl was injected.

Patient was turned immediately to supine position on the operating table after the administration of the drugs and monitored.

Outcome variables

Sensory block was assessed using alcohol swab in mid-axillary line. T_{10} was taken as the level for onset of sensory blockade and recovery time for sensory blockade was defined as two dermatome regression of anaesthesia from the highest level achieved. When sensory levels were not equal bilaterally, the higher level was used for statistical analysis .The operation was allowed to start once sensory block reached at least T_{10} but general anaesthesia was induced if this did not occur after 20 minutes.

Motor block was assessed immediately after sensory block assessment using a Modified Bromage scale.

Bromage 0:- Free movement of legs and with ability to raise extended leg.

Bromage 1:-Inability to raise extended leg and knee flexion is decreased, but full flexion of ankle and feet is present.

Bromage 2:-Inability to raise leg or flex knees, flexion of ankle and feet present.

Bromage 3:-Inability to raise leg, flex knee or ankle or move toes.

Motor block onset was taken as the time to reach modified Bromage score 3 and total duration of motor block was taken as the time for return to modified Bromage score 0.

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

The end of the study period was defined as the longer of the times at which the sensory block would regress below the T_{10} dermatome or at which Bromage score would be 0.

Any complications associated with these drugs if seen were noted.

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

Hypotension was defined as decrease in systolic B.P by 20% from baseline values or a systolic B.P less than 90 mm of Hg and was treated with incremental intravenous boluses of ephedrine 5 to 10 mg and a bolus administration of 250 ml of Ringer Lactate solution over 10 minutes.

Bradycardia was defined as decrease in heart rate less than 50 beats per minute and was treated with intravenous Atropine 0.6 mg.

Supplementary oxygen was given through face mask.

Statistical Methods

The data was tabulated and master chart was prepared (Annexure IV). The categorical data was expressed as rates, ratios and percentages and the continuous data was expressed as mean ± standard deviation Significance was assessed at five percent level of significance. Student unpaired‘t’ test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups. Chi-square test was used to find association between the classes of variables.

RESULTS

This one year clinical trial was conducted in the Department of Anaesthesiology, during the period of January 2014 to December 2014 at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi attached to Jawaharlal Nehru Medical College, Belagavi.

A total of 80 patients undergoing lower abdominal surgeries under spinal anaesthesia were randomly allocated into one of the two groups by computer generated randomization:

- Group LF (n=40) Patients received 3 ml of 0.5 % isobaric levobupivacaine + 0.5 ml (25 mcg) fentanyl intrathecally.
- Group RF (n=40) Patients received 3 ml of 0.5 % isobaric ropivacaine + 0.5 ml (25 mcg) fentanyl intrathecally.

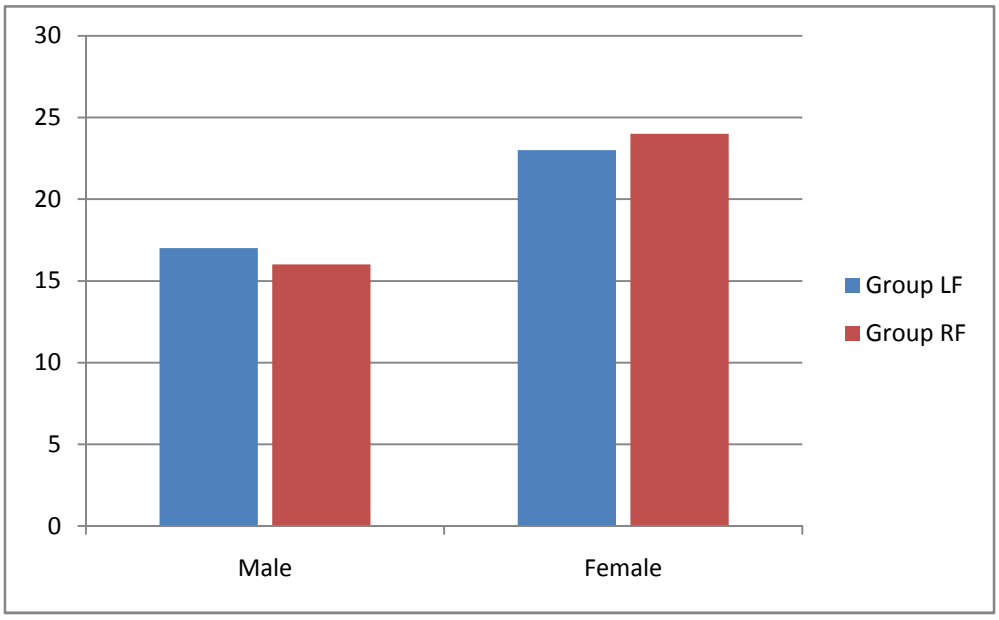
Data obtained was coded and analyzed as below.

Table 1: Sex Distribution

Sex	Group LF (n=40)		Group RF (n= 40)	
	Number	Percent	Number	Percent
Female	23	57.5	24	60
Male	17	42.5	16	40
Total	40	100.00	40	100.00

$\chi^2 = 0.052$ p=0.820

Graph 1: Sex Distribution



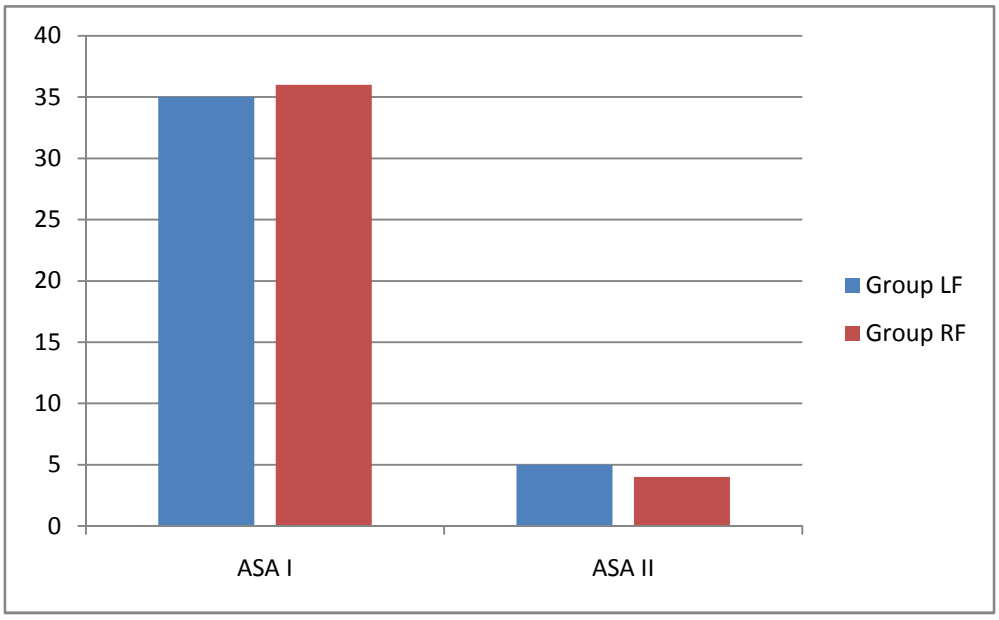
In this study 42.5% were males and 57.5% were females in group LF and 40 % were males and 60 % were females in group RF, suggesting both the groups had comparable demographic characteristics (p=0.820).

Table 2: ASA grade

ASA grade	Group LF (n=40)		Group RF (n=40)	
	Number	Percent	Number	Percent
Grade I	35	87.5	36	90
Grade II	5	12.5	4	10
Total	40	100	40	100

x^2=0 p=1

Graph 2: ASA Grade

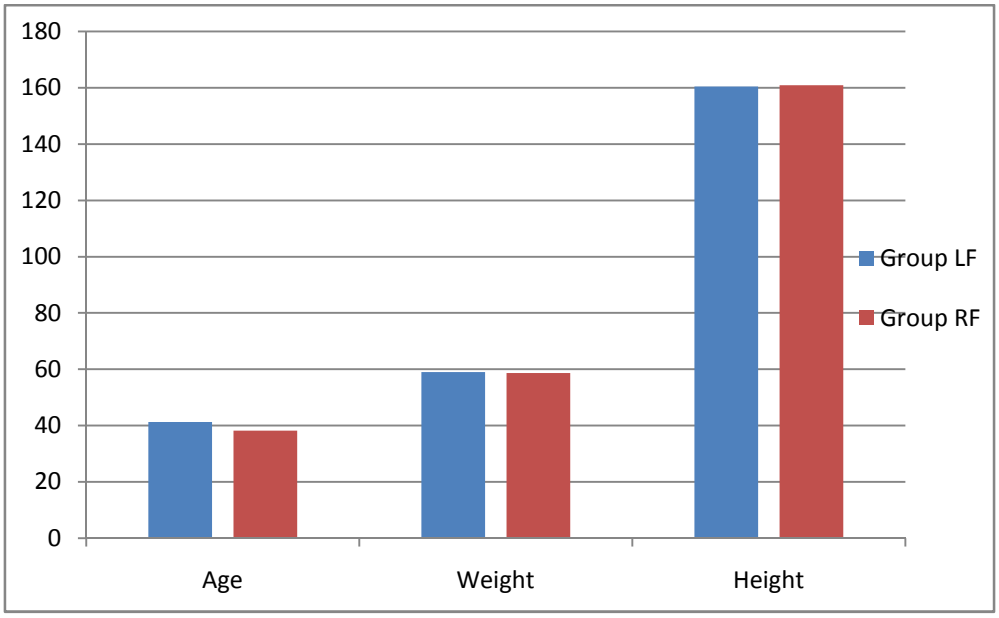


In Group LF, 87.5 % patients were ASA Grade I and 12.5 % were ASA Grade II. In Group RF, 90 % patients were ASA Grade I and 10 % were ASA Grade II, suggesting that ASA Grades in both groups were comparable (p=1).

Table 3: Mean age, weight and height

Parameters	Group LF		Group RF		p value
	Mean	Standard deviation	Mean	Standard deviation	
Age (years)	41.30	12.09	38.23	13.87	0.29
Weight (kgs)	59.03	8.25	58.68	7.64	0.84
Height (cms)	160.45	6.93	160.88	6.31	0.77

Graph 3: Mean age, weight and height

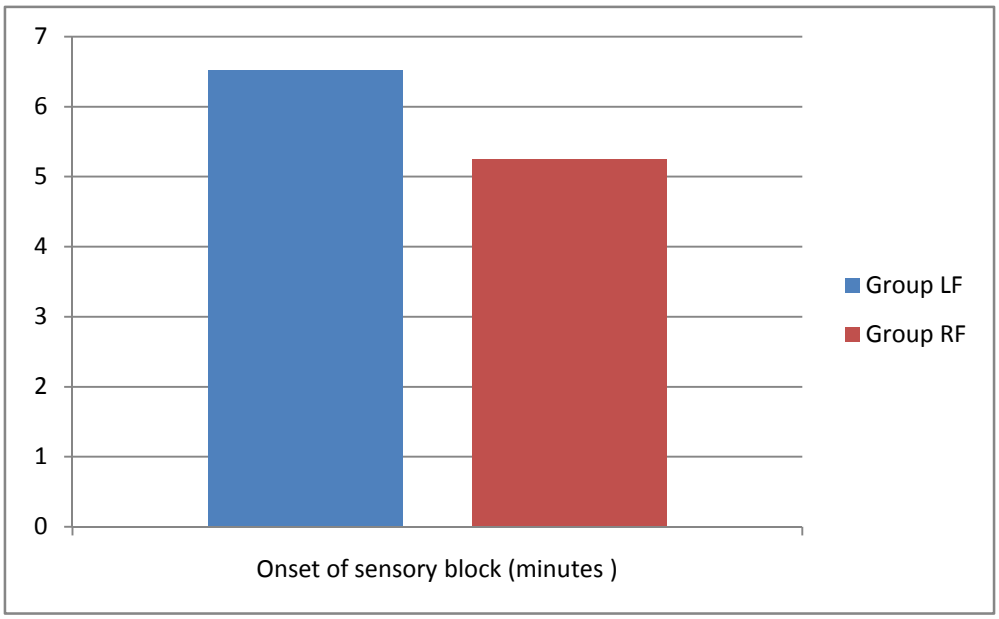


In the present study no statistically significant difference was observed between group LF and group RF with regards to mean age (41.30 ± 12.09 and 38.23 ± 13.87 years respectively; p = 0.29), mean weight (59.03 ± 8.25 and 58.68 ± 7.64 kg respectively; p = 0.84) and mean height (160.45 ± 6.93 and 160.88 ± 6.31 cm respectively; p = 0.77)

Table 4: Onset and duration of sensory block

Group	Onset (minutes)		Duration(minutes)	
	Mean	Standard deviation	Mean	Standard deviation
Group LF	6.53	0.51	169.5	7.15
Group RF	5.25	0.74	144.25	5.94
p value	< 0.001		< 0.001	

Graph 4: Onset of sensory block



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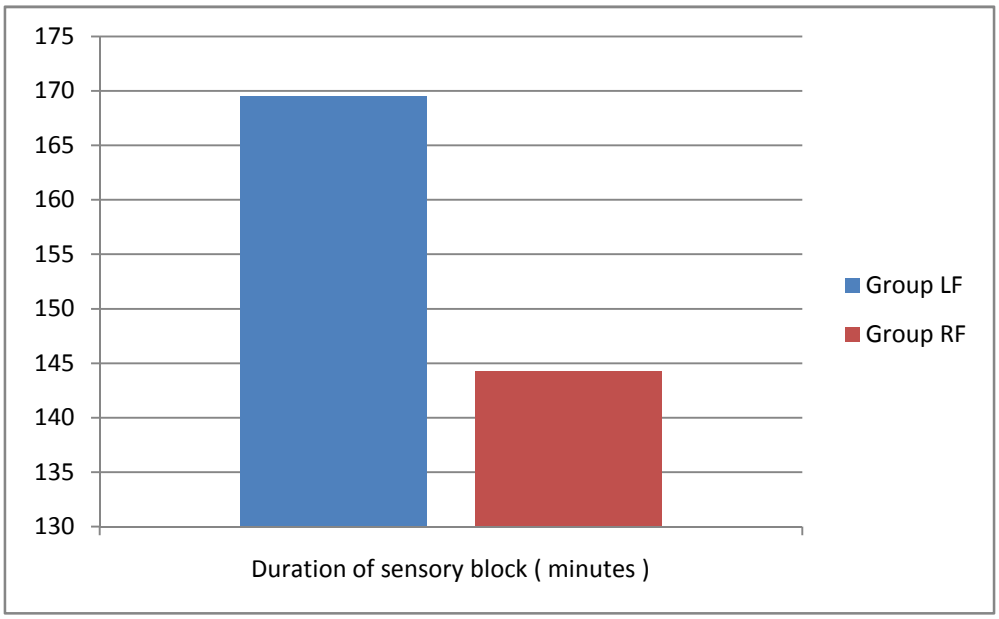
Graph 5: Duration of sensory block



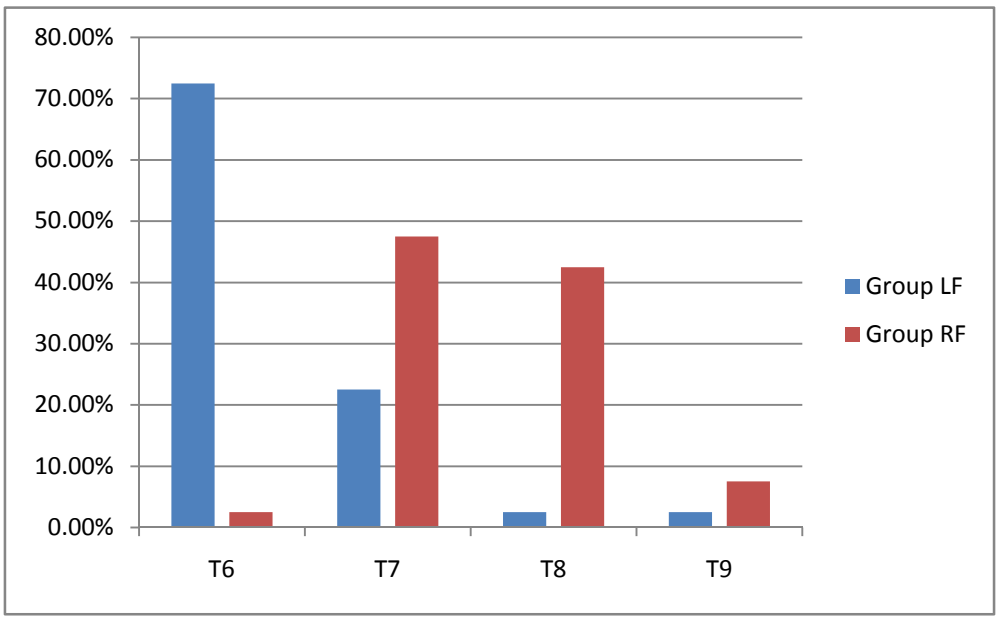
In the present study, mean onset of sensory block was faster in Group RF (5.25 ± 0.74 min) than in Group LF (6.53 ± 0.51 min) and was statistically significant (p value < 0.001) The mean duration of sensory block was longer in Group LF (169.5 ± 7.15 min) than in Group RF (144.25 ± 5.94 min) and was statistically significant (p value < 0.001).

Table 5: Highest sensory dermatome block level

Highest Sensory block level	Group LF		Group RF	
	Number	Percentage	Number	Percentage
T_6	29	72.5	1	2.5
T_7	9	22.5	19	47.5
T_8	1	2.5	17	42.5
T_9	1	2.5	3	7.5

$x^2 = 44.93$ $p < 0.001$

Graph 6: Highest sensory dermatome block level

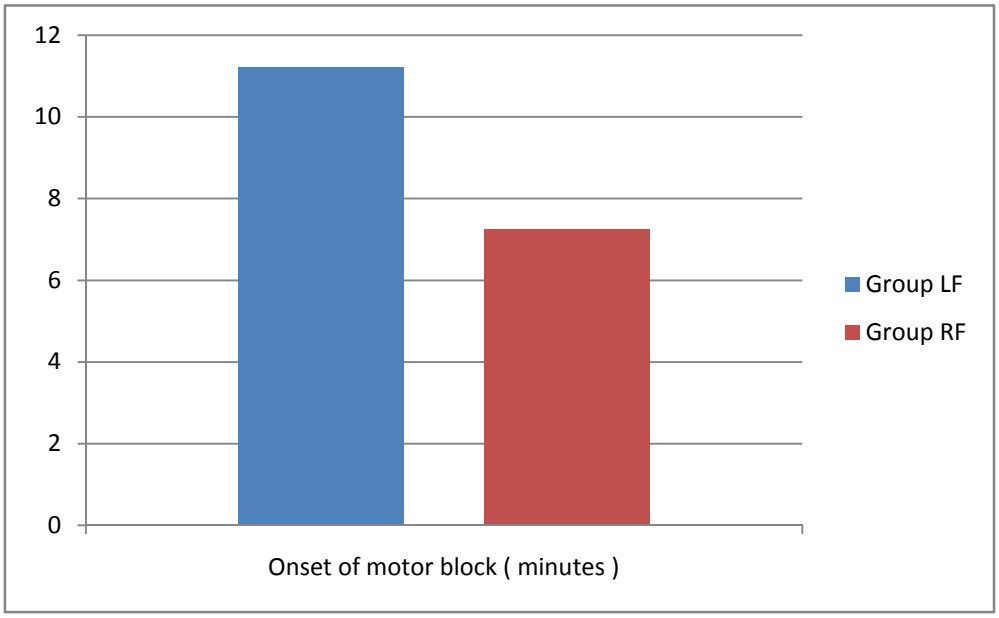


In the present study higher number of patients were noted with T_6 sensory dermatome level block in group LF (72.5%) compared to group RF (2.5%) and was statistically significant (p value < 0.001).

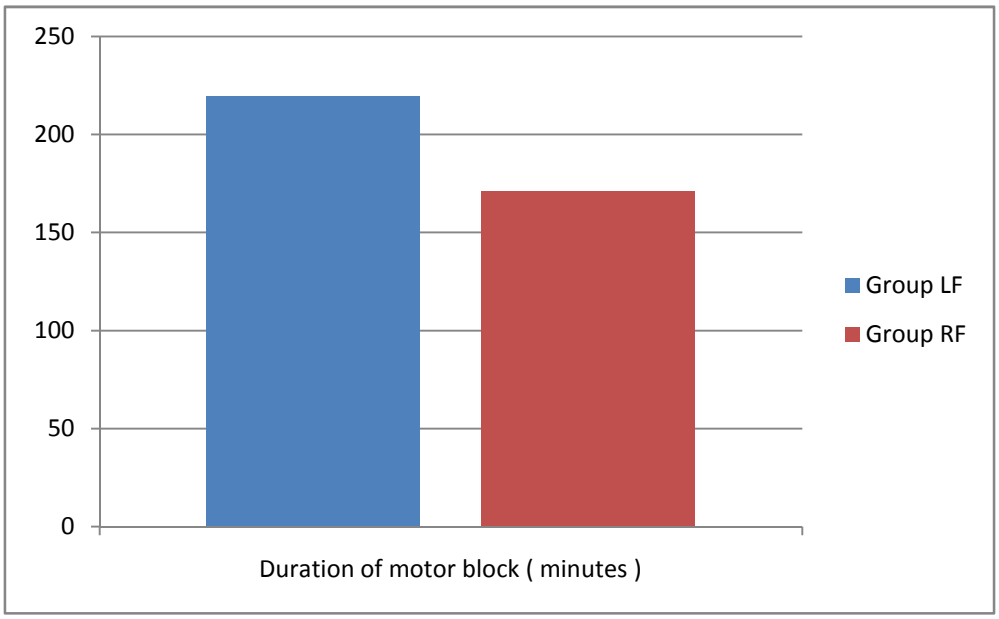
Table 6: Onset and duration of motor block

Group	Onset (minutes)		Duration(minutes)	
	Mean	Standard deviation	Mean	Standard deviation
Group LF	11.2	0.61	219.5	6.39
Group RF	7.25	0.98	171.25	7.23
p value	< 0.001		< 0.001	

Graph 7: Onset of motor block



Graph 8: Duration of motor block

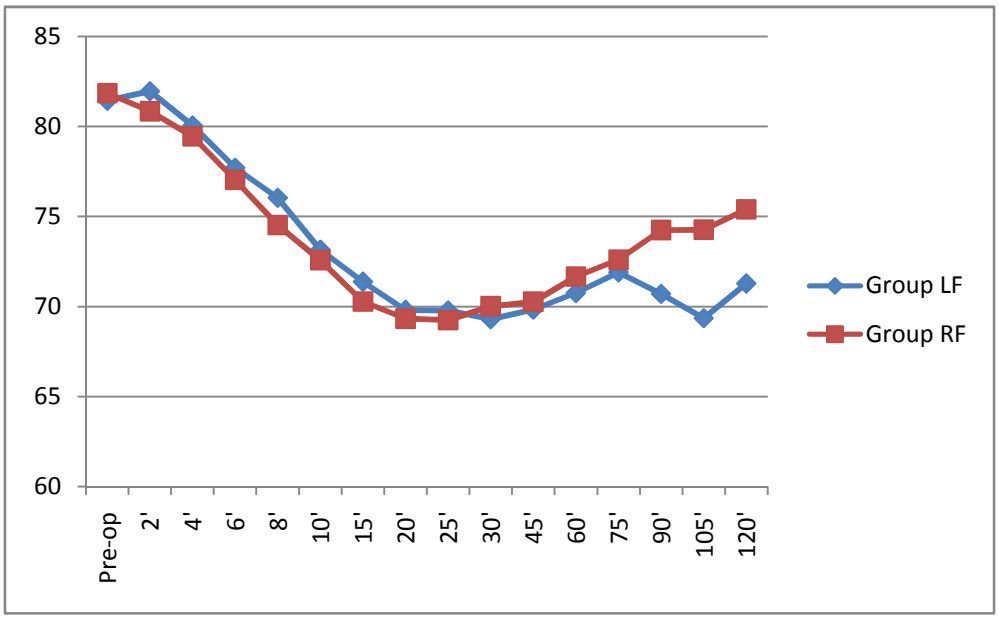


In the present study, mean onset of motor block was faster in Group RF (7.25 ± 0.98 min) than in Group LF (11.2 ± 0.61 min) and was statistically significant (p value < 0.001) The mean duration of motor block was longer in Group LF (219.5 ± 6.39 min) than in Group RF (171.25 ± 7.23 min) and was statistically significant (p value < 0.001).

Table 7: Comparison of mean heart rate at different intervals (bpm)

Intervals	Group LF (n=40)		Group RF (n=40)		p value
	Mean	SD	Mean	SD	
Pre op	81.43	8.18	81.85	8.78	0.82
2 Minutes	81.95	9.00	80.85	9.08	0.59
4 Minutes	80.05	9.53	79.45	8.87	0.77
6 Minutes	77.70	9.38	77.03	9.17	0.75
8 Minutes	76.03	9.00	74.53	8.89	0.46
10 Minutes	73.15	8.76	72.58	8.27	0.76
15 Minutes	71.38	8.95	70.28	7.98	0.56
20 Minutes	69.80	8.47	69.33	7.53	0.79
25 Minutes	69.78	8.31	69.25	7.71	0.77
30 Minutes	69.30	7.62	70.02	7.09	0.89
45 Minutes	69.83	7.28	70.27	6.62	0.98
60 Minutes	70.75	8.38	71.67	6.88	0.60
75 Minutes	71.90	10.83	72.6	6.91	0.52
90 Minutes	70.70	9.56	74.25	6.69	0.25
105 Minutes	69.35	8.76	74.27	7.20	0.89
120 Minutes	71.28	7.45	75.4	6.55	0.98

Graph 9: Comparison of mean heart rate at different intervals (bpm)

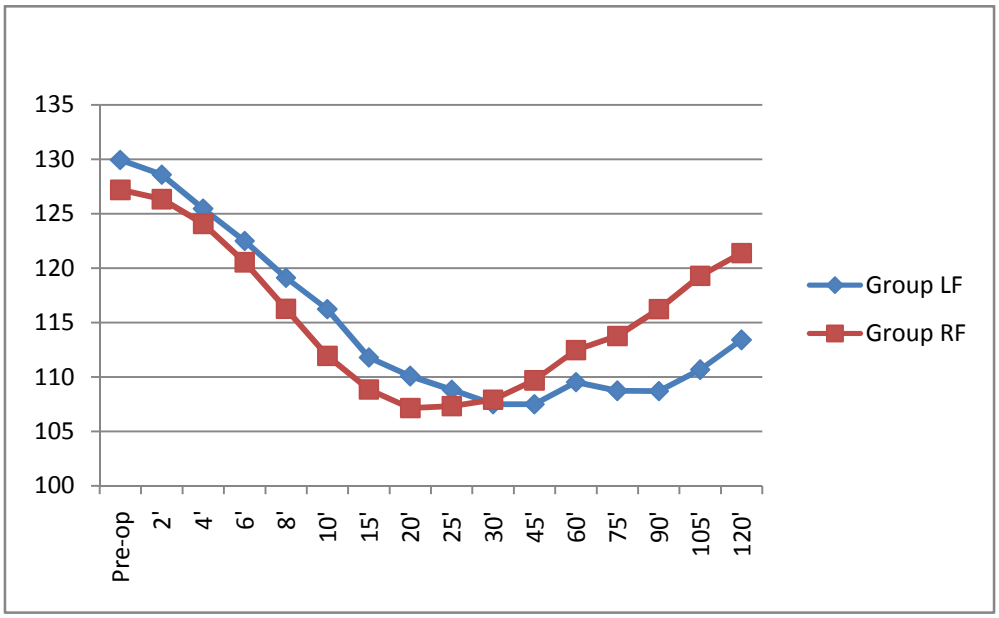


In this study the mean heart rate in group LF at beginning was noted as 81.43 ± 8.18 bpm which decreased to 70.75 ± 8.38 bpm at 60 minutes interval and reached 71.28 ± 7.45 bpm at 120 minutes. In group RF, the mean heart rate at beginning was 81.85 ± 8.78 bpm which reduced to 71.67 ± 6.88 bpm at 60 minutes interval and reached 75.4 ± 6.55 at 120 minutes. However at all the intervals the mean heart rate in group LF and RF was comparable ($p > 0.05$)

Table 8: Comparison of mean systolic blood pressure at different intervals (mm Hg)

Intervals	Group LF (n=40)		Group RF (n=40)		p value
	Mean	SD	Mean	SD	
Pre op	129.95	8.39	127.20	9.15	0.16
2 Minutes	128.60	8.15	126.35	8.95	0.24
4 Minutes	125.48	7.51	124.08	9.38	0.46
6 Minutes	122.50	7.27	120.55	9.16	0.29
8 Minutes	119.13	8.16	116.27	9.38	0.15
10 Minutes	116.25	8.38	111.95	9.03	0.03
15 Minutes	111.80	7.58	108.85	8.08	0.09
20 Minutes	110.08	7.10	107.15	7.06	0.06
25 Minutes	108.83	10.60	107.33	6.73	0.33
30 Minutes	107.50	14.31	107.92	6.63	0.97
45 Minutes	107.65	12.91	109.70	6.13	0.47
60 Minutes	109.53	12.88	112.48	5.90	0.32
75 Minutes	108.73	11.16	113.78	5.42	0.79
90 Minutes	108.72	10.30	116.25	5.78	0.70
105 Minutes	110.67	6.66	119.3	5.91	0.69
120 Minutes	113.40	8.73	121.4	5.52	0.83

Graph 10: Comparison of mean systolic blood pressure at different intervals (mm Hg)

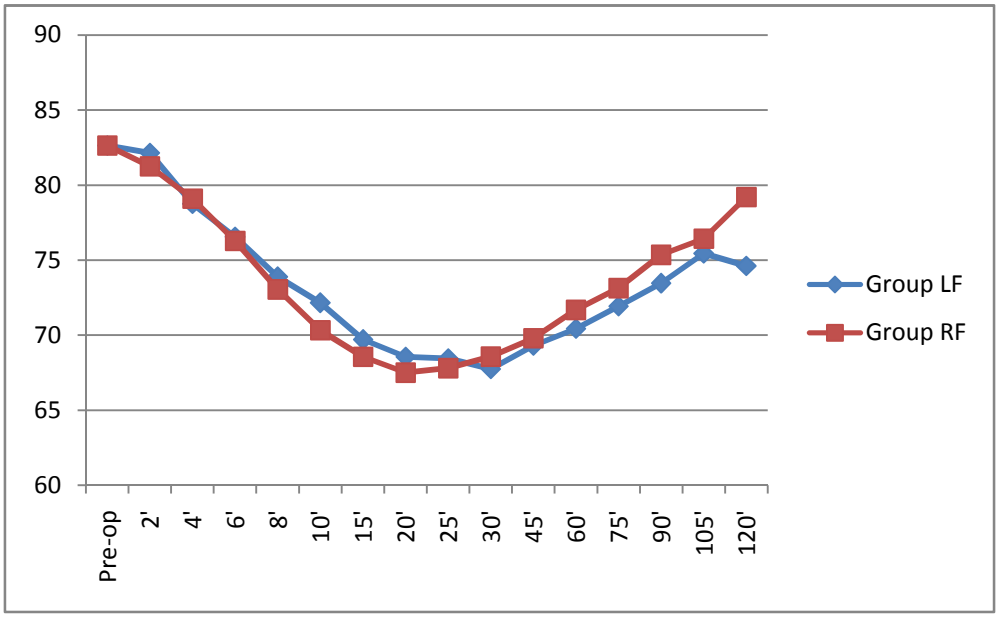


In this study, the mean systolic blood pressure in group LF, at two minutes interval was 128.60 ± 8.15 mm Hg which decreased to 116.25 ± 8.38 mm Hg at 10 minutes interval and reached 113.40 ± 8.73 mm Hg at 120 minutes. Similarly, in group RF, the systolic blood pressure at two minutes interval was 126.35 ± 8.95 mm Hg which decreased to 111.95 ± 9.03 mm Hg at 10 minutes interval and reached 121.40± 5.52 mm Hg at 120 minutes. However the mean systolic blood pressure at all the intervals in group LF and RF were comparable ($p > 0.05$) except at 10 minutes duration when it was significant. (p value = 0.03)

Table 9: Comparison of mean diastolic blood pressure at different intervals (mm Hg)

Intervals	Group LF (n=40)		Group RF (n=40)		p value
	Mean	SD	Mean	SD	
Pre op	82.63	7.15	82.63	8.78	1.00
2 Minutes	82.15	6.78	81.25	8.34	0.60
4 Minutes	78.75	6.88	79.1	8.04	0.83
6 Minutes	76.55	6.96	76.28	7.62	0.87
8 Minutes	73.88	6.73	73.05	6.94	0.59
10 Minutes	72.15	5.94	70.33	6.60	0.19
15 Minutes	69.70	5.29	68.55	6.17	0.37
20 Minutes	68.56	5.49	67.50	6.56	0.44
25 Minutes	68.45	5.91	67.80	6.10	0.63
30 Minutes	67.75	5.89	68.57	5.91	0.53
45 Minutes	69.30	4.91	69.80	5.70	0.69
60 Minutes	70.43	4.47	71.68	5.19	0.25
75 Minutes	71.93	4.73	73.13	4.63	0.25
90 Minutes	73.45	5.06	75.35	4.12	0.07
105 Minutes	75.45	4.56	76.43	5.24	0.43
120 Minutes	74.61	4.27	79.20	6.38	0.06

Graph 11: Comparison of mean diastolic blood pressure at different intervals (mm Hg)

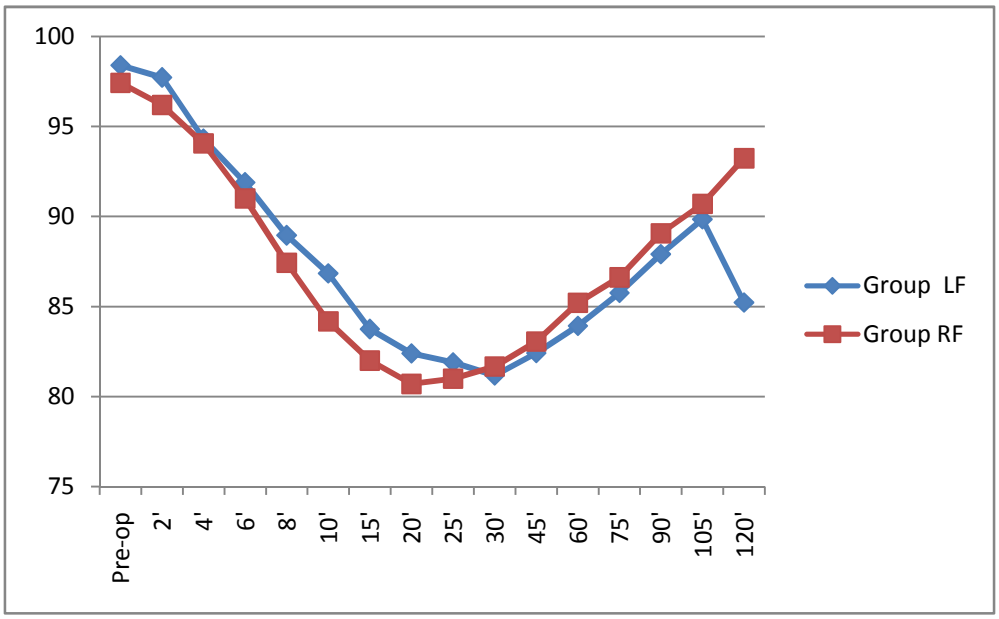


In the present study, preoperatively the mean diastolic blood pressure in group LF and RF was almost similar and hence statistically not significant (82.63 ± 7.15 and 82.63 ± 8.78 mm Hg respectively; p = 1). There was a decrease in mean diastolic blood pressure at 30 minutes interval that is, 67.75± 5.90 mm Hg in group LF and 68.57 ± 5.91 mm Hg in group RF but this difference was statistically not significant (p = 0.53). Further at 120 minutes also the mean diastolic blood pressure in group LF and RF were comparable (74.61 ± 4.27 and 79.20 ± 6.38 mm Hg respectively; p = 0.06).

Table 10: Comparison of mean MAP at different intervals (mm Hg)

Intervals	Group LF (n=40)		Group RF (n=40)		p value
	Mean	SD	Mean	SD	
Pre op	98.40	6.71	97.42	8.42	0.57
2 Minutes	97.71	6.61	96.19	8.00	0.36
4 Minutes	94.33	6.43	94.06	8.07	0.87
6 Minutes	91.88	6.46	91.00	7.70	0.58
8 Minutes	88.95	6.58	87.43	7.21	0.33
10 Minutes	86.84	6.03	84.18	6.88	0.06
15 Minutes	83.74	5.41	82.00	6.35	0.19
20 Minutes	82.40	5.30	80.70	6.36	0.20
25 Minutes	81.90	5.75	80.99	5.86	0.53
30 Minutes	81.17	6.43	81.67	5.83	0.69
45 Minutes	82.41	4.88	83.06	5.56	0.57
60 Minutes	83.93	4.73	85.20	4.98	0.24
75 Minutes	85.76	4.63	86.62	4.61	0.41
90 Minutes	87.91	5.17	89.06	4.34	0.28
105 Minutes	89.84	4.31	90.70	4.82	0.46
120 Minutes	85.22	4.08	93.23	5.84	0.15

Graph 12: Comparison of mean MAP at different intervals (mm Hg)



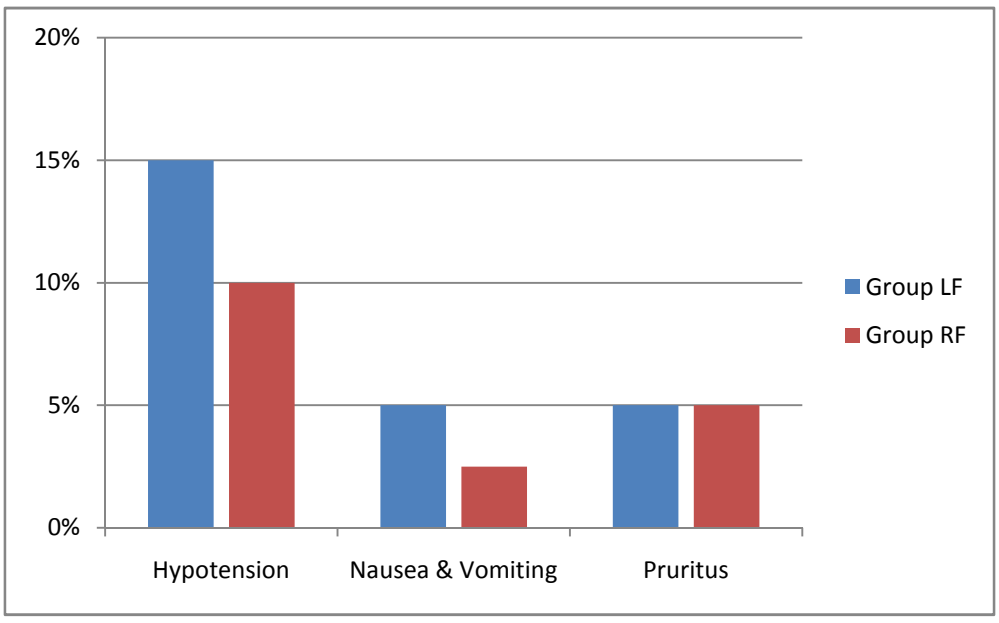
In the present study, preoperatively the mean MAP in group LF and RFwas almost similar and hence statistically not significant (98.40 ± 6.71 and 97.42 ± 8.42 mm Hg respectively ; p value = 0.57). There was a decrease in mean MAP at 30 minutes interval , 81.17 ± 6.43 mm Hg in group LF and 81.67 ± 5.83 mm Hg in group RF but this difference was statistically not significant (p = 0.69). Further at 120 minutes also the mean MAP in group LF and RF were comparable (85.22 ± 4.08 and 93.23 ± 5.84 mm Hg respectively; p = 0.15).

Table 11: Complications/ Side – Effects observed

	Group LF (n=40)	Percentage	Group RF (n=40)	Percentage
Hypotension	6	15	4	10
Nausea & Vomiting	2	5	1	2.5
Pruritus	2	5	2	5
Bradycardia	-		-	
Sedation	-		-	
Shivering	-		-	

In 15% of the cases in group LF and 10% of the cases in group RF, hypotension was observed. Other incidences observed were nausea and vomiting and pruritus in the two groups.

Graph 13: Complications / Side Effects observed



DISCUSSION

Spinal administration of local anaesthetics is the choice of anaesthesia technique for surgeries of lower abdomen, pelvis and lower limbs. Spinal anaesthesia has a quick onset, provides good relaxation with adequate sensory blockade. Hence it is one of the most commonly performed anaesthetic procedures in today's times.

With the advancement of technology and availability of better equipment, surgeries have become faster. However the patient's safety has always been the primordial importance. Hence research and development in the field of pharmacology has been encouraged for the discovery of newer, safer and better drugs.

Bupivacaine, the most commonly used local anaesthetic in spinal anaesthesia, is as a racemic mixture (50:50) of its two enantiomers, levobupivacaine, S (−) isomer and dextrobupivacaine, R (+) isomer. Adverse reactions involving central nervous system and cardiovascular system have been reported in literature. These adverse reactions have been attributed to the R (+) isomer of bupivacaine. The levorotatory isomer has a safer pharmacological profile. The decreased toxicity of levobupivacaine is due to its faster protein binding rate.

The pure S (−) enantiomer of bupivacaine, levobupivacaine, and pure S (−) enantiomer of propivacaine, ropivacaine, have thus been introduced into clinical practice. Levobupivacaine has been recently introduced in India and is being widely used. Hence an increased usage mandates documentation of evidence based literature with the risks, safety concerns and clinical issue related to levobupivacaine.[31]

Ropivacaine is a well-tolerated local anaesthetic effective for surgical anaesthesia. It has a high pKa and low lipid solubility. Hence it blocks Aδ and C fibres (pain fibres) to a greater degree than large myelinated Aβ (motor fibres). It produces an equivalent sensory block but shorter duration of motor block than intrathecal bupivacaine and thus a quicker regression of motor block, early mobilization and early recovery.[33]

Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without increasing the sympathetic block while achieving satisfactory quality of spinal anaesthesia at a much lower dose of local anaesthetic.

Current literature comparing 0.5% levobupivacaine - fentanyl and 0.5% ropivacaine - fentanyl administered intrathecally are few and hence we compared the above drugs in patients posted for elective lower abdominal surgeries.

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi during the period of January 2014 to December 2014. A total of 80 patients undergoing lower abdominal surgeries under spinal anaesthesia were randomly allocated into one of the two groups by computer generated randomization: Group LF (n=40; patients received 3 ml of isobaric 0.5% levobupivacaine + 0.5 ml (25 mcg) fentanyl) or Group RF (n=40; patients received 3 ml of isobaric 0.5% Ropivacaine + 0.5 ml (25 mcg) fentanyl).

In our study demographic parameters like age, sex, weight, height and ASA status were comparable between the two groups.

In our study, onset of sensory block was defined as the time taken to achieve T_{10} block level, mean onset of sensory block was faster in Group RF (5.25 ±0.74 min) than in Group LF (6.53 ±0.51 min) and was statistically significant (p value <0.001).

Jagtap et al in their study compared sixty patients, undergoing major lower limb orthopaedic surgery, who were randomly allocated to receive either intrathecal 3.0 ml of 0.5% isobaric ropivacaine + 0.5 ml fentanyl or 3.0 ml of 0.5% isobaric bupivacaine with 25 mcg fentanyl. Time to reach peak sensory level (min) in ropivacaine - fentanyl group was 6.86±3.73 minutes while in bupivacaine - fentanyl group was 7.07±2.99 minutes.[36]Hence their results were quite similar to our study.

Breebaart el al conducted a study in 2003 of 60 patients undergoing ambulatory knee arthroscopy under spinal anaesthesia. In this study, they compared 10 mg levobupivacaine with 15 mg ropivacaine given intra-thecally. The onset of sensory block found by them was 8 minutes for levobupivacaine group and 7 minutes for ropivacaine group.[37] Considering the fact that a different dose with no added adjuvant was used in their study, hence a slight difference can be noted in the onset of sensory block between that and our study.

Şimşek et al conducted a study on 40 patients undergoing inguinal herniorrhaphy under spinal anaesthesia. Patients were randomly divided into two groups receiving either 15 mg of 0.5 % levobupivacaine or 12.5 mg of levobupivacaine + 25 mcg fentanyl. The onset of sensory block at T_{10} was found to be 6.80 ± 3.75 minutes and 5.70 ± 2.01 minutes respectively[35], which was quite similar to our study.

In our study, duration of sensory block was defined as two dermatome regression of anaesthesia from the highest level. It was longer in Group LF (169.5 ± 7.15 minutes) than in Group RF (144.25 ± 5.94 minutes) and was statistically significant (p value < 0.001). Majority of patients had T_6 sensory dermatome block level in Group LF while T_7 sensory dermatome block level was observed in Group RF.

A study was done by Mantouvalou et al, in 2008, comparing characteristics of spinal anaesthesia in patients undergoing lower abdominal surgery. They compared 15 mg of levobupivacaine with 15 mg of bupivacaine and 15 mg ropivacaine. The duration of sensory block in that study was 230 minutes, 240 minutes and 200 minutes respectively.[38] Considering the fact there was no added adjuvant in that study and total duration of sensory block was measured and not just two segment regression , hence a slight difference can be noted in the duration between that and our study.

In the aforementioned study of Jagtap et al, that compared intrathecally administered 15 mg of 0.5% ropivacaine + 25 mcg fentanyl with 15 mg of 0.5% bupivacaine + 25 mcg fentanyl, time to sensory regression to L_1 dermatome was 226±46.98 minutes in the former group and 229.33±50.5 minutes in the latter.[36] Considering the fact that different drugs and different end points were chosen, hence a variation is noted in the duration of sensory block with our study.

Breebaart et al, in their study, concluded that the total duration of sensory block with 10 mg of levobupivacaine and 15 mg of ropivacaine was 173 ± 47 minutes and 167 ± 49 minutes,[37] which was quite similar to our study.

In our study, onset of motor block was defined as the time to reach Modified Bromage Grade 3. The mean onset of motor block was faster in Group RF (7.25 ± 0.98 min) than in Group LF (11.2 ± 0.61 min) and was statistically significant (p value < 0.001)

Glaser et al, in 2002, in their study on 80 patients undergoing hip surgery under spinal anaesthesia, administered 3.5 ml of levobupivacaine or 3.5 ml of bupivacaine. The onset of motor block observed in their study was 10 ± 7 minutes and 9 ± 7 minutes, [39] the results quite similar our study, although no adjuvant was used in their study.

A study was done by Fattorini et al in 2006 on 60 patients undergoing hip or knee replacement surgery. They compared 3 ml of levobupivacaine with 3 ml of bupivacaine and concluded that onset of motor block was 11 ± 6 minutes and 8 ± 4 minutes respectively[40], the results being similar to our study, although no adjuvant was used in their study.

In the aforementioned study of Jagtap et al, that compared intrathecally administered 15 mg 0.5% isobaric ropivacaine + 25 mcgfentanyl with 15 mg 0.5% isobaric bupivacaine + 25 mcg fentanyl, the time to reach peak motor block Grade 3 was 6.02±2.1 minutes and 6±3.6 minutes respectively[36].

Total duration of motor block was defined as the time for return to Modified Bromage Grade 0 in our study. It was longer in Group LF (219.5 ± 6.39 min) than in Group RF (171.25 ± 7.23 min) and was statistically significant (p value < 0.001).

In the aforementioned study of Şimşek at al , that compared intra-thecally administered 15 mg 0.5 % levobupivacaine with 12.5 mg 0.5 % levobupivacaine + 25

mcg fentanyl in patients undergoing herniorrhapphy , it was observed that the time to return of motor function was longer in the former group (267±64.2 minutes) than in the latter group (224 ±86.2 minutes).[35]

Varun et al conducted a study on 100 patients undergoing lower abdomen and lower limb surgeries under spinal anaestheisa. The patients were randomly divided into two groups receiving either 3 ml 0.5% isobaric bupivacaine + 20 mcg fentanyl or 3 ml 0.5% isobaric ropivacaine + 20 mcg fentanyl. Time for Motor recovery to Modified Bromage scale 0 was 180.20±41.66 minutes in the former group and 173.00±17.76 minutes in the latter group, the results being similar to our study.[20]

In our study, the baseline hemodynamic parameters i.e., mean heart rate, mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure were comparable in Group LF and Group RF at all the intervals since beginning (p value> 0.05). Hypotension was observed in 15 % of the patients in Group LF while 10 % of the patients in Group RF had hypotension. It was corrected with 5 mg of ephedrine and 250 ml of fluid bolus. Similar hemodynamics were observed in the study by Jagtap et al.[36] Hypotension requiring treatment was observed in 3.3% patients in Group Ropivacaine-Fentanyl as compared to 10% patients in Group Bupivacaine Fentanyl.

The other side effects observed were nausea and vomiting and pruritus in the two groups. Group LF had an incidence of 5 % of nausea and vomiting while Group RF had an incidence of 2.5 % of nausea and vomiting. Similar results were observed in the study by Jagtap et al where the incidence of nausea and vomiting was 3.3% in Ropivacaine - fentanyl group[36]. It was treated with Inj. ondansetron 4 mg i/v in our study. Pruritus was observed in 5 % in both the groups in our study. Jagtap et al had

observed an incidence of 10 % in their study[36]. Patients complaining of pruritus were treated with Inj. Hydrocortisone sodium 100 mg i/v and Inj. Chlorpheniramine maleate 10 mg i/v in our study.

Levobupivacaine has not entirely replaced bupivacaine in clinical anaesthesia practice. It was believed that levobupivacaine and bupivacaine produce comparable surgical sensory block. But the equipotency of the two drugs has been recently questioned. It has therefore prompted clinicians to increase the dose of levobupivacaine in an attempt to ensure adequate anesthesia and analgesia and offsetting the advantages of less motor block with levobupivacaine.

To evaluate the pharmacodynamic effects of different intrathecal drugs, a clinical model should be developed to determine the relative potencies of local anesthetics with adjuvants. This involves the estimation of the median effective dose (ED_{50}) to determine the spinal potency ratios for sensory and motor block. Ropivacaine, levobupivacaine, and bupivacaine belong to the pipecolylxylidine homologous series of local anesthetics that have an ability to cause differential sensory and motor neural blockade. Previous studies have compared ED_{50} values of levobupivacaine/ropivacaine and ropivacaine/ bupivacaine when given intrathecally for surgical anesthesia. However most of these studies have been done without the use of fentanyl as adjuvant. Hence more studies need to be done with fentanyl to add to the already existing knowledge.

This study was done using isobaric solutions. In current clinical practice hyperbaric bupivacaine is most commonly used for intrathecal administration. It would be useful to do further study comparing hyperbaric levobupivacaine, hyperbaric ropivacaine and hyperbaric bupivacaine for intrathecal usage.

CONCLUSION

Our study showed that intrathecal 0.5% isobaric levobupivacaine + fentanyl is more potent than intrathecal 0.5 % isobaric ropivacaine + fentanyl with respect to the duration of sensory and motor block with no significant hemodynamic changes in lower abdominal surgeries. Intrathecal 0.5 % isobaric ropivacaine + fentanyl provides satisfactory anaesthesia with shorter duration of motor block compared to intrathecal 0.5% isobaric levobupivacaine + fentanyl which is a desirable feature for early ambulation. Both the drugs can be used as alternative to bupivacaine intrathecally with no risk of major side effects / complications.

SUMMARY

Spinal administration of local anaesthetics is the choice of anaesthesia technique for surgeries of lower abdomen, pelvis and lower limbs. Spinal anaesthesia has a quick onset, provides good relaxation with adequate sensory as well as motor blockade. Pure S-enantiomers, ropivacaine and levobupivacaine, have been introduced into clinical practice and are a good alternative to bupivacaine. It has been well documented that the combination of opioids and local anesthetics administered intrathecally has a synergistic analgesic effect. Fentanyl, itself a short acting opioid, potentiates afferent sensory blockade of local anaesthetic and provides an acceptable surgical anaesthesia. Moreover, the adjuvant fentanyl does not prolong recovery.

This one year randomized controlled trial was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, during the period January 2014 to December 2014. A total of 80 patients undergoing lower abdominal surgeries under spinal anaesthesia were allocated into two groups namely, Group LF (n =40 , Patients received 3.0 ml of 0.5 % isobaric levobupivacaine + 0.5 ml (25mcg) fentanyl intrathecally) or Group RF (n =40 , Patients received 3.0 ml of 0.5 % isobaric ropivacaine + 0.5 ml (25 mcg) fentanyl intrathecally). Sensory and motor block characteristics like onset and duration were studied. Hemodynamic parameters like heart rate, blood pressure and oxygen saturation were monitored continuously.

Demographic parameters were comparable in both the groups. In this study, onset of sensory block was significantly faster in Group RF (5.25 ± 0.74 min) than in Group LF (6.53 ± 0.51 min). Duration of sensory block was significantly longer in Group LF (169.5 ± 7.15 min) than in Group RF (144.25 ± 5.94 min). Onset of motor block was significantly faster in Group RF (7.25 ± 0.98 min) than in Group LF (11.2

± 0.61 min). Duration of motor block was significantly longer in Group LF (219.5 ± 6.39 min) than in Group RF (171.25 ± 7.23 min). Hemodynamic parameters were comparable between the two groups with no major side effects / complications observed.

Overall, based on the findings of this study it may be concluded that intrathecal 0.5 % isobaric levobupivacaine - fentanyl is more potent than intrathecal 0.5 % isobaric ropivacaine- fentanyl with respect to the duration of sensory and motor block with no significant hemodynamic changes. Both the drugs can be used as alternative to bupivacaine intrathecally with no risk of major side effects / complications.

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ANNEXURE -I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll yourself in study titled **"COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUAL DOSES OF ISOBARIC LEVOBUPIVACAINE 0.5% -FENTANYL AND ISOBARIC ROPIVACAINE 0.5%-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL"** conducted by

Respected Sir/Madam we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in 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.

The purpose of research is to compare the duration of action between levobupivacaine and ropivacaine after the addition of fentanyl to both in spinal anaesthesia in patients undergoing lower abdominal surgeries.

Procedure Involved:

If you agree to enroll yourself in my study, you will be interviewed regarding your present, past and family history, then you will be clinically examined in detail and investigated accordingly. You will receive 3.0 ml of 0.5% isobaric Levobupivacaine + 0.5 ml of (25 mcg) fentanyl or 3.0 ml of 0.5% isobaric Ropivacaine + 0.5 ml of (25 mcg) fentanyl as spinal anaesthesia.

Benefits and Risks

The benefits of taking part in this research are that we can avoid GA with good quality of analgesia and early ambulation. The risks are minimal which include hypotension, bradycardia, headache, backache, syncope, paraesthesia. There are no observable risks associated with the study.

Voluntary participation / Withdrawal

Taking part in the study is voluntary; you may choose not to enroll in this study. Your decision will not change present or future health care services offered to you at Dr. Prabhakar Kore Hospital.

Alternatives

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

Confidentiality

All information collected about you during the course of the study will be kept Confidential. The code numbers will identify you in this Study records and the

information from this study may be published but your identity will be confidential in any publication. The only people to know that you are a research subject are members of the research team. No information about you or 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 you will remain 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 at Dr. Prabhakar Kore Hospital and MRC, Belagavi. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

If you have any queries about your rights as a study subject, you may call Dr. Ganga Pilli, Prof. & Head of Pathology as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.9448863866 or Extension-4052 at J. N. Medical College, Belagavi

Consent for participation in research trial

I, _____ voluntarily agree for the participation 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 form 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 : _____

Date: _____

Witness Name : _____ Signature: _____ Date:

Investigators Name: _____ Signature: _____

Date:

Place : _____

ANNEXURE -II

PROFORMA

"COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUAL DOSES OF ISOBARIC LEVOBUPIVACAINE 0.5% -FENTANYL AND ISOBARIC ROPIVACAINE 0.5%-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL"

Patient Name: IP No.:

Age: Gender:

Height: Weight:

Date of Operation: Occupation:

Address: Anaesthesiologist:

Preanesthetic Evaluation:

Chief Complaints:

Past History:

a. HTN / DM / Asthma / Epilepsy / Rx allergy

b. Drug therapy

c. Previous exposure to Anesthesia

Family history

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Lymphadenopathy / Edema

PR : BP :

RR : Temp :

Musculoskeletal examination

Jaw movements : Teeth :

Airway assessment : Spine :

Systemic Examination

RS : CNS :

CVS : Abdominal :

Investigations

Hb : Total Leukocyte Count :

S.urea : Platelet Count:

S.creatinine: Urine routine:

ECG : Chest X-Ray:

RBS:

Preoperative physical status: ASA Grade I, II

Diagnosis

Proposed Surgery

Preoperative baseline values

HR: BP:

Monitors attached

Pulse oximetry : NIBP :

ECG:

Vital parameters:

Time (min)	BP (mm Hg)	PR (bpm)

Sensory Block

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

Motor Block

a) Onset (mins.)	
b) Total duration of motor block	

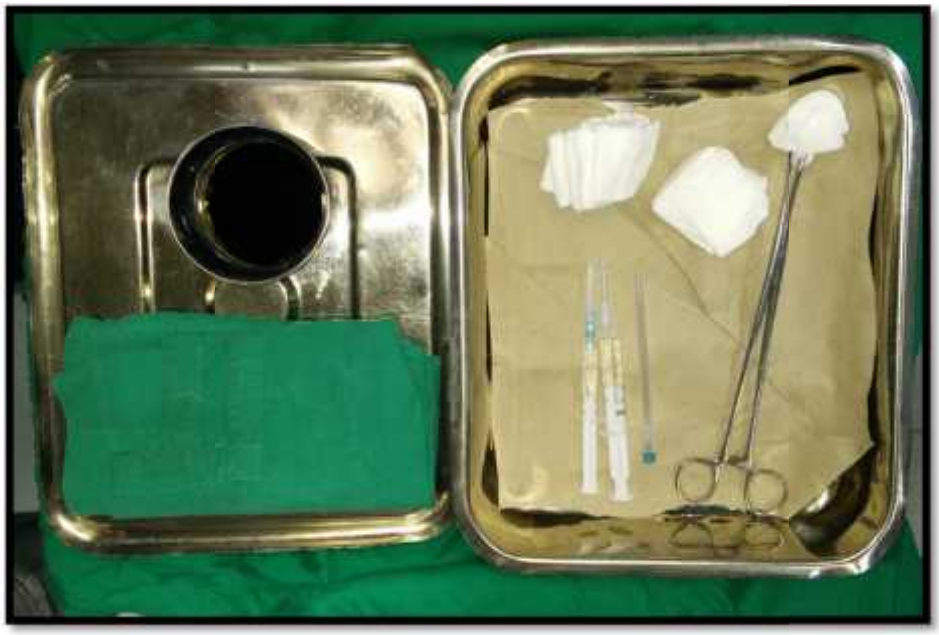
Side Effects:

ANNEXURE – III - PHOTOGRAPHS

Photograph 1: Ropivacaine ampoule

Photograph 2: Levobupivacaine ampoule

Photograph 3: Fentanyl ampoule



Photograph 4: Spinal tray

Photograph 5: Procedure of spinal anaesthesia

Photograph 6: Monitoring during the surgery

KEY TO MASTER CHART

ASA	-	American Society of Anaesthesiologists
F	-	Female
M	-	Male
HR	-	Heart Rate (bpm)
Systolic	-	Systolic Blood Pressure (mm Hg)
Diastolic	-	Diastolic Blood Pressure (mm Hg)
MAP	-	Mean Arterial Pressure (mm Hg)
SpO_2	-	Saturation of peripheral oxygen
T	-	Thoracic sensory dermatomal level