"COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUIPOTENT DOSES OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA – A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL STUDY"

REG. NO. BA0111002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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APRIL - 2014

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ENDORSEMENT BY THE HOD/PRINCIPAL/ HEAD OF THE INSTITUTION

This is to certify that the dissertation entitled **"COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUIPOTENT DOSES OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA - A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL STUDY"** is a bonafide research work done by **CANDIDATE REG. NO. BA0111002**.

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

Date:
Place: Belgaum

Dr. A. S. GODHI MS, FICS
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

ASA	-	American Society of Anaesthesiologists
Bpm	-	Beats per minute
C	-	Cervical
cc	-	Cubic centimeter
CNS	-	Central nervous system
CSF	-	Cerebrospinal fluid
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ED	-	Effective dose
GA	-	General anaesthesia
HCL	-	Hydrochloric Acid
HCO_3	-	Bicarbonate
HR	-	Heart rate
I.V	-	Intravenous
KCl	-	Potassium chloride
kg	-	Kilogram
L	-	Lumbar
m	-	Meters
MAP	-	Mean arterial pressure
Mcg	-	Microgram
mg	-	Milligram
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
T	-	Thoracic
TNS	-	Transient neurological symptoms
v/s	-	Versus
α	-	Alpha
β	-	Beta
δ	-	Delta
μ	-	Micro

ABSTRACT

Background and Objectives

Effective analgesia with early ambulation is becoming more important, especially for day care patients. Hence the present study was undertaken to compare the isobaric 0.75% Ropivacaine with isobaric 0.5% Bupivacaine after the addition of Fentanyl to both the groups.

Methods

This one year hospital based randomized clinical study was conducted from January 2012 to December 2012 in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, on 80 patients, undergoing elective lower abdominal surgeries under spinal anaesthesia. Patients were distributed into two groups of 40 each i.e Group B (2.5 cc of 0.5% Bupivacaine plus 0.5 cc of Fentanyl) and Group R (2.5 cc of 0.75% Ropivacaine plus 0.5 cc Fentanyl).

Results

Both groups were comparable with respect to demographic data and hemodynamic parameters. Mean onset time of sensory block was significantly high in group R (7.68±1.02 v/s 5.08±0.83 minutes; $p<0.001$). In group R, majority of the patients (90%) achieved T_6 to T_8 whereas in group B, majority of the patients (75%) achieved T_4 to T_6 highest sensory block level. The duration of sensory block in group R was comparable to group B (133.25±11.85 v/s 137.50±11.04 minutes; $p=0.101$). Time taken for onset of motor block was significantly high in group R (8.78±0.89 v/s 6.65±0.92 minutes; $p<0.001$). The duration of total motor block (144.75±10.86 v/s 189.75±16.09 minutes; $p<0.001$)

was significantly less in group R and the time to request for first post-operative rescue analgesia (230.25 ± 20.69 v/s 238.75±24.72 minutes p> 0.05) was comparable in both the groups.

Conclusion and interpretation

To conclude, Ropivacaine-Fentanyl required more time for onset of sensory and motor block and provided lower block level. The duration of motor block was less with comparable duration of sensory block and the time to request for first post-operative rescue analgesia in comparison to intrathecal Bupivacaine-Fentanyl.

Keywords

Bupivacaine; Fentanyl; Ropivacaine; Spinal anaesthesia;

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Chapter 1

Introduction

INTRODUCTION

Spinal anaesthesia is the most commonly used anaesthetic technique for patients undergoing lower abdominal surgeries. Augustus Bier performed the first spinal anaesthesia using cocaine in 1889. Since his first report, regional anaesthesia including spinal has gained widespread popularity in the developed world. Spinal anaesthesia is a form of regional anaesthesia where conduction block of nerve roots is achieved by injecting 10-20 mg of local anaesthetic solution into the subarachnoid fluid through a lumbar puncture.[1]

Central neuraxial blockade is probably the most widely used form of regional anaesthesia today. A number of clinical studies suggest that spinal anaesthesia may be superior to general or epidural anaesthesia for certain patients and for certain surgical procedures. The endocrine-metabolic response to surgery appears to be blunted when spinal anaesthesia is employed compared to the response during general anaesthesia.[2]

Reducing the duration of motor block is becoming more important, especially for day care patients. Therefore in surgeries, performed under spinal anaesthesia, early ambulation as a consequence of shorter duration of motor block is considered desirable.

Since the development of spinal anaesthesia technique various local anaesthetics such as cocaine, procaine, etidocaine, tetracaine, lignocaine, bupivacaine were tried and studied for their effects. The choice depends on the duration of operation and the quality of the aftercare available for those patients whose operations end before their blocks wear off.[1]

In the past hyperbaric 5% lignocaine was commonly used for spinal anaesthesia for short surgical procedures, but its use has declined because of concerns about cauda equina syndrome and transient neurological symptoms.[3] Currently the local anaesthetic drugs like Bupivacaine and Ropivacaine have been used intrathecally for these surgical procedures.[4]

A number of deaths from cardiac arrest were reported in association with regional anaesthesia using Bupivacaine. All appeared to be caused by accidental intravenous injection of these long acting local anaesthetics. The doses required to produce cardiotoxicity seemed to be close to the convulsant doses. These deaths and subsequent recommendations of the United States Food and Drug Administration provided the impetus to develop a safer drug. It was postulated that a less fat soluble drug than bupivacaine would be less cardiotoxic.[5]

It was noted in 1977 that the propyl derivative of the pipecoloxylidides was less toxic than the butyl derivative (bupivacaine). Further work revealed that the nerve blocking properties of the R and S enantiomers were similar but this S-enantiomer was less cardiotoxic. Thus the S enantiomer of the propyl derivative (Ropivacaine) was chosen for further development.[5]

Ropivacaine is an amide local anaesthetic with properties similar to those of Bupivacaine. Ropivacaine produces an equivalent sensory block but shorter duration of motor block than intrathecal bupivacaine and thus quicker regression of motor block, early mobilisation and early recovery.[4,6] Ropivacaine produces CNS and cardiovascular toxicity at a higher plasma concentration than Bupivacaine and thus the incidence is lower than Bupivacaine.[7,8]

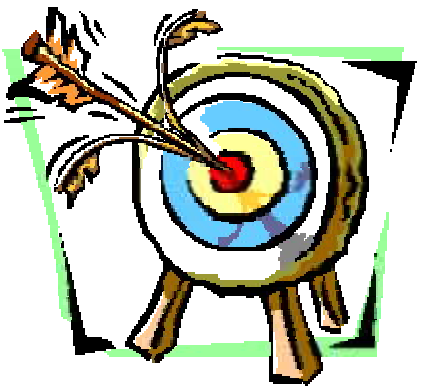
Opioid analogues have been used as additives in spinal anaesthesia to improve the onset of action, prolong the duration of block and to improve the quality of perioperative analgesia.[9-12]

Intrathecal opioids enhance analgesia from subtherapeutic doses of local anaesthetic and make it possible to achieve successful spinal anaesthesia using what would otherwise be an inadequate dose of local anaesthetic.[7]

However most of the studies comparing Ropivacaine-Fentanyl and Bupivacaine-Fentanyl have been conducted in the orthopaedic settings with few involving lower abdominal surgeries. Hence, the present study was undertaken to compare the isobaric Ropivacaine with isobaric Bupivacaine after the addition of Fentanyl to both the groups in patients undergoing lower abdominal surgeries under spinal anaesthesia.

Chapter 2

Objectives



OBJECTIVES

The objectives of the present study were;

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

Secondary objective: Time to request for first post operative rescue analgesia between Ropivacaine-Fentanyl and Bupivacaine-Fentanyl in patients posted for elective lower abdominal surgeries under spinal anaesthesia.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

Spinal anaesthesia, also referred to as 'subarachnoid block' (SAB), or 'intrathecal analgesia', was the first major regional technique attempted. Spinal anaesthesia is a form of regional anaesthesia where conduction block of nerve roots is achieved by injecting local anaesthetic solution into the subarachnoid fluid through a lumbar puncture. It produces complete analgesia with profound muscle relaxation, quiet respiration and small contracted bowel.[1]

The first spinal anaesthesia was administered in 1885 by James Leonard Corning (1855–1923), when he accidentally pierced the dura mater while experimenting with cocaine on the spinal nerves of a dog.[13]

Quincke in 1891 demonstrated a safe, predictable means of performing lumbar puncture. The first planned spinal anaesthesia for surgery in man was performed in 1898 by August Karl Bier in Germany.[13] Bier and his assistant Hildebrandt tried spinal anaesthesia by injecting cocaine into each others theca.[14] The first phase in the history of spinal anaesthesia, from 1899 to 1905, was characterized by the use of only cocaine for spinal anaesthesia.[15]

In 1905, Heinrich Braun, a German surgeon, reported the use of procaine for operative spinal anaesthesia. Means for controlling levels of anaesthesia by making procaine solutions hyperbaric by adding glucose, was first reported by Barker in 1907. Synthesis of tetracaine in 1931 and its introduction into clinical practice by Sise in 1935, synthesis of dibucaine and its introduction into clinical practice by Jones in 1930 popularized spinal anaesthesia. Continuous spinal anaesthesia was demonstrated by Lemmon in 1940 and Tuohy in 1945. In 1945,

Prickett and associates published their report on the neurologic safety of intrathecal epinephrine to prolong the duration of spinal anaesthesia.[16]

By the mid 1940's spinal anaesthesia reached a peak of its popularity, a popularity soon followed by almost equally widespread avoidance and neglect. The pharmacological explosion in anaesthesia between 1945 and 1965 made spinal anaesthesia appear unnecessarily demanding, inconvenient and tedious, as well as, at least medico legally unsafe.

In the following years, the technique was found to be safe in expert hands and preferred over general anaesthesia for operations involving lower limbs and lower abdomen.

Spinal anaesthesia has many advantages like ease of administration and rapid onset of action. The main disadvantages are its limited duration of action and hence lack of postoperative analgesia without the use of adjuvants.

Spinal anaesthesia is best reserved for operations below the umbilicus e.g. hernia repairs, gynaecological, urological, perineum or genitalia procedures. It is indicated with special consideration for those with systemic disease such as chronic respiratory disease, hepatic, renal and endocrine disorders such as diabetes.

It is suitable for managing patients with trauma if they are haemodynamically stable. There are definite advantages for both mother and baby in using spinal anaesthesia for caesarean section. However, special considerations apply to managing spinal anaesthesia in pregnant patients.

Local anaesthetic agents are either hyperbaric, hypobaric, or isobaric. Hyperbaric solutions tend to spread below the level of the injection. It is easier to predict the spread of spinal anaesthesia when using a hyperbaric agent. Isobaric preparations may be made hyperbaric by the addition of dextrose.

Since the development of spinal anaesthesia technique various local anaesthetics such as cocaine, procaine, etidocaine, tetracaine, lignocaine, Bupivacaine were tried and studied for their effects. The choice depends on the duration of operation and the quality of the aftercare available for those patients whose operations end before their blocks wear off.[1]

In the past hyperbaric lignocaine 5% was commonly used for spinal anaesthesia for short surgical procedures, but its use has declined because of concerns about cauda equina syndrome and transient neurological symptoms.[3] Currently the local anaesthetic drugs like Bupivacaine and Ropivacaine have been used intrathecally for these surgical procedures. Opioid analogues have been used as additives in spinal anaesthesia to improve the onset of action, prolong the duration of block and to improve the quality of perioperative analgesia.[9-12]

Intrathecal opioids enhance analgesia from subtherapeutic doses of local anaesthetics making it possible to achieve successful spinal anaesthesia using what would otherwise be an inadequate dose of local anaesthetic.[5] Most of the studies comparing Ropivacaine-Fentanyl and Bupivacine-Fentanyl have involved orthopaedic surgeries, with few involving lower abdominal surgeries.Hence the present study was carried out to compare Ropivacaine-Fentanyl and Bupivacaine-

Fentanyl in patients undergoing lower abdominal surgeries under spinal anaesthesia.

A randomised, double-blind study[18] comparing equipotent doses of plain Ropivacaine and Bupivacaine (19.5 mg and 13 mg respectively), both with Fentanyl 20 mcg, for spinal anaesthesia in lower abdominal surgery found that all patients achieved sensory block to T_{10} or higher. The level of sensory block was significantly higher in group B (T_4 [T_3 to T_7] vs T_7 [T_4 to T_9], $P < 0.05$). There was no difference in the onset time of motor block. The duration of motor block (Bromage score >0) was shorter in group R (139 ± 39 minutes vs group B 182 ± 46 minutes, $P < 0.05$). The duration and intensity of complete motor block (Bromage score=3) was also shorter in group R (90 ± 25 minutes vs 130 ± 40 minutes, $P < 0.05$). Study concluded that, plain Ropivacaine 19.5 mg plus Fentanyl 20 mcg is associated with a lower level of sensory block and a shorter duration of motor block when compared to Bupivacaine 13 mg plus Fentanyl 20 mcg for spinal anaesthesia in lower abdominal surgery.

Another prospective randomized double-blind study[19] comparing plain Ropivacaine 10 mg and plain Bupivacaine 10 mg, both with Fentanyl 15 mcg, for spinal anaesthesia in urological surgery reported that, the duration of motor block, was shorter in the Ropivacaine group (median, 126 minutes; interquartile range, 93-162 minutes) compared with the Bupivacaine group (median, 189 minutes; interquartile range, 157-234 minutes; difference between medians, 71 minutes; 95% confidence interval, 28-109 minutes; $P = 0.003$). The duration of complete motor block was also shorter in the Ropivacaine group compared with the Bupivacaine group. There was no difference in the onset time of motor block.

The characteristics of sensory block and the haemodynamic changes were similar between the groups. The study concluded that, plain Ropivacaine 10 mg plus Fentanyl 15 mcg provided similar sensory anaesthesia, but with a shorter duration of motor block, compared with plain Bupivacaine 10 mg plus Fentanyl 15 mcg when used for spinal anaesthesia in urological surgeries.

In a randomized, single-blinded study[20] comparing the effects of intrathecal Ropivacaine with Bupivacaine in a dose ratio of 2:1 for outpatient arthroscopic knee surgery concluded that isobaric Ropivacaine 15 mg provided a higher sensory block level and shorter sensory onset and faster regression time than did 7.5 mg of isobaric Bupivacaine and hemodynamic changes were similar between the groups.

In a study[21] comparing the regression of sensory and motor block, and the analgesia during continuous epidural infusion of Ropivacaine and Fentanyl with other local anesthetics in two studies. Study 1: Eighty patients were scheduled for orthopedic procedures of the lower extremity under lumbar epidural anaesthesia. Following the operation, continuous infusion of a randomized solution (0.2% Ropivacaine, 0.125% Bupivacaine, 0.5% Lidocaine, or 0.2% Ropivacaine with 2.5 µg/mL Fentanyl) was commenced at a rate of 6 mL/h.. Study 2: After gynecologic abdominal surgery, 39 patients were randomized to one of the three epidural infusion groups: 0.2% Ropivacaine, 0.125% Bupivacaine, or 0.2% Ropivacaine with 2.5 µg/mL Fentanyl at a rate of 6 mL/h with an additional bolus injection of 3 mL, which can be used when patients have pain. VAS was compared among the groups. In Study 1, the level of sensory block in all the groups appeared to decrease progressively. However, the regression of sensory

block was significantly prolonged in patients treated with Ropivacaine. The addition of Fentanyl to Ropivacaine augmented this prolonged analgesic effect. In Study 2, VAS after the bolus in the Ropivacaine and the Ropivacaine + Fentanyl groups were significantly lower than that in the Bupivacaine group. Patients in the Ropivacaine + Fentanyl group required significantly fewer supplemental bolus injections. Continuous epidural infusion of Ropivacaine may induce a slower regression of sensory blockade compared with Bupivacaine and lidocaine. The addition of Fentanyl to Ropivacaine can enhance this prolonged analgesic effect with little effect on motor blockade. Epidural infusion of Ropivacaine with Fentanyl provides effective pain relief, possibly because of the maintenance of sensory blockade by Ropivacaine and Fentanyl.

In another study[22] comparing between 0.08% Ropivacaine and 0.06% Levobupivacaine for epidural analgesia during nulliparous labor in a retrospective study in a single center. Computer records of 392 Asian nulliparous parturients, who had presented with spontaneous labor or spontaneous rupture of the membranes, and had received epidural analgesia, were retrospectively reviewed. In the Levobupivacaine group, the parturients required top-up boluses of local anesthetics more frequently (1.4 ± 1.6 vs. 0.9 ± 1.3, $p< 0.001$), and the incidence of temporary maternal fever (25 % vs. 15%, $p = 0.024$) and the cost of local anesthetic were higher (292 ± 183 NTD vs. 146 ± 104 NTD, $p< 0.001$). However, the amount of local anesthetic administered during labor was lower (79 ± 49 mg vs. 114 ± 81 mg, $p< 0.001$) than for the Ropivacaine group. 0.06 % Levobupivacaine was as effective as 0.08% Ropivacaine, when both were used with 0.0002% Fentanyl for labor epidural analgesia of nulliparous women.

In another study[23] comparing low-dose Ropivacaine and Levobupivacaine in walking spinal anaesthesia in ambulatory inguinal herniorrhaphy, CSEA was performed. Adult patients were randomly allocated to receive 5 mg 0.5% Ropivacaine plus 25 mcg Fentanyl (group RF, n = 25) or 3.75 mg 0.75% Levobupivacaine plus 25 mcg Fentanyl (group LF, n = 25). They found that sensory block onset time and time to reach the T_6 dermatome were significantly shorter in LF group, whereas time to the two-segment regression and time to first analgesic requirement were significantly shorter in group RF. All patients in group LF were Bromage 0. Time to home discharge was shorter in group LF, but this difference was not statistically significant. They suggested that both local anesthetics can be used in walking spinal technique. Levobupivacaine may be an alternative local anesthetic for walking spinal anaesthesia as it provides minimum motor block and a long duration of postoperative analgesia, even if its use is not associated with a shorter home discharge time.

Chapter 4

Basic Sciences

BASIC SCIENCES

APPLIED ANATOMY

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

Vertebral column

Main function of vertebral column is to protect the spinal cord. There are 33 vertebrae in vertebral column which includes;[24]

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

Curves of spine

In adults, curves of vertebral column have significant effect on spread of drugs in sub arachnoid space and these curves are:[24]

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

Cervical (C) five and lumbar (L) five are the highest points of cervical and lumbar curves in supine position and the lowest points of thoracic and sacral are at thoracic (T) five and sacral (S) two respectively.[24]

Vertebral ligaments[25]

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

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

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

Ligamentum flavum: This ligament comprises yellow elastic fibres and connects adjacent 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 2).

Longitudinal ligaments: There are two longitudinal ligaments (anterior and posterior) that bind vertebral bodies together (Figure 2).

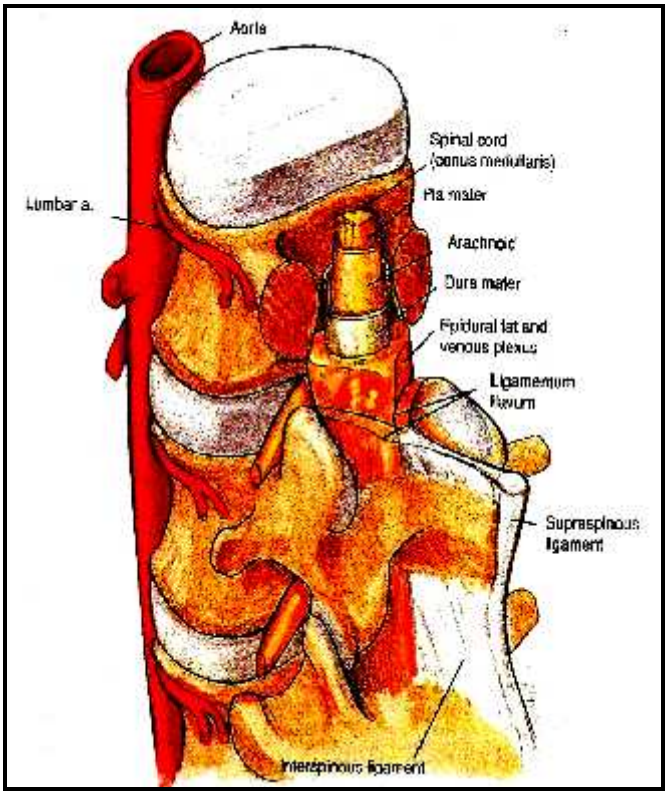


Figure 1. Vertebral Column

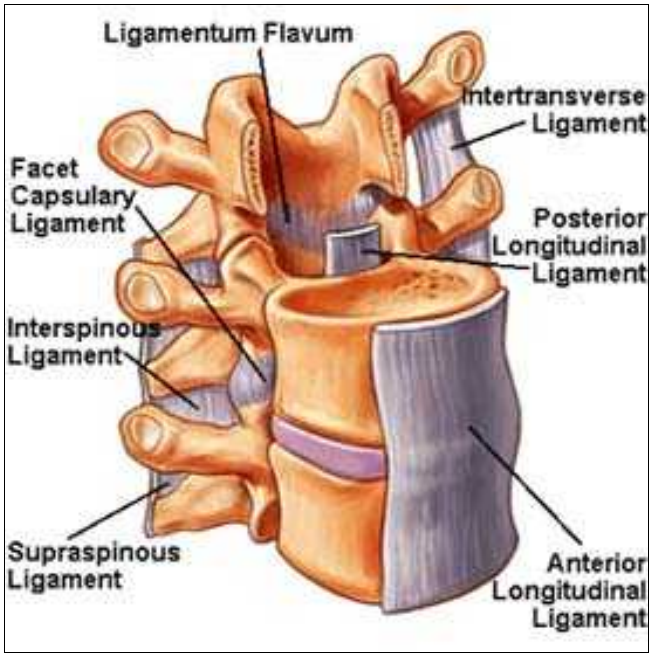


Figure 2. Spinal Ligaments

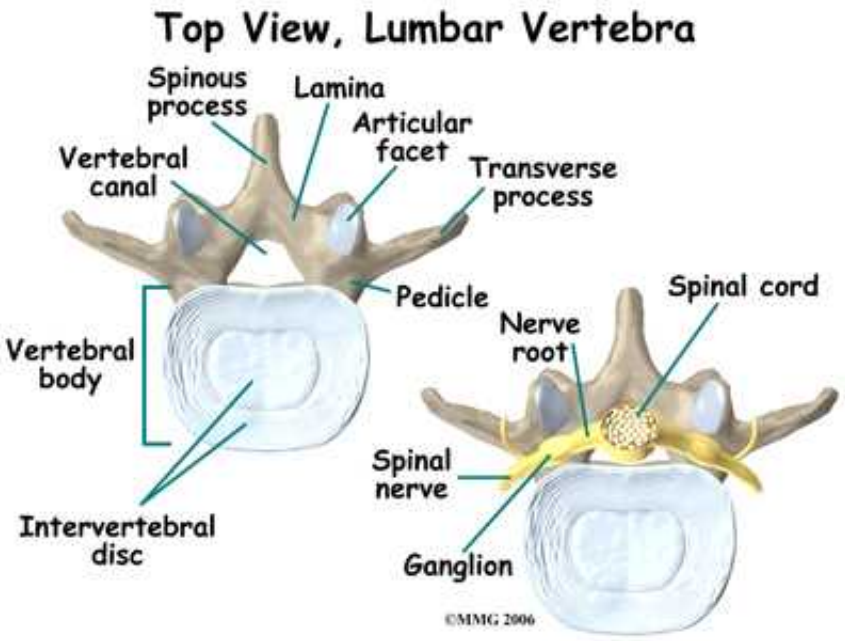


Figure 3. Typical Lumbar Vertebra

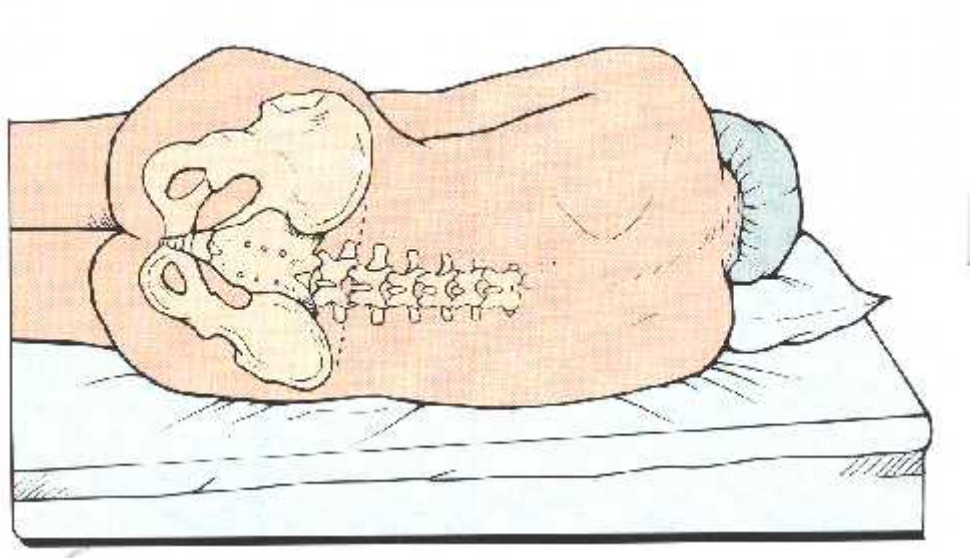


Figure 4. Line of Tuffier

Intervertebral Discs[13]

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

Topographical Line of Tauffier[26]

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

Lumbar vertebrae[13]

A typical lumbar vertebrae consists of (Figure 3);

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

Vertebral canal

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

Spinal cord[24]

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

The spinal cord is a continuation of the medulla oblongata below the level of foramen magnum and it tapers off into a conical extremity known as conus medullaris. Filum terminale descends to the back of first segment of coccyx from apex of conus medullaris.

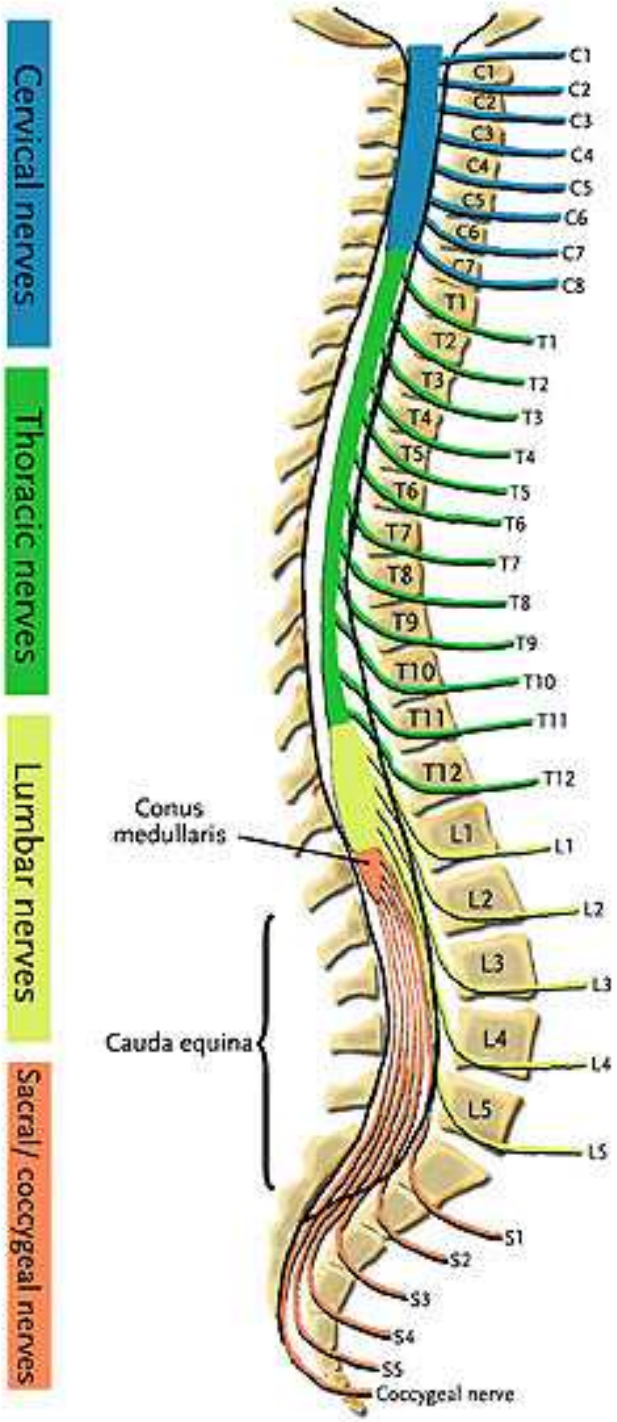


Figure 5. Spinal nerve roots

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

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

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

Amount of white matter decline progressively from the cervical down to the lumbar region. The gray matter is greately increased in the both the lumbar and cervical enlargement

Blood Supply of Spinal Cord[22]

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

There are two posterior spinal arteries-one on each side. They are derived from the vertebral artery or more often from a primary branch of each vertebral

artery. They supply the posterior one-third of the spinal cord. This supply is augmented by spinal branches of vertebral, ascending cervical, posterior intercostals, lumbar and lateral sacral arteries, which pass through the intervertebral foramina.

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

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

Meninges[26]

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

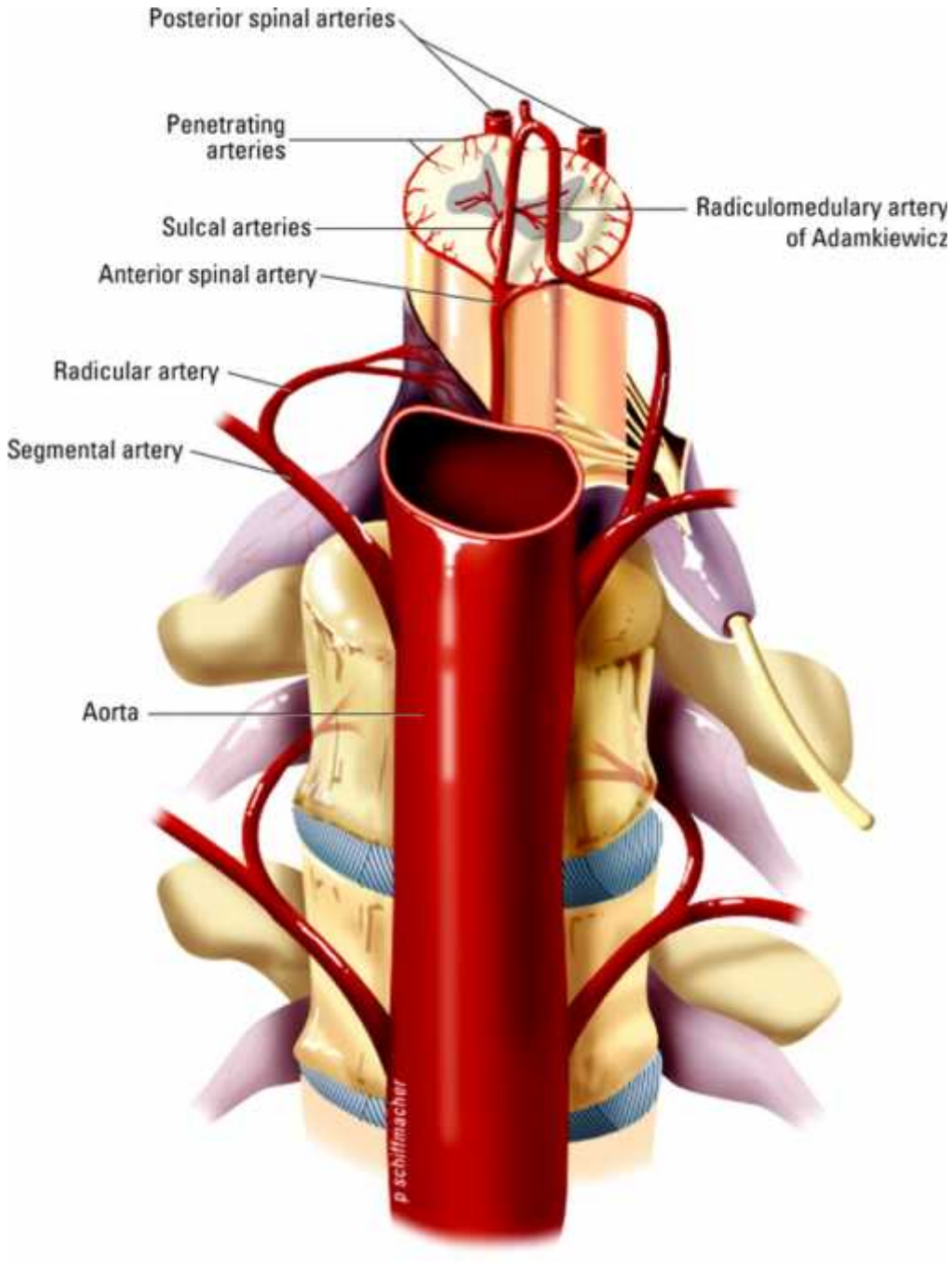


Figure 6. Blood Supply of Spinal Cord

Duramater[27]

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

Arachnoid Mater[27]

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

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

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

Subarachnoid Space[27]

Subarachnoid space is the space between the arachnoid and pia mater. It is filled with cerebrospinal fluid and contains numerous arachnoid trabeculae which form delicate sponge like mass. This space has three divisions which are free

communications to 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 cerebrospinal fluid. 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 mater continues as perineural epithelium of peripheral nerve.

Pia Mater[27]

The pia mater is the innermost membrane which closely invests the brain and spinal cord.

Cerebrospinal Fluid[27]

It is a clear colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles. Cerebrospinal fluid is mainly formed by either secretion or ultrafiltration from the choroidal plexus of lateral ventricles. It 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 cerebromedullary 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/L
- Sodium : 135 to 145 mEq/L
- Magnesium : 2 to 2.5 mEq/L
- Chloride : 15 to 20 mEq/L
- Calcium : 2 to 3 mEq/L
- Phosphorous : 1.6 mg/dl
- Proteins : 23 to 38 mg/dl

It is important to know that certain drugs alter the rate of formation of CSF. Carbonic anhydrase inhibitors like acetazolamide reduces the rate of CSF formation by as much as 50%. Furosemide in large doses may reduce the CSF formation. Inhalational anaesthetics like isoflourane and vasoconstrictors decrease the CSF formation. CSF formation is decreased when the serum osmolality is increases and increases when the serum is made hypotonic. During equilibrium, rate of formation equals the rate of absorption (500 mL/day).

PHYSIOLOGY OF SUB ARACHNOID BLOCK

The well recognized physiological effects of subarachnoid block are often mistakenly termed as complications. It is imperative to make a clear distinction between the physiologic effects of an anaesthetic technique and complications that implies some harm to the patients. The various factors, which control the different effects of a spinal anesthetic technique are;[28]

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

Following are the factors which affects the spread of local anaesthetics;[29,30]

- Patient factors:
- Age
- Height
- Position
- Cerebrospinal fluid volume
- Spinal column configuration
- Site of injection
- Technical factors

- Needle direction
- Spread of injection
- Local anesthetic volume
- Local anesthetic baricity

The sensory and motor blockade results from the direct effects of local anesthetic on the spinal nerve roots. The primary 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 extent two to four segments above motor block. The sympathetic fibers are affected first and last to recover, on the other hand motor nerve blockade is usually last to be affected and first to recover.

Sequence of spinal anaesthesia (SA)[31]

- 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 physiological response to spinal anesthesia.

Cardiovascular effects of spinal anesthesia[32]

The most important physiologic response to spinal anesthesia involves the cardiovascular system. As sympathetic denervation is responsible for the genesis of cardiovascular changes during spinal anesthesia, the effect of spinal anaesthesia on the sympathetic nervous system warrants discussion before consideration of the cardiovascular responses themselves.

Sympathetic blockade

Because the level of sympathetic denervation under Sub Arachnoid Block determines the magnitude of cardiovascular responses to spinal anesthesia, it might be anticipated that higher the level of neural blockade, the greater would be the change in the cardio-circulatory parameters. In the presence of partial sympathetic blockade, a reflex increase in sympathetic activity occurs in sympathetically intact areas. The result is vasoconstriction that tends to compensate for the peripheral vasodilatation-taking place in the sympathetically denervated areas. This can be seen in the changes in the arterial pressure waveforms and in the cutaneous blood flow in the upper extremities in the presence of low or midthoracic sensory levels of spinal anaesthesia. Of even greater importance is the fact that the most cephalad preganglionic sympathetic fibers exit the spinal cord at the level of T1. Since sympathetic denervation is complete at the T1 level, cardiovascular changes are no greater with mid cervical sensory levels of anesthesia than they are with T1 levels.

Functional Anatomy of Sympathetic Nervous System[33]

The sympathetic nervous system originates from spinal cord in the thoracolumbar region, from the first thoracic through the second lumbar segment. The preganglionic neurons have cell bodies within the intermediolateral columns of the spinal gray matter. Nerve fibers from these cell bodies extend to three types of ganglia grouped as paired sympathetic chains, various unpaired distal plexus or terminal or collateral ganglia near the target organs. The 22 paired ganglia lie along either side of vertebral column. Nerve trunks connect these ganglia to each other and gray rami communicants connect the ganglia to the spinal nerves. The preganglionic fibers leave the cord in the anterior nerve roots, join the spinal nerve trunks and enter the ganglion at that level via white ramus. Leaving the ganglion, postsynaptic fibers re enter the spinal nerve via gray ramus, then go on to innervate pilomotor and sudomotor effectors and blood vessels of skeletal muscle and skin. Sympathetic innervation of trunk and limbs is thus carried by the spinal nerves.

The sympathetic distribution to head and neck comes from the three ganglia of cervical sympathetic chain. The unpaired pre vertebral ganglia reside in the abdomen and pelvis anterior to the vertebral column and are primarily the celiac, superior mesenteric, aorticorenal, and inferior mesenteric ganglia. Celiac ganglia is innervated by T5 – T12 and innervates the liver, spleen, kidney, pancreas, small bowel, and proximal colon .The superior mesenteric ganglion innervates the distal colon, whereas inferior mesenteric ganglion innervates rectum, bladder, and genitals. Adrenal medulla and other chromaffin tissue are homologous to sympathetic ganglia.

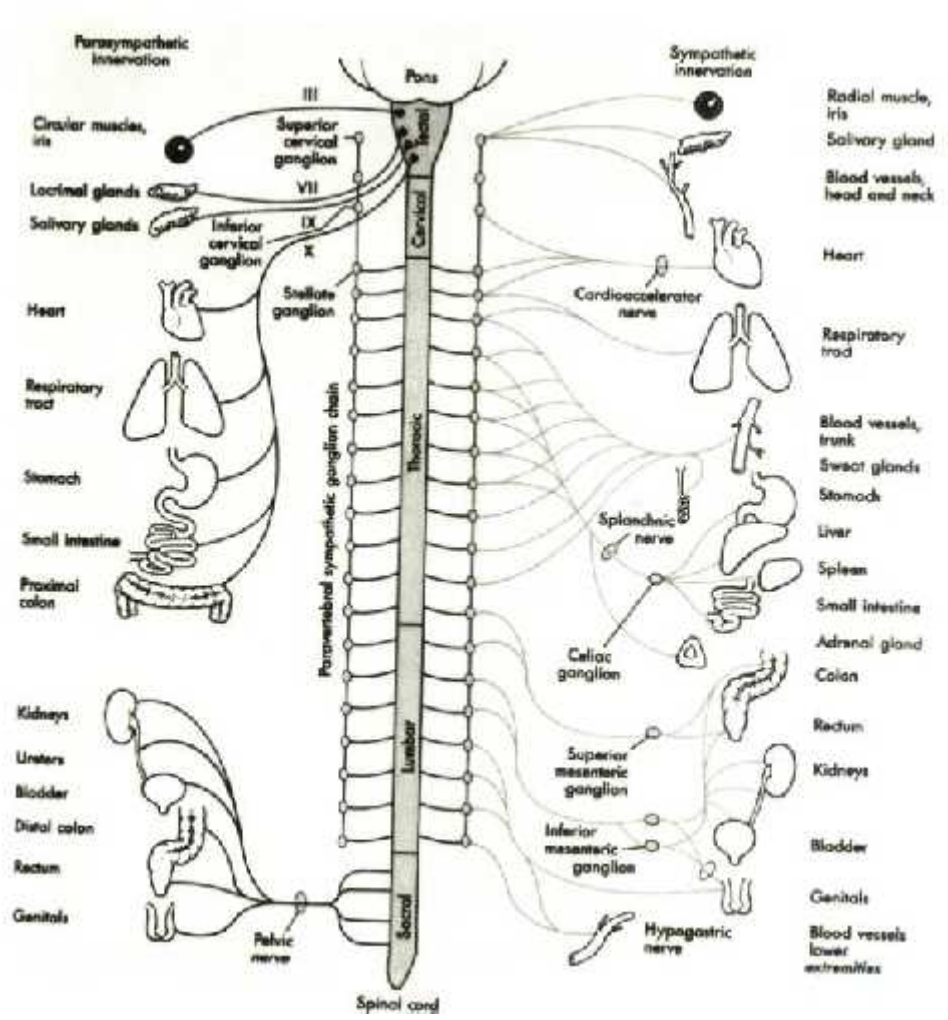


Figure 7. Schematic Representation of Autonomic Nervous System

Sympathetic pre-ganglionic fibers are relatively short because sympathetic ganglia are generally close to the CNS, but they are distant from the effector organs. Therefore, post-ganglionic fibers run a long course before innervating effector organs.

Arterial Circulation

Sympathetic denervation produces arterial vasodilatation. Arterial smooth muscle retains a significant degree of autonomous tone following acute,

pharmacologically induced sympathetic denervation. As a result, total peripheral vascular resistance (TPVR) decreases only modestly, about 15 to 18% in normal subjects even in the presence of total sympathetic denervation, provided cardiac output, the other determinant of blood pressure, is kept normal. Because TPVR decreases only 15 to 18%, mean arterial pressure decreases only 15 to 18% in the presence of a normal cardiac output.

Venous Circulation

Veins and venules, with only few smooth muscles in their walls, retain no significant residual tone following acute pharmacologic denervation and so they can vasodilate maximally. Whether they do so or not is determined by intraluminal hydrostatic pressure. Intraluminal hydrostatic pressure on the venous side of the circulation depends on the gravity. If the denervated veins lie below the right atrium, gravity causes peripheral pooling of blood in these venous capacitance vessels and if above, gravity causes the blood to flow back to the heart. Preload therefore depends on the position of the patient during spinal anesthesia.

Cardiac Output

Preload is an important determinant of cardiac output. During levels of spinal anesthesia high enough to produce total sympathetic denervation, cardiac output remains unchanged in normovolemic patients as long as they are positioned with the legs elevated above the level of the heart.

Heart Rate

Heart rate characteristically decreases during spinal anesthesia in the absence of autonomically active drugs. The bradycardia is due to blockade of preganglionic cardiac accelerator fibers arising from T1 to T4 during high levels of spinal anesthesia. The bradycardia is also mediated by significant decrease in the right atrial pressure and pressure in the great vessels as they enter the right atrium. Placing the patient in a slight head down position increases the venous return, which in turn increases the heart rate. The direct relationship between the right atrial pressure and heart rate during high spinal anesthesia is mediated by the intrinsic chronotropic stretch receptors located in the right atrium and adjacent great vessels. Heart rate decreases moderately (10 to 15%) in response to total sympathetic denervation. The mechanism responsible for such cardiovascular responses have been described as the Bezold – Jarisch reflex.[34]

Hypotension

The preceding indicates that slight decreases in the arterial pressure in the range of 15% or so during high spinal anesthesia in normovolemic patients can be ascribed to decreases in after load that is decreases in TPVR. Severe hypotension, however, can be due to decreases in cardiac output secondary to decreases in preload associated with peripheral pooling of blood in vasodilated capacitance vessels or to hypovolemia, or to both.

Myocardial Oxygenation

Myocardial oxygen demand decreases during hypotension associated with spinal anesthesia because of the following reasons:

- After load decreases: the resistance against which the left ventricle ejects blood during systole decreases.
- Preload decreases: as venous return and cardiac output decreases, which further decreases the work load of both the ventricles.
- Heart rate decreases.

Cerebral Blood Flow

Cerebrovascular autoregulatory mechanisms maintain cerebral blood flow in humans at constant levels even in the presence of wide fluctuations of mean arterial pressure and this autoregulation is independent of the sympathetic nervous system.

Respiratory System

The phrenic nerve supplying the diaphragm arises from the anterior root, root of C3 to C5 and should not be encroached on in spinal anaesthesia, but phrenic paralysis can occur. Medullary ischaemia or toxic effects of the drug in extradural block can produce apnea. During spinal anaesthesia breathing becomes quite and tranquil. This is not only due to motor blockade but also due to reduction of sensory input to the respiratory center. Lowered arterial and venous tone also lessens the work of the heart and tends to relieve any existing pulmonary congestion. The ventilation perfusion relationship during extradural

block is not greatly altered and the effect on respiratory function is relatively small with no evidence of change in functional residual capacity (FRC) or ventilation / perfusion (V/Q) ratio. 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, as it's innervations is by vagus. The small gut is contracted as sympathetic inhibitory impulses are removed, the vagus being all-powerful. The sphincters are relaxed and peristalsis is active although not more frequent. Pressure within the bowel lumen is increased. Handling of small bowel by the surgeon may cause it to dilate, as may the injection of atropine before the operation. Nausea and vomiting due to the hypotension may occur and usually comes on in waves lasting a minute or so and passes away spontaneously.

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

Spleen

The spleen enlarges 2-3 times in high blocks when its sympathetic efferent fibers are paralyzed. Colonic blood supply and oxygen availability are increased in animal following spinal anaesthesia, perhaps an important factor in the prevention of anastamotic breakdown following gut resection.

Liver

There are no effects of major significance. If the liver is diseased, a decrease in the mean arterial pressure (MAP) affects the liver blood flow and also the metabolism of amide anesthetics.

Endocrine System

Spinal block delays adrenal responses to injury and trauma, so there is no change in the levels of 17- hydroxy corticosteroids.

Spinal block suppresses the hyperglycaemic response to surgery and stress and so is useful in diabetic patients. The response to insulin is augmented, one should be aware of possibility of hypoglycaemia. Infused glucose is well utilised.

Genitourinary System

Sympathetic supply to kidney is from T11 to L1 via the lower splanchnic nerve. Any effects on renal function are solely due to hypotension, renal blood flow is decreased but does not cease until blood pressure has fallen to about 80 mm Hg. These changes are transient and disappear when blood pressure (BP)

rises again. The penis is often engorged and flaccid due to paralysis of nervi erigenti (S2 to S3) and this is also a positive sign of a successful block.

Post spinal retention of urine may be moderately prolonged as S2 to S3 contain small autonomic fibers and their paralysis lasts longer than that of larger sensory and motor fibers.

Uterus

The tone of uterus is not greatly altered after spinal analgesia in pregnancy. Block of nerves from T11 downwards results in painless labour. In late pregnancy, smaller doses of local anesthetics are required because of decreased extradural space.

Body Temperature

Vasodilatation favours heat loss, absence of sweating favours hyperpyrexia in hot environment and depressed secretion of catacholamine prevents heat loss.

BUPIVACAINE[35]

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. Superior penetration or 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.

Bupivacaine (Marcain, Marcaine and Sensorcaine)

Bupivacaine, an amino amide local anesthetic was first synthesized in Sweden by A.F Ekenstam and his colleagues in 1957. First report of its use was in 1963 by L.J Teluvio. It is one of the long acting local anesthetic agents available, which is extensively used for intrathecal, extradural and peripheral nerve blocks.

Chemistry

The molecular weight of chloride salt is 325 and that of base form is 288. pH of plain solutions varied between 4.5 to 6 and pKa 8.16. Bupivacaine HCl is

chemically designated as 2-piperidinecarboxamide, 1-butyl-N-(2,6-dimethylphenyl), monohydrochloride, monohydrate and has the following structure:

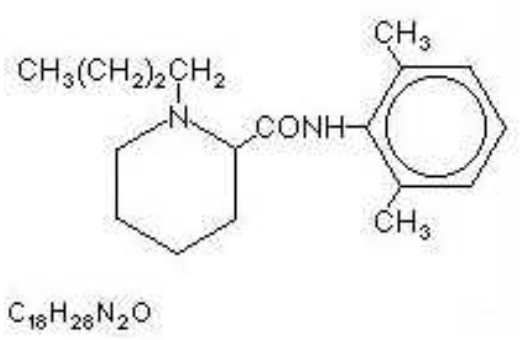


Figure 8. Chemical structure of bupivacaine

Presentation

Bupivacaine is available as 2.5 mg/ml, 5 mg/ml and 7.5 mg/ml solutions. Bupivacaine is also also available as 5 mg/ml with 80 mg/ml dextrose in a 4 ml clear ampule.

Chemical Structure

Bupivacaine has an IUPAC nomenclature of 1-butyl-n-(2, 6-dimethylphenyl) piperidine-2-carboxamide.

Dosage

Bupivacaine can be used in a dose for block upto a maximum of 2 mg/kg depending on the type and duration of surgery.

Properties

The base is sparingly soluble, but the hydrochloride salt is readily soluble in water. In spinal anesthesia, the onset of action is about three to four minutes and complete anesthesia occurs in five minutes and lasts for 3.5 to 4 hours. Because bupivacaine is an amide, the liver is the primary site of metabolism. Most of the drug is metabolized by N-dealkylation.

Physiochemical Properties

- Molecular formula C_{18} H_{28} N_2O
- Molecular weight 288.43 g/mol
- Solubility in water 25 mg/ml
- pH of saturated solution 5.2
- pKa 8.1
- Specific gravity 1.021 at 37°c

Mechanism of Action

Mechanism of action is similar to that of any other local anesthetic. The primary action is on the cell membrane axon, on which it produces electrical stabilization. Bupivacaine prevents the generation and the conduction of the nerve impulse. Bupivacaine blocks conduction by decreasing or preventing the large transient increase in permeability of excitable membranes to sodium that normally is produced by a slight depolarization of the membrane. This action of Bupivacaine is due to its direct interaction with the voltage gated sodium channels. As the anaesthetic action progressively develops in a nerve, the

threshold for electrical excitability gradually decreases, the rate of rise of the action potential declines, impulse conduction slows, and the safety factor for conduction decreases, these factors decrease the probability of propagation of the action potential and nerve conduction fails. The mechanism by which local anaesthetics block sodium conductance is as follows:

Local anesthetics in the cationic form act on the receptors within the sodium channels on cell membrane and block it. The local anesthetics can reach the sodium channel either via the lipophilic pathway directly across the lipid membrane, or via the axoplasmic opening. This mechanism accounts for 90% of the nerve blocking effects of amide local anesthetics.

The second mechanism of action is by membrane expansion. This is a non-specific drug receptor interaction. Bupivacaine is available in the following concentrations:

- 0.25%. 0.5% and 1%
- 0.25% and 0.5% solution in isotonic saline
- 0.5% solution in 8% dextrose
- Dosage for nerve blocks is two mg/kg limited to 150 mg in four hours.
- The intrathecal dosage is 0.1 to 0.3 mg/kg.

Basic Pharmacology

Bupivacaine hydrochloride is 2-piperidine carboxamide, 1 butyl N-2, 6 dimethyl phenyl, monohydrochloride, monohydrate. Bupivacaine 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.

Structure – Activity relationship

Bupivacaine being more lipophilic (because of butyl group) is very potent and produces longer lasting blocks.

pKa of any drug is defined as the hydrogen ion concentration specific for each drug at which the concentration of local anaesthetic base is equal to the concentration of charged cation. pKa of bupivacaine hydrochloride is 8.1 at 36ºC.

Anaesthetic Potency

Hydrophobicity appears to be a primary determinant of intrinsic anesthetic potency and Bupivacaine 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

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

Pharmacokinetics

The concentration of Bupivacaine in blood is determined by the amount injected, the rate of absorption from the site of injection, the rate of tissue distribution and the rate of biotransformation and excretion of Bupivacaine.

Absorption

The site of injection, dose and addition of a vasoconstrictor determine the systemic absorption of Bupivacaine .The maximum blood level of Bupivacaine 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 describe this. 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. Bupivacaine is rapidly excreted by lung tissue. Though skeletal muscle does not show any particular affinity for bupivacaine, it is the largest reservoir of the drug.

Distribution Characteristics

- T1/2 α 2-7 minutes (uptake by rapid equilibrium tissue)
- T1/2 β 28 minutes (distribution by slowly perfused tissues)
- T1/2 γ 3-5 hours (metabolism and elimination)
- VDSS 72 liters (volume of distribution at steady state)

Clinical Pharmacology

1. Anaesthetic potency: Hydrophobicity is a major determinant of intrinsic anaesthetic potency and bupivacaine 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 bupivacaine:*** As the dosage of bupivacaine is increased, the probability and duration of satisfactory analgesia will increase and the time of onset of block will be shortened.
2. ***Addition of vasoconstrictors:*** Addition of adrenaline does not significantly increases the duration of action of bupivacaine.
3. ***Site of action:*** The latency and duration are long when given for brachial block and epidural block.
4. ***Compounding of local anaesthetics:*** The basis for this practice is rapid onset of one agent. e.g., lidocaine and longer duration of action of other agent, e.g. bupivacaine.

5. ***Pregnancy:*** The spread and depth of spinal and epidural anaesthesia are greater in pregnant patients than in non-pregnant women.
6. ***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 power and more availability of diffusible base of the local anaesthetic. When pH of the solution is equal to pKa of local anaesthetic solution, half of the drug is present as ionized water-soluble cation and rest half as lipid soluble unionized base since this non-ionised soluble form is permeable to nerve cell membrane; it has a major role in penetration.

   Alkalinisation of local anaesthetic solution acts by

   - A direct depressant effect of CO_2 on the axon.
   - Concentrating 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 bupivacaine increases the pH of the solution without affecting its chemical stability.

Actions

Central Nervous System

Bupivacaine readily crosses the blood brain barrier causing CNS depression following higher doses. The initial symptoms involve feeling of light-headedness 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 still higher doses, cardiovascular or respiratory arrest may occur. Acidosis increases the risk of CNS toxicity from Bupivacaine, since an elevation of $PaCO_2$ enhances cerebral blood flow, so that more anesthetic is delivered rapidly to the brain

Autonomic nervous system

Bupivacaine does not inhibit the Nor Adrenaline uptake and hence has no sympathetic potentiating effect. Myelinated preganglionic B fibers have a faster conduction time and are more sensitive to action of Bupivacaine. When used for conduction blockade, Bupivacaine produces faster sensory block compared to motor block.

Cardiovascular System

The primary cardiac electrophysiological effect of a local anesthetic is a decrease in the maximum rate of depolarization in Purkinje fibers and ventricular muscle. This action by Bupivacaine is far greater compared to Lignocaine. Also, the rate of recovery of block is slower with Bupivacaine. Therefore there is

complete restoration of Vmax between action potential particularly at higher rates. Bupivacaine reduces the cardiac contractility. This is by blocking the calcium transport. Low concentration of Bupivacaine produces vasoconstriction whereas high doses causes vasodilatation.

Respiratory System

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

Biotransformation And Excretion

Bupivacaine 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 Bupivacaine 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 n-dealkylated metabolite of bupivacaine. 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

CNS: Nervousness, dizziness, blurring of vision or tremors, drowsiness, convulsions and respiratory arrest.

CVS: Myocardial depression, hypotension, arrhythmia, ventricular type conduction defect, Sino Atrial node depression and cardiac arrest

Allergic reactions: Urticaria, bronchospasm, hypotension

Other: Constriction of pupil and tinnitus

ROPIVACAINE

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 same group as that of bupivacaine and mepivacaine, pipecoloxylidides local anaesthetics, ropivacaine was introduced to clinical practice in 1996.

It was found that “propyl derivatives” of pipecoloxylidides were less toxic than ‘butyl derivatives’ (bupivacaine). Thus Ropivacaine was developed after bupivacaine was noted to be associated with significant number of cardiac arrests.[7] 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)[37]It is used as local anaesthestic including infiltration, nerve block, epidural and for intrathecal anaesthesia. It is also used for peripheral nerve blocks and caudal epidural in children for surgical pain relief.

CHEMICAL STRUCTURE

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

a molecular weight of 328.89. The chemical structure is given in the figure 9.

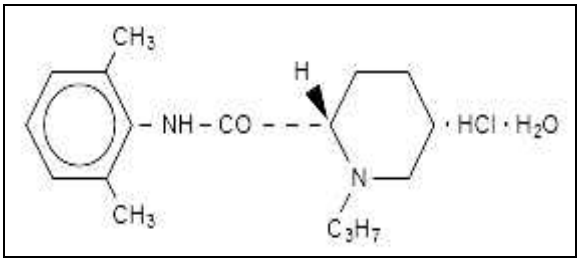


Figure 9. Chemical structure of ropivacaine

Physical Properties

At 25°C ropivacaine HCL has a solubility of 53.8 mg/mL in water, a distribution ratio between n-octanol and phosphate buffer at pH 7.4 of 14:1 and a pKa of 8.07 in 0.1 M KCl solution. The pKa of ropivacaine is approximately the same as bupivacaine (8.1). However, ropivacaine has a lower lipid solubility (substitution of pipecoloxylidine with a 3-carbon side chain instead of a 4–carbon side chain)[38] compared to bupivacaine and mepivacaine. Usually sodium hydroxide or hydrochloric acid is added to adjust pH of the compound. Ropivacaine is preservative free and is available in single dose containers in 2 (0.2%), 5 (0.5%), 7.5 (0.75%) and 10 mg/mL (1%) concentrations .The specific gravity of solutions range from 1.002 to 1.005 at 25°C.

Mechanism of Action

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

a. Block generation and conductance of nerve impulses.
b. Slows propagation of nerve impulses

c. Reduces the rate of rise of action potential

Most local anaesthetics block the unmyelinated C and myelinated Aδ fibers that transmit pain impulses at the same rate. However the rate of blockade of Aα and Aβ (that carry motor impulses) depends on the physicochemical properties, Pka and lipid solubility of the individual local anaesthetic drugs. As ropivacaine is less lipid soluble when compared to bupivacaine , the blockade of Aα and Aβ is slow and hence produce less motor blockade than bupivacaine. Studies of lumbar epidural block in humans have confirmed that equal volumes and concentrations of bupivacaine and ropivacaine produce similar degree of sensory block while the motor block produced by ropivacaine is slower in onset, less in intensity and short in duration. Clinically the order of blockade of nerve fibres is autonomic, sensory and motor, while the disappearance occurs in reverse order. The order of the loss of nerve function is

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

Pharmacokinetics

Absorption

The systemic concentration of ropivacaine is dependent on the total dose and concentration of drug given, the route of administration, the patient's

haemodynamic condition and the vascularity of the site of administration. Ropivacaine from the epidural space shows complete and biphasic absorption. The half lives of the 2 phases (mean ± SD) are 14 ± 7 minutes and 4.2 ± 0.9 h, respectively.

Distribution

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

Metabolism

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

Elimination

Ropivacaine metabolites are mainly excreted via kidney. After I.V administration 86% of the dose is excreted in urine of which only 1% is in unchanged form. Following I.V administration ropivacaine has a mean ± SD total plasma clearance of 387 ± 107 mL/min, an unbound plasma clearance of 7.2 ±

1.6 L/min and a renal clearance of 1 mL/min. The mean ± SD terminal half life is 1.8 ± 0.7 h and 4.2 ±1.0 h after I.V and epidural administration respectively.

POTENCY[38]

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 less molecules are required for conduction blockade resulting in enhanced potency. For this reason, a strict correlation between the lipid solubility of the local anaesthetic and its potency and toxicity exists. Mc Donald et al[39] compared three intrathecal doses of ropivacaine and bupivacaine (4, 6 and 8 mg) in healthy volunteers and reported that ropivacaine is half as potent as bupivacaine.

Using the same up-down sequential technique for determining the minimum local anaesthetic concentration (MLAC) producing adequate pain control in 50% of patients receiving an epidural for labour pain[40] and found nearly 50% higher MLAC values[41] for ropivacaine when compared to bupivacaine. A study[42] determined the minimum volume of local anaesthetic to produce an effective block of femoral nerve in 50% of patients within 20 min after the injection similar to that required when using 0.5% bupivacaine.

Intrathecal administration

Intrathecal anaesthesia is useful for ambulatory anaesthesia, requirements of which are a sensory and motor block of adequate duration for the procedure and a fast regression of the motor block to assist mobilisation. The majority of

data relating to the efficacy of intrathecal ropivacaine for regional anaesthesia to date are derived from studies of patients undergoing caesarean section or orthopaedic surgery. Ropivacaine has also shown efficacy in several trials in other types of surgery such as perineal surgery,[43] inguinal herniorrhaphy,[44] other lower abdominal or gynaecological procedures[45] and anorectal surgery.[46]

Adverse effects

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

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

Management of complications

Discontinuation of ropivacaine should be done at the first sign of toxicity. As no specific antidote is available, symptomatic and supportive management should be done promptly. Any change in mentation need oxygen administration. Secure airway and provide assisted ventilation if any signs of respiratory depression are observed. Convulsions can be treated with barbiturates, specific anticonvulsants or neuromuscular blockers. In case of cardiac arrest ,prolonged resuscitative efforts might be required.

Drug interactions

Ropivacaine should be used with caution in patients receiving other local anaesthetics or agents structurally related to amide-type local anaesthetics, as these are additives. Strong inhibitors of cytochrome P4501A2, such as fluvoxamine can interact with ropivacaine leading to increased ropivacaine plasma levels. Drug interactions can also occur with the drugs known to be metabolized by cytochrome P1A2 via competitive inhibition such as theophylline and imipramine.

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 op 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.

The extensive clinical use of ropivacaine through various routes for a variety of surgeries have confirmed a long lasting block similar to that provided by racemic bupivacaine. Another clinically relevant advantage with ropivacaine is greater differentiation between sensory and motor blockade, that is particularly useful if early mobilization is needed to enhance postoperative recovery. Though 40 to 50% less potent than bupivacaine, ropivacaine in a equipotency ratio of 1.5:1 produces results in a similar clinical profile with good preservation of motor function. Ropivacaine is the only local anaesthetic that is specifically approved for use by infusion.[47]

FENTANYL[48,49]

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

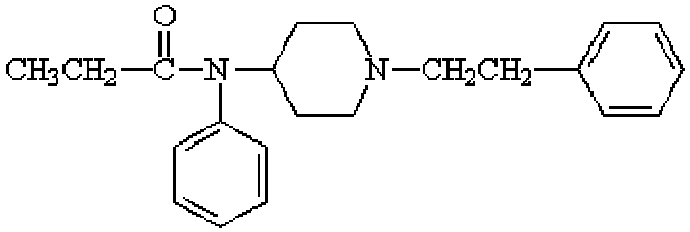


Figure 10. Chemical Structure of Fentanyl

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

Physiochemical properties

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 presynaptic and postsynapatic 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 much more rapid with shorter duration of action. The effect site equilibration time between blood and the brain is 6.4 minutes. Its rapid onset of action reflects the greater lipid solubility.

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 Literskg^{-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 litershour^{-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 return of Opioid from peripheral tissues to the plasma.

DRUG INTERACTIONS

There are 3 general types of mechanism of drug interactions pharmaceutical, pharmacokinetic, and pharmacodynamic.

Sedatives and hypnotics

Benzodiazepines potentiate the effects of Fentanyl for loss of consciousness.

Thiopental or Propofol with Opioids produce hypotension due to venodilatation and decreased cardiac filling, so induction doses are reduced when administered along with Fentanyl.

Inhaled Anaesthetics

Volatile anaesthetics requirement is reduced in low dose (One third of MAC) with Fentanyl to ensure amnesia and haemodynamic stability.

Muscle relaxant

Combination of high doses of Opioid and Vecuronium produce negative ionotropic and chronotropic effect on the heart.

Calcium channel blockers

Calcium channel blockers Potentiate the actions of Fentanyl

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 ventilatory centres to carbondioxide.

Central nervous system

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

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. Pruritis produced by neuraxial Opioids is likely due to cephalad migration of opioids in cerebrospinal fluid and subsequent interaction with opioid receptors in trigeminal nucleus. Pruritis is more likely to be localized to face, neck and upper thorax.

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.

Mechanism responsible for tolerance and physical dependence is determined to be down regulation in the number of opioid receptors in the brain.

Chapter 5

Methodology

METHODOLOGY

Study design

A one year hospital based randomized clinical study.

Study Period

One year from January 2012 to December 2012.

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, Belgaum

Source of Data

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

Sampling procedure

Based on the results of previous studies considering time for duration of motor block as 182 ± 46 minutes for Bupivacaine with Fentanyl and 139 ± 39 minutes for Ropivacaine with Fentanyl and based on the statistical formula the sample size was calculated as below.

$$\text{Sample Size (n)} = \frac{2 \times (Z\alpha + Z\beta)^2 (S_1^2 + S_2^2)}{(\bar{X}_1 - \bar{X}_2)^2}$$

Where,

Level of significance was considered as 5%

Power of the test used as 80%

Hence, $Z\alpha = 1.96$

$Z\beta = 0.84$

$2s^2 = (46)^2 + (39)^2$

$\bar{X}_1 = 182$

$\bar{X}_2 = 139$

With these values, the minimum sample size was obtained as 37 for each group. Further for the sake of consistency in results the sample size was considered as 40 in each group.

Sample Size

A total of 80 patients distributed into two groups of 40 each undergoing elective lower abdominal surgeries under spinal anaesthesia were enrolled.

Selection Criteria

Inclusion criteria

- ASA Grade I and II patients.
- Aged between 20 to 60 years group.

- Patients undergoing lower abdominal surgeries lasting 60 to 120 minutes.

Exclusion criteria

- Patient refusal.
- Contraindications to sub arachnoid block.
- Pre-existing neurological deficits in lower extremities
- Pre-existing deficits in the following systems;
    - Cardiovascular
    - Respiratory
    - Neurological
    - Psychological
    - Hepatic
    - Renal

Ethical clearance

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

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).

Randomization

Patients were randomized based on computerized generated randomization into two groups.

- Group B (n=40)
- Group R (n=40)

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

Preanaesthetic Examination and Preparation

Overnight fasting status was confirmed. Anaesthetic techniques were standardized for all patients. Preanaesthetic check up was done one day prior to the surgery. Patients were evaluated for any systemic diseases and laboratory investigations were recorded.

Before shifting to the operation theatre, I.V access was obtained with 18 Gauge I.V cannula and patients were preloaded with intravenous infusion of 10 mL/Kg of ringers lactate solution 30 minutes prior to surgery.

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 B

Under all aseptic precautions, L_{3-4} space identified, a 23G Quincke's spinal needle was inserted into L_{3-4} space and 2.5 cc (12.5 mg) of 0.5% Bupivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl was injected into the space. Patients were turned immediately to supine position.

Group R

Under all aseptic precautions, L_{3-4} space identified and a 23G Quincke's spinal needle inserted into L_{3-4} space and 2.5 cc (18.75 mg) of 0.75% Ropivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl was injected into the space. Patients were turned immediately to supine position.

Hypotension

Hypotension was defined as decrease in systolic blood pressure by 30% from baseline values or a systolic blood pressure less than 90 mm of Hg and was treated with incremental intravenous boluses of mephentermine 6 to 12 mg and a bolus administration of 250 ml of ringer lactate solution over 10 minutes.

Bradycardia

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

Outcome variables

- Sensory block: Sensory block was assessed bilaterally, using alcohol swab in mid axillary line. Sensory block onset was defined as the time taken to achieve T_{10} block level and duration of sensory block was defined as two dermatome regression of anaesthesia from the highest level. The surgery was allowed to start once sensory block reached at least T_{10} but general anaesthesia was induced if this did not occur after 15 minutes.

- Motor block: Motor block was assessed immediately after sensory block using a Modified Bromage Grade. Onset of motor block was defined as the time to reach Modified Bromage Grade 1 and Total duration of motor block was defined as the time for return to Modified Bromage Grade 0.

    - Bromage 0, free movement of legs and feet, 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.

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

- Systolic blood pressure, Diastolic blood pressure, Mean arterial pressure and Heart rate were recorded at 2, 4, 6, 8, 10, 15, 20, 25, 30 minutes and every 15 minutes till the end of surgery.

- Time to request for first post operative rescue analgesia – In the post anaesthesia care unit, time to request for first post-operative rescue analgesia was noted . Post-operative pain score was measured by using VAS of ‘zero’ to ‘ten’ where ‘zero’ indicated no pain and ‘ten’ indicated worst imaginable pain. Rescue analgesia of injection paracetamol 1gram intravenously was given if the VAS score was more than three.

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.

Chapter 6

Results

RESULTS

The present one year hospital based study was conducted in the Department of Anaesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. during the period of January 2012 to December 2012.

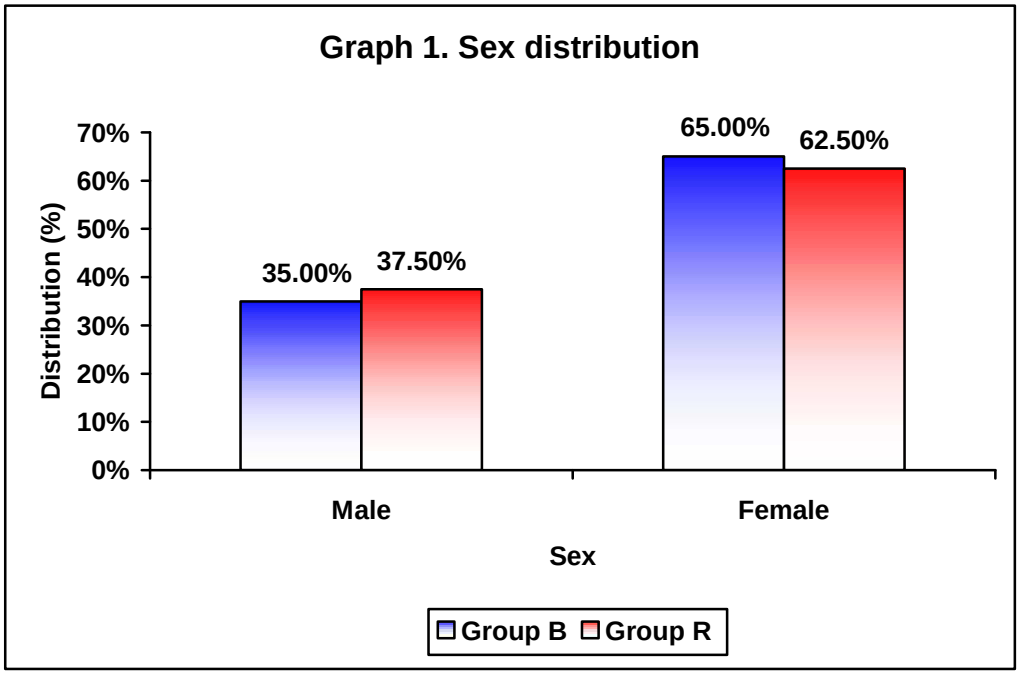
A total of 80, ASA Grade I and II, aged between 20 to 60 years of either gender were distributed into two groups of 40 each, Group B recieved 2.5 cc (12.5 mg) of 0.5% Bupivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl and Group R received 2.5 cc (18.75 mg) of 0.75% Ropivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl.

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

Table 1. Sex distribution

Sex	Group B (n=40)		Group R (n=40)	
	Number	**Percentage**	**Number**	**Percentage**
Male	14	35.00	15	37.50
Female	26	65.00	25	62.50
Total	**40**	**100.00**	**40**	**100.00**

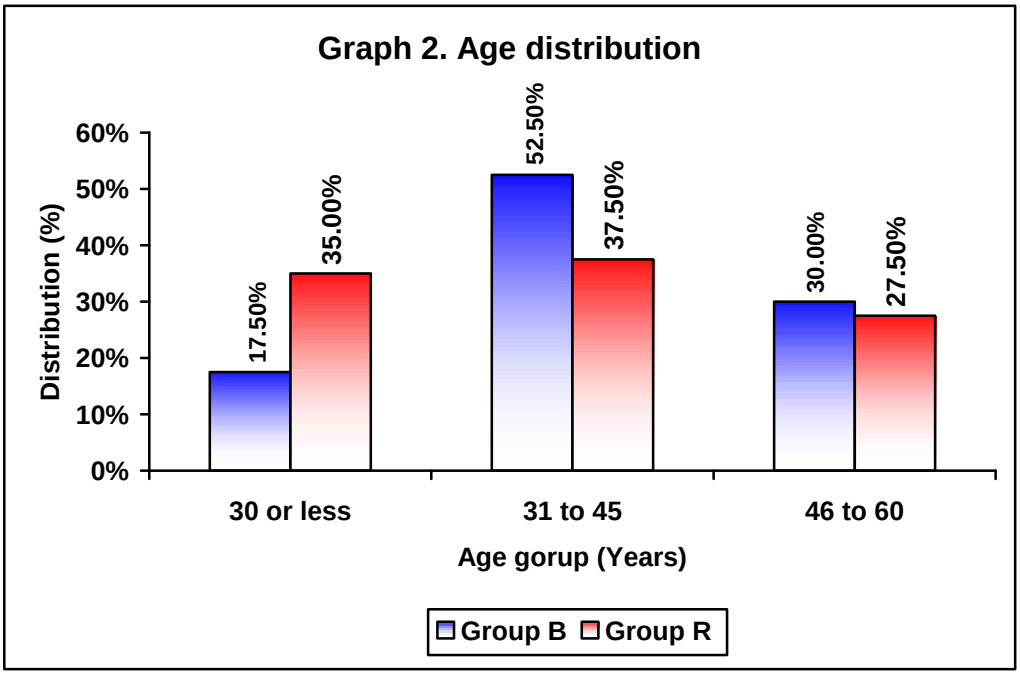
X^2= 0.054 **p = 0.816**



In the present study, 65% of patients in group B were females compared to 62.50% in group R. The male to female ratio was 1:1.85 in group B and in group R it was 1:1.66. However the sex distribution in group B and R was comparable (p =0 .816).

Table 2. Age distribution

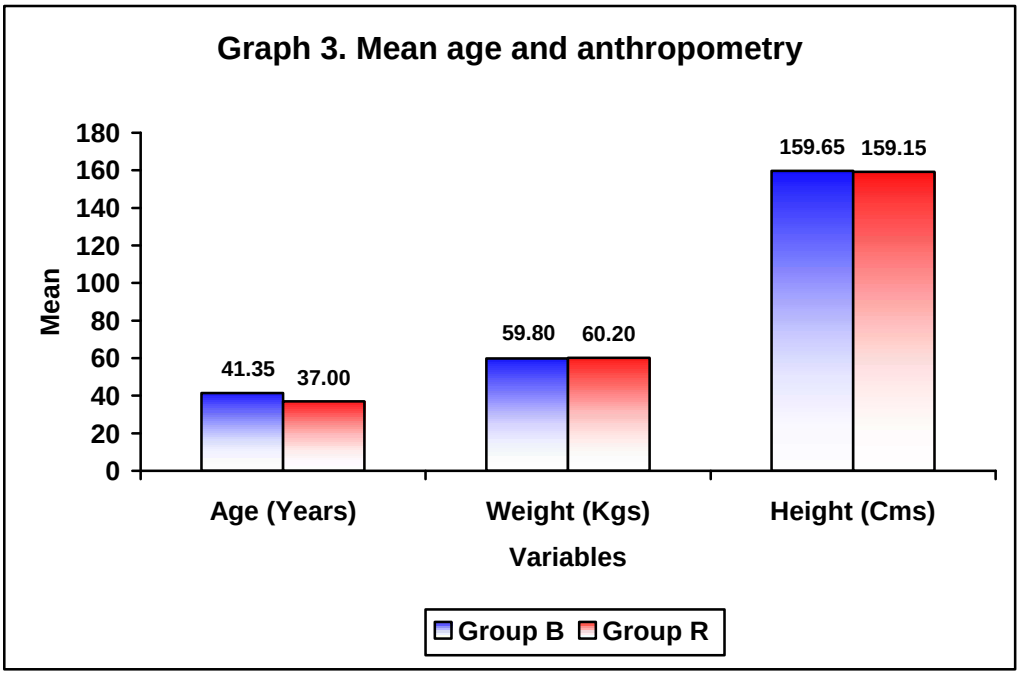
Age group (Years)	Group B (n=40)		Group R (n=40)	
	Number	**Percentage**	**Number**	**Percentage**
30 or less	7	17.50	14	35.00
31 to 45	21	52.50	15	37.50
46 to 60	12	30.00	11	27.50
Total	**40**	**100.00**	**40**	**100.00**



In this study most of the patients in group B (52.5%) and R (37.5%) were aged between 31 to 45 years.

Table 3. Mean age and anthropometry

Variables	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Age (Years)	41.35	10.84	37.00	12.24	0.096
Weight (Kgs)	59.80	8.27	60.20	7.47	0.821
Height (Cms)	159.65	6.77	159.15	5.76	0.723

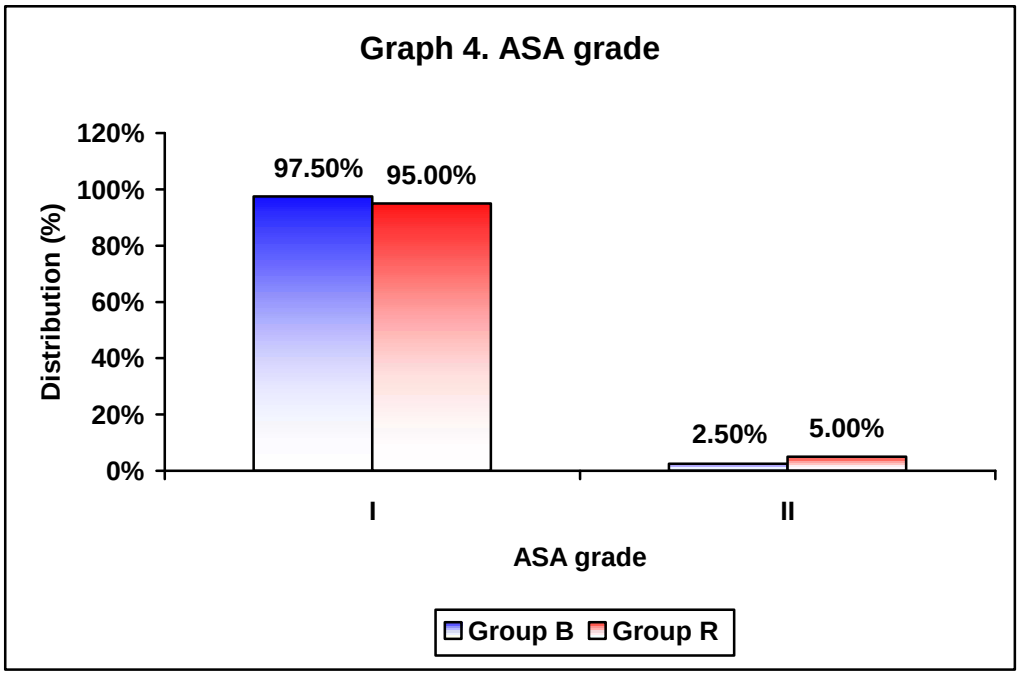


In the present study no statistically significant difference was observed between group B and group R with regard to mean age (41.35 ± 10.84 and 37.00 ± 12.24 years respectively; p = 0.096), mean weight (59.80 ± 8.27 and 60.20 ± 7.47 Kgs respectively; p = 0.821) and mean height (159.65 ± 6.77 and 159.15 ± 5.76 Cms respectively; p = 0.723)

Table 4. ASA grade

ASA grade	Group B (n=40)		Group R (n=40)	
	Number	Percentage	Number	Percentage
I	39	97.50	38	95.00
II	1	2.50	2	5.00
Total	**40**	**100.00**	**40**	**100.00**

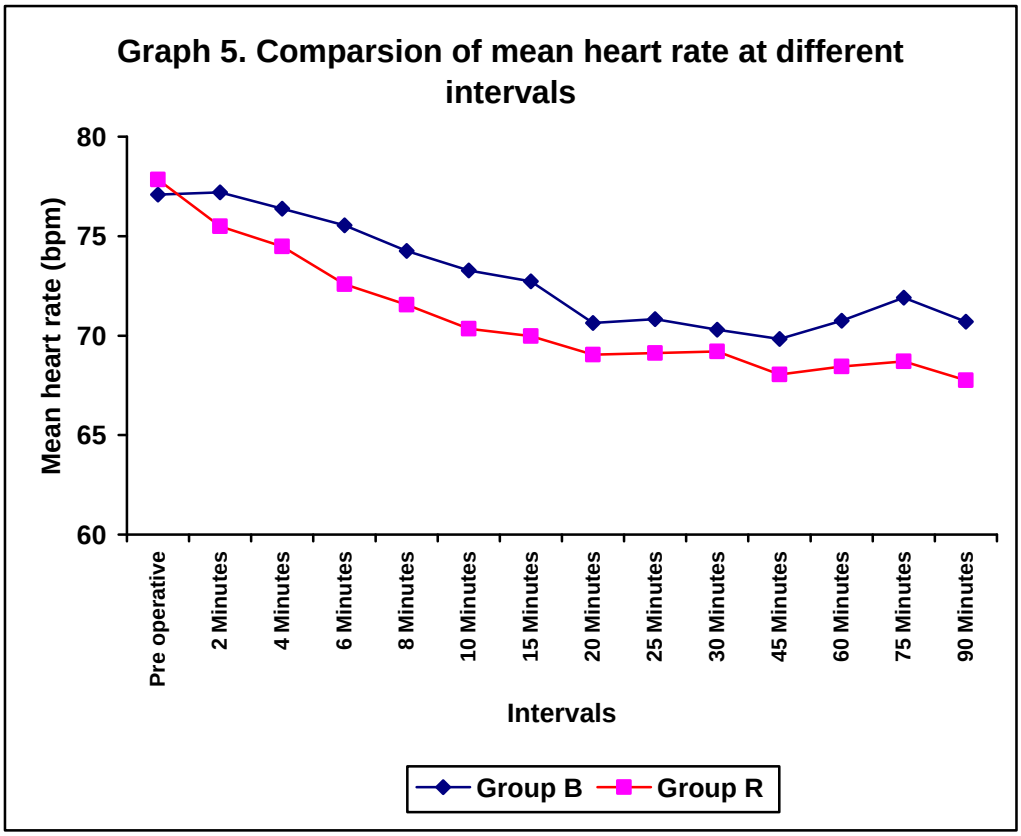
x^2 = 0.0 (With Yate's correction) **p = 1.000**



In this study, in group B, 97.5% patients had ASA class I and in group B it was noted among 95% of patients.

Table 5. Comparison of mean heart rate at different intervals (bpm)

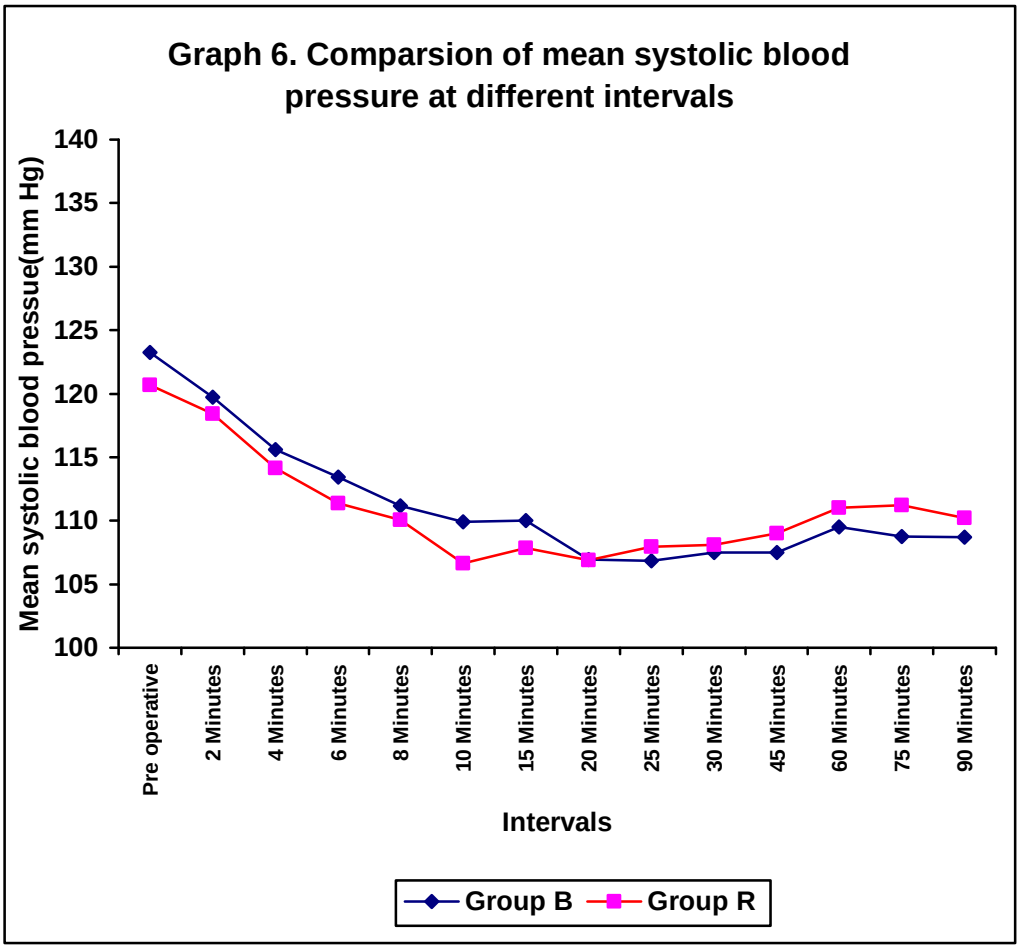
Intervals	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Pre operative	77.08	7.37	77.85	8.76	0.670
2 Minutes	77.20	9.69	75.50	7.65	0.387
4 Minutes	76.38	10.49	74.48	8.33	0.373
6 Minutes	75.55	9.22	72.58	6.61	0.102
8 Minutes	74.25	8.86	71.55	8.06	0.158
10 Minutes	73.28	7.92	70.35	8.40	0.113
15 Minutes	72.73	9.46	69.98	8.35	0.172
20 Minutes	70.63	7.78	69.05	6.69	0.335
25 Minutes	70.83	7.62	69.13	7.04	0.303
30 Minutes	70.30	8.65	69.20	6.89	0.531
45 Minutes	69.83	7.28	68.05	8.06	0.305
60 Minutes	70.75	8.38	68.45	5.72	0.156
75 Minutes	71.90	10.83	68.70	6.78	0.118
90 Minutes	70.70	10.56	67.76	7.67	0.158



In this study the mean heart rate in group B at beginning was noted as 77.08 ± 7.37 bpm which decreased upto 69.83 ± 7.28 bpm at 45 minutes interval and reached 70.70 ± 10.56 bpm at 90 minutes. In group R, the mean heart rate at beginning was 77.85 ± 8.76 bpm which reduced to 69.05 ± 6.69 bpm at 20 minutes intervals and further reduced to 67.76 ± 7.67 at 90 minutes. However at all the intervals the mean heart rate in group B and R was comparable ($p > 0.05$)

Table 6. Comparison of mean systolic blood pressure at different intervals (mm Hg)

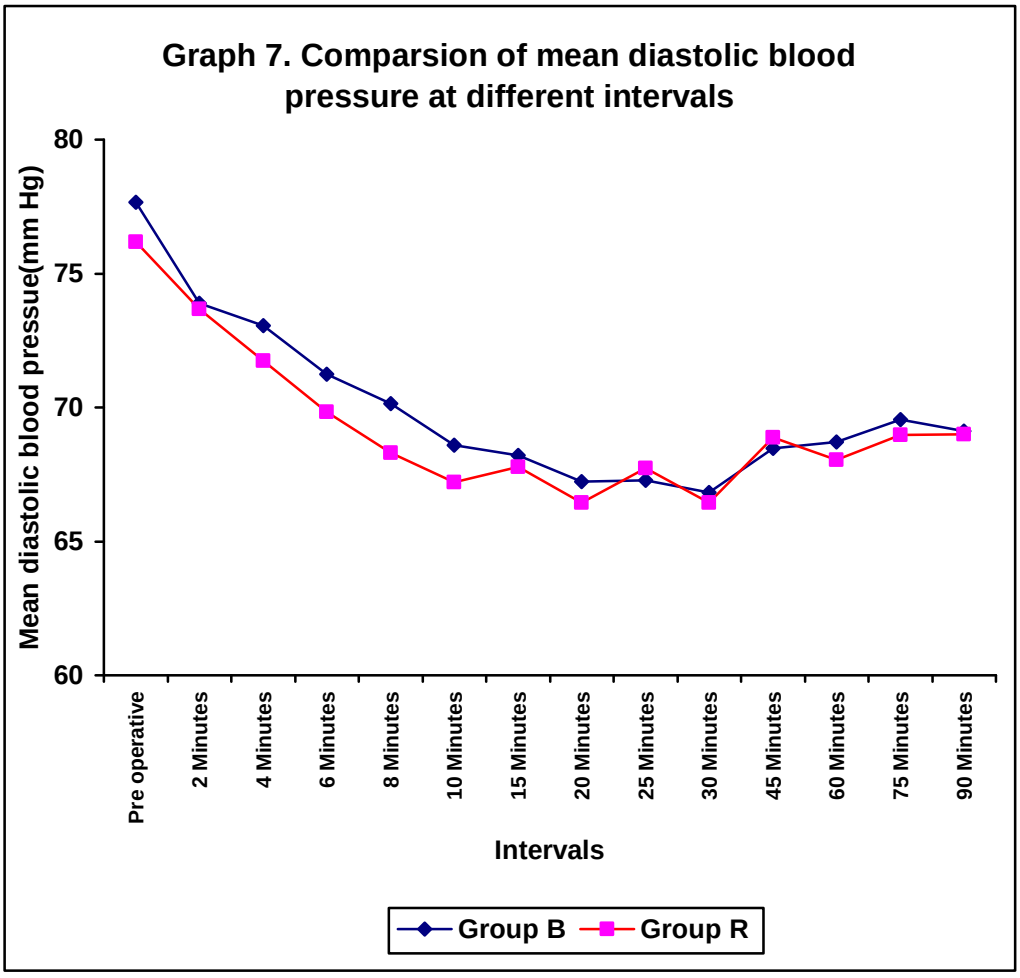
Intervals	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Pre operative	123.25	10.19	120.70	8.29	0.223
2 Minutes	119.70	10.57	118.43	8.56	0.555
4 Minutes	115.58	12.71	114.13	9.38	0.563
6 Minutes	113.43	12.47	111.35	8.62	0.390
8 Minutes	111.15	10.74	110.05	10.36	0.642
10 Minutes	109.90	13.60	106.63	19.35	0.384
15 Minutes	110.00	12.76	107.83	11.10	0.419
20 Minutes	106.95	12.96	106.90	11.58	0.986
25 Minutes	106.85	15.58	107.95	10.47	0.712
30 Minutes	107.50	14.31	108.08	8.75	0.829
45 Minutes	107.50	12.91	109.03	10.05	0.557
60 Minutes	109.53	12.88	111.00	7.35	0.532
75 Minutes	108.73	11.16	111.20	7.64	0.251
90 Minutes	108.72	10.30	110.20	7.18	0.459



In this study, the mean systolic blood pressure in group B, at two minutes interval was 119.70 ± 10.57 mm Hg which, reduced upto 106.95 ± 12.96 mm Hg at 20 minutes duration and further slight rise was noted at 90 minutes duration that is 108.72 ± 10.30 mm Hg. Similarly, in group R, the systolic blood pressure at two minutes duration was 118.43 ± 8.56 mm Hg which gradually reduced to 106.63 ± 19.35 mm Hg at 10 minutes duration and further slight increase upto 110.20 ± 7.18 mm Hg was noted at 90 minutes duration. However the mean systolic blood pressure at all the intervals in group B and R were comparable ($p > 0.05$).

Table 7. Comparison of mean diastolic blood pressure at different intervals (mm Hg)

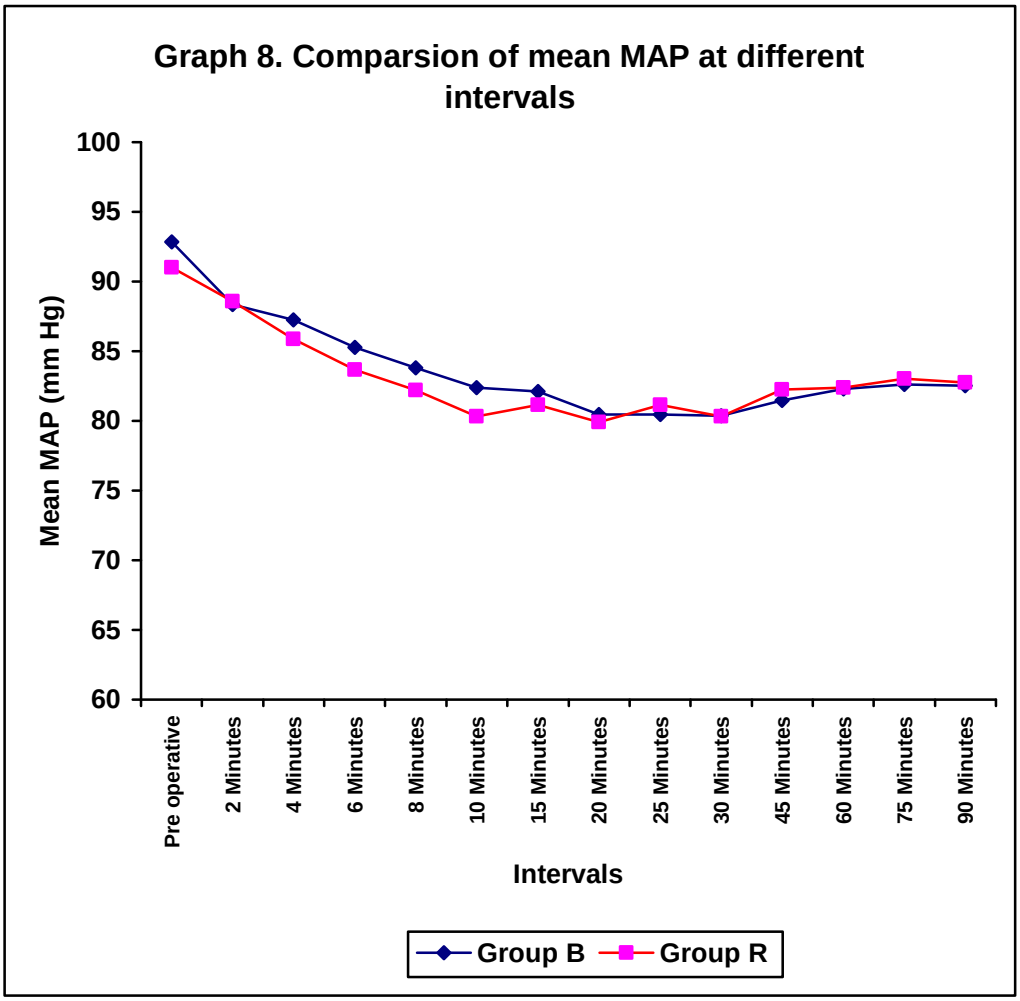
Intervals	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Pre operative	77.65	7.12	76.18	6.28	0.329
2 Minutes	73.90	7.56	73.68	8.66	0.902
4 Minutes	73.05	9.09	71.75	8.12	0.502
6 Minutes	71.23	8.65	69.83	8.11	0.457
8 Minutes	70.15	7.62	68.30	7.81	0.287
10 Minutes	68.60	9.62	67.20	8.81	0.499
15 Minutes	68.20	10.11	67.78	11.12	0.858
20 Minutes	67.23	10.30	66.45	9.27	0.725
25 Minutes	67.28	11.28	67.73	7.83	0.836
30 Minutes	66.83	11.02	66.45	7.52	0.859
45 Minutes	68.48	9.61	68.88	8.25	0.842
60 Minutes	68.70	9.38	68.05	5.52	0.707
75 Minutes	69.55	8.97	68.98	6.27	0.741
90 Minutes	69.11	9.10	69.00	6.28	0.953



In the present study, preoperatively the mean diastolic blood pressure in group B and R differed slightly but the difference was statistically not significant (77.65 ± 7.12 and 76.18 ± 6.28 mm Hg respectively; p = 0.329). There was a decrease in mean diastolic blood pressure at 30 minutes interval that is, 66.83 ± 11.02 mm Hg in group B and 66.45 ± 7.52 mm Hg in group R but this difference was statistically not significant (p = 0.859). Further at 90 minutes also the mean systolic blood pressure in group R and B were comparable (69.11 ± 9.10 and 69.00 ± 6.28 mm Hg respectively; p = 0.953).

Table 8. Comparison of mean MAP at different intervals (mm Hg)

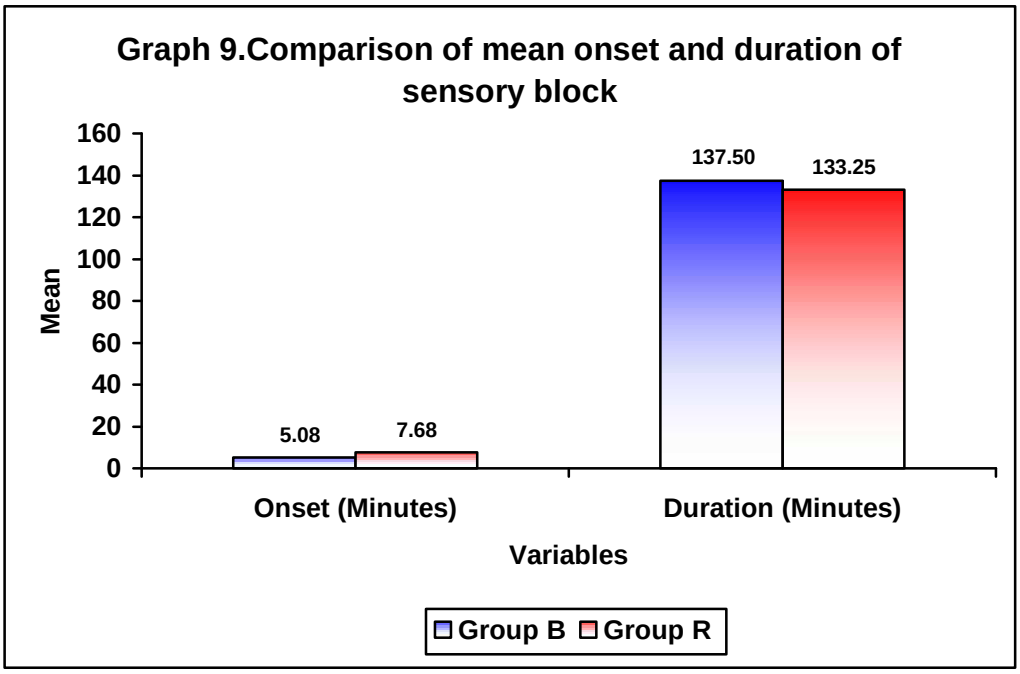
Intervals	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Pre operative	92.85	7.64	91.02	6.40	0.248
2 Minutes	88.34	10.09	88.59	8.04	0.903
4 Minutes	87.23	9.74	85.88	7.97	0.500
6 Minutes	85.29	9.56	83.67	7.57	0.402
8 Minutes	83.82	8.02	82.22	8.03	0.376
10 Minutes	82.37	10.26	80.34	10.28	0.381
15 Minutes	82.13	10.53	81.13	9.24	0.650
20 Minutes	80.47	10.72	79.93	9.28	0.813
25 Minutes	80.47	12.23	81.13	7.90	0.773
30 Minutes	80.38	11.60	80.33	6.94	0.978
45 Minutes	81.48	10.22	82.26	8.08	0.708
60 Minutes	82.31	10.12	82.37	5.30	0.974
75 Minutes	82.61	8.54	83.05	6.10	0.791
90 Minutes	82.51	9.00	82.73	5.97	0.896



In this study, the mean MAP in group B, at two minutes interval was 88.34 ± 10.09 mm Hg which, reduced upto 80.38 ± 11.60 mm Hg at 30 minutes interval and further slight rise was noted at 90 minutes duration that is 82.51 ± 9.00 mm Hg. Similarly, in group R, the mean MAP at two minutes duration was 88.59 ± 8.04 mm Hg which gradually reduced to 79.93 ± 9.28 mm Hg at 20 minutes duration and further slight increase upto 82.73 ± 5.97 mm Hg was noted at 90 minutes duration. However the mean MAP at all the intervals in group B and R were comparable ($p > 0.05$).

Table 9. Comparison of mean onset and duration of sensory block

Variables	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Onset (Minutes)	5.08	0.83	7.68	1.02	**<0.001**
Duration (Minutes)	137.50	11.04	133.25	11.85	0.101

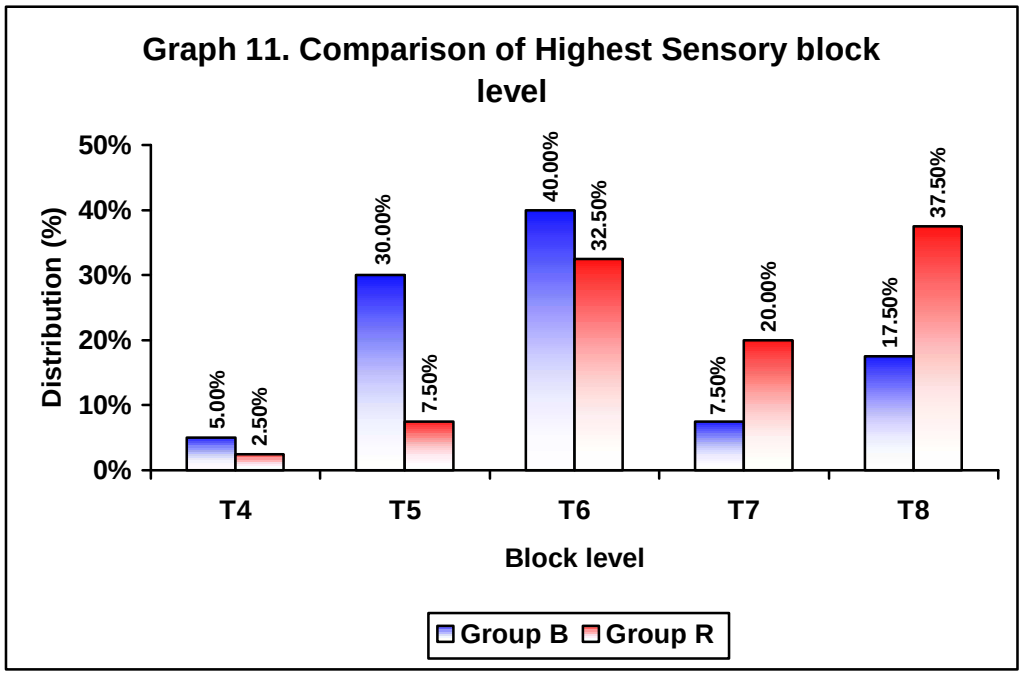


In this study, there was a significant delay in mean onset time of sensory block in group R compared to group B (7.68 ± 1.02 v/s 5.08 ± 0.83 minutes; $p < 0.001$). With regard to duration of sensory block, it was comparable in group B and R (137.50 ± 11.04 v/s 133.25 ± 11.85 minutes; $p = 0.101$).

Table 10. Comparison of highest sensory block level

Highest Sensory Block level	Group B (n=40)		Group R (n=40)	
	Number	Percentage	Number	Percentage
T_4	2	5.00	1	2.50
T_5	12	30.00	3	7.50
T_6	16	40.00	13	32.50
T_7	3	7.50	8	20.00
T_8	7	17.50	15	37.50
Total	**40**	**100.00**	**40**	**100.00**

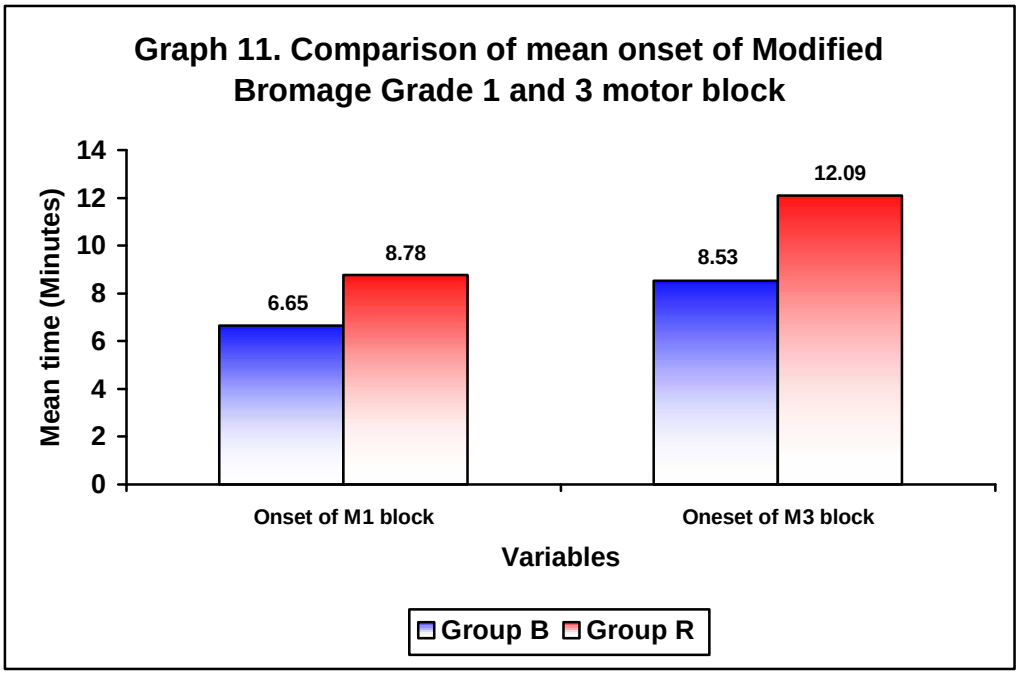
x^2 = 11.225 **p = 0.024**



In the present study, in group R, more number of patients i.e 32.5%, 20% and 37.5% achieved T_6, T_7 and T_8 as highest level of sensory block, whereas in group B more number of patients i.e 30% and 40% achieved T_5, T_6 as highest level of sensory block (p = 0.024).

Table 11. Comparison of mean onset of Modified Bromage Grade 1 and 3 motor block

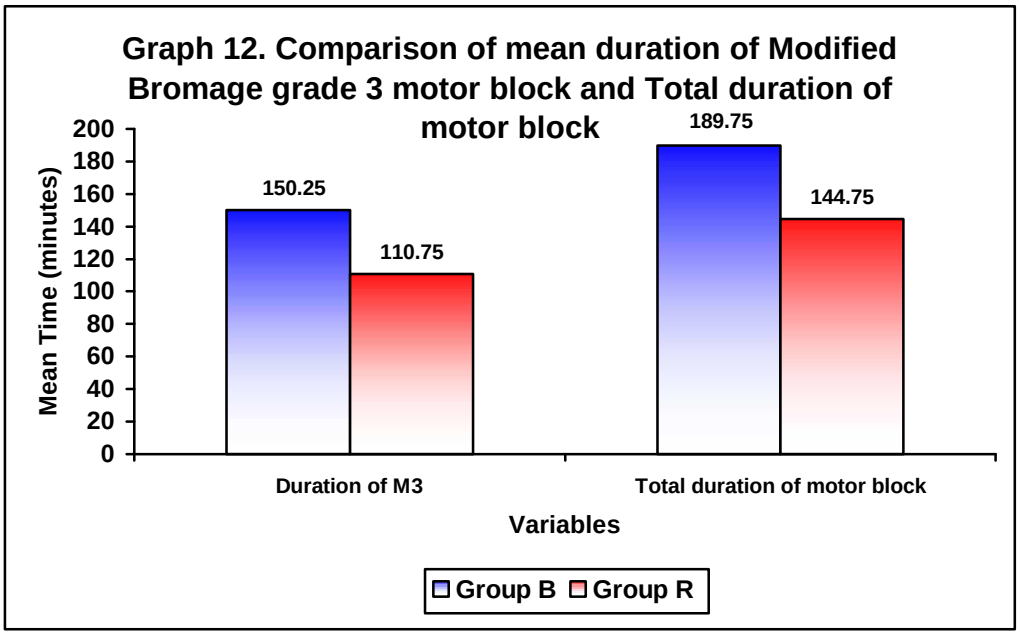
Variables (Minutes)	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Onset of M_1 block	6.65	0.92	8.78	0.89	**<0.001**
Onset of M_3 block	8.53	0.99	12.09	1.19	**<0.001**



In this study, time taken for onset of Modified Bromage Grade l motor block (M_1) (8.78 ± 0.89 v/s 6.65 ± 0.92 minutes) and Modified Bromage Grade 3 motor block (M_3) (12.09 ± 1.19 v/s 8.53 ± 0.99 minutes) were significantly delayed in group R compared to group B ($p < 0.001$).

Table 12. Comparison of mean duration of Modified Bromage grade 3 (M_3) and Total duration of motor block

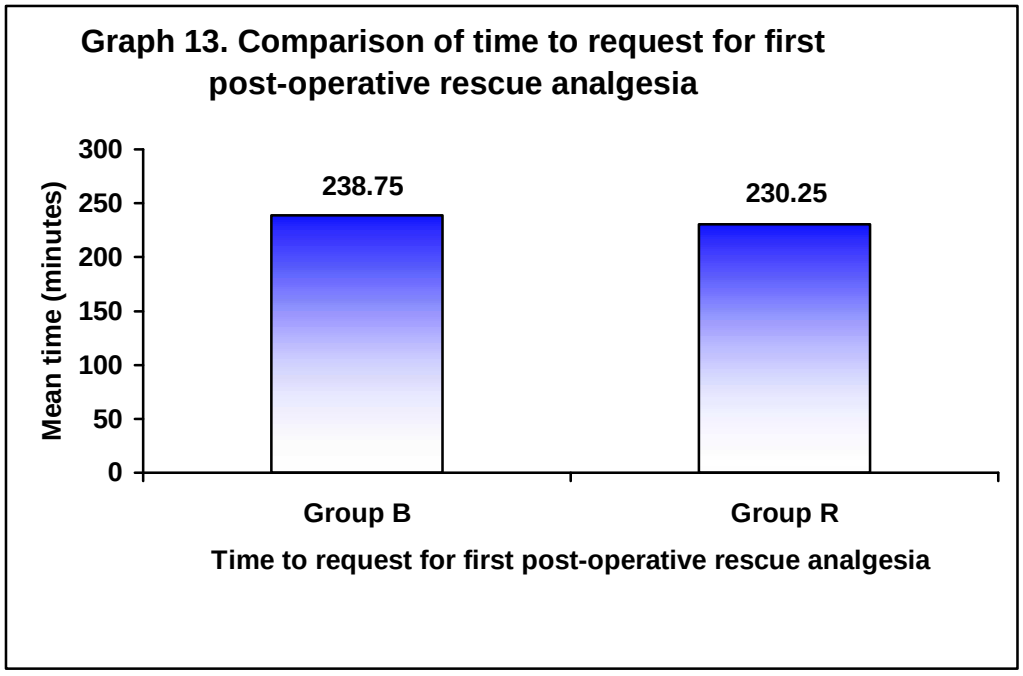
Variables (Minutes)	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Duration of M_3 block	150.25	13.87	110.75	8.88	**<0.001**
Total Duration of motor block	189.75	16.09	144.75	10.86	**<0.001**



In this study, the mean duration of M_3 motor block (110.75 ± 8.88 v/s 150.25 ± 13.87 minutes) and duration of total motor block (144.75 ± 10.86 v/s 189.75 ± 16.09 minutes) were significantly less in group R compared to group B ($p < 0.001$).

Table 13. Comparison of time to request for first post operative rescue analgesia

Time to request for first post operative rescue analgesia	Group B (n=40)		Group R (n=40)		p value
	Mean	SD	Mean	SD	
Time (Minutes)	238.75	24.72	230.25	20.69	0.100



In this study the comparison of time to request for first post operative rescue analgesia was comparable in both the groups i.e 238.75 ± 24.72 minutes in group B compared to 230.25 ± 20.69 minutes in group R (p = 0.100).

Chapter 7

Discussion

DISCUSSION

Spinal anaesthesia is an accepted technique for lower abdominal surgeries. The local anaesthetic drugs like Bupivacaine and Ropivacaine have been used intrathecally for these surgical procedures.

Bupivacaine, an amide type local anaesthetic, has high potency, slow onset and long duration of action but has been associated with prolonged motor block, CNS and cardiac toxicity.

Ropivacaine is an amide local anaesthetic with properties similar to those of Bupivacaine.[4,50] Ropivacaine produces an equivalent sensory block but shorter duration of motor block than intrathecal Bupivacaine and thus quicker regression of motor block, early mobilisation and early recovery.[51] Ropivacaine produces CNS and cardiovascular toxicity at a higher plasma concentration than Bupivacaine and thus the incidence is lower than Bupivacaine.[7,8]

Opioid analogues have been used as additives in spinal anaesthesia to improve the onset of action, prolong the duration of block and to improve the quality of perioperative analgesia.[9-12]

Fentanyl (a lipophilic opioid) has a rapid onset and shorter duration of action following intrathecal administration. The co-administration of opioids reduces the total dose of local anaesthetics required for anaesthesia and significantly prolongs the duration of complete and effective analgesia without prolonging the duration of motor block[9-12]. It reduces analgesic requirement in early postoperative period following spinal block.[52]

Presently most of the studies comparing Ropivacaine-Fentanyl and Bupivacaine-Fentanyl have been conducted in the orthopaedic settings. Hence, the present study was planned to assess the onset and duration of motor and sensory block, level of sensory block and time to request for first post operative rescue analgesia requirement between Ropivacaine-Fentanyl and Bupivacaine-Fentanyl in patients posted for lower abdominal surgeries under spinal anaesthesia.

The present one year hospital based randomized clinical study was conducted during the period of January 2012 to December 2012. A total of 80 patients distributed into two groups of 40 each undergoing elective lower abdominal surgeries, aged between 20 to 60 years of either gender, belonging to ASA Grade I and II, posted in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were studied.

In the present study no statistically significant difference was observed between group B and group R with regard to distribution of sex ($p > 0.05$), mean age (41.35 ± 10.84 and 37.00 ± 12.24 years respectively; $p > 0.05$), mean weight (59.80 ± 8.27 and 60.20 ± 7.47 Kgs respectively; $p > 0.05$) and mean height (159.65 ± 6.77 and 159.15 ± 5.76 Cms respectively; $p > 0.05$)

These above findings suggests, that the demographic and pre anaesthetic characteristics in group B and R were comparable ($p > 0.05$).

In the present 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 B and R at all the intervals since

beginning (P > 0.05). Similar findings were reported in a study by Ogun et al,[53] where mean pulse rate was comparable in both the groups throughout the study and the MAP was also comparable in the two groups except at one minute interval after the block where MAP was significantly lower in Bupivacaine group. Similar findings were reported in a study by Varun S et al,[17] where in the mean pulse rate was comparable in the two groups throughout the study period and the MAP was also comparable($p > 0.05$) in both the groups except between 10 minutes to 30 minutes intervals where the MAP was relatively lower in group B ($P < 0.05$) .

In the present study, mean onset time of sensory block was 7.68 ± 1.02 minutes in group R compared to 5.08 ± 0.83 minutes in group B suggesting significantly higher onset time of sensory block in group R ($p < 0.001$).In the present study, in group R, significantly higher number of patients i.e 90% of the patients achieved T_6 to T_8 as highest level of sensory block , whereas in group B, significantly higher number of patients i.e 75% achieved T_4 to T_6 as highest level of sensory block ($P < 0.05$). The duration of sensory block in group B was comparable to group R i.e, 137.50 ± 11.04 v/s 133.25 ± 11.85 minutes ($p > 0.05$).

Gunaydin et al,[54] in their study, used 10 mg of isobaric Bupivacaine and 15 mg isobaric Ropivacaine with 20 mcg Fentanyl for elective caesarean sections. They concluded that both the drug solutions achieved T_6 dermatome level but time taken to achieve sensory block till T_6 level was significantly longer (7.5 ± 5.5 minutes) in Ropivacaine group; which is comparable to the present study.

Ogun et al,[53] compared the combinations of intrathecal isobaric Bupivacaine-morphine with isobaric Ropivacaine-morphine (15 mg and 150 mg respectively in both groups) for caesarean sections. They observed that mean time to achieve T_5 sensory block was 4.9 ± 2.0 minutes in Bupivacaine- morphine group and 6.1 ± 2.5 minutes in Ropivacaine-morphine group with no statistical difference which is in contrast to the present study.

Koltka et al,[18] using 19.5 mg isobaric Ropivacaine and 13 mg isobaric Bupivacaine with 20 mcg Fentanyl for lower abdomen surgery, showed that all patients achieved T_{10} level or higher and the level of sensory block was higher in Bupivacaine group as compared to Ropivacaine group which is comparable to the present study and the duration of sensory block at T_{10} level was 185 ± 40 minutes in Bupivacaine- Fentanyl group and 160 ± 40 minutes in Ropivacaine-Fentanyl group with no statistical difference which is comparable to the present study.

Lee et al,[19] used 10 mg isobaric Bupivacaine and 10 mg isobaric Ropivacaine with 15 mg Fentanyl for urological surgery. They observed that all patients achieved sensory block upto T_{10} dermatome or higher after 15 mins of intrathecal injection and the level of sensory block was higher in Bupivacaine group as compared to Ropivacaine group which is comparable to the present study.

In the present study, time taken for onset of Modified Bromage Grade 1 block and Modified Bromage Grade 3 motor block were high in group R (8.78 ± 0.89 and 12.09 ± 1.19 minutes respectively) compared to group B (6.65 ± 0.92 and 8.53 ± 0.99 minutes respectively). This difference between Ropivacaine and

Bupivacaine group was statistically significant ($p < 0.001$). The mean duration of Modified Bromage Grade 3 motor block in Ropivacaine group was significantly less compared to Bupivacaine group i.e, 110.75 ± 8.88 v/s 150.25 ± 13.87 minutes ($p < 0.001$). Similarly, the duration of total motor block in group R was also significantly less compared to group B i.e, 144.75 ± 10.86 v/s 189.75 ± 16.09 minutes ($p < 0.001$).

In a study by Varun S, et al,[17] as compared to Bupivacaine group, the time taken to achieve maximum grade of motor block (Modified Bromage Grade = 3) was significantly more in Ropivacaine group ($p < 0.001$) which was similar to that of Ogun et al,[53] where the mean time to achieve complete motor block was 4.0 ± 2.0 minutes in Bupivacaine group and 5.9 ± 3.3 minutes in Ropivacaine group which was statistically significant.

The findings of the present study were comparable with both the studies done by Varun S et al,[17] and Ogun et al[53] whereas in contrast another study by Koltka et al,[18] showed no significant difference in onset time of motor block between the two groups.

The results of the present study was similar with a study by Lee et al[14] which concluded that duration of motor block was shorter in Ropivacaine group (median 126, interquartile range 93-162 minutes) as compared to Bupivacaine group (median 189, interquartile range 157-234 minutes).

Gunaydin et al[54] showed that duration of motor block was shorter in Ropivacaine group 121.6 ± 33.7 minutes v/s Bupivacaine group 149.7 ± 46.0 minutes i.e. early motor recovery in Ropivacaine group. Another study by Koltka

et al[18] observed that duration of Modified Bromage Grade 3 motor block in Bupivacaine group was 130 ± 40 minutes (median time) and 90 ± 25 minutes (median time) which is comparable to the present study. Ogun et al[54] concluded that mean time to complete recovery was 220.0 ± 32.4 minutes and 200.2 ± 34.9 minutes in Bupivacaine and Ropivacaine groups respectively, which was statistically significant. In contrast, a study by Varun S et al,[17] showed that, though motor regression to Modified Bromage Grade 0 was faster in Ropivacaine group as compared to Bupivacaine group but, it was statistically not significant.

In the present study, time to request for first post operative rescue analgesia was 238.75 ± 24.72 minutes in group B compared to 230.25 ± 20.69 minutes in group R ($p > 0.05$). These findings suggests that, the time to request for first post operative rescue analgesia was comparable in both the groups. In a study by Ogun et al,[54] mean time to request for first postoperative rescue analgesia was comparable in both the groups which is comparable to the present study. In contrast, a study by Varun S et al.,[17] reported that, the mean time to request for first post operative rescue analgesia was 241.80 ± 42.10 minutes in Bupivacaine-Fentanyl group and 227 ± 19.85 minutes in Ropivacaine-Fentanyl group, showing a statistically significant intergroup difference ($P < 0.05$).

Chapter 8

Conclusion

CONCLUSION

Based on the study results it may be concluded that, intrathecal administration of Ropivacaine-Fentanyl required more time for onset of sensory and motor block, provided lower level of sensory block and lesser duration of motor block, with similar duration of sensory block and time to request for first post-operative rescue analgesia compared to intrathecal Bupivacaine-Fentanyl in patients undergoing elective lower abdominal surgeries under spinal anaesthesia. However larger studies need to be conducted to confirm these findings.

Chapter 9

Summary

SUMMARY

Spinal anaesthesia, is the most commonly used anaesthetic technique in patients undergoing lower abdominal surgeries. Ropivacaine is an amide local anaesthetic with properties similar to those of Bupivacaine. Opioid analogues have been used as additives in spinal anaesthesia to improve the onset of action, prolong the duration of block and to improve the quality of perioperative analgesia. The present study was aimed to compare the isobaric Ropivacaine with isobaric Bupivacaine after the addition of Fentanyl to both the groups.

The present one year hospital based randomized clinical trial was conducted during the period of January 2012 to December 2012 in KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 80 patients, belonging to ASA Grade I and II, aged between 20 to 60 years of either gender undergoing elective lower abdominal surgeries under spinal anaesthesia were studied. Patients were distributed into two groups of 40 each namely group B [2.5 cc (12.5 mg) of 0.5% Bupivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl] and group R [2.5 cc (18.75 mg) of 0.75% Ropivacaine (plain) plus 0.5 cc (25 mcg) Fentanyl].

In group B and R, 65% and 62.5% of patients were females. Most of the patients (52.5% in group B and 37.5% in group R) were aged between 31 to 45 years. The mean age in group B was 41.35 ± 10.84 years compared to 37.00 ± 12.24 years in group R. No statistically significant difference was observed between demographic and preanaesthetic characteristics ($p > 0.05$). The heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure

were comparable in Group B and R at all the intervals since beginning ($p > 0.05$). Mean onset time of sensory block was 7.68 ± 1.02 minutes in group R compared to 5.08 ± 0.83 minutes in group B ($p < 0.001$). In group R majority of the patients (90%) had achieved T_6 to T_8 whereas in group B majority of the patients (75%) had achieved T_4 to T_6 as highest level of sensory block. The duration of sensory block in group B was comparable to group R that is, 137.50 ± 11.04 v/s 133.25 ± 11.85 minutes ($p = 0.101$). The time taken for onset of Modified Bromage Grade 1 and 3 motor block were significantly delayed in group R (8.78 ± 0.89 and 12.09 ± 1.19 minutes respectively) compared to group B (6.65 ± 0.92 and 8.53 ± 0.99 minutes respectively) ($p < 0.001$). The mean duration of Modified Bromage Grade 3 motor block in group R was significantly less compared to group B (110.75 ± 8.88 v/s 150.25 ± 13.87 minutes; $p < 0.001$). Duration of total motor block in group R was significantly less compared to group B (144.75 ± 10.86 v/s 189.75 ± 16.09 minutes; $p < 0.001$). Time to request for first post operative rescue analgesia was comparable in both the groups i.e 238.75 ± 24.72 minutes in group B compared to 230.25 ± 20.69 minutes in group R ($p = 0.100$).

Overall, Intrathecal Ropivacaine-Fentanyl required more time for onset of sensory and motor block and provided lower level of sensory block with lesser duration of motor block compared to intrathecal Bupivacaine-Fentanyl. The duration of sensory block and time to request for first post operative rescue analgesia were comparable in both the groups.

Chapter 10

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

A study, "**COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUIPOTENT DOSES OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA – A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL STUDY"** is being conducted by Dr. *******, Post Graduate in Anaesthesiology at Jawaharlal Nehru Medical College Belgaum, Karnataka. Under guidance of Dr. ***** ******* Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Belgaum, under KLE University, Belgaum.

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

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

Objective of the study

Objective of my study is to assess the effect of 2.5 cc of 0.75% Ropivacaine (Plain) plus 0.5 cc of 25 mcg Fentanyl and 2 cc of 0.5% Bupivacaine (plain) plus 0.5 cc of 25 mcg Fentanyl on onset and duration of motor block, onset, duration and level of sensory block and time to request for first post operative rescue analgesia in elective lower abdominal surgeries under spinal anaesthesia.

Procedure involved

If you agree to enrol yourself in my study, you will be interviewed regarding your present, past and family history, then you will be clinically examined in detail and investigated accordingly. You will receive either 2.5 cc of 0.75% Ropivacaine (Plain) plus 0.5 cc of 25 mcg Fentanyl or 2.5 cc of 0.5% Bupivacaine (Plain) plus 0.5 cc of 25 mcg Fentanyl.

Benefits and Risks

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

Voluntary participation / Withdrawal

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

Belgaum.

Alternatives

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

Confidentiality

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

Financial Incentives for participation

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

Compensation

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

Queries/ Contact details

If you have any queries, in future or in case of study related injury or

illness, you may contact Dr. **** at Department of Anesthesiology, KLES Dr. Prabhakar Kore Hospital and Medical Research Center, Belgaum Mobile Number – ********** or Dr. **** ******, Professor, Department of Anaesthesiology, Jawaharlal Nehru Medical College, Belgaum Mobile Number - *********. If you have any queries about your rights as a study subject, you may call Dr. **** *****, Prof. and Head of Pathology as Chairman of Jawaharlal Nehru Medical College Institutional Ethical Committee of Human Subjects Research, Mobile Number - ********** at Jawaharlal Nehru Medical College, Belgaum.

CONSENT TO PARTICIPATE IN A RESEARCH STUDY:

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

Signature of the participant: _____

Witness name: _____

Signature of the participant: _____

Date: _____

Place: _____

Signature of Investigator: _____

Annexures

Annexure II

ANNEXURE II – PROFORMA

STUDY: "COMPARISON OF ONSET AND DURATION OF BLOCKADE BETWEEN EQUIPOTENT DOSES OF ROPIVACAINE-FENTANYL AND BUPIVACAINE-FENTANYL IN LOWER ABDOMINAL SURGERIES UNDER SPINAL ANAESTHESIA- A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL STUDY".

Patient Name: **IP No.:**

Age: **Weight:**

Height: **Gender:**

Date of Operation: **Occupation:**

Address: **Anaesthesiologist:**

Preanesthetic Evaluation:

Chief Complaints:

Past History:

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

Family history

General physical examination

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

PR : BP :

RR : Temp :

Musculoskeletal disorders

Jaw movements : Teeth :

Airway assessment : Spine :

Systemic Examination

RS : CNS :

CVS : GIT :

Investigations

Hb : Total Count :

DC : BT :

Urine routine : CT :

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

Diagnosis

Proposed Surgery

Preoperative baseline values

HR: BP:

Monitors attached

Pulse oxymetry : NIBP :

ECG :

I. Group:

II. Vital parameters :

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

III. Sensory Block

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

IV. Motor Block

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

V. Post operative analgesia

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

Annexures

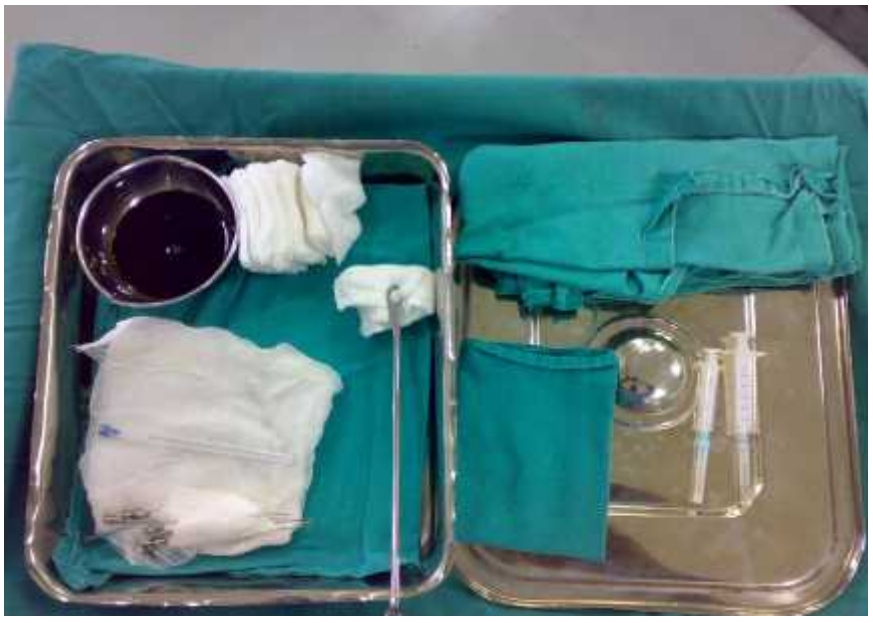
Annexure III

ANNEXURE III – PHOTOGRAPHS

Photograph 1. Isobaric Ropivacaine (0.75%)

Photograph 2. Isobaric Bupivacaine (0.5%)

Photograph 3. Fentanyl



Photograph 4. Spinal tray

Photograph 5. Procedure of spinal anaesthesia

Photograph 6. Monitoring

Annexures

Annexure IV

ANNEXURE IV – KEY TO MASTER CHART

ABH	-	Abdominal hysterectomy
ASA	-	American Society of Anaesthesiologists
Bpm	-	Beats per minute
Cms	-	Centimeters
F	-	Female
HR	-	Hernia repair
Kgs	-	Kilograms
Mins	-	Minutes
mm Hg	-	Millimeters of mercury
M	-	Male
OA	-	Open appendicectomy
SPO_2	-	Oxygen saturation

ANNEXURE IV - MASTER CHART - GROUP B

Serial Number	Randomization number	In patient number	Sex	Age (Years)	Weight (Kgs)	Height (Cms)	ASA grade	Proposed surgery	Vitals at different time intervals (Min)																																							
									Preoperative					2					4					6					8					10					15					20				
									HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm		MAP (mm Hg)	SpO_2
										Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic		
1	58	462800	F	32	65	158	I	OA	89	115	84	94	100	86	124	73	90	99	82	114	66	82	99	78	112	69	83	100	78	104	64	77	100	78	101	62	75	100	74	103	62	76	100	70	99	59	72	100
2	72	463494	F	28	50	148	I	HR	96	120	78	92	100	106	122	84	97	100	109	111	80	90	100	96	93	58	70	100	94	109	76	87	100	91	124	59	81	100	104	129	84	99	100	91	129	75	93	100
3	10	479628	M	58	70	166	I	HR	78	134	80	98	100	81	131	79	96	100	79	140	82	101	100	71	141	84	103	100	78	129	83	98	100	77	134	82	99	100	67	129	78	95	100	76	133	81	98	100
4	32	484551	M	35	60	158	I	HR	70	130	70	90	100	110	140	75	97	100	120	158	92	114	100	114	153	88	110	99	116	146	81	103	100	112	155	90	112	99	108	150	93	112	100	96	154	92	113	100
5	62	485485	F	35	50	158	I	ABH	104	150	97	115	100	107	146	91	109	100	94	123	82	96	100	100	99	64	76	100	83	104	70	81	100	78	99	63	75	100	76	94	58	70	100	72	95	52	66	100
6	48	486076	M	52	68	166	I	HR	72	142	83	103	100	70	94	61	72	100	62	88	56	67	98	78	103	66	78	98	76	97	62	74	99	79	78	54	62	99	90	104	67	79	99	89	105	65	78	98
7	20	486116	F	42	55	160	I	ABH	78	140	90	107	100	77	125	84	98	100	76	102	62	75	100	75	111	73	86	100	74	106	71	83	100	73	102	66	78	100	75	94	60	71	100	73	101	76	84	100
8	38	486779	M	34	68	164	I	HR	72	144	88	107	100	72	128	69	89	100	72	118	66	83	100	74	112	64	80	99	70	107	58	74	100	69	108	65	79	100	68	104	57	73	100	67	100	63	75	100
9	52	486580	F	35	55	155	I	ABH	78	114	70	85	100	80	111	65	80	100	78	103	61	75	100	87	109	62	78	100	86	102	61	75	100	76	102	60	74	100	85	105	59	74	100	48	100	54	69	100
10	54	486934	M	57	82	168	I	HR	78	110	70	83	100	72	105	59	74	100	71	107	64	78	100	70	102	61	75	100	73	103	61	75	100	68	94	51	65	100	66	92	48	63	100	69	92	51	65	100
11	6	487607	F	28	55	162	I	HR	70	120	70	87	100	72	120	66	84	100	72	123	73	90	100	71	121	73	89	99	66	118	69	85	100	70	121	69	86	100	71	120	69	86	99	68	119	73	88	100
12	46	488093	M	59	65	164	I	HR	80	112	70	84	100	80	110	65	47	100	78	104	61	75	100	72	109	62	78	100	83	102	61	75	100	74	102	60	74	100	78	107	64	78	100	71	105	59	74	100
13	30	488239	M	58	68	168	I	HR	78	130	80	97	100	72	130	73	92	100	71	124	77	93	100	73	123	76	92	100	70	123	73	90	100	68	113	67	82	100	69	118	73	88	100	68	107	60	76	100
14	2	488855	F	51	50	154	I	ABH	74	136	90	105	100	68	130	79	96	100	69	132	79	97	100	63	127	76	93	100	66	126	77	93	100	72	128	81	97	100	62	135	81	99	100	63	114	70	85	99
15	8	486968	F	55	55	185	I	ABH	78	120	70	87	100	68	112	66	81	100	69	118	66	83	100	70	108	68	81	100	66	114	65	81	100	71	107	60	76	99	68	104	57	73	99	67	107	60	76	100
16	64	489172	F	43	58	158	I	ABH	76	120	70	87	100	68	128	70	89	100	70	110	68	82	100	72	106	64	78	100	70	104	62	76	100	69	102	64	77	100	66	106	60	75	100	67	104	68	80	100
17	18	489221	F	42	55	156	I	ABH	70	115	83	94	100	68	124	72	89	100	70	114	66	82	100	71	112	69	83	99	71	104	64	77	99	70	103	62	76	100	69	99	59	72	100	68	96	59	71	100
18	40	489420	F	40	56	160	I	HR	73	112	70	84	100	73	112	66	81	100	72	118	71	87	100	71	114	65	81	100	73	107	60	76	100	72	108	63	78	100	72	112	60	77	100	70	100	70	80	100
19	14	489370	M	22	70	166	I	OA	70	110	70	83	100	78	112	69	83	100	71	104	64	77	100	73	101	62	75	100	68	103	62	76	100	69	99	59	72	100	70	92	57	69	100	71	94	64	74	100
20	68	489437	M	51	72	168	I	HR	70	136	80	99	100	79	139	73	95	100	88	144	90	108	100	78	145	95	112	100	73	140	78	99	100	76	136	78	97	100	68	124	73	90	100	73	123	93	103	100
21	22	487819	F	35	54	156	I	ABH	72	110	70	83	100	72	110	78	89	100	71	98	64	75	100	69	103	65	78	100	68	106	70	82	99	64	101	62	75	99	63	98	58	71	100	66	92	52	65	100
22	26	488555	F	50	56	154	I	ABH	78	120	80	93	100	78	118	80	93	100	74	117	85	96	100	71	122	79	93	100	76	122	81	95	99	78	122	84	97	99	77	111	80	90	99	76	93	58	70	100
23	78	499846	F	26	58	150	I	OA	74	120	80	93	100	76	123	70	88	100	76	117	70	86	100	75	114	71	85	100	73	111	70	84	100	74	117	62	80	100	72	113	72	86	100	71	107	70	82	100
24	16	500614	F	45	59	156	I	ABH	80	124	78	93	100	79	117	80	92	100	76	122	79	93	100	78	122	81	95	100	75	111	80	90	100	74	109	76	87	100	73	104	67	79	100	68	103	66	78	100
25	80	501799	M	58	68	162	I	HR	77	110	70	83	100	74	105	61	76	100	73	102	61	75	100	74	94	59	71	99	72	98	60	73	99	71	92	56	68	100	70	94	57	69	100	68	93	59	70	100
26	76	501726	F	22	58	155	I	OA	73	112	72	85	100	71	111	74	86	100	70	106	71	83	100	71	107	66	80	100	72	104	63	77	100	68	110	64	79	100	66	112	63	79	100	65	103	68	80	100
27	74	501638	F	36	58	156	I	ABH	73	120	70	87	100	72	110	71	84	100	71	104	67	79	100	70	108	63	78	100	68	100	71	81	100	68	98	70	79	99	69	92	69	77	99	65	88	61	70	100
28	66	501813	F	35	61	158	I	ABH	73	120	76	91	100	78	118	84	95	100	75	111	81	91	100	76	109	74	86	100	73	107	74	85	100	71	110	79	89	100	72	111	78	89	100	73	113	77	89	99
29	44	502129	F	25	56	158	I	HR	96	120	77	91	100	78	120	83	95	100	76	114	80	91	100	77	111	79	90	100	73	109	76	87	100	72	111	80	90	100	73	122	81	95	100	71	114	79	91	100
30	50	502863	F	45	56	164	I	ABH	76	130	78	95	100	70	122	76	91	100	68	114	73	87	100	66	107	71	83	100	65	109	67	81	100	67	104	69	81	100	66	107	62	77	99	65	106	60	75	100
31	60	505607	M	59	68	163	I	HR	74	118	76	90	100	74	114	67	83	100	73	110	66	81	100	70	109	67	81	100	68	107	66	80	100	66	106	65	79	100	65	104	65	78	100	64	101	60	74	100
32	28	506234	M	50	68	166	I	HR	78	120	74	89	100	78	123	70	88	100	79	111	64	80	100	76	106	60	75	100	74	104	60	75	100	73	103	59	74	100	70	101	62	75	100	68	98	58	71	100
33	42	505624	F	40	58	158	I	ABH	79	126	70	89	100	78	115	70	85	100	81	113	70	84	100	72	107	70	82	100	68	107	67	80	99	64	101	64	76	99	63	98	58	71	100	64	97	56	70	100
34	36	510534	F	38	58	165	I	HR	74	124	82	96	100	76	119	81	94	100	77	118	80	93	100	75	123	82	96	100	77	114	79	91	100	75	115	80	92	100	76	115	83	94	100	72	117	80	92	100
35	24	511658	F	36	40	152	I	ABH	78	136	90	105	100	78	137	87	104	100	77	130	83	99	100	79	122	83	96	100	73	124	83	97	100	76	125	82	96	100	75	123	76	92	100	75	123	76	92	100
36	4	510951	F	42	75	154	II	ABH	78	130	86	101	100	76	126	83	97	100	75	123	88	100	100	78	125	78	94	100	72	121	77	92	100	73	118	79	92	100	71	118	74	89	100	73	112	70	84	100
37	12	511543	F	45	50	152	I	HR	70	120	76	91	100	72	108	73	85	100	73	113	76	88	100	71	106	73	84	100	72	104	73	83	100	71	101	69	80	100	70	109	73	85	100	72	106	70	82	100
38	70	512691	M	40	52	154	I	HR	75	120	78	92	100	75	114	76	89	100	72	116	82	93	100	73	115	78	90	100	72	115	78	90	100	71	111	79	90	100	70	115	82	93	100	72	114	79	91	100
39	34	512343	M	28	60	160	I	OA	78	120	80	93	100	73	115	75	88	100	71	114	79	91	100	72	111	80	90	100	73	114	80	91	100	72	116	81	93	100	71	114	78	90	100	70	115	77	90	100
40	56	511678	F	42	52	151	I	ABH	73	120	80	93	100	73	120	78	92	100	74	115	77	90	100	72	115	71	86	100	72	111	73	86	100	71	110	69	83	100	71	118	71	87	100	70	106	69	81	100

ANNEXURE IV - MASTER CHART - GROUP B

Serial Number	Vitals at different time intervals (Min)																																								Sensory block			Motor block				Time to request for first post-operative rescue analgesia
	25					30					45					60					75					90					105					120												
	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg) Systolic	BP (mm Hg) Diastolic	MAP (mm Hg)	SpO_2	Onset (min)	Duration (min)	Highest level	Onset of M1 (min)	Onset of M3 (min)	Grade 3 block duration (min)	Total duration (min)	
1	70	96	59	71	99	62	92	57	69	100	60	94	64	74	100	60	96	64	75	100	62	98	66	77	100	61	97	67	77	100	62	98	68	78	100	-	-	-	-	-	5	130	T6	6	8	170	210	230
2	102	127	85	99	100	106	122	81	95	100	102	122	80	94	100	106	122	84	97	100	109	111	80	90	100	107	110	81	90	100	-	-	-	-	-	-	-	-	-	-	5	130	T6	6	8	150	200	270
3	75	136	82	100	100	74	135	80	98	100	77	142	81	101	100	78	153	90	111	100	75	128	80	96	100	74	127	81	96	100	76	129	83	98	100	-	-	-	-	-	4	130	T5	6	8	160	200	290
4	92	160	93	115	99	98	164	92	116	99	92	149	89	109	100	92	149	90	110	99	83	141	91	108	100	81	140	92	108	100	80	138	91	107	100	-	-	-	-	-	4	140	T5	7	8	150	180	280
5	64	85	52	63	100	67	88	54	65	100	67	89	54	66	100	67	91	56	68	100	62	98	65	76	100	61	97	66	76	100	-	-	-	-	-	-	-	-	-	-	5	130	T4	8	10	180	220	290
6	84	101	64	76	96	80	104	65	78	98	74	106	69	81	98	86	117	73	88	100	85	118	86	82	100	88	116	65	82	100	87	114	68	77	100	-	-	-	-	-	6	120	T6	8	10	130	180	240
7	68	110	70	83	100	72	99	66	77	99	77	102	60	74	100	75	94	61	72	100	74	112	70	84	99	73	111	71	84	99	-	-	-	-	-	-	-	-	-	-	5	130	T8	6	9	140	170	220
8	66	102	62	75	100	66	101	63	76	99	65	105	60	75	99	64	108	63	78	99	64	107	64	78	100	63	106	65	78	100	62	104	64	77	100	-	-	-	-	-	5	130	T8	7	8	130	170	230
9	69	94	51	65	100	66	92	48	63	100	64	92	51	65	100	63	93	49	64	100	70	94	57	69	100	69	93	58	69	100	-	-	-	-	-	-	-	-	-	-	5	140	T6	5	8	150	190	230
10	70	93	49	64	100	71	94	57	69	100	70	92	51	65	100	72	102	60	74	100	71	102	61	75	100	70	101	62	75	100	68	104	64	77	100	-	-	-	-	-	5	130	T6	6	8	150	180	240
11	67	116	64	81	100	66	119	60	80	100	66	118	75	89	100	68	118	69	85	100	65	117	68	84	100	67	118	68	85	100	64	124	67	86	100	-	-	-	-	-	6	140	T5	6	8	170	210	260
12	77	100	54	69	100	68	94	51	65	100	69	94	57	69	100	71	93	58	70	100	75	97	62	74	100	74	96	63	74	100	-	-	-	-	-	-	-	-	-	-	6	150	T5	6	7	160	200	270
13	69	105	59	74	100	70	100	54	69	100	66	102	61	75	100	68	109	62	78	100	70	104	61	75	100	69	103	62	75	100	72	108	65	79	100	-	-	-	-	-	4	150	T5	8	10	160	200	270
14	74	123	80	94	100	62	121	82	95	100	69	110	70	83	100	61	104	80	88	99	60	108	76	87	99	59	107	77	87	99	61	109	78	88	99	-	-	-	-	-	6	130	T7	8	10	130	170	230
15	66	108	63	78	100	67	100	70	80	100	68	100	82	88	100	69	112	60	77	100	69	112	66	81	100	68	111	67	81	100	-	-	-	-	-	-	-	-	-	-	5	140	T5	6	7	170	210	240
16	66	102	63	76	100	65	106	60	75	100	64	103	66	78	99	65	102	64	77	99	66	105	60	75	100	65	104	61	75	100	66	106	62	77	100	-	-	-	-	-	5	130	T6	7	8	150	190	220
17	66	101	62	75	99	64	92	57	69	100	66	94	64	74	100	68	96	64	75	100	69	103	62	76	100	68	102	63	76	100	-	-	-	-	-	-	-	-	-	-	3	150	T6	7	8	150	200	230
18	66	100	82	88	100	68	104	57	73	100	69	98	70	79	100	66	108	62	77	100	67	112	60	77	100	66	111	59	76	100	68	116	62	80	100	-	-	-	-	-	5	150	T6	8	10	150	180	220
19	68	96	64	75	100	69	96	59	71	100	70	103	62	76	100	70	104	64	77	100	72	102	66	78	100	71	101	65	77	100	-	-	-	-	-	-	-	-	-	-	5	150	T4	6	8	180	220	270
20	75	130	73	92	100	82	124	77	93	100	68	123	73	90	100	82	113	67	82	100	83	122	71	88	100	82	121	70	87	100	-	-	-	-	-	-	-	-	-	-	4	120	T8	5	7	130	160	220
21	65	90	52	65	100	64	90	51	64	100	66	97	56	70	100	68	101	62	75	100	69	98	58	71	100	68	97	57	70	100	66	95	61	72	100	-	-	-	-	-	7	140	T6	7	8	150	200	250
22	75	98	60	73	100	71	110	70	83	100	68	121	80	94	100	69	122	81	95	99	70	122	80	94	100	69	121	79	93	100	68	126	82	97	100	-	-	-	-	-	5	130	T5	6	8	160	210	270
23	72	109	73	85	100	73	106	70	82	100	70	104	68	80	100	74	108	74	85	100	74	108	74	85	100	73	107	73	84	100	74	108	75	86	100	-	-	-	-	-	7	150	T5	8	10	180	220	280
24	66	98	67	77	100	65	96	66	76	100	66	104	67	79	100	66	105	68	80	100	66	105	68	80	100	65	104	67	79	100	-	-	-	-	-	-	-	-	-	-	6	150	T6	8	10	150	180	230
25	69	86	53	64	99	66	110	60	77	100	68	104	62	76	99	67	108	61	77	100	67	108	61	77	100	66	107	60	76	100	68	108	62	77	100	-	-	-	-	-	5	120	T5	6	7	150	200	240
26	66	102	62	75	100	64	108	67	81	100	68	110	67	81	100	69	107	66	80	100	69	107	66	80	100	68	106	65	79	100	-	-	-	-	-	-	-	-	-	-	5	150	T5	7	8	150	190	240
27	64	106	70	82	100	63	104	68	80	100	66	110	70	83	100	67	112	70	84	100	67	112	70	84	100	66	111	69	83	100	-	-	-	-	-	-	-	-	-	-	4	150	T5	6	8	150	200	240
28	74	118	76	90	99	72	108	75	86	99	72	104	76	85	100	71	107	74	85	100	71	107	74	85	100	70	106	73	84	100	68	108	74	85	100	-	-	-	-	-	4	150	T6	6	8	140	180	230
29	70	115	80	92	100	69	119	78	92	100	70	120	76	91	100	71	122	80	94	100	71	122	80	94	100	70	121	79	93	100	-	-	-	-	-	-	-	-	-	-	5	150	T5	8	10	150	190	230
30	64	105	70	82	100	65	112	69	83	100	66	114	72	86	100	67	113	71	85	100	67	113	71	85	100	66	112	70	84	100	65	110	68	82	100	-	-	-	-	-	4	140	T6	6	9	130	170	240
31	63	98	59	72	100	62	97	57	70	100	61	95	58	70	100	62	100	60	73	100	62	100	60	73	100	61	99	59	72	100	60	98	60	73	100	-	-	-	-	-	5	120	T6	6	9	150	190	240
32	67	92	52	65	100	69	94	54	67	100	68	93	55	68	100	66	98	60	73	100	67	97	55	69	100	66	96	54	68	100	-	-	-	-	-	-	-	-	-	-	5	150	T6	8	10	140	180	240
33	63	72	52	59	100	68	99	55	70	100	69	97	58	71	100	70	99	60	73	100	70	99	60	73	100	69	98	59	72	100	72	102	62	75	100	-	-	-	-	-	5	150	T7	6	9	140	180	210
34	74	119	78	92	100	75	116	85	95	100	72	117	81	93	100	70	114	79	91	100	73	110	75	87	100	68	123	87	99	100	70	125	89	101	100	-	-	-	-	-	5	140	T6	6	9	150	190	220
35	73	121	76	91	100	70	120	78	92	100	69	121	79	93	100	72	122	79	93	100	73	123	81	95	100	72	122	80	94	100	70	124	78	93	100	-	-	-	-	-	5	120	T6	7	8	160	200	220
36	74	108	72	84	100	73	114	74	87	100	72	111	73	86	100	70	113	70	84	100	73	119	88	98	100	72	118	87	97	100	-	-	-	-	-	-	-	-	-	-	6	130	T8	8	10	140	170	200
37	73	107	70	82	100	71	109	73	85	100	70	105	72	83	100	69	105	71	82	100	71	113	70	84	100	70	112	69	83	100	72	114	72	86	100	-	-	-	-	-	6	150	T8	6	8	140	180	210
38	69	119	84	96	100	68	117	83	94	100	69	114	81	92	100	70	116	81	93	100	71	114	78	90	100	71	118	80	93	100	-	-	-	-	-	-	-	-	-	-	6	130	T8	6	8	130	160	200
39	69	117	82	94	100	71	111	79	90	100	72	113	76	88	100	72	113	70	84	100	72	113	70	84	100	71	112	69	83	100	69	116	72	87	100	-	-	-	-	-	5	140	T7	7	8	150	180	210
40	69	109	72	84	100	70	113	71	85	100	68	108	73	85	100	69	112	71	85	100	69	112	71	85	100	68	111	70	84	100	-	-	-	-	-	-	-	-	-	-	5	120	T8	6	8	140	180	200

ANNEXURE IV - MASTER CHART - GROUP R

Serial Number	Randomization number	In patient number	Sex	Age (Years)	Weight (Kgs)	Height (Cms)	ASA grade	Proposed surgery	Vitals at different time intervals (Min)																																			
									Preoperative					2				4				6				8				10				15				20				
									HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2
										Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic		
1	79	460248	F	38	59	152	I	ABH	80	120	70	87	100	78	111	64	80	100	81	106	60	75	100	73	104	58	73	100	72	101	62	75	100	66	98	58	71	100	68	97	56	70	99	67	92	52	65	99
2	37	461119	M	24	56	164	I	HR	68	130	82	98	100	69	132	78	96	100	66	132	77	95	100	63	127	76	93	100	62	132	79	97	100	61	125	73	90	100	63	123	69	87	100	61	126	77	93	99
3	71	461606	M	48	68	160	I	HR	86	120	82	95	100	86	123	82	96	100	86	104	70	81	100	81	99	63	75	100	84	94	58	70	100	80	95	52	66	100	72	91	56	68	100	78	91	57	68	100
4	13	462093	M	24	74	168	I	OA	78	110	70	83	100	78	123	72	89	100	79	116	70	85	99	72	114	59	77	100	70	122	73	89	100	68	120	66	84	100	68	121	70	87	100	64	120	67	85	99
5	3	462122	M	21	64	162	I	HR	72	124	80	95	100	70	122	76	91	99	67	114	73	87	100	65	112	69	83	99	64	114	71	85	100	69	117	62	80	100	66	107	71	83	100	61	109	67	81	100
6	19	462634	F	22	60	158	I	OA	78	126	80	95	100	79	130	92	105	100	78	124	80	95	100	68	114	70	85	100	71	112	66	81	100	66	118	66	83	100	73	108	66	80	100	68	114	65	81	100
7	49	462863	M	22	68	162	I	HR	66	128	83	98	100	65	124	67	86	100	63	120	66	84	100	72	123	73	90	100	64	121	73	89	100	60	118	69	85	100	66	118	75	89	100	65	121	69	86	100
8	7	463459	M	40	72	166	I	HR	74	124	80	95	100	70	122	76	91	99	67	114	73	87	100	66	107	71	83	100	61	109	67	81	100	62	114	69	84	100	63	109	73	85	100	61	106	60	75	100
9	57	463376	F	30	54	152	I	ABH	88	110	76	87	100	68	108	60	76	100	66	104	57	73	100	65	107	60	76	100	61	108	63	78	100	68	120	68	85	100	64	112	60	77	100	66	100	70	80	100
10	69	464582	F	21	55	148	I	ABH	86	128	68	88	100	78	101	62	75	100	81	98	58	71	99	72	97	56	70	99	66	92	52	65	100	68	99	54	69	100	64	110	72	85	100	63	114	69	84	100
11	51	465378	F	60	58	155	I	ABH	78	124	70	88	100	78	124	80	95	100	68	114	70	85	100	71	112	66	81	100	66	118	66	83	100	73	108	66	80	100	66	114	65	81	100	65	107	60	76	100
12	41	483480	M	60	68	165	I	HR	72	124	76	92	100	68	122	79	93	100	69	122	81	95	100	80	111	80	90	100	72	93	58	70	100	68	109	76	87	100	69	117	85	96	100	70	120	82	95	100
13	75	484096	M	48	78	170	I	HR	96	124	78	93	100	98	117	85	96	100	94	111	80	90	100	81	109	76	87	100	88	122	81	95	100	96	93	58	70	100	91	110	78	89	100	81	124	59	81	99
14	39	483546	F	30	65	150	I	OA	98	119	79	92	100	102	118	80	93	100	107	117	85	96	100	102	122	79	93	100	106	122	81	95	100	106	122	84	97	100	109	111	80	90	100	96	93	58	70	100
15	29	483976	F	50	57	155	II	ABH	110	150	96	114	100	84	144	94	111	100	78	141	87	105	100	73	130	84	99	100	66	110	78	89	100	64	98	64	75	100	61	84	54	64	100	84	103	65	78	100
16	67	484142	F	55	55	153	I	ABH	72	110	70	83	100	72	110	70	83	100	80	106	70	82	100	77	101	67	78	99	74	90	62	71	100	80	80	50	60	100	78	102	66	78	100	74	84	52	63	100
17	17	486019	M	50	65	162	I	OA	65	124	90	101	100	65	124	67	86	100	67	120	66	84	100	68	123	73	90	100	72	121	73	89	100	63	118	69	85	100	68	129	69	89	100	66	120	69	86	100
18	23	486051	F	28	58	155	I	OA	74	110	70	83	100	72	106	70	82	100	71	101	67	78	100	72	106	77	87	100	73	102	66	78	100	69	99	66	77	100	74	91	56	68	100	70	90	60	70	100
19	61	485326	F	35	55	158	I	ABH	66	110	70	83	100	68	110	70	83	100	66	108	60	76	100	65	104	57	73	100	69	108	63	78	100	64	107	60	76	99	63	100	70	80	98	62	100	82	88	100
20	65	484769	F	35	50	158	I	ABH	80	120	80	93	100	80	124	59	81	100	78	122	84	97	100	76	111	80	90	100	80	109	76	87	100	71	129	84	99	99	76	129	25	60	99	74	127	85	99	100
21	11	486565	M	35	68	162	I	OA	69	132	80	97	100	68	131	79	96	100	66	134	82	99	100	64	133	81	98	100	61	128	80	96	100	64	127	81	96	100	63	129	78	95	100	66	127	81	96	100
22	63	487151	F	45	56	156	I	ABH	75	130	80	97	100	68	127	76	93	100	69	126	77	93	100	70	128	81	97	100	68	114	70	85	100	68	121	82	95	100	69	110	70	83	100	70	104	80	88	100
23	31	488203	F	47	56	158	I	ABH	74	110	70	83	100	70	110	68	82	100	68	106	64	78	100	72	104	62	76	100	71	102	64	77	100	73	98	60	73	100	71	96	56	69	100	70	97	61	73	99
24	33	489601	F	24	52	154	I	OA	80	120	70	87	100	78	111	64	80	100	81	106	60	75	100	73	104	58	73	100	72	101	62	75	100	66	98	58	71	100	68	97	56	70	99	67	92	52	65	99
25	1	489467	F	35	58	160	I	ABH	72	110	70	83	100	73	110	60	77	100	72	106	64	78	100	73	104	62	76	100	72	102	64	77	100	71	106	60	75	100	70	104	62	76	100	73	106	60	75	100
26	53	488789	F	42	56	154	I	HR	74	120	70	87	100	72	122	84	97	100	71	111	80	90	100	72	109	76	87	100	73	124	59	81	100	71	129	84	99	100	70	127	85	99	100	68	122	81	95	100
27	27	500591	M	20	66	168	I	OA	72	120	84	96	100	76	118	68	85	100	75	116	64	81	100	73	114	62	79	100	72	113	66	82	99	70	115	65	82	99	69	111	68	82	100	68	112	67	82	100
28	35	500777	F	36	52	160	I	ABH	76	124	76	92	100	76	111	72	85	100	73	106	70	82	100	72	102	65	77	100	68	98	67	77	100	67	94	61	72	99	66	98	63	75	99	64	104	62	76	100
29	9	501715	F	36	60	158	I	ABH	78	114	72	86	100	78	104	62	76	100	77	98	60	73	100	71	108	64	79	100	70	112	60	77	99	72	106	65	79	99	72	94	60	71	99	73	98	62	74	100
30	25	501882	M	60	68	162	I	HR	76	128	76	93	100	76	123	81	95	100	74	121	73	89	100	70	118	69	85	100	71	116	64	81	100	72	114	66	82	99	70	111	70	84	100	68	108	65	79	100
31	73	504403	F	20	52	154	I	OA	75	118	70	86	100	74	113	67	82	100	71	112	69	83	100	72	104	65	78	99	70	101	66	78	100	68	98	60	73	100	67	96	59	71	100	64	92	57	69	100
32	77	505428	F	50	56	158	I	ABH	76	128	76	93	100	76	122	77	92	100	74	112	72	85	100	75	111	73	86	100	76	110	71	84	99	73	106	71	83	99	72	107	72	84	99	70	104	71	82	100
33	15	505814	M	34	72	168	I	OA	84	128	80	96	100	80	116	71	86	100	76	114	69	84	100	70	115	67	83	100	69	106	66	79	100	70	104	65	78	100	71	101	65	77	100	68	98	64	75	100
34	47	506649	F	35	60	160	I	HR	78	118	80	93	100	78	115	70	85	100	77	108	68	81	100	75	103	67	79	100	76	98	64	75	100	72	92	62	72	100	60	94	65	75	99	67	104	62	76	99
35	55	506997	M	22	70	172	I	HR	80	110	70	83	100	70	109	64	79	100	68	110	70	83	100	67	107	61	76	100	68	104	58	73	100	67	112	62	79	100	66	100	82	88	100	64	108	68	81	99
36	5	506487	F	30	54	160	I	ABH	80	118	70	86	100	78	120	82	95	100	76	116	80	92	100	72	109	77	88	100	70	122	85	97	100	68	123	80	94	100	66	111	80	90	100	65	96	50	65	100
37	21	508581	M	57	60	156	I	HR	80	120	80	93	98	70	120	79	93	100	70	116	74	88	100	68	110	70	83	100	68	115	72	86	100	66	11	73	52	100	68	110	70	83	100	69	118	72	87	100
38	43	508035	F	42	52	150	I	ABH	72	116	78	91	100	72	116	80	92	100	71	114	79	91	100	73	113	80	91	100	70	118	80	93	100	70	110	75	87	100	71	111	81	91	100	69	117	82	94	100
39	45	508678	F	37	56	158	I	ABH	80	120	76	91	100	78	121	78	92	100	77	116	79	91	100	79	109	78	88	100	76	103	67	79	100	69	105	69	81	99	72	112	81	91	100	71	102	68	79	100
40	59	507559	F	32	50	165	II	ABH	76	109	69	82	100	81	123	82	96	100	81	123	82	96	100	80	116	81	93	100	80	115	79	91	100	75	109	75	86	100	76	111	72	85	100	72	106	68	81	100

ANNEXURE IV - MASTER CHART - GROUP R

Serial Number	Vitals at different time intervals (Min)																																								Sensory block			Motor block				Time to request for first post-operative rescue analgesia
	25					30					45					60					75					90					105					120												
	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	HR (bpm)	BP (mm Hg)		MAP (mm Hg)	SpO_2	Onset (min)	Duration (min)	Highest level	Onset of M1 (min)	Onset of M3 (min)	Grade 3 block duration (min)	Total duration (min)	
		Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic				Systolic	Diastolic										
1	66	90	52	65	99	67	109	73	85	99	64	114	69	84	99	66	122	70	87	99	65	117	66	83	99	64	116	76	89	99	63	113	73	86	99	-	-	-	-	-	8	120	T7	8	11	120	150	240
2	64	129	75	93	99	66	128	78	95	99	63	135	81	99	100	65	123	80	94	100	65	123	80	94	100	64	122	79	93	100	62	120	81	94	100	-	-	-	-	-	7	140	T6	8	11	120	150	260
3	73	98	65	76	100	76	92	56	68	100	79	104	72	83	100	80	112	75	87	100	71	110	70	83	100	70	109	71	83	100	-	-	-	-	-	-	-	-	-	-	6	120	T6	10	13	110	150	220
4	64	120	66	84	100	67	113	70	84	100	61	104	58	73	100	63	106	66	79	100	64	104	67	79	100	63	103	68	79	100	62	106	71	83	100	-	-	-	-	-	7	140	T8	10	13	110	150	210
5	61	115	69	84	100	62	114	69	84	100	63	109	73	85	100	61	106	60	75	100	63	107	70	82	100	62	106	71	82	100	-	-	-	-	-	-	-	-	-	-	9	120	T4	9	11	130	170	270
6	66	107	60	76	100	65	104	57	73	99	61	107	60	76	100	68	108	63	78	100	66	119	67	84	100	64	112	60	77	100	67	101	74	83	100	-	-	-	-	-	6	150	T6	10	12	130	160	230
7	62	120	69	86	100	66	119	73	88	100	64	119	68	85	100	63	116	64	81	100	63	119	60	80	100	62	118	61	80	100	94	121	64	83	100	-	-	-	-	-	7	150	T6	7	11	100	140	210
8	63	107	70	82	100	69	117	62	80	100	64	114	71	85	100	65	112	69	83	99	67	114	73	87	100	66	113	74	87	100	-	-	-	-	-	-	-	-	-	-	9	120	T8	9	14	100	130	200
9	67	100	82	88	100	79	112	60	77	100	64	108	68	81	100	66	114	65	81	100	68	104	58	73	100	67	103	59	73	100	68	106	62	77	100	-	-	-	-	-	8	150	T6	8	11	110	150	220
10	72	98	58	71	100	64	101	62	75	100	61	90	52	65	100	72	107	70	82	100	77	107	67	80	100	75	106	68	80	100	-	-	-	-	-	-	-	-	-	-	7	140	T7	8	11	100	140	230
11	61	104	57	73	100	66	107	60	76	100	64	104	57	73	100	67	119	67	84	100	68	112	60	77	100	67	111	61	77	100	66	114	64	81	100	-	-	-	-	-	8	120	T6	10	13	120	150	230
12	72	102	77	85	100	66	120	60	80	100	63	122	81	95	100	68	122	80	94	100	62	129	84	99	99	61	128	85	99	99	64	132	86	101	100	-	-	-	-	-	9	150	T5	9	11	120	160	270
13	76	129	75	93	99	68	111	80	90	98	70	107	74	85	99	68	111	79	90	100	69	111	76	88	100	68	110	77	88	100	-	-	-	-	-	-	-	-	-	-	7	130	T8	8	11	100	130	210
14	94	109	76	87	100	91	124	59	81	100	106	129	84	99	100	91	129	75	93	100	102	127	85	99	100	106	122	81	95	100	102	122	80	94	100	-	-	-	-	-	9	140	T5	10	12	120	160	270
15	94	110	70	83	99	97	107	63	78	100	90	108	64	79	99	83	106	70	82	99	81	104	69	81	100	84	110	70	83	100	92	130	71	91	100	-	-	-	-	-	6	120	T7	8	13	110	140	240
16	71	99	66	77	100	67	91	56	68	100	68	82	49	60	100	62	90	60	70	100	61	90	58	69	100	60	89	59	69	100	-	-	-	-	-	-	-	-	-	-	8	130	T6	8	14	120	160	230
17	65	119	73	88	99	68	116	64	81	99	70	119	60	80	100	66	118	75	89	100	65	118	69	85	100	64	117	70	85	100	68	122	74	90	100	-	-	-	-	-	8	120	T8	10	13	100	130	200
18	72	94	60	71	100	73	102	66	78	99	72	106	75	85	99	71	110	70	83	100	73	106	74	85	100	72	105	75	85	100	-	-	-	-	-	-	-	-	-	-	7	140	T8	10	12	110	140	220
19	65	108	68	81	100	63	104	56	72	100	66	100	81	87	100	65	108	70	83	100	68	114	65	81	100	67	113	66	81	100	65	118	63	81	100	-	-	-	-	-	9	120	T8	9	11	100	130	230
20	76	122	81	95	100	71	122	80	94	100	70	121	81	94	100	73	110	70	83	100	76	114	74	87	100	74	113	75	87	100	72	116	78	91	100	-	-	-	-	-	7	150	T7	8	11	100	140	240
21	68	120	81	94	100	64	116	64	81	100	63	118	78	91	100	64	118	69	85	100	62	114	68	83	100	61	113	69	83	100	-	-	-	-	-	-	-	-	-	-	7	130	T6	8	14	110	140	240
22	71	108	76	87	100	66	102	61	75	100	65	109	62	78	100	68	113	67	82	100	69	110	70	83	100	68	109	71	83	100	72	106	74	85	100	-	-	-	-	-	9	120	T5	9	11	120	160	280
23	68	100	60	73	99	66	102	60	74	99	69	106	70	82	100	70	102	64	77	100	69	106	68	81	100	68	105	69	81	100	-	-	-	-	-	-	-	-	-	-	9	120	T7	9	11	120	150	210
24	66	90	52	65	99	67	109	73	85	99	66	122	70	87	99	65	117	66	83	99	64	116	76	89	99	63	115	77	89	99	68	126	80	95	100	-	-	-	-	-	8	130	T8	9	13	110	160	210
25	71	104	60	75	100	66	103	66	78	100	65	102	64	77	100	69	105	60	75	100	70	106	62	77	100	73	110	67	81	100	72	114	70	85	100	-	-	-	-	-	8	140	T7	9	11	110	150	260
26	66	122	80	94	100	64	122	84	97	99	63	111	80	90	99	65	124	59	81	100	68	129	75	93	100	67	128	74	92	100	-	-	-	-	-	-	-	-	-	-	7	150	T6	10	14	120	150	240
27	67	110	68	82	100	68	108	67	81	99	66	106	66	79	99	64	110	66	81	99	67	109	65	80	100	66	108	64	79	100	64	110	68	82	100	-	-	-	-	-	7	130	T8	9	14	100	130	230
28	65	98	61	73	99	66	94	60	71	100	63	94	62	73	100	67	105	67	80	99	67	105	67	80	99	66	104	66	79	99	-	-	-	-	-	-	-	-	-	-	7	120	T7	10	13	110	140	220
29	74	97	63	74	100	71	103	65	78	100	70	108	65	79	100	69	109	62	78	100	68	110	66	81	100	67	109	65	80	100	-	-	-	-	-	-	-	-	-	-	6	120	T6	7	11	110	140	230
30	69	104	64	77	100	68	107	66	80	100	67	110	64	79	100	68	112	63	79	100	68	112	63	79	100	67	111	62	78	100	72	119	69	86	100	-	-	-	-	-	9	150	T8	9	11	100	130	220
31	63	95	59	71	100	64	99	60	73	99	65	103	60	74	100	66	102	61	75	100	66	102	61	75	100	65	101	60	74	100	68	109	64	79	100	-	-	-	-	-	9	120	T8	10	14	100	130	210
32	68	109	70	83	100	69	103	70	81	100	70	105	71	82	100	70	107	70	82	100	71	110	71	84	100	70	109	70	83	100	-	-	-	-	-	-	-	-	-	-	8	140	T7	9	11	120	150	230
33	69	96	65	75	100	68	97	66	76	100	67	94	67	76	100	66	101	64	76	100	65	105	67	80	100	64	104	66	79	100	69	112	68	83	100	-	-	-	-	-	7	150	T6	8	14	110	150	250
34	68	96	64	75	99	69	97	68	78	99	70	108	66	80	100	71	112	70	84	100	71	112	70	84	100	70	111	69	83	100	-	-	-	-	-	-	-	-	-	-	7	130	T6	8	11	120	150	230
35	65	114	65	81	100	65	105	60	75	100	66	107	71	83	100	67	108	64	79	100	67	108	64	79	100	66	107	63	78	100	64	109	68	82	100	-	-	-	-	-	8	150	T8	8	11	110	140	220
36	60	109	77	88	100	64	113	81	92	100	66	118	78	91	100	67	110	77	88	100	67	110	77	88	100	66	109	76	87	100	64	112	78	89	100	-	-	-	-	-	7	140	T8	8	14	100	130	220
37	70	120	68	85	100	72	107	70	82	100	68	105	75	85	100	66	110	70	83	100	66	110	70	83	100	65	109	69	82	100	-	-	-	-	-	-	-	-	-	-	9	140	T6	9	13	110	140	250
38	70	113	76	88	100	71	109	78	88	100	72	111	73	86	100	71	110	71	84	100	71	110	71	84	100	70	109	70	83	100	69	112	74	87	100	-	-	-	-	-	8	120	T8	8	11	100	130	200
39	71	113	65	81	100	73	109	65	80	99	68	118	69	85	100	66	113	69	84	100	66	113	69	84	100	65	112	68	83	100	68	110	66	81	100	-	-	-	-	-	6	130	T8	8	14	110	150	220
40	72	120	66	84	100	76	105	70	82	100	70	104	66	79	100	76	103	65	78	100	72	102	67	79	100	68	101	65	77	100	-	-	-	-	-	-	-	-	-	-	9	130	T8	9	11	110	140	210