"COMPARISON OF 0.5% HYPERBARIC BUPIVACAINE AND 0.5% HYPERBARIC LEVOBUPIVACAINE WITH BUPRENORPHINE AS AN ADJUVANT FOR SPINAL ANAESTHESIA IN ADULTS UNDERGOING INFRAUMBILICAL SURGERIES – A ONE YEAR HOSPITAL BASED RANDOMIZED CONTROL TRIAL"

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BELAGAVI, KARNATAKA

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KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH,

BELAGAVI, KARNATAKA

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KAHER * BELAGAVI * J.N. MEDICAL COLLEGE

DR. RAJESH MANE MD, DNB
Professor and Head,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date: 25/3/2025
Place: Belagavi

Dr. N.S. MAHANTSHETTI MD
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

PRINCIPAL
Jawaharlal Nehru Medical College
BELAGAVI

Date: 25/3/2025
Place: Belagavi

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JAWAHARLAL NEHRU MEDICAL COLLEGE

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Accredited 'A+' Grade by NAAC (3rd Cycle) **Placed in Category 'A' by MoE (GoI)**

Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu rincipal@jnmc.edu

Ref No: MDC/PG/ Date: 21-03-2025

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Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

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Reg. No. BA0122015
Postgraduate Student,
2022-23 Batch,
Department of Anaesthesiology
J. N. Medical College, Belagavi.

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

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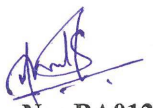

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(Deemed – to- be- University)
Accredited 'A++' Grade by NAAC in (3rd Cycle) Placed in Category 'A' by MHRD (GoI)
JNMC INSTITUTIONAL ETHICS COMMITTEE
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref No.MDC/JNMCIEC/ 55 **Date: 24/03/2023**

To,

REG NO: BA0122015
PG Student in Anaesthesiology
J. N. Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF 0.5% HYPERBARIC BUPIVACAINE AND 0.5% HYPERBARIC LEVOBUPIVACAINE WITH BUPRENORPHINE AS AN ADJUVANT FOR SPINAL ANESTHESIA IN ADULTS UNDERGOING INFRAUMBILICAL SURGERIES- A ONE YEAR HOSPITAL BASED RANDOMIZED CONTROL TRIAL",** is ethical and justifiable.

The proposed research project has been cleared by the JNMC Institutional Ethics Committee.

(Dr. Smita Sonoli)
Member Secretary
JNMC Institutional Ethics Committee
J.N.Medical College, Belagavi.

(Dr. Harsha Hegde)
Chairman,
JNMC Institutional Ethics Committee
J.N.Medical College, Belagav

LIST OF ABBREVIATIONS

ASA	-	American Society of Anesthesiologists
SA	-	Spinal anesthesia
SAB	-	Subarachnoid Block
LA	-	Local Anaesthetic
SAS	-	Subarachnoid Space
CSF	-	Cerebrospinal Fluid
CVS	-	Cardiovascular system
CNS	-	Central Nervous System
HR	-	Heart Rate (bpm)
SBP	-	Systolic Blood Pressure (mmHg)
DBP	-	Diastolic Blood Pressure (mmHg)
MAP	-	Mean Arterial Pressure (mmHg)
SpO2	-	Saturation of peripheral oxygen (%)
Inj	-	Injection
IV	-	Intravenous
L	-	Lumbar vertebra
ml	-	milliliter
mcg	-	micrograms
mg	-	milligram
kgs	-	kilograms
cms	-	centimeters
g/cm	-	grams per centimeter
mEq/L	-	milliequivalents per litre
mg/dl	-	milligrams per decilitre

mcg/ml	-	micrograms per millilitre
g/mol	-	grams per mol
mins	-	minutes
L/min	-	Litres per minute
RCT	-	Randomized controlled trial
CBC	-	Complete Blood Count
BG	-	Blood Grouping
RBS	-	Random Blood Sugar
LFT	-	Liver Function Test
RFT	-	Renal Function Test
SD	-	Standard Deviation
vs	-	Versus

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ABSTRACT

Title:

Comparison of 0.5% hyperbaric bupivacaine and 0.5% hyperbaric levobupivacaine with buprenorphine as an adjuvant for spinal anaesthesia in adults undergoing infraumbilical surgeries-a one year hospital based randomized control trial.

Context:

Spinal anaesthesia with hyperbaric bupivacaine is commonly used, while hyperbaric levobupivacaine is less studied. We aimed to compare hemodynamic effects and the onset of sensory and motor block between these formulations when used with buprenorphine.

Aims:

To assess hemodynamic parameters and to compare onset of sensory and motor block of buprenorphine with hyperbaric formulations of bupivacaine and levobupivacaine in spinal anaesthesia for infraumbilical surgeries.

Settings & Design: A one year hospital based randomized control trial.

Methods:

102 patients (18-60 years) undergoing elective infraumbilical surgeries under spinal anaesthesia were randomly assigned to 2 groups of 51 each - Group BB (15mg of 0.5% Hyperbaric Bupivacaine with 60mcg Buprenorphine) and Group LB (15mg of 0.5% Hyperbaric Levobupivacaine with 60mcg Buprenorphine). Intraoperative hemodynamic parameters and onset of sensory and motor block and were assessed.

Results:

Significant differences were noted in hemodynamic parameters at certain time intervals between both groups where group LB showed better hemodynamic profile. In contrast, a faster onset of sensory and motor block was seen in group BB when compared to group LB.

Conclusion:

When compared to Hyperbaric Bupivacaine with Buprenorphine, Hyperbaric Levobupivacaine with Buprenorphine demonstrated better hemodynamic profile in the intraoperative period. A quicker onset of sensory and motor block was demonstrated by Hyperbaric Bupivacaine with Buprenorphine group thereby concluding that both groups have an advantage of their own.

Keywords:

Spinal anesthesia, Hyperbaric, Bupivacaine, Levobupivacaine, Buprenorphine.

INTRODUCTION

Spinal anesthesia (SA) is a highly utilized anesthetic procedure in individuals who need to undergo a surgery below the umbilicus. A local anesthetic (LA) medication is administered in the subarachnoid space (SAS) to cause sensory-motor and sympathetic blockade, either with or without an adjuvant. With the added benefits of patients being exposed to less number of drugs and patients who are conscious and breathing spontaneously, this treatment is economical and relatively safer.

Spinal anesthesia with bupivacaine is commonly used for operations involving the lower abdomen and lower limbs due to its long-lasting effects and the ability to block both sensory and motor functions.[1] However, bradycardia and hypotension are most frequent side effects of SAB. In particular, severe hypotension can be life-threatening, especially in old patients with limited cardiac reserve. [2]

The pure S enantiomer of racemic bupivacaine is called levobupivacaine. It was just recently approved for use as a long-acting local anesthetic in therapeutic settings. Reports of levobupivacaine toxicity are uncommon, and when they do happen, it is usually manageable with slightest effort and without fatal results. Levobupivacaine hasn't entirely substituted bupivacaine, yet. [3]

Commonly used spinal anesthetic medications include levobupivacaine, ropivacaine, and bupivacaine. Additives including fentanyl, dexmedetomidine, and buprenorphine are utilized to extend the analgesic effect. [4] There was significant heterogeneity in the efficacy results in different clinical populations, even though its clinical effects in comparison studies did not differ significantly from those of bupivacaine. [5]

According to the clinical investigations that are now available, intrathecal anesthesia with levobupivacaine produces acceptable surgical anesthesia but has an

uncertain distribution of sensory blockade. [4] A common approach to enhance effects of intrathecal LA is by adding an adjuvant. Neuraxial opioids are frequently used to provide pain relief during and after the operation while minimizing the extension of sympathetic and motor blockade. [6,7] Nevertheless, no research has examined effects of intrathecal buprenorphine as an adjuvant in SAB for people undergoing infraumbilical procedures in comparison to 0.5% bupivacaine (H) and 0.5% levobupivacaine (H).

This study aims to evaluate and compare the effects of adding intrathecal buprenorphine to 0.5% bupivacaine (H) versus 0.5% levobupivacaine (H) for spinal anesthesia in patients undergoing infraumbilical surgeries.

AIMS AND OBJECTIVES

- Primary objective – To study the effect of intrathecal buprenorphine as an adjuvant to 0.5% hyperbaric bupivacaine and 0.5% hyperbaric levobupivacaine on hemodynamic parameters (HR, SBP, DBP, MAP, SpO_2) in adults undergoing infraumbilical surgeries under spinal anesthesia.
- Secondary objective- To evaluate and compare the onset of sensory and motor blockade of intrathecal buprenorphine as an adjuvant to 0.5% hyperbaric bupivacaine and 0.5% hyperbaric levobupivacaine in adults undergoing infraumbilical surgeries under spinal anesthesia.

REVIEW OF LITERATURE

Neuraxial anesthesia is a process of administering a LA into or close to the nervous system. The most common anesthetic approach for patients having surgery on areas below the umbilicus, such as the lower abdomen wall, perineal area, and lower limbs, is spinal anesthesia, which is a type of neuraxial anesthesia. [11]

"A more dependable block with a lower profile of adverse symptoms, such as hypotension, high block, pruritis, vomiting, and nausea, is expected with hyperbaric solutions. Furthermore, as "TJ Scull et al." noted in their study, they may cause sudden cardiac arrest due to cephalad extension of sympathetic block." [12]

Low dosages of opioids, such as fentanyl, sufentanil, and morphine, are added when giving LA in SAB to improve the quality of analgesia during and after the procedure and lessen the possibility of complications from the local anesthetic. [13] [14]

A randomized controlled trial conducted by "Bidikar M, Mudakanagoudar MS, and Santhosh MC" in 2017 compared intrathecal levobupivacaine and levobupivacaine combined with fentanyl for cesarean sections, with the aim of promoting early ambulation. Study found that mixture of intrathecal levobupivacaine and fentanyl not only prolonged sensory blockade but also reduced the need for additional pain relief, without affecting the motor blockade duration.[1]

When fentanyl (10 µg) and buprenorphine (60 µg) were used as adjuvants to 0.75% isobaric ropivacaine in intrathecal administration, they resulted in longer-lasting and higher-quality postoperative analgesia compared to ropivacaine alone. However, buprenorphine demonstrated a superior competence to increase the span of sensory blockade and provided better postoperative pain relief outcomes than fentanyl.

Limitations of study:

Buprenorphine was employed in this investigation at a maximum dose of 60 µg, which was shown to have more negative effects than desired in this specific study subjects. Additionally, they didn't investigate how addition of buprenorphine affected intraoperative hemodynamic variables and motor block characteristics. Although umbilical cord blood gas analysis might have been less subjective, neonatal effects were evaluated using the Apgar score.

In 2016, "Arvinder Pal Singh, Ravinder Kaur, Ruchi Gupta, and Anita Kumari" conducted a prospective double-blind study to compare effects of intrathecal buprenorphine and fentanyl as adjuncts to 0.75% ropivacaine in lower extremity operations. Their findings indicated both buprenorphine and fentanyl enhanced postoperative pain relief without extending the motor blockade duration. However, buprenorphine was found to be more effective than fentanyl in prolonging the sensory block and providing satisfactory pain relief. [3]

A systematic review and meta-analysis of randomized controlled trials with trial sequential analysis on the effectiveness of intrathecal fentanyl for cesarean birth was carried out in 2020 by "Uppal V, Retter S, Casey M, Sancheti S, Matheson K, and McKeen DM." Conclusion was combination of fentanyl and intrathecal bupivacaine alone decreased incidence of nausea and vomiting during the procedure, lengthened the time before first analgesic request, and decreased need for intraoperative supplemental analgesia. Initiation of hypotension, start of sensory blockade, and length of motor block do not seem to be impacted by intrathecal fentanyl. Adding fentanyl to intrathecal morphine–bupivacaine, benefits were comparable and requirement for additional intraoperative analgesia was significantly decreased. [5]

A randomized prospective study comparing the effects of buprenorphine and dexmedetomidine as additives to bupivacaine spinal anesthesia in elderly male participants undergoing transurethral resection of the prostate was carried out in 2017 by "Navdeep Kaur, Umesh Goneppanavar, Ramkumar Venkateswaran, and Sadasivan Shankar Iyer." They came to the conclusion that giving older male patients with TURP intrathecal bupivacaine plus either buprenorphine (60 mcg) or dexmedetomidine (5 mcg) produced a similar intraoperative and postoperative profile while extending the period for the initial analgesic dosage. [8]

Limitations of study:

Dexmedetomidine causes significant hypotension and bradycardia. Hence, further studies were conducted.

A randomized controlled trial comparing intrathecal dexmedetomidine and buprenorphine as adjuvants to bupivacaine in SAB was carried out in 2014 by "Gupta M, Shailaja S, and Hegde KS." In contrast to intrathecal buprenorphine, they found that intrathecal dexmedetomidine results in longer lasting anesthesia and analgesia, requiring fewer sedatives and rescue analgesics. [9]

Limitations of the study:

- They didn't conduct a statistical power assessment.
- A control group was not included, limiting the ability to compare the effects of the drugs independently.
- The study focused on participants aged 42–47 years, preventing an evaluation of intrathecal dexmedetomidine's impact on older individuals.

Study by “Tanvi A Dhawale and K R Sivashankar” (2021) compares efficacy of intrathecal fentanyl and buprenorphine as adjuvants to 0.5% bupivacaine (H) in SAB. Previous study has shown that opioid adjuvants like fentanyl and buprenorphine may increase quality of spinal anesthesia by improving pain relief plus prolonging its duration. Fentanyl, a potent μ-opioid receptor agonist, is widely used, but concerns about adverse effects such as hypotension and respiratory depression persist. Buprenorphine, a partial agonist, has been explored as an alternative with a potentially lower side-effect profile. This study adds to the ongoing investigation into optimizing spinal anesthesia for improved patient outcomes while minimizing complications. [10]

The article by “McDonald SB”, *"Spinal anesthesia and intrathecal opioids for ambulatory surgery,"* published in *Current Opinion in Anaesthesiology* (2001), reviews the role of spinal anesthesia combined with intrathecal opioids in enhancing analgesia for ambulatory surgeries. The use of spinal anesthesia in outpatient procedures offers rapid onset and effective pain control, but its duration may limit its effectiveness for longer procedures. Intrathecal opioids, such as morphine or fentanyl, when used as an additive, provide increased analgesia after procedure while reducing need for systemic opioids. The article discusses various studies showing improved pain relief and earlier discharge with this combination. Study reviews safety profile of intrathecal opioids, noting potential risks like respiratory depression or pruritus, and emphasizes the importance of careful patient selection and dosing to balance benefits and risks in ambulatory surgical settings. [15]

The article by “Burlacu CL”, *"Update on local anesthetics: focus on levobupivacaine,"* published in *Therapeutics and Clinical Risk Management* (2008), provides an overview of the characteristics and advantages of levobupivacaine. Levobupivacaine, the S-enantiomer of bupivacaine, is associated with a reduced risk

of cardiotoxicity and neurotoxicity, making it a preferable choice for various regional anesthesia techniques. The review highlights several studies comparing levobupivacaine with other local anesthetics, emphasizing its efficacy in providing effective, long-lasting anesthesia with a more favorable safety profile. Additionally, the article explores the potential benefits of levobupivacaine in both inpatient and outpatient surgical settings, particularly for its reduced side effect profile. [16]

The article by "Gupta RK", *"Comparative evaluation of intrathecal bupivacaine with fentanyl and buprenorphine for infraumbilical surgeries: A double-blind study,"* published in *Anesthesia Essays and Research* (2016), compares the efficacy of intrathecal bupivacaine combined with either fentanyl or buprenorphine for analgesia in infraumbilical surgeries. The study evaluates parameters such as onset and duration of anesthesia, postoperative relief from pain and side effects. Results indicate that both fentanyl and buprenorphine enhance the analgesic effect of bupivacaine, with buprenorphine offering a longer duration of pain relief and fewer side effects compared to fentanyl. The article highlights the potential of buprenorphine as a safer alternative to fentanyl in providing effective spinal anesthesia with improved postoperative outcomes. [17]

The article by "Glasser SA", *"Levobupivacaine: Is it time to replace bupivacaine?"* published in *Journal of Clinical Anesthesia* (2001), discusses the advantages of levobupivacaine over bupivacaine as a local anesthetic. Levobupivacaine, the S-enantiomer of bupivacaine, is highlighted for its improved safety profile, particularly its reduced cardiotoxicity and neurotoxicity. The review summarizes studies showing that levobupivacaine offers similar efficacy in terms of anesthesia quality and duration but with a lower incidence of adverse effects. The article suggests that levobupivacaine could be a better alternative to bupivacaine,

particularly in high-risk patients, though further clinical studies are needed for broader adoption. [18]

The article by “Lee YY”, *"Randomized double-blind comparison of levobupivacaine vs. bupivacaine for spinal anesthesia in foot and ankle surgery,"* published in *British Journal of Anaesthesia* (2003), compares the efficacy and safety of levobupivacaine and bupivacaine for spinal anesthesia in foot and ankle surgeries. The study found that levobupivacaine provided similar anesthesia quality and onset time as bupivacaine, but with a significantly lower incidence of cardiovascular and neurological side effects. The review highlights that levobupivacaine, as the S-enantiomer of bupivacaine, offers a safer alternative, particularly in high-risk patients. However, the authors suggest that further research is needed to confirm these findings across a broader range of surgical procedures. [19]

BASIC SCIENCES

Subarachnoid Block also known as Spinal Anaesthesia is the anaesthesia of choice for surgeries of the lower abdominal wall, the perineum and the lower limbs. It causes sensory, motor and sympathetic blockade. The main advantage of spinal anaesthesia is the avoidance of the usage of multiple drugs and manipulation of the airway as it is done in general anaesthesia. It also causes reduction in the metabolic stress response to surgery, reduction in pulmonary compromise as well as reduction in blood loss.

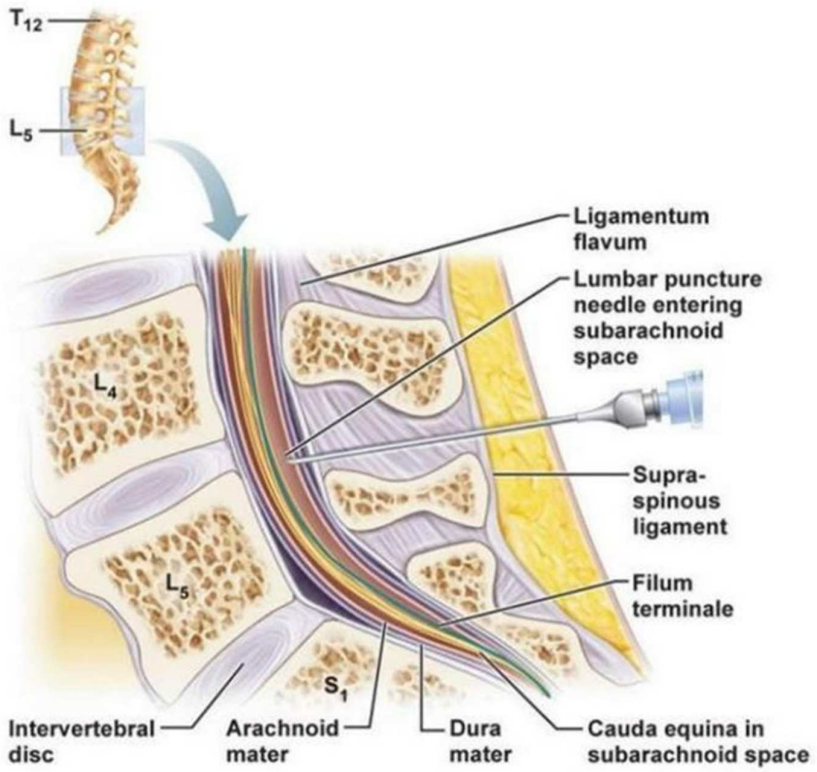


Fig 1: Subarachnoid Block

Spinal anaesthesia is administered only in the lumbar region, specifically the mid to low lumbar levels in order to avoid damaging the spinal cord. This also prevents intrathecally injected drugs from having any activity in the upper thoracic and cervical regions. [11]

CONTRAINDICATIONS OF SPINAL ANESTHESIA:

Absolute contraindications of spinal anaesthesia comprise of refusal by the patient, infection at the injection site, uncorrected hypovolemia, increased intracranial pressure, allergies to local anaesthetics.

Relative contraindications of spinal anaesthesia include coagulopathies, indeterminate neurological disease, fixed cardiac output states, septic shock.

COMPLICATIONS OF SPINAL ANESTHESIA:

Minor: Nausea, vomiting, mild hypotension, shivering, itching, urinary retention and transient hearing impairment.

Moderate: Failed spinal block, Post-dural puncture headache (PDPH).

Major: Direct needle trauma, spinal cord ischaemia, infection (abscess, meningitis), vertebral canal hematoma, cauda equina syndrome, arachnoiditis, peripheral nerve injury, total spinal anaesthesia, cardiovascular collapse, death.

ANATOMY

For a successful spinal anaesthesia, it is important for the anaesthesiologist to have a detailed knowledge of the anatomy of the vertebral column, spinal cord and spinal nerves.

VERTEBRAL COLUMN:

The main function of the vertebral column is to protect the spinal cord. There are a total of 33 vertebral bodies that make up the vertebral column which includes the following: [11]

- Cervical - 07
- Thoracic - 12
- Lumbar - 05
- Sacral - 05 (fused)
- Coccyx - 04 (fused)

CURVATURES OF SPINE:

The vertebral column has four curves in adults.

- Cervical curve - Convex anterior
- Thoracic curve- Concave anterior
- Lumbar curve - Convex anterior
- Sacral curve -Concave anterior

The curves of the spine are important when the patient is in supine position. The highest point of cervical and lumbar curves in supine position are at cervical-C5 and lumbar-L5, lowest points of thoracic and sacral at T5 and S2 respectively. Spread of local anaesthetic in the subarachnoid space is determined by the vertebral column curves, baricity of the local anaesthetic solution and positioning of the patient.

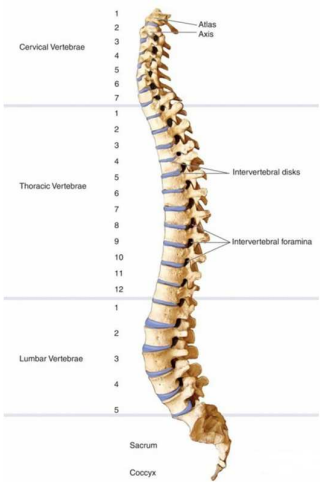


Fig 2: Vertebral Column

VERTEBRAL LIGAMENTS:

Vertebral column is bound by the following ligaments that give it stability and elasticity.

Supraspinous Ligament: It is a strong fibrous ligament which connects the apices of the spinous processes from the C7 vertebra to the Sacrum. It is also known as LIGAMENTUM NUCHAE in the area above C7 vertebra.

Interspinous Ligament: It is a thin membranous ligament which connects the spinous processes and it blends anteriorly with ligamentum flavum and posteriorly with supraspinous ligament.

Ligamentum Flavum: It comprises of yellow elastic fibres and connects the adjacent lamina. It begins laterally at the root of the articular processes and extends posteriorly and medially to the point where laminae join to form spinous process.

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

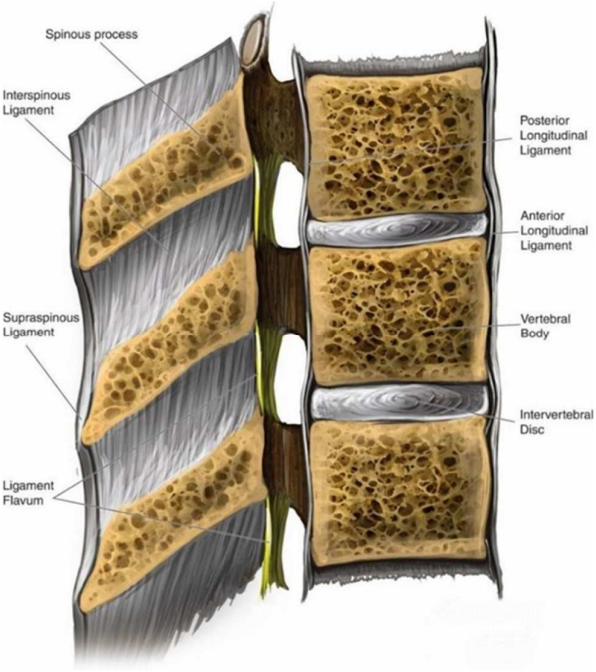


Fig 3: Ligaments of Spine

LUMBAR VERTEBRAE:

A typical lumbar vertebra consists of:

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

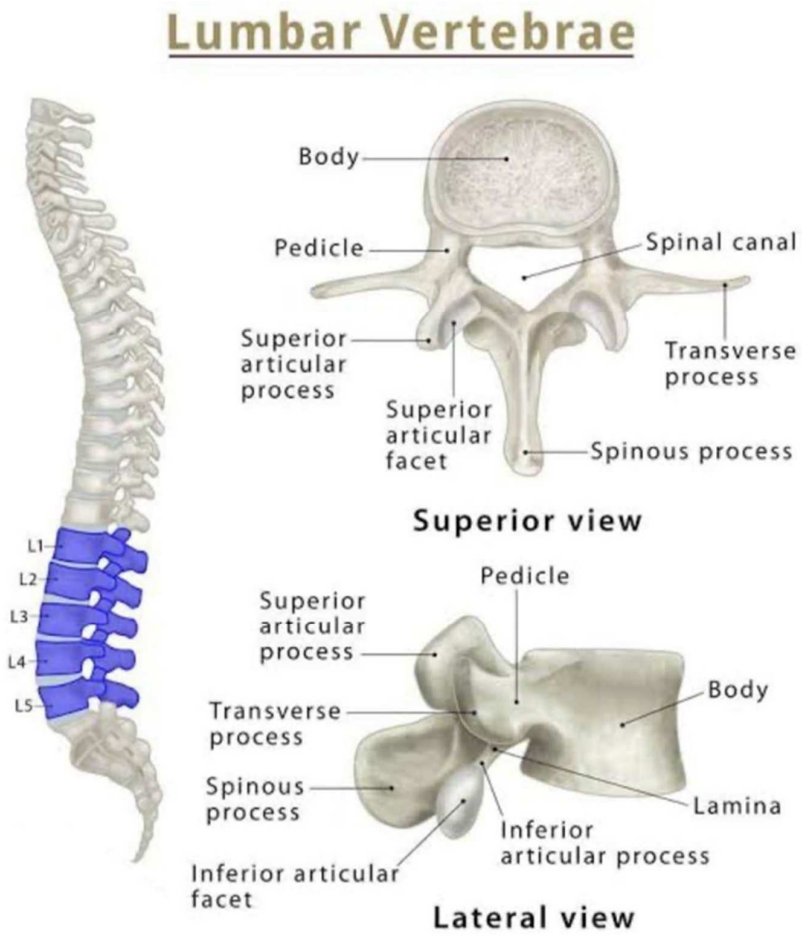


Fig 4: Lumbar Vertebrae

TUFFIER'S LINE:

It is an imaginary line that passes between the highest points of the iliac crests which crosses the spine of the fourth lumbar vertebra in the upright position. When the patient is in lateral decubitus position it may pass through the L4-L5 interspace. The lumbar spaces are identified by using the superior iliac crest.

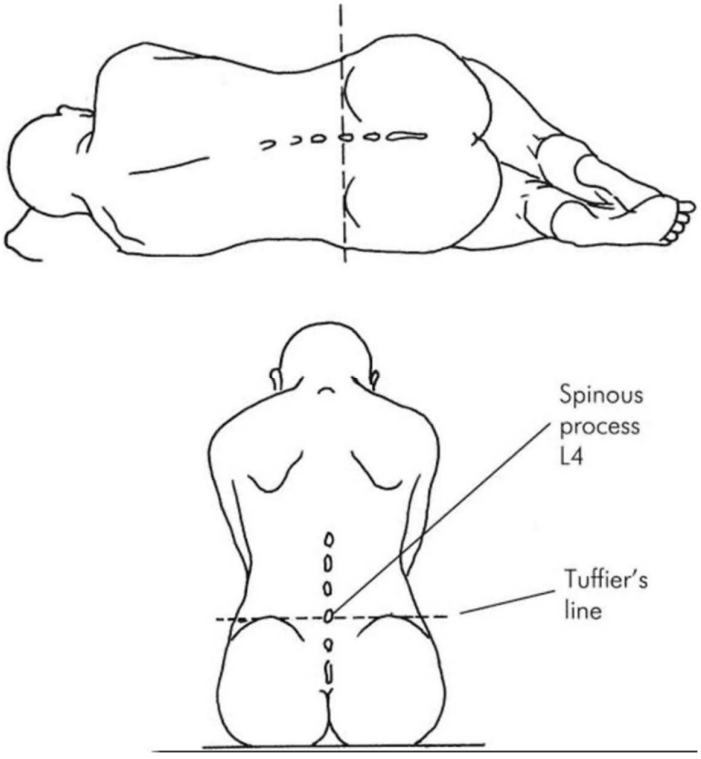


Fig 5: Topographical line of Tuffier

VERTEBRAL BODY:

Vertebral canal is bound posteriorly by the spinous processes and interspinous ligaments, laterally by the pedicles, postero-laterally by the laminae and the ligamentum flavum. Superiorly it extends from foramen magnum and terminates inferiorly in the sacral hiatus.

Its contents are:

- spinal cord
- dorsal root ganglia
- ventral rootlets
- roots of the spinal nerves
- sympathetic trunk
- rami communicantes
- adipose tissue

- CSF
- blood vessels and
- spinal membranes

SPINAL CORD:

The spinal cord is the continuation of medulla oblongata below the level of foramen magnum and it tapers off into a conical extremity known as conus medullaris. A delicate fibrous filament descends to the back of the first segment of the coccyx from the apex of conus medullaris which is called *filum terminale* which is a continuation of the pia mater. The average length of the spinal cord in males is 45 cm and 42 cm. The length of the spinal cord differs according to age. In the first trimester, the foetal spinal cord extends up till the end of the spina; column. As the foetus grows the vertebral column lengthens more than the length of the spinal cord. At birth, the spinal cord ends approximately at the L3 space and in adults it ends approximately at the upper border of the L1 vertebra.

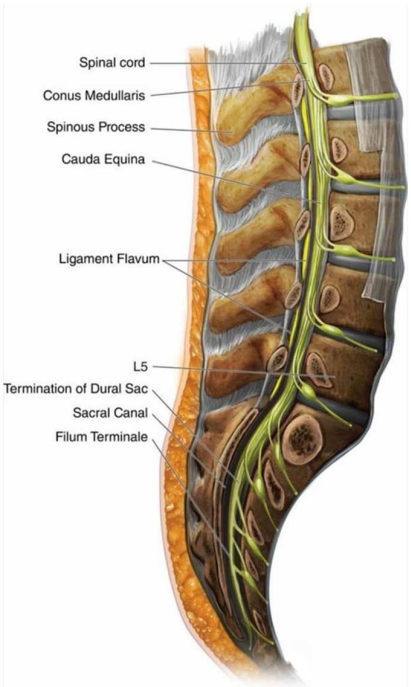


Fig 6: Spinal cord at Lumbo-sacral region

BLOOD SUPPLY OF SPINAL CORD:

The spinal cord is supplied by three arteries: One anterior spinal artery and two posterior spinal arteries.

Anterior Spinal Artery is a single vessel lying in the substance of the pia mater overlying the anterior median fissure. It supplies the lateral and anterior columns which comprises the three quarters of the substance of the cord. Thrombosis of this artery leads to Anterior spinal artery syndrome. [20]

There are two pairs of *Posterior Spinal Arteries* one pair on each side of the spinal cord arising from the posterior cerebellar arteries at the level of foramen magnum. They supply the posterior column of the spinal cord. [20]

There is no anastomosis between the anterior and posterior spinal arteries.

Anterior and posterior plexus of veins in the neck, azygos veins in the thorax, lumbar veins in the abdomen, lateral sacral veins in the pelvis are responsible for the venous drainage of the spinal cord.

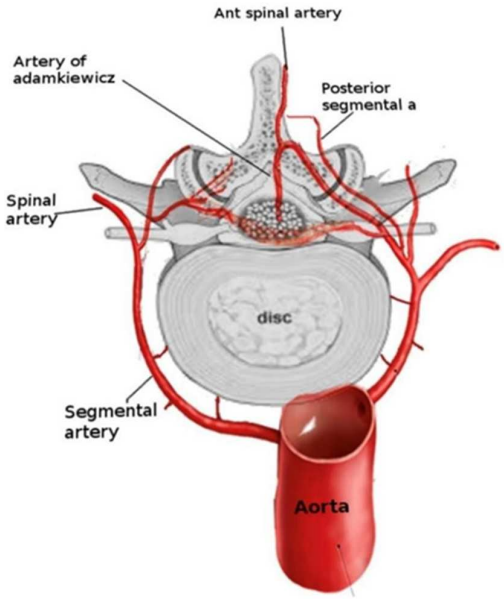


Fig 7: Blood supply of the Spinal cord (transverse view)

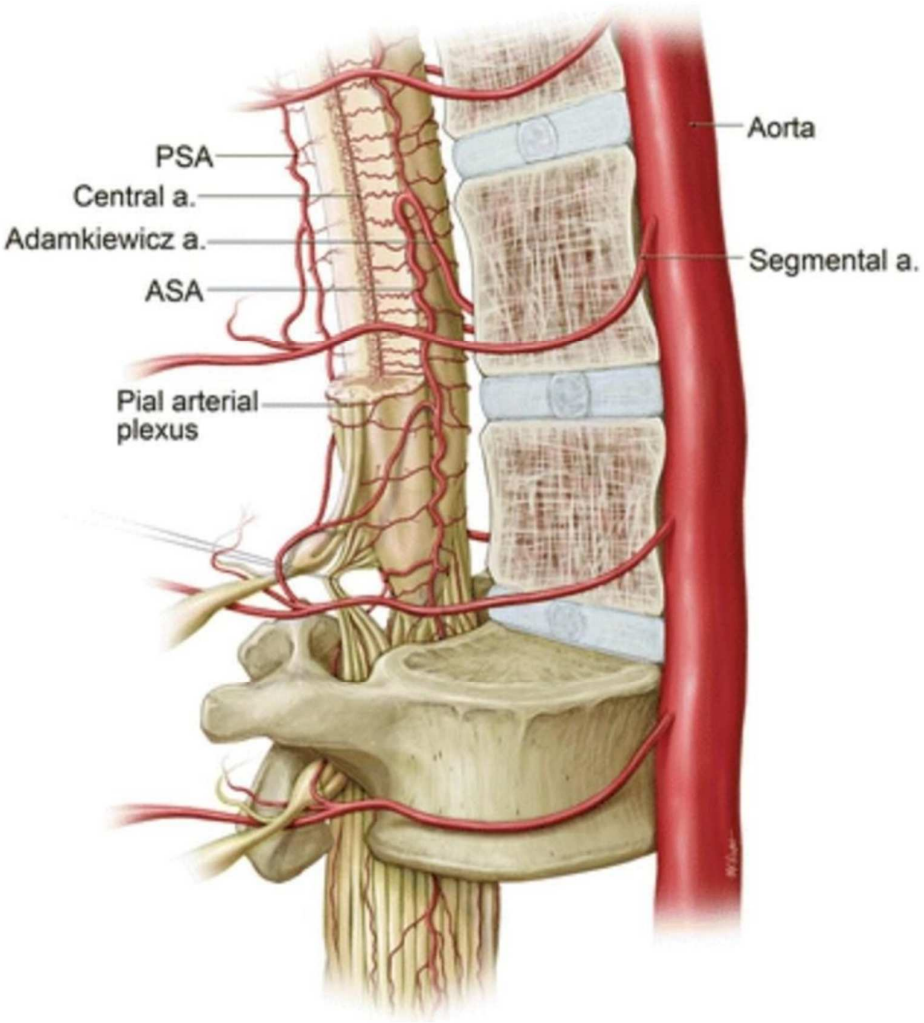


Fig 8: Blood supply of the spinal cord (lateral view)

SPINAL MENINGES:

Spinal cord is also protected by three connective tissue coverings called *Meninges*- Dura mater, Pia Mater and Arachnoid mater.

DURA MATER: It is a tough outermost fibro-elastic covering which consists of an outer endosteal layer and an inner meningeal layer. The fibres of the dura mater are aligned longitudinally. The dural sac ends at the lower border of S2 where it is pierced by the filum terminale.

ARACHNOID MATER: It is a delicate, non-vascular, middle layer and is closely attached to the dura mater. There is a potential space between the dura mater and arachnoid mater called the subdural space and it contains serous fluid. PIA MATER: It is the innermost membrane and is a vascular sheath which closely invests the brain and spinal cord. It continues till the coccyx as filum terminale.

SUBARACHNOID SPACE: It is the space between the arachnoid mater and the pia mater and is filled with cerebrospinal fluid (CSF) along with numerous arachnoid trabeculae which form a delicate sponge like mass. This space has three divisions that are in continuation with each other: Cranial (surrounding the brain), Spinal (surrounding the spinal cord) and Root (surrounding the ventral and dorsal nerve roots). In the spinal cord, these nerves are covered only by pia mater and bathed in CSF. As these spinal nerve roots pass beyond the spinal dura and traverse the epidural space, they carry with them all the three layers of the meninges and have a distinct epidural, subdural, subarachnoid and subpial spaces. The subarachnoid space extends separately along both the dorsal and ventral roots to the level of dorsal root ganglion where the arachnoid and pia continue as perineural epithelium of peripheral nerves.

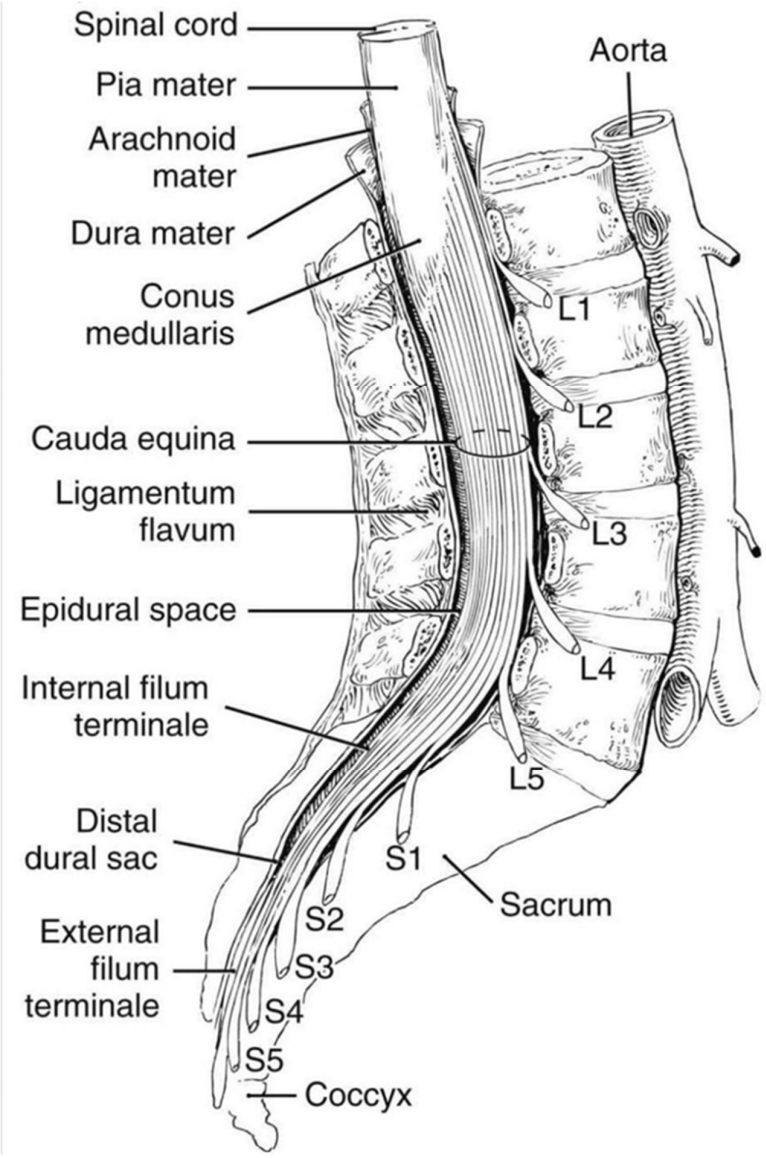


Fig 9: Spinal cord with its meningeal layers at Lumbo-sacral level

CEREBROSPINAL FLUID:

It is a clear, colourless fluid found in the cranial and spinal subarachnoid spaces and in the ventricles. It is mainly formed by either secretion or ultrafiltration from the choroidal plexus of the lateral ventricles. It flows from the lateral ventricles into the third ventricle through the Foramen of Monroe and then into the fourth ventricle through the Aqueduct of Sylvius. CSF then flows into the Cisterna Magna (cerebro-medullary cisterna) through the Foramen of Magendie and Foramen of Lushka. From the Cisterna Magna, CSF enters the Subarachnoid Space where it flows over the surface of cerebral cortex and spinal cord before it is absorbed into the arachnoid granulations which are present over the cerebral hemispheres and the finally into the cerebral venous system. [21]

COMPOSITION OF CSF:

- Specific Gravity : 1.003 to 1.00 g/cm at 37°C
- Volume : 120 ml to 150 ml (25 ml to 35 ml in the spinal space)
- CSF pressure : 60-80 mmHg in the Lumbar space
- pH : 7.27 to 7.37
- PCO2 : 48 mmHg
- HCO3 : 23 mEq/L
- Sodium : 135-145 mEq/L
- Calcium : 2-3 mEq/L
- Phosphorus : 1.6 mg/dl
- Magnesium : 2-2.5 mEq/L
- Chloride : 15-20 mEq/L
- Proteins : 23-38 mg/dl

PHYSIOLOGY OF SUBARACHNOID BLOCK:

The various factors that control the different effects of a spinal anaesthetic technique are as follows:

The amount and the type of drug

- Volume of the drug solution
- The site of injection
- The rate of injection
- Specific gravity of the solution- baricity and density
- Barbottage.

The factors that affect the spread of local anaesthetics are:

1. Patient factors:

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

2. Technical Factors:

- Site of injection
- Direction of the needle
- Dose of the local anaesthetic
- Baricity of the local anaesthetic
- Volume of the local anaesthetic

The nerve roots as well as spinal cord take up the local anaesthetics after injection into the subarachnoid space. More the surface area of exposure of the nerve root, more is the uptake of the drug. There are two mechanisms by which the local anaesthetic gets taken up:

- The first mechanism is by diffusion from the CSF into the pia mater and into the spinal cord. This is a slow process and only the most superficial portion of the spinal cord is affected.
- The second mechanism of local anaesthetic uptake is by extension into the spaces of Virchow-Robin which is the area of pia mater that surround the blood vessels which penetrate the Central Nervous System. These spaces connect with perineural clefts that surround the nerve cell bodies in the spinal cord.

The site of action is on both the anterior and posterior nerve roots, affecting the smaller nerve fibres first and the thick large motor nerve fibres last.

The sympathetic fibres are affected first and are last to recover. The sympathetic blockade is more diffuse and extends two to four segments above the motor block. Sympathetic blockade is the major determinant of physiologic response to spinal anaesthesia. The motor blockade is usually the last to be affected and first to recover.

SEQUENCE OF SPINAL ANESTHESIA:

- Vasomotor Block: Dilatation of skin vessels and increase cutaneous blood flow.
- Temperature Fibres: Cold sensation lost first followed by warm sensation.
- Loss of temperature discrimination
- Pain- Pin prick sensation lost first
- Loss of tactile sensation

- Motor paralysis
- Loss of pressure sensation
- Loss of proprioception and vibratory sensation

SYMPATHETIC BLOCKADE:

Sympathetic fibres are usually blocked two to three segments above the sensory blockade and sensory blockade is two segments higher than motor blockade. Since the level of sympathetic denervation determines the magnitude of cardiovascular response to subarachnoid block, it could be anticipated that higher the level of neural blockade, greater would be the changes in the cardiovascular and hemodynamic parameters.

CARDIOVASCULAR EFFECTS OF SPINAL ANESTHESIA:

The autonomic denervation that accompanies spinal anaesthesia affects the cardiovascular system in the following ways:

- Vasodilation of resistance and capacitance vessels
- Blockade of cardiac efferent sympathetic fibres from T1-T4 resulting in loss of chronotropic and inotropic drive and fall in cardiac output.
- Bainbridge reflex causing bradycardia
- Depression of vascular smooth muscles and beta-adrenergic blockade of the myocardium with fall in cardiac output following systemic absorption of local anaesthetic drug.

extending above T4 level is associated with fall in Blood Pressure. Bradycardia occurs if any of the anterior roots carrying the sympathetic cardiac accelerator fibres are blocked, which may happen in high spinal block above T4-T5. Bradycardia may

also be due to lowering in blood pressure in the right atrium consequent to diminished venous return.

THEORIES OF CAUSATION OF HYPOTENSION:

- Reduced venous return leading to diminished cardiac output
- Dilation of post-arteriolar capillaries and small venules
- Paralysis of sympathetic nerve supply to the heart
- Paralysis of the sympathetic nerve supply to the adrenal glands leading to catecholamine depletion.

CEREBRAL BLOOD FLOW:

Due to the presence of cerebral autoregulatory mechanism in humans, cerebral blood flow is maintained at constant levels.

RESPIRATORY SYSTEM:

Breathing becomes quiet and tranquil during spinal anaesthesia. This is due to differentiation with reduction of sensory input to respiratory centre along with motor blockade. Intercostal muscle paralysis is compensated by increased descent of diaphragm which is enabled by the lax abdomen. However, the pulmonary gas-exchange is preserved.

GASTROINTESTINAL SYSTEM:

Pre-ganglionic sympathetic fibres extending from T5 to L1 are inhibitory to the gut with no effect on oesophagus which has vagal nerve innervation. Neuraxial block-induced sympathectomy causes Vagal dominance which leads to small, contracted bowel with active peristalsis. The pressure in the bowel lumen increases. There is relaxation of sphincters.

NAUSEA & VOMITING:

Following are the causes:

- Hypotension
- Hypoxia
- Traction on nerve endings (especially the Vagus nerve)
- Increased peristalsis
- Relaxation of pyloric sphincter leading to presence of bile in stomach which causes nausea and vomiting
- Psychological effects
- Opioid analgesics that are used as a part of pre-medication.

GENITOURINARY SYSTEM:

Renal blood flow is maintained through autoregulation with little effect on kidney function with normal systemic blood pressure. Neuraxial anaesthesia at the lumbar and sacral levels blocks both sympathetic and parasympathetic control of bladder function.

Urinary retention post spinal anaesthesia may be moderately prolonged due to involvement of autonomic fibers of S2 to S3. Their paralysis lasts longer than that of larger sensory and motor fibers. Due to the paralysis of *nervi arigentes* (S2 to S3), the penis becomes engorged and flaccid.

UTERUS:

Uterus muscle tone is not greatly altered after spinal anesthesia in pregnancy.

NEUROENDOCRINE SYSTEM:

Neuroendocrine stress response by activation of somatic and visceral afferent nerve fibers along with localized inflammatory response occurs with surgical trauma. Neuraxial blockade can partially suppress or completely block the neuroendocrine stress response.

BODY TEMPERATURE:

Hypothermia is a common occurrence. Neuraxial anaesthesia reduces the threshold for shivering by inhibiting the central thermoregulatory control. Block of peripheral sympathetic and motor nerves prevents vasoconstriction and shivering. Heat loss continues through convection, evaporation and radiation. Catecholamine secretion is depressed, hence less heat is produced by metabolism.

PHARMACOLOGY:

LOCAL ANESTHETICS:

Local anaesthetic drugs are the drugs that case reversible blockade of conduction of nerve impulses. The properties of an ideal local anaesthetic agent are:

- Short latency
- High potency
- High diffusion
- Low toxicity
- Complete reversibility of its actions
- Prolonged duration of action
- No tachyphylaxis
- Stability and ability withstand heat sterilization

CLASSIFICATION:

They are divided into two groups depending on the link between the aromatic portion and the intermediate chain- the amino-ester group and the amino-amide group.

The amino-ester group has an ester link and they are Procaine, Chlorprocaine and Amethocaine.

The amino-amide group has an amide link between the aromatic head and the intermediate chain and they are Lignocaine, Bupivacaine, Levobupivacaine, Mepivacaine, Prilocaine, Ropivacaine and Etidocaine.

PHARMACOLOGY OF LOCAL ANESTHETICS:

These drugs produce reversible blockade of nerve conduction along the central and peripheral nerve pathways. When their concentration is increased gradually, the transmission of autonomic, somatic sensory and somatic motor impulses is interrupted in the same sequence. This leads to autonomic blockade, sensory anaesthesia and muscle paralysis in the area supplied. These drugs get gradually removed by absorption into the systemic circulation which leads to the reversal of the blockade.

MOLECULAR STRUCTURE:

Local anaesthetics have a lipophilic group (usually an aromatic benzene ring) separated from a hydrophilic group (usually a tertiary amine) by an intermediate chain that includes an ester or amide linkage, which forms the basis of its classification as either esters or amides.

BUPIVACAINE ($C_{18}H_{28}N_{20}$)

CHEMICAL STRUCTURE:

Fig 10: Chemical structure of Bupivacaine

Bupivacaine is a long acting, amide local anaesthetic. It was first prepared by A.F. Ekenstam in 1957 and introduced by Telivuo in 1963. It is chemically related to lignocaine and its structure is similar to that of Mepivacaine except for the amide containing group is a butyl piperidine. Its potency is approximately four times that of Lignocaine.

It is a popular drug for its long duration of action along with its tendency to provide both sensory and motor block and prolonged analgesia during the post-operative period.

Bupivacaine can be used to provide effective analgesia for several days through the use of indwelling catheters and continuous infusions.

PHYSIOCHEMICAL PROPERTIES:

- Chemical Name: 1-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide
- Molecular weight: 288.4 g/mol
- pKa: 8.1

- Half-life: 1.5 to 5.5 hours in adults and 8.1 hours in neonates
- Specific gravity: 1.026 at 37°C

PHARMACOLOGY:

The addition of a butyl group to the piperidine Nitrogen of Mepivacaine makes Bupivacaine 35 times more lipid soluble.

POTENCY:

It is approximately 3-4 times more potent than Mepivacaine or Lignocaine.

ONSET & DURATION OF ACTION:

The onset of action of Bupivacaine is between 5-7 minutes and the maximum anaesthesia is achieved in 15-20 minutes.

The duration of action depends on the type of block- average duration of epidural block is 2.5-4 hours and average duration of spinal block is 2-3 hours.

MECHANISM OF ACTION:

The mechanism of action of Bupivacaine is similar to that of Lignocaine.

Local anaesthetics bind to a specific site in the voltage gated sodium channels and block it thereby preventing sodium ion influx through the individual channels and preventing impulse propagation. Local anaesthetic binding to sodium channels does not alter the resting membrane potential. As a consequence of more channels binding a local anaesthetic, the threshold for excitation and impulse conduction in the nerves increase and the rate of rise and magnitude of the action potential decrease and impulse conduction velocity slows. When a large amount of local anaesthetic concentrations, action potentials can no longer be generated and impulse propagation is abolished.

The mechanism of sodium conductance blockade:

- The cationic form of local anaesthetic drug acts on the receptors within the Na^+ channels on the cell membrane and block it. The local anaesthetic can reach the Na^+ channel either via the lipophilic pathway directly across the lipid membrane or via the axoplasmic opening.
- The second mechanism is a non-specific action, i.e. by membrane expansion.

AVAILABLE CONCENTRATIONS OF BUPIVACAINE:

0.25% and 0.5%

DOSAGE OF BUPIVACAINE:

Maximum dosage: 3 mg/Kg body weight.

Adrenaline prolongs its action only marginally, if at all. Tachyphylaxis is much less likely than with Lignocaine.

METABOLISM & ELIMINATION:

Bupivacaine gets metabolised by the following mechanisms:

- Aromatic hydroxylation
- N-dealkylation
- Amide hydrolysis
- Glucuronide- conjugation

The chief mechanism is N-dealkylation and the metabolite is N-desbutyl Bupivacaine. The mean total of urinary excretion of Bupivacaine and its dealkylation and hydroxylation metabolites account for >40% of the total anaesthetic dose.

ACTIONS:

ON CENTRAL NERVOUS SYSTEM

Over-dosage concentrations of Bupivacaine produce dizziness and light-headedness followed by visual and auditory disturbances such as difficulty to focus and tinnitus. Shivering and muscular tremors and tremors of facial muscles can occur.

The plasma concentration of Bupivacaine that is associated with seizures is 4.5 to 5.5mcg/ml.

ON CARDIOVASCULAR SYSTEM

Usually, the cardiovascular system is more resilient to the toxic effects of high plasma concentrations of local anaesthetics. Lignocaine concentrations <5mcg/ml is devoid of adverse effects but causes decrease in automaticity. Lignocaine concentrations of 5-10 mcg/ml can produce profound hypotension due to arteriolar vascular smooth muscle relaxation direct myocardial depression.

Blockade of cardiac Na^+ channels by local anaesthetics contributes to anti-dysrhythmic properties. With increase in concentration, more Na^+ channels get blocked and conduction and automaticity become affected adversely. This is evident by prolongation of PR interval and QRS complexes.

Accidental injection of Bupivacaine may result in precipitous hypotension, cardiac dysrhythmias and AV heart block. Most common dysrhythmias include widening of QRS complexes, premature ventricular contractions and Ventricular tachycardia.

Cardiotoxicity with Bupivacaine is seen when its plasma concentration is 8-10 mcg/ml. Pregnancy may increase sensitivity to the cardiotoxic effects of Bupivacaine.

Cardiotoxic threshold of Bupivacaine may be decreased in patients being treated with drugs like Digitalis, Calcium Channel Blockers and Beta Blockers. Epinephrine and Phenylephrine can increase cardiotoxicity of Bupivacaine-induced inhibition of catecholamine-induced production of cyclic AMP.

Bupivacaine blocks cardiac Na+ channels during systole but due to its high lipid solubility it gets dissociated during diastole. This explains its persistent depressant effect on Vmax and hence greater cardiotoxicity. The R-enantiomer of Bupivacaine is more cardiotoxic. Tachycardia can enhance frequency dependent blockade of cardiac Na+ channels by Bupivacaine.

TREATMENT OF BUPIVACAINE TOXICITY:

Bretyllium 20 mg/Kg IV reverses Bupivacaine-induced cardiac depression and increases the threshold for ventricular tachycardia.

Lipid Emulsion is also used for the treatment of cardiotoxicity with its usage recommended at the earliest sign of toxicity. Initial bolus of 1.5 ml/Kg of 20% Lipid Emulsion followed by 0.25 ml/Kg/min infusion should be continued for at least 10 minutes after the circulatory stability is established.

RESPIRATORY SYSTEM:

Local anaesthetics in very high plasma levels depress medullary respiratory centre which can precipitate decreased oxygenation.

TOXICITY OF BUPIVACAINE:

The toxic plasma concentration of Bupivacaine is >3 mcg/ml. The cardiotoxic effects of Bupivacaine become evident when the plasma concentration becomes 8-10 mcg/ml.

PHARMACOKINETICS:

Bupivacaine levels are detectable in the blood 5 minutes after infiltration. Peak blood concentrations depend on the total dosage given and ranges between 0.14 to 0.18 mcg/ml. These levels are from 5 minutes to 2 hours of infiltration and reduces to 0.1 to 0.34 mcg/ml in approximately 4 hours. Liver is the primary site of metabolism of Bupivacaine. Bupivacaine crosses placenta in very little concentrations with feto-maternal circulation ratios ranging from 0.2 to 0.4. It is also secreted in the breast milk.

HYPERBARIC BUPIVACAINE:

Isobaric Bupivacaine (Plain) has density equal to that of CSF. Hyperbaric Bupivacaine is prepared by the addition of Glucose (80 mg/ml) to the Isobaric Bupivacaine, with a density heavier than CSF. The difference in densities between the two is believed to effect their diffusion patterns and thus determine the spread, effectiveness and side-effect of the drugs.

Baricity is defined as the ratio of density (mass/volume) of the local anaesthetic's solution to that of the CSF at 37°C. It influences the distribution of local anaesthetic solution in the CSF, the spread and height of the block since gravity causes hyperbaric solutions to settle downward in the CSF and hypobaric solutions tend to rise. In contrast, gravity has no effect on the distribution of a truly isobaric solution.

LEVOBUPIVACAINE ($C_{18}H_{28}N_{20}$)

INTRODUCTION:

Levobupivacaine is the S(–)-enantiomer of the local anaesthetic bupivacaine. Racemic bupivacaine has traditionally been the longest acting local anaesthetic commercially available and widely used. Levobupivacaine's clinical profile closely resembles that of bupivacaine. However, current preclinical safety and toxicity data show an advantage for levobupivacaine over bupivacaine.

CHEMICAL STRUCTURE:

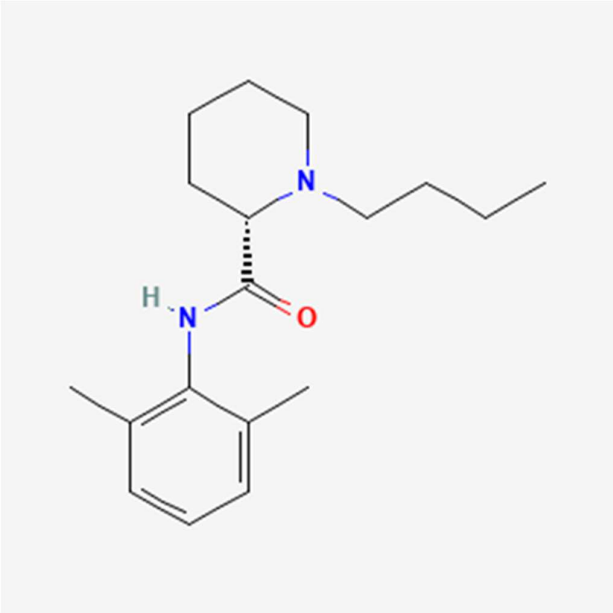


Fig 11: Chemical structure of Levobupivacaine

PHYSIOCHEMICAL PROPERTIES:

- Chemical Name: (2S)-1-butyl-N-(2,6_dimethylphenyl)piperidine-2-carboxamide
- Molecular weight: 288.4 g/mol
- pKa: 8.1

MECHANISM OF ACTION & CO-RELATION WITH ITS STRUCTURE:

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

PHARMACOKINETICS:

ABSORPTION:

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

DISTRIBUTION:

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

METABOLISM & EXCRETION:

Levobupivacaine is extensively metabolized with no unchanged Levobupivacaine detected in urine or feces. In vitro studies using Levobupivacaine

showed that CYP3A4 isoform and CYP1A2 isoform mediate the metabolism of Levobupivacaine to Desbutyl Levobupivacaine and 3-hydroxy Levobupivacaine, respectively.

In vivo, the 3-hydroxy Levobupivacaine appears to undergo further transformation to glucuronide and sulfate conjugates. Metabolic inversion of levobupivacaine to R(+)- Bupivacaine was not evident both in vitro and in vivo.

Following intravenous administration, recovery of the radio-labelled dose of Levobupivacaine was essentially quantitative with a mean total of about 95% being recovered in urine and feces in 48 hours. Of this 95%, about 71% was in urine while 24% was in feces. The mean half-life is 3.3 hours.

PHARMACODYNAMICS:

CENTRAL NERVOUS SYSTEM & CARDIOVASCULAR SYSTEM:

The risk of CNS toxicity was less with Levobupivacaine than with Bupivacaine in human volunteers. Central or peripheral nervous system disorders were experienced by 36% of Levobupivacaine recipients in the study where volunteers received intravenous doses of Levobupivacaine (mean 67.7mg).

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

Levobupivacaine also showed less depressant effect on the atrioventricular conduction and QRS complex duration, and provoked less impairment of the

contractile function of the isolated animal heart. Levobupivacaine is also less potent in blocking cloned human heart sodium and potassium channels.

POTENCY:

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

ADVERSE EFFECTS:

- Cardiovascular system toxicity: bradycardia, hypotension, sudden cardiovascular collapse
- Gastrointestinal system toxicity: nausea (12%), vomiting (14%), constipation (7%),
- Central nervous system toxicity: Headache (7%) disorientation, drowsiness, slurred speech, which may culminate with tonic-clonic seizures
- Hematological: Anemia (12%), increased serum albumin level, leukocytosis and purpura

ADVANTAGES OVER OTHER LOCAL ANESTHETICS:

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

OPIOD RECEPTORS:

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

MECHANISM OF ACTION OF OPIODS:

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

It also leads to the reduced neuronal firing. It reduces the action potential plateau and thereby reducing the calcium influx and the neurotransmitter release. Contrary to the above- mentioned receptors, κ receptors, shut the calcium channels.

BUPRENORPHINE:

INTRODUCTION:

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

CHEMICAL STRUCTURE:

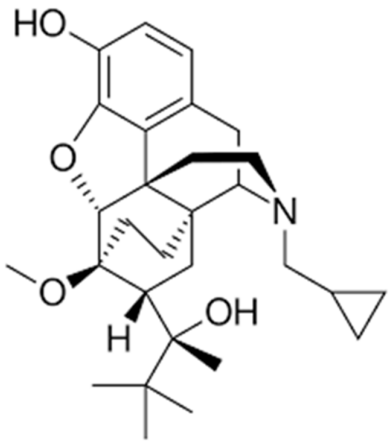


Figure 12: Chemical structure of Buprenorphine

Molecular weight of Buprenorphine is 467.6 g/mol)

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

Buprenorphine also has the following characteristics:

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

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

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

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

PHYSICAL PROPERTIES:

MECHANISM OF ACTION & CO-RELATION WITH STRUCTURE:

Buprenorphine is a partial agonist at the mu receptor, meaning that it only partially receptor agonist. It is a potent analgesic that acts on the central nervous system (CNS). The partial agonism at the mu receptor is a unique quality to buprenorphine. The feature gives its many unique properties specifically that its analgesic effects plateau at higher doses, and then its effects become antagonistic. [22] Buprenorphine exhibits ceiling effects on respiratory depression, which means that it is safer than methadone for agonist substitution treatment in addiction. [23, 24]

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

PHARMACOKINETICS:

ABSORPTION:

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

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

Coadministration with naloxone does not affect the pharmacokinetics of buprenorphine.

DISTRIBUTION:

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

MECHANISM & EXCRETION:

Buprenorphine is metabolized to norbuprenorphine via Cytochrome P450 3A4/3A5-mediated N-dealkylation. Buprenorphine and norbuprenorphine both also

undergo glucuronidation to the inactive metabolites buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, respectively.

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

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

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

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

Buprenorphine demonstrates slow dissociation kinetics (~166 min), which contributes to its long duration of action and allows for once-daily or even every-

second-day dosing.In clinical trial studies, the half-life of sublingually administered buprenorphine/naloxone 2mg/0.5mg was found to be 30.75 hours. Clearance may be higher in children than in adults. Plasma clearance rate, IV administration, anaesthetized patients = 901.2 ± 39.7 mL/min; Plasma clearance rate, IV administration, healthy subjects = 1042 - 1280 mL/min.

PHARMACODYNAMICS:

Buprenorphine interacts predominately with the opioid mu-receptor. These mu-binding sites are discretely distributed in the human brain, spinal cord, and other tissues. In clinical settings, buprenorphine exerts its principal pharmacologic effects on the central nervous system. Its primary actions of therapeutic value are analgesia and sedation. In addition to analgesia, alterations in mood, euphoria and dysphoria, and drowsiness commonly occur. Buprenorphine depresses the respiratory centers, depresses the cough reflex, and constricts the pupils.

DEPENDENCE:

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

WITHDRAWAL:

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

Precipitation of Opiod Withdrawal Signs & Symptoms:

If buprenorphine is started in opioid-dependent individuals, it will displace the other opioids and cause a phenomenon known as "precipitated withdrawal" which is characterized by a rapid and intense onset of withdrawal symptoms. Individuals must therefore be in a state of mild to moderate withdrawal before starting therapy with buprenorphine. Because it contains naloxone, buprenorphine and naloxone sublingual tablets are also highly likely to produce marked and intense withdrawal signs and symptoms if misused parenterally by individuals dependent on full opioid agonists such as heroin, morphine, or methadone.

GASTROINTESTINAL EFFECTS:

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

EFFECTS ON ENDOCRINE SYSTEM:

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date. Patients presenting with symptoms of androgen deficiency should undergo laboratory evaluation.

Adrenal Insufficiency:

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

Orthostatic Hypotension:

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

Elevation of Cerebrospinal Fluid Pressure:

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

Elevation of Intracholedochal Pressure:

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

ADVERSE EFFECTS:

Cardiovascular system toxicity: hypertension and peripheral edema

Gastrointestinal system toxicity: nausea, constipation, diarrhea

Central nervous system toxicity: fatigue, headache, dizziness, drowsiness, anxiety, opioid withdrawal syndrome

Hematologic: Anemia and bruise

Metabolic disorders: Hot flushes

MATERIALS AND METHODS

Title: "Comparison of 0.5% hyperbaric bupivacaine and 0.5% hyperbaric levobupivacaine with buprenorphine as an adjuvant for spinal anesthesia in adults undergoing infraumbilical surgeries – a one year hospital based randomized control trial."

Source of Data:

"Patients recruited were between the age group of 18-60 years, of either gender, belonging to American Society of Anesthesiologists (ASA) grade I-II, undergoing infraumbilical surgeries under spinal anesthesia at KLE's Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi from February 2024 to February 2025."

Study Design: One year hospital based randomized controlled trial (RCT)

Study Period: February 2024 to February 2025

Sample Size: 102. Group BB = 51 patients and Group LB = 51 patients

At 95% confidence interval and 90% power

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 \ (SD_1{}^2 + SD_2{}^2)}{(X_1 - X_2)^2} \text{ X } 1.10$$

N = 102

X_1 = 82.8 (baseline DBP)

X_2 = 75 (At 15 min DBP)

SD_1 = 13.5

SD_2 = 10.6

$Z_{1-\alpha/2}$ = 1.96

$Z_{1-\beta}$ = 1.29

SD= Standard deviation

Sample size was determined according to prior study - "Tanvi A Dhawale, K R Sivashankar. Comparison of Intrathecal Fentanyl and Buprenorphine as an Adjuvant to 0.5% Hyperbaric Bupivacaine for Spinal Anesthesia. 2021; Anesth Essays Res.2021 Jan-Mar; 15(1):126-132. The minimum sample size needed to conduct the study was 102 cases. 102 cases will be selected and allocated them into two groups (51 in each group) based on computer generated randomized method."

Sampling technique:

Patients who conformed to eligibility criteria and gave consent were allocated between BB and LB through a computer generated randomization process.

Group BB: who received 15mg of 0.5% bupivacaine (H) + 60mcg buprenorphine

Group LB: who received 15mg of 0.5% levobupivacaine (H) + 60mcg buprenorphine

For this purpose, each patient was assigned to one group using computer generated randomization table. This action was repeated until the sample size was reached. The allocations were concealed to the patients.

Inclusion Criteria:

- Age 18-60 years
- Either gender
- American Society of Anesthesiologists (ASA) grade I and II patients

- Patients who underwent infraumbilical surgeries under spinal anesthesia

Exclusion Criteria:

- Patients with American Society of Anesthesiologists (ASA) grade III or more
- Patients with allergy to study drug

Study protocol:

"18–60-year old adults, either male or female, who underwent infraumbilical surgeries under spinal anesthesia at KLE's Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru Nagar, Belagavi."

Data collection procedure:

After ethical committee approval and obtaining written informed consent, 102 participants scheduled for non-emergency surgery under spinal anesthesia were enrolled. A comprehensive pre-anesthetic evaluation was conducted a day before surgery. On the surgery day, an 18G or 20G IV cannula was inserted to establish intravenous access, and intravenous fluids were administered. Patient was preloaded with 8 ml/kg of fluids for 20 minutes. Standard monitoring equipment, including NIBP, HR, ECG, and SpO2, was applied before induction of anesthesia. Baseline measurements of NIBP and HR were recorded. Under sterile and aseptic conditions, a 25G spinal needle was advanced in SAS at appropriate level. SAB was given with participant in a sitting position using a midline approach at L3-4 intervertebral space. Once clear CSF was observed, study drug was slowly injected at 0.2 mL per second. Spinal needle bevel was oriented upwards, and LA solution was administered without aspiration or barbotage.

After informed consent was taken and inclusion and exclusion criteria were satisfied, study subjects were assigned to one of two groups:

- **Group BB:** Patients were administered 15mg of 0.5% bupivacaine (H) + 60mcg buprenorphine.
- **Group LB:** Patients were administered 15mg of 0.5% levobupivacaine (H) + 60mcg buprenorphine.

After injection of LA, subjects were repositioned face-up. HR and NIBP were measured. Onset, duration, peak level of sensory block, time taken to reach the highest dermatomal level of sensory blockade, the onset of motor block, the time required for complete recovery of motor block, and the total span of subarachnoid block were all documented. Sensory block was assessed in the midclavicular line bilaterally using 24G hypodermic needle pin prick. Sensory block onset was determined as time from intrathecal injection to the loss of sensation at T8 dermatome. Highest level of sensory block was assessed every 2 minutes for first 20 minutes post-injection and then at 15-minute intervals thereafter.

Sensory block duration was defined as time of regression of two segments in the maximum block height, which was evaluated by pin prick.

Motor blockade was assessed using the modified Bromage score, where 0 indicated full movement in the hip, knee, and ankle; 1 indicated no movement in the hip but movement in knee and ankle; 2 indicated no movement in hip and knee but movement in ankle; and 3 indicated no movement in hip, knee, and ankle. Onset of motor block was defined as time at which modified Bromage score reached 3, while complete recovery was considered when score returned to 0.

The duration of the subarachnoid block was defined as the time interval from the intrathecal injection to the first instance when the patient reported pain during the postoperative period. All time durations were calculated with the

intrathecal injection time set as time zero.

Surgery was allowed to begin on achieving adequate sensory block height (T8). Hemodynamic variables (SBP, DBP, MAP, HR and SpO2) measured prior intrathecal injection and at every 5 minutes intervals till 30 minutes after intrathecal injection.

Data processing and analysis/statistical analysis:

The study is focused on comparing 2 groups.

Qualitative variable was represented in the form of frequency and percentage.

Association between variables was assessed with Chi Square Test.

Numerical variable was represented as Mean & Sd. Comparison of groups was done with unpaired t test.

A P value of <0.05 was considered statistically significant.

Statistical analysis was evaluated with IBM SPSS Version 22 for windows.

RESULTS

Table 4.1: Age Group Distribution (BB versus LB Comparison)

	GROUP		Total
AGE	BB	LB	
21 - 30	9	4	13
31 - 40	13	13	26
41 - 50	15	15	30
51 - 60	14	19	33
Total	51	51	102
Pearson chi-square = 2.681, p-value = 0.444			

INTERPRETATION:

The age distribution between BB and LB groups showed no statistically significant difference (p=0.444), with the highest frequency observed in the age group of 51–60 years (LB=19, BB=14).

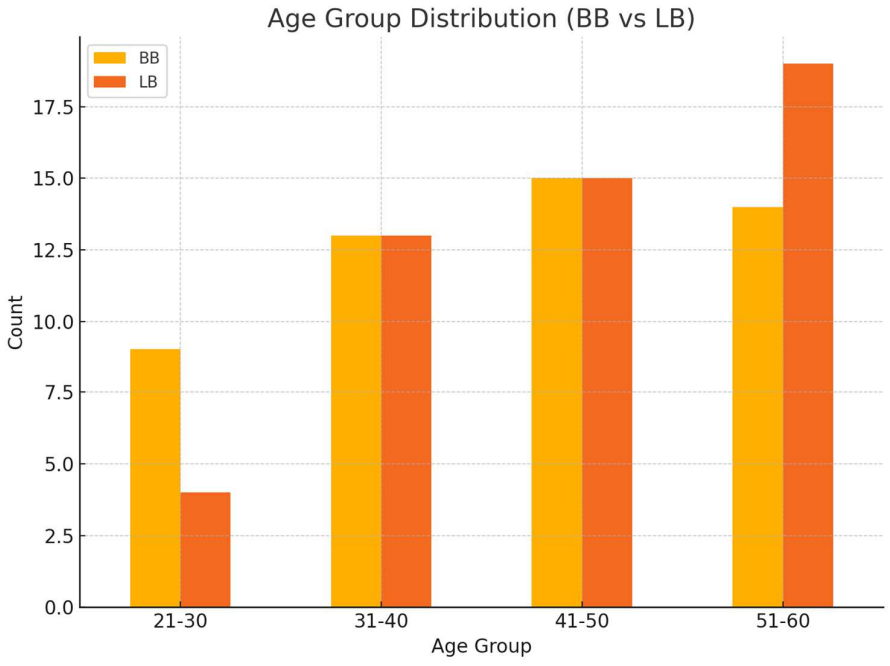


Table 4.2: Sex Distribution (BB vs LB Comparison)

	GROUP		Total
SEX	BB	LB	
Female	18	12	30
Male	33	39	72
Total	51	51	102
Pearson chi-square = 1.700, p-value = 0.192			

INTERPRETATION:

Sex distribution was comparable between the groups without statistical significance (p=0.192), although males were predominant (BB=33, LB=39).

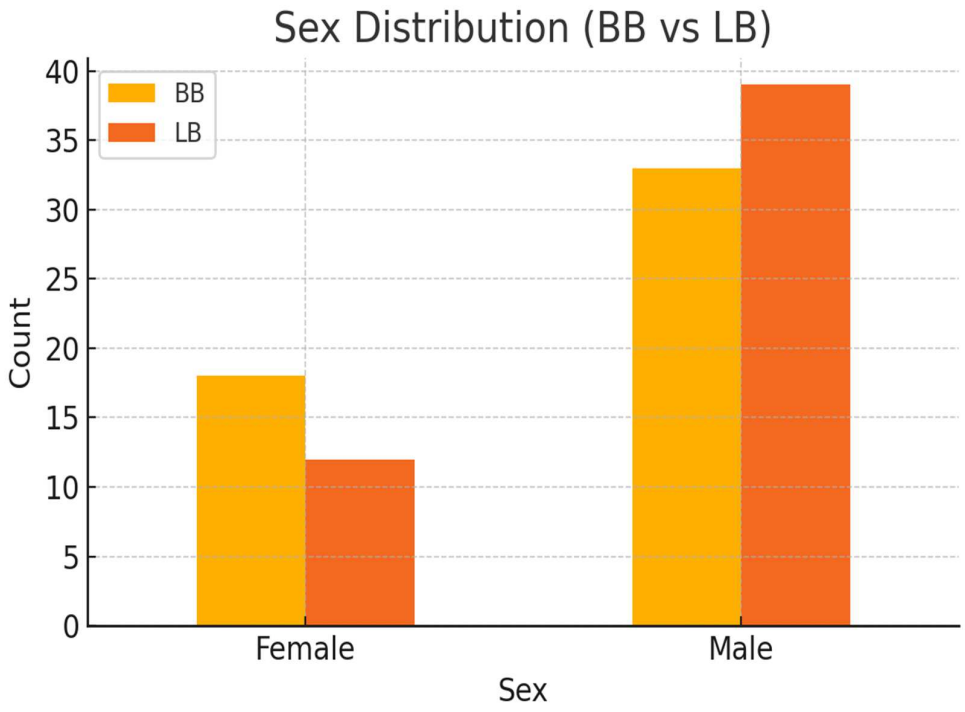


Table 4.3: ASA Classification (BB vs LB Comparison)

	GROUP		Total
ASA	BB	LB	
I	33	27	60
II	18	24	42
Total	51	51	102
Pearson chi-square = 1.457, p-value = 0.227			

INTERPRETATION:

No significant difference was found in ASA classification between groups (p=0.227); however, most participants belonged to ASA Class I (BB=33, LB=27).

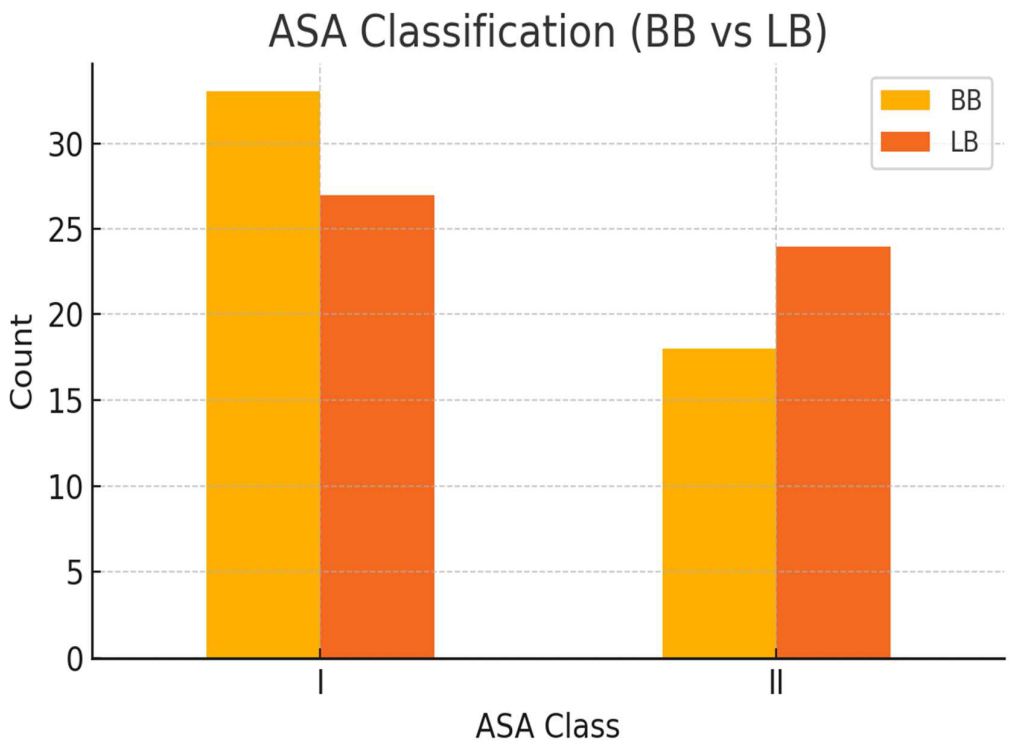


Table 4.4: Baseline Vitals - (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
BASELINE VITALS					
HR (bpm)	BB	51	81.63	8.256	0.214
	LB	51	78.06	9.764	
SBP	BB	51	134.00	10.475	0.329
	LB	51	133.04	11.581	
DBP	BB	51	84.00	9.722	0.327
	LB	51	83.14	8.584	
MAP	BB	51	100.76	9.11	0.992
	LB	51	99.78	8.89	
SpO2	BB	51	100.00	0.000[b]	1.0000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

Baseline vital parameters were statistically comparable between BB and LB groups, with no significant differences noted for Heart Rate (BB=81.63 bpm, LB=78.06 bpm; p=0.214), Systolic Blood Pressure (BB=134.00 mmHg, LB=133.04 mmHg; p=0.329), Diastolic Blood Pressure (BB=84.00 mmHg, LB=83.14 mmHg; p=0.327), Mean Arterial Pressure (BB=100.76 mmHg, LB=99.78 mmHg; p=0.992), and SpO2 levels (both groups=100%; p=1.000). Overall, baseline vital signs were well-matched, indicating comparable clinical status at initiation between the groups.

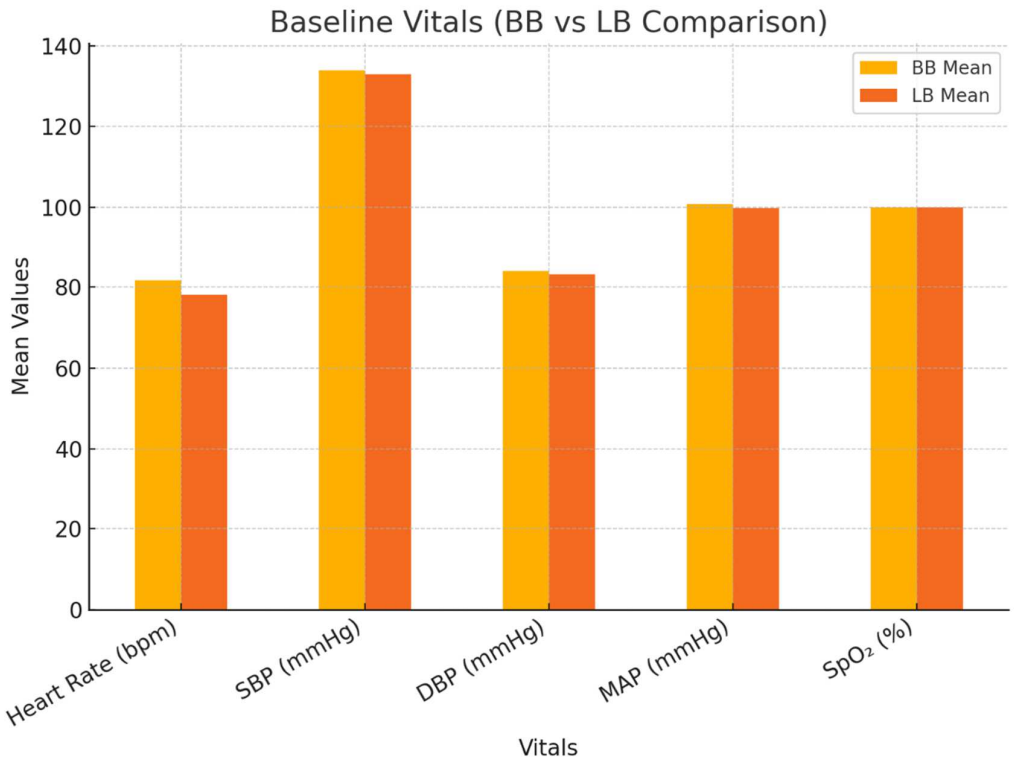

Baseline Vitals (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
120
140
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.5: Vitals at 0 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	Std. Error Mean
VITALS AT 0 MINUTES					
HR (bpm)	BB	51	79.33	8.402	0.521
	LB	51	77.51	9.144	
SBP	BB	51	128.00	12.598	0.825
	LB	51	130.73	14.168	
DBP	BB	51	80.31	11.196	0.939
	LB	51	82.35	11.185	
MAP	BB	51	95.92	11.142	0.911
	LB	51	98.47	11.38	
Spo2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 0 minutes, vital parameters were comparable between BB and LB groups. The mean Heart Rate (BB=79.33 bpm, LB=77.51 bpm), Systolic Blood Pressure (BB=128.00 mmHg, LB=130.73 mmHg), Diastolic Blood Pressure (BB=80.31 mmHg, LB=82.35 mmHg), Mean Arterial Pressure (BB=95.92 mmHg, LB=98.47 mmHg), and SpO2 (both groups=100%) did not differ significantly. This indicates equivalent vital stability in both groups at the onset of assessment.

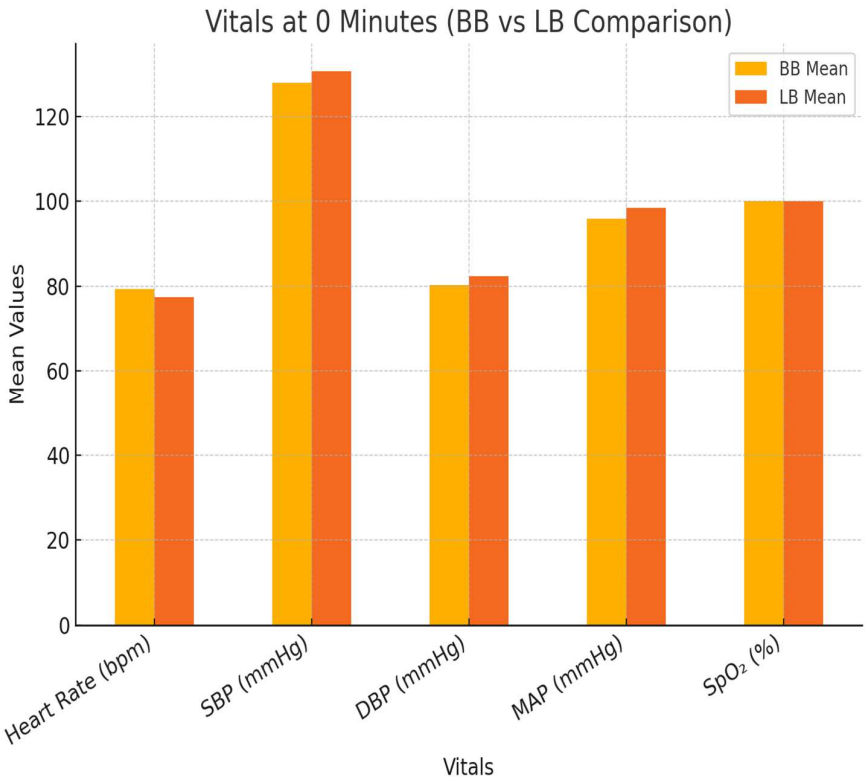

Vitals at 0 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
120
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.6: Vitals at 5 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 5 MINUTES					
HR (bpm)	BB	51	67.65	7.691	0.031
	LB	51	71.53	9.124	
SBP	BB	51	104.51	8.744	0.046
	LB	51	116.25	12.558	
DBP	BB	51	64.08	8.733	0.812
	LB	51	73.73	8.352	
MAP	BB	51	77.78	8.19	0.521
	LB	51	87.67	9.33	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 5 minutes, statistically significant differences emerged in Heart Rate (LB=71.53 bpm vs. BB=67.65 bpm; p=0.031) and Systolic Blood Pressure (LB=116.25 mmHg vs. BB=104.51 mmHg; p=0.046), with higher values observed in the LB group. Although differences in Diastolic Blood Pressure (LB=73.73 mmHg, BB=64.08 mmHg) and Mean Arterial Pressure (LB=87.67 mmHg, BB=77.78 mmHg) were clinically notable, they did not reach statistical significance. Both groups maintained optimal SpO2 at 100%.

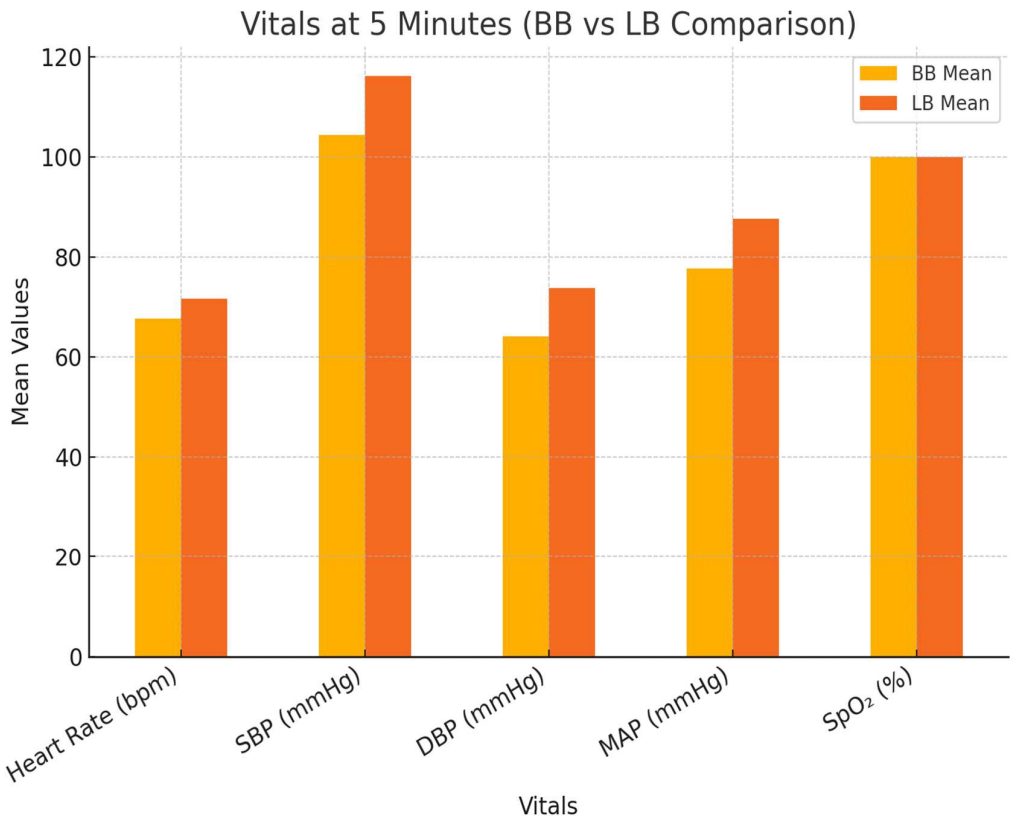

Vitals at 5 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
120
100
80
60
40
20
0
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.7: Vitals at 10 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 10 MINUTES					
HR (bpm)	BB	51	60.14	7.324	0.136
	LB	51	67.20	8.861	
SBP	BB	51	89.49	11.030	0.349
	LB	51	105.98	9.665	
DBP	BB	51	54.63	9.113	0.378
	LB	51	66.33	7.919	
MAP	BB	51	66.17	9.12	0.178
	LB	51	79.52	7.29	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 10 minutes, although no statistically significant differences were found, clinically notable variations existed between BB and LB groups. The LB group showed higher mean values for Heart Rate (LB=67.20 bpm vs. BB=60.14 bpm), Systolic Blood Pressure (LB=105.98 mmHg vs. BB=89.49 mmHg), Diastolic Blood Pressure (LB=66.33 mmHg vs. BB=54.63 mmHg), and Mean Arterial Pressure (LB=79.52 mmHg vs. BB=66.17 mmHg). Both groups maintained optimal SpO2 levels at 100%. The observed differences suggest clinically relevant trends, though statistically non-significant.

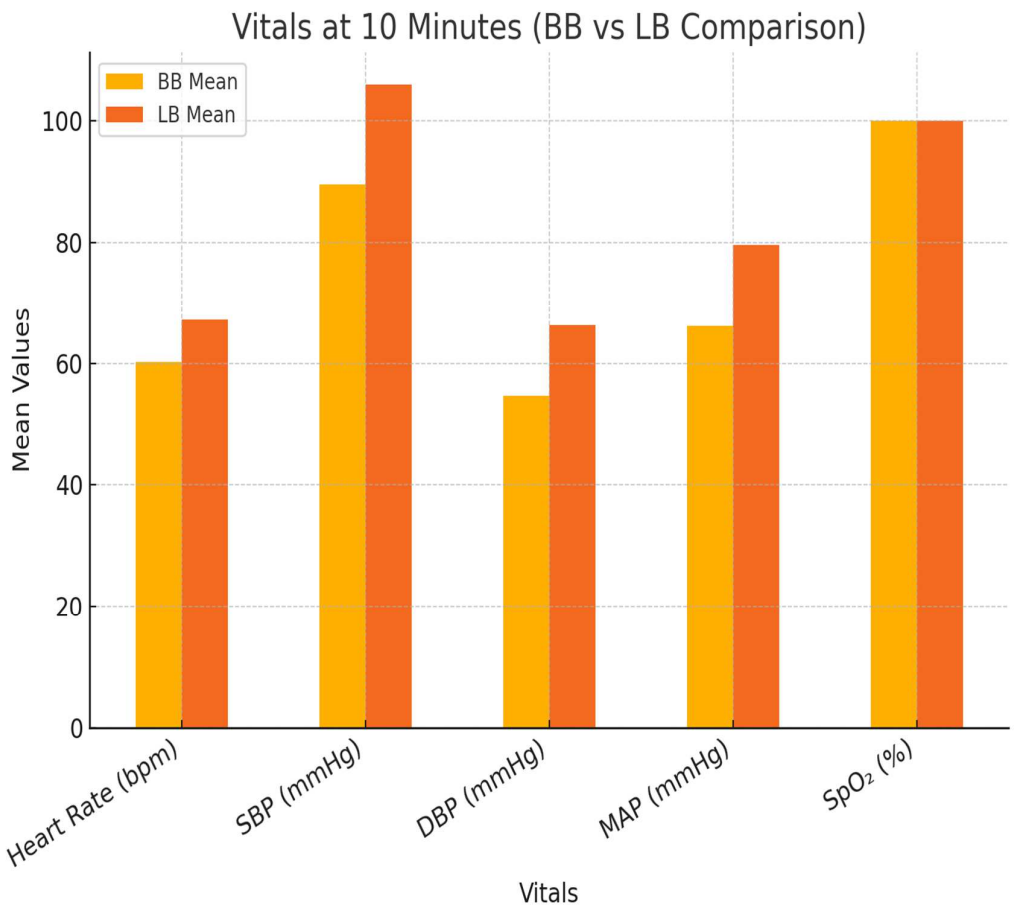

Vitals at 10 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.8: Vitals at 15 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 15 MINUTES					
HR (bpm)	BB	51	57.51	6.354	0.348
	LB	51	65.02	7.146	
SBP	BB	51	91.96	11.139	0.040
	LB	51	103.69	8.157	
DBP	BB	51	60.18	10.332	0.045
	LB	51	66.76	7.876	
MAP	BB	51	70.80	10.018	0.016
	LB	51	79.05	6.88	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 15 minutes, statistically significant differences were evident between BB and LB groups for Systolic Blood Pressure (LB=103.69 mmHg vs. BB=91.96 mmHg; p=0.040), Diastolic Blood Pressure (LB=66.76 mmHg vs. BB=60.18 mmHg; p=0.045), and Mean Arterial Pressure (LB=79.05 mmHg vs. BB=70.80 mmHg; p=0.016), with higher mean values consistently observed in the LB group. Although the Heart Rate was also higher in the LB group (LB=65.02 bpm vs. BB=57.51 bpm), this difference was not statistically significant (p=0.348). Both groups maintained optimal SpO2 levels at 100%. These findings suggest clinically and statistically significant hemodynamic differences between groups at this interval.

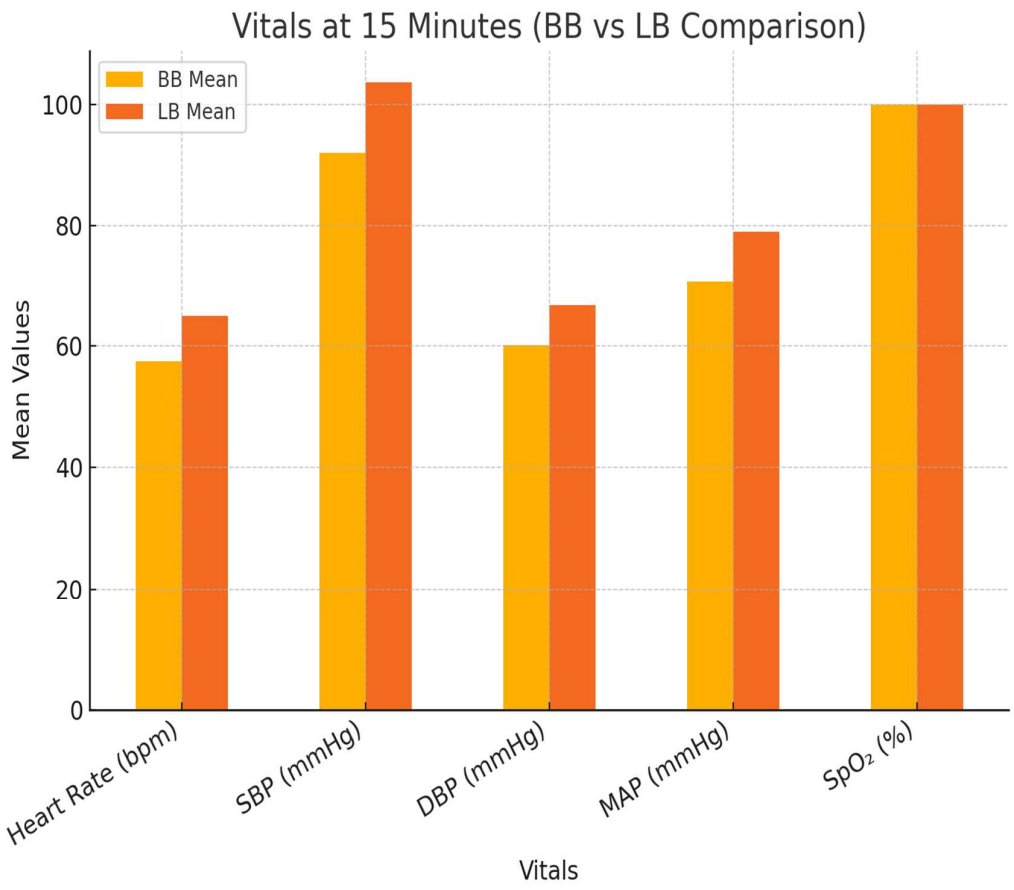

Vitals at 15 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.9: Vitals at 20 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 20 MINUTES					
HR (bpm)	BB	51	60.41	5.675	0.201
	LB	51	64.55	6.379	
SBP	BB	51	100.76	8.327	0.317
	LB	51	107.31	6.950	
DBP	BB	51	68.61	7.676	0.589
	LB	51	70.25	7.686	
MAP	BB	51	79.235	7.095	0.504
	LB	51	82.568	6.420	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 20 minutes, vital parameters remained statistically comparable between BB and LB groups. Although the LB group had slightly higher mean values for Heart Rate (LB=64.55 bpm vs. BB=60.41 bpm), Systolic Blood Pressure (LB=107.31 mmHg vs. BB=100.76 mmHg), Diastolic Blood Pressure (LB=70.25 mmHg vs. BB=68.61 mmHg), and Mean Arterial Pressure (LB=82.57 mmHg vs. BB=79.24 mmHg), these differences were not statistically significant ($p>0.05$). Both groups consistently maintained optimal SpO2 levels at 100%.

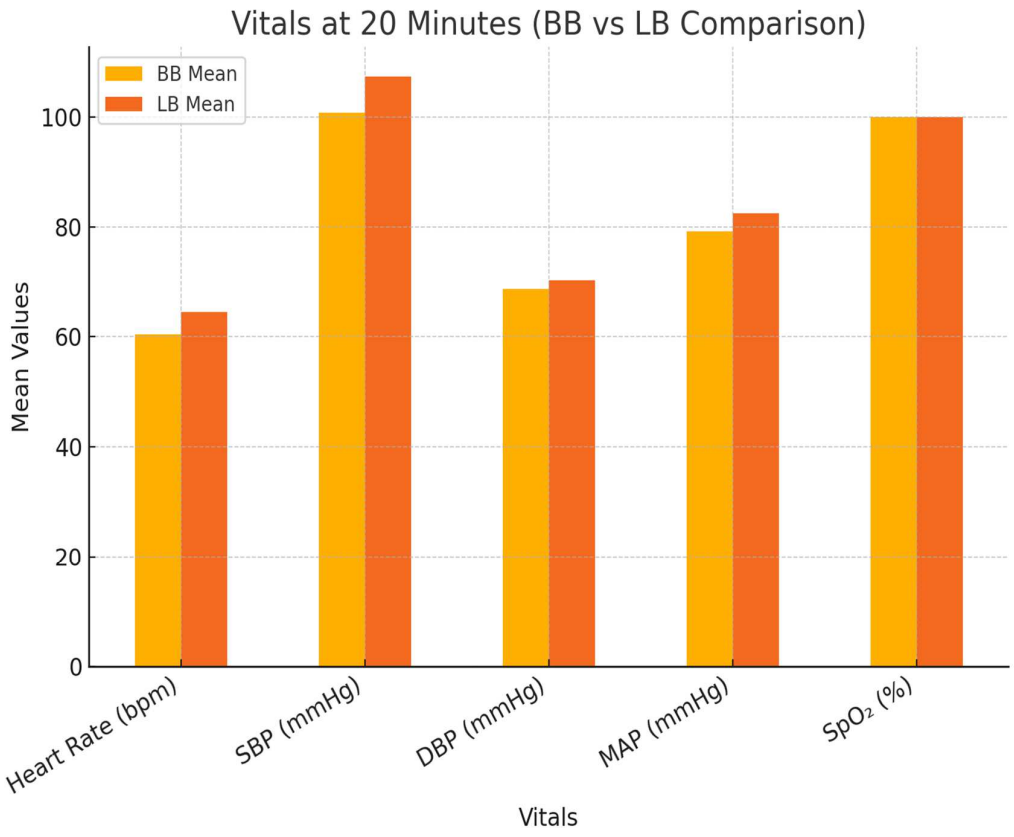

Vitals at 20 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.10: Vitals at 25 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 25 MINUTES					
HR (bpm)	BB	51	63.10	5.561	0.457
	LB	51	65.78	5.576	
SBP	BB	51	107.39	7.518	0.709
	LB	51	108.35	7.688	
DBP	BB	51	70.76	6.787	0.049
	LB	51	68.29	7.852	
MAP	BB	51	82.90	5.58	0.033
	LB	51	81.5	6.72	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 25 minutes, statistically significant differences were observed between groups in Diastolic Blood Pressure (BB=70.76 mmHg vs. LB=68.29 mmHg; p=0.049) and Mean Arterial Pressure (BB=82.90 mmHg vs. LB=81.50 mmHg; p=0.033), with slightly higher values noted in the BB group. Heart Rate (BB=63.10 bpm, LB=65.78 bpm) and Systolic Blood Pressure (BB=107.39 mmHg, LB=108.35 mmHg) were comparable and did not significantly differ. Both groups maintained optimal SpO2 levels at 100%. These findings highlight subtle but statistically significant hemodynamic variations at this time point.

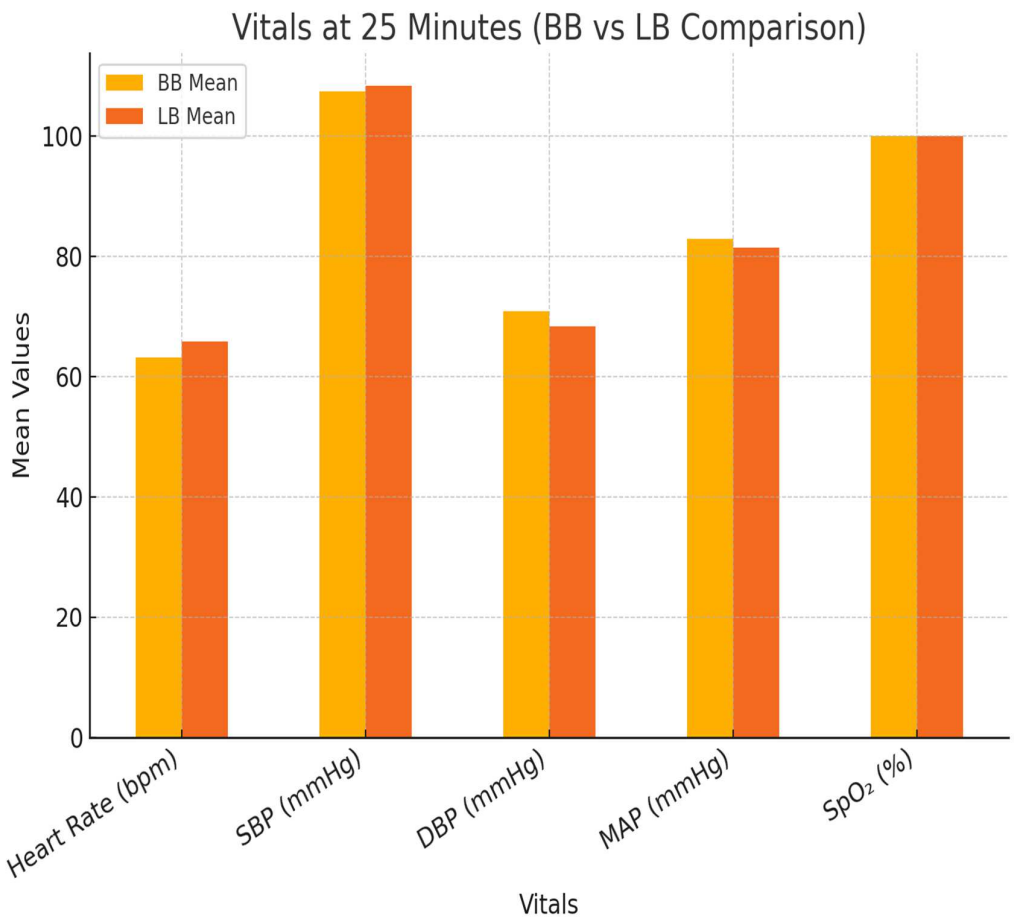

Vitals at 25 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.11: Vitals at 30 Minutes (BB vs LB Comparison)

	GROUP	N	Mean	Std. Deviation	P value
VITALS AT 30 MINUTES					
HR (bpm)	BB	51	64.80	5.940	0.764
	LB	51	67.86	6.248	
SBP	BB	51	111.63	7.419	0.112
	LB	51	112.27	8.658	
DBP	BB	51	73.71	6.100	0.392
	LB	51	73.65	7.618	
MAP	BB	51	86.15	5.47	0.129
	LB	51	86.52	7.095	
SpO2	BB	51	100.00	0.000[b]	1.000
	LB	51	100.00	0.000[b]	

INTERPRETATION:

At 30 minutes, vital parameters showed no statistically significant differences between the BB and LB groups. Mean values for Heart Rate (BB=64.80 bpm, LB=67.86 bpm), Systolic Blood Pressure (BB=111.63 mmHg, LB=112.27 mmHg), Diastolic Blood Pressure (BB=73.71 mmHg, LB=73.65 mmHg), and Mean Arterial Pressure (BB=86.15 mmHg, LB=86.52 mmHg) were comparable across both groups. Both groups consistently maintained optimal SpO2 levels at 100%, indicating stable and balanced hemodynamic parameters at this assessment point.

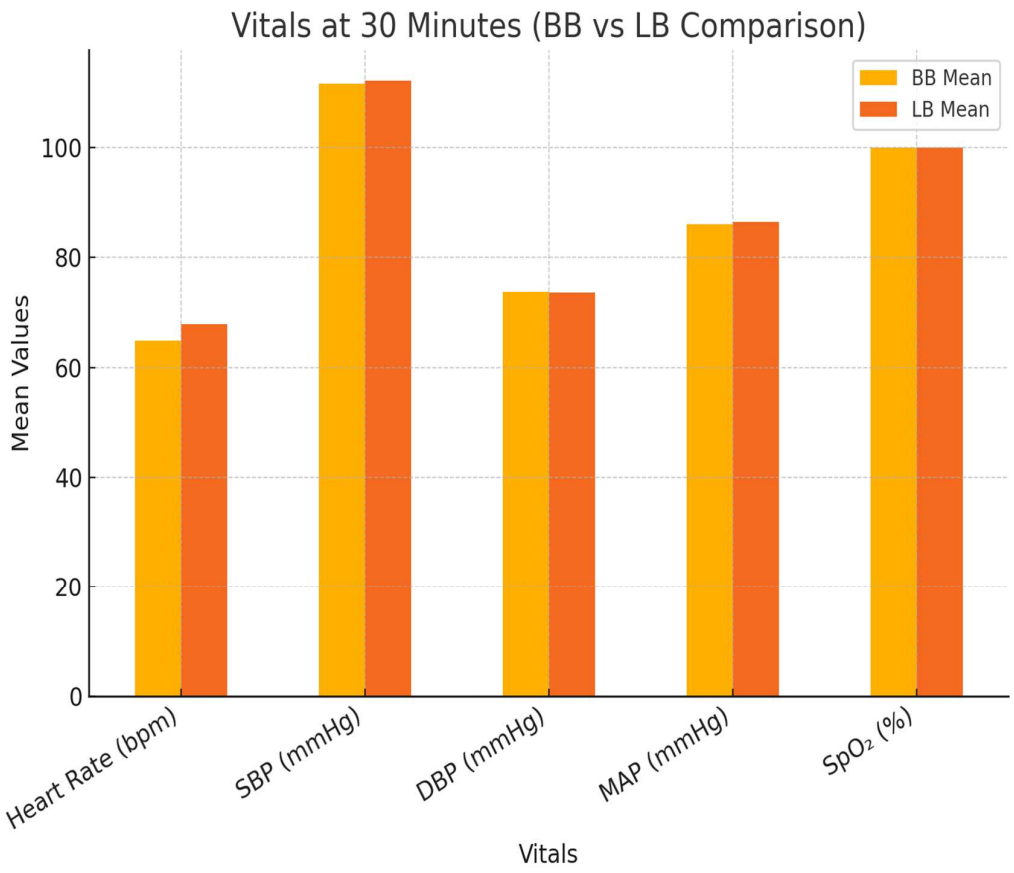
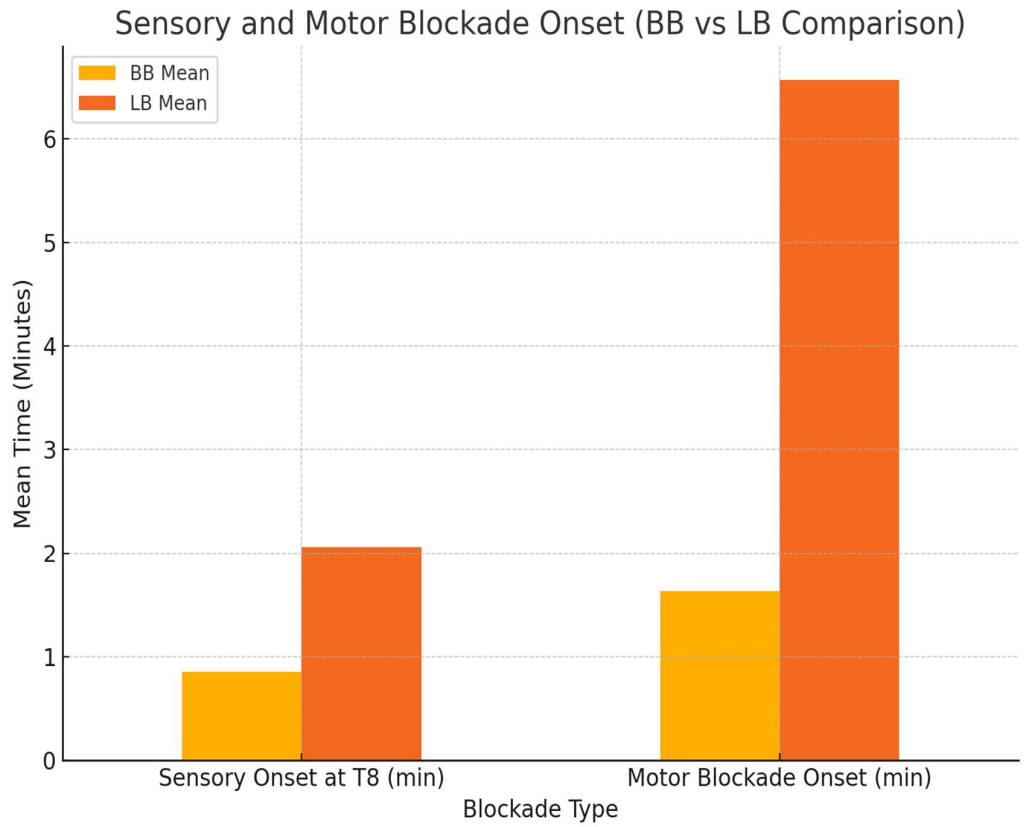

Vitals at 30 Minutes (BB vs LB Comparison)
BB Mean
LB Mean
Mean Values
0
20
40
60
80
100
Heart Rate (bpm)
SBP (mmHg)
DBP (mmHg)
MAP (mmHg)
SpO₂ (%)
Vitals

Table 4.12: Sensory Blockade Onset at T8 Level (Minutes) and Onset of Complete Motor Blockade (Minutes) - BB vs LB Comparison

	GROUP	N	Mean	Std. Deviation	P value
SENSORY BLOCKADE: Onset at T8 Level (minutes)	BB	51	0.853	0.2880	0.006
	LB	51	2.059	0.5352	
MOTOR BLOCKADE: Onset of Complete Motor Blockade	BB	51	1.627	0.3853	<0.001
	LB	51	6.559	1.2714	

INTERPRETATION:

The onset times for sensory and motor blockade were drastically lesser in the BB group compared to the LB group. Sensory blockade onset at T8 level was significantly faster in the BB group (0.853 minutes) than in the LB group (2.059 minutes; p=0.006). Similarly, the onset of complete motor blockade was markedly quicker in the BB group (1.627 minutes) compared to the LB group (6.559 minutes; p<0.001), highlighting superior blockade efficiency in the BB group.


Sensory and Motor Blockade Onset (BB vs LB Comparison)
BB Mean
LB Mean
Mean Time (Minutes)
0
1
2
3
4
5
6
Sensory Onset at T8 (min)
Motor Blockade Onset (min)
Blockade Type

DISCUSSION

Spinal anesthesia remains a cornerstone in modern surgical practice for infraumbilical procedures, offering profound sensory and motor blockade with relative simplicity and a favorable safety profile. Local anesthetics, particularly bupivacaine, have been widely used for this purpose due to their potent anesthetic properties and acceptable side-effect profiles [15]. However, interest in potentially safer alternatives has fueled the emergence of levobupivacaine—the S (-) enantiomer of bupivacaine—which promises reduced cardiotoxicity and neurotoxicity without compromising anesthetic efficacy [16]. Simultaneously, the addition of opioid adjuvants such as buprenorphine to intrathecal local anesthetic solutions has garnered attention for their ability to enhance both intraoperative and postoperative analgesia [25]. This synergy between local anesthetics and opioids holds the potential for superior patient comfort with less reliance on systemic analgesics [26].

Despite bupivacaine's established profile, questions remain about its comparative performance against levobupivacaine in terms of hemodynamic stability, onset characteristics, and overall duration of analgesia. Indeed, while levobupivacaine is often described as having fewer cardiovascular side effects, some clinicians have observed slight differences in block onset and density relative to bupivacaine [18]. Moreover, although intrathecal opioids, including buprenorphine, can substantially improve perioperative pain control, the extent to which they alter the hemodynamic effects and clinical onset characteristics of different local anesthetics remains a subject of ongoing investigation [27].

Several recent randomized trials and observational studies have examined hyperbaric levobupivacaine versus hyperbaric bupivacaine for lower limb or infraumbilical surgeries [28]. Generally, they suggest that levobupivacaine provides

block quality comparable to bupivacaine, albeit sometimes with a slightly slower onset, along with a potentially safer pharmacologic profile. The addition of buprenorphine intrathecally has further been shown to prolong analgesia and reduce the requirement for rescue analgesics, leading to improved patient satisfaction [17]. However, consensus on optimal dosing and comparative outcomes remains elusive, particularly regarding the magnitude of any hemodynamic advantages or differences in speed of onset between these two agents.

In this one-year, hospital-based randomized control trial, we compared 0.5% hyperbaric bupivacaine (BB) and 0.5% hyperbaric levobupivacaine (LB) when used alongside intrathecal buprenorphine for infraumbilical surgeries. The discussion that follows integrates our study's findings with those of existing literature—both supportive and contradictory—to contextualize the demographic profiles, hemodynamic responses, and block characteristics observed. Each key variable from our results section is examined in turn. We also comment on the study's limitations and suggest directions for future investigations. Ultimately, understanding whether levobupivacaine genuinely offers a safer or equally efficacious, clinical alternative to bupivacaine— particularly when combined with intrathecal buprenorphine—will guide clinicians seeking to optimize the anesthetic management of patients undergoing infraumbilical surgeries [19].

Our data address whether levobupivacaine's reputed advantages in cardiotoxic safety, combined with opioid-based analgesic enhancement, translate into meaningful clinical benefit or whether the longstanding familiarity and rapid onset of bupivacaine is preferable. By exploring these questions, this work aims to illuminate best practices for intrathecal anesthesia and encourage further research focused on long-term safety, postoperative analgesia, and cost-effectiveness within this domain [29].

In our study, no statistically significant difference was observed in the age distribution between the BB (0.5% hyperbaric bupivacaine plus buprenorphine) and LB (0.5% hyperbaric levobupivacaine plus buprenorphine) groups ($p = 0.444$). This similarity implies successful randomization, reducing the likelihood that age skewed the comparison of anesthetic outcomes.

Previous randomized controlled trials have likewise reported minimal age-related differences when comparing bupivacaine and levobupivacaine [30]. Furthermore, although advanced age might predispose to more pronounced hemodynamic changes under subarachnoid block [31], the presence of an intrathecal opioid adjuvant such as buprenorphine tends to offer stable intraoperative analgesia across different age brackets [32]. Consequently, with both arms displaying a comparable mean age profile, any variations observed in our key outcomes can be more confidently attributed to the anesthetic agents themselves rather than patient age.

The overall sample demonstrated a male preponderance (72 males vs. 30 females), yet this difference between BB and LB groups was not statistically significant ($p = 0.192$). Male predominance for infraumbilical surgeries, especially orthopedic and urological, is a commonly reported demographic phenomenon [33]. Importantly, no substantive evidence suggests that sex differences alter the comparative efficacy of bupivacaine and levobupivacaine in spinal anesthesia, aside from isolated reports indicating minor variations in local anesthetic requirements [34]. In our trial, the random distribution of males and females further validates the internal consistency of the comparison.

Patients in both groups were predominantly ASA I or II (60 and 42, respectively), and no statistically significant intergroup difference existed ($p = 0.227$). This typical profile for elective infraumbilical surgery patients indicates a relatively

healthy study cohort. Within the ASA I–II range, major differences in block characteristics generally arise from technique and drug pharmacodynamics rather than from comorbid conditions [35]. Hence, similarity in ASA classification between the groups helps ensure fair comparisons.

At baseline, no statistically significant difference emerged in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), or oxygen saturation (SpO2) between the groups ($p > 0.05$). This parallels previous comparative trials, which also reported comparable starting vitals across bupivacaine and levobupivacaine arms [38]. Consequently, subsequent hemodynamic differences can be reliably attributed to the distinct pharmacologic attributes of the two agents rather than an imbalance at baseline.

Hemodynamic fluctuations following intrathecal anesthesia often occur within the first 15–20 minutes, owing to sympathectomy.

1. Heart Rate

- At 5 minutes, BB showed a significantly lower mean HR (67.65 bpm) relative to LB (71.53 bpm, $p = 0.031$).
- Although p-values at 10 and 15 minutes varied (with $p = 0.136$ and $p = 0.348$), the mean HR generally remained lower in the BB group.

This tendency toward bradycardia aligns with earlier reports indicating that bupivacaine may induce deeper sympathetic blockade than levobupivacaine, at least in the initial phase of the block [39]. Buprenorphine's influence on heart rate is typically minimal, and it is more recognized for its analgesic potentiation rather than direct chronotropic effects [40].

2. Blood Pressure (SBP, DBP and MAP)

- At 5 minutes, BB exhibited a significantly lower mean SBP (104.51 mmHg) compared to LB (116.25 mmHg, p = 0.046).
- This more pronounced early drop in SBP for BB remained evident at 15 minutes (p = 0.040 for SBP and p = 0.045 for DBP). MAP at 15 minutes was also significantly lower in the BB group (p = 0.016).

Several investigators have observed that hyperbaric bupivacaine, due to its potency and profile, may cause a more abrupt sympathectomy, thus magnifying the initial hypotensive response [41]. Levobupivacaine, conversely, appears to cause less hemodynamic perturbation in the early phase [42]. Clinically, however, these differences are often well-managed with standard intraoperative monitoring and interventions, such as fluid boluses and vasoactive medications, mitigating any tangible harm.

Overall, our findings indicate that while both local anesthetics are safe and effective for infraumbilical surgery, bupivacaine may trigger a more pronounced early bradycardia and hypotension, consistent with previous comparative reports [43]. Levobupivacaine's potentially milder initial sympathectomy could be beneficial in patients where hemodynamic stability is paramount, though in typical practice these effects are usually controllable.

Two key parameters—time to T8 sensory block and time to complete motor blockade—demonstrated statistically significant differences:

- **Sensory Block Onset**: BB reached T8 in 0.85 minutes on average, whereas LB took 2.06 minutes ($p = 0.006$).
- **Motor Block Onset**: BB achieved complete motor blockade in 1.63 minutes, considerably faster than LB at 6.56 minutes ($p < 0.001$).

These results confirm existing evidence that bupivacaine generally offers a faster onset of block than levobupivacaine [44]. The stereoselective properties of levobupivacaine are believed to contribute to its comparatively slower onset, though clinically the difference of a few minutes may be acceptable, particularly if patient safety is improved [45]. Additionally, hyperbaricity in both solutions is created to facilitate predictable spread, yet the inherent pharmacological differences between racemic bupivacaine and levobupivacaine remain relevant.

The addition of buprenorphine does not significantly alter onset times, functioning primarily to extend analgesic duration and quality [46]. Hence, the differences observed in our study are consistent with known pharmacologic distinctions rather than any opioid-induced modulation.

In sum, hyperbaric levobupivacaine combined with buprenorphine appears to offer a comparable anesthetic depth to hyperbaric bupivacaine, but with a slower onset and milder early cardiovascular effects. Bupivacaine, on the other hand, delivers a quicker onset but may induce steeper early hemodynamic fluctuations. Both agents remain viable, safe, and effective choices when guided by appropriate clinical judgement.

Limitations:

1. **Single-Center Design and Sample Size**

   Although powered for detecting onset and hemodynamic differences, our single-center design limits generalizability. Larger, multicenter trials could validate or refine these findings among different populations and surgical contexts.

2. **Infraumbilical Surgeries Only**

   Our findings may not extrapolate to upper abdominal or thoracic procedures, where the required level and spread of anesthesia differ. Additional research is needed to compare bupivacaine and levobupivacaine in other surgical domains and in patients with higher ASA classes.

Future Scope:

1. **Dosing Strategies**

   Future studies could explore varying concentrations of bupivacaine or levobupivacaine and incremental doses of buprenorphine to identify the optimal combination balancing rapid onset, hemodynamic stability, and prolonged pain relief.

2. **Enhanced Recovery Pathways**

   As healthcare systems increasingly adopt enhanced recovery after surgery (ERAS) pathways, there is potential for levobupivacaine plus buprenorphine to serve as a key component of multimodal analgesia, reducing length of stay and improving patient satisfaction. Evaluating these regimens within ERAS frameworks would further guide best-practice protocols.

In conclusion, our randomized control trial indicates that both hyperbaric bupivacaine and hyperbaric levobupivacaine, administered intrathecally with buprenorphine, offer safe and effective anesthesia for infraumbilical surgeries. Key differences include a more rapid onset and more pronounced early hemodynamic changes with bupivacaine versus a slower onset and milder hemodynamic shifts with levobupivacaine. Tailoring the choice of local anesthetic to patient comorbidities, surgical urgency, and institutional expertise remains integral. Future large-scale, multicenter, and longer-term studies can further delineate the optimal role of levobupivacaine in modern regional anesthesia practice, especially as part of comprehensive perioperative pain management strategies.

CONCLUSION

In conclusion, our one-year, hospital-based randomized control trial confirms that both 0.5% bupivacaine (H) and 0.5% levobupivacaine (H), each administered with buprenorphine intrathecally, offer effective anesthesia for infraumbilical surgical procedures with manageable side effects, albeit with meaningful differences in onset speed and initial hemodynamic impact; thus, while bupivacaine may be favored in instances where a rapid and profound block is prioritized, levobupivacaine's comparative cardiovascular stability could be advantageous in patients with compromised hemodynamic reserve, ultimately underscoring the importance of individualizing anesthetic selection to optimize patient safety and outcomes.

SUMMARY

Spinal anesthesia has been a reliable mainstay for infraumbilical surgeries owing to its simplicity, rapid onset, and high level of patient satisfaction. However, the choice of local anesthetic and the incorporation of adjuvants significantly influence clinical outcomes. Against this backdrop, our thesis sought to compare the efficacy of 0.5% hyperbaric bupivacaine (BB) and 0.5% hyperbaric levobupivacaine (LB) when combined with buprenorphine for subarachnoid block in adult patients undergoing diverse infraumbilical procedures. The impetus behind examining levobupivacaine specifically relates to its reputation for reduced cardiotoxicity while maintaining a comparably effective sensory and motor blockade profile to bupivacaine. Meanwhile, intrathecal buprenorphine has garnered favor for prolonging perioperative analgesia, potentially decreasing the need for additional postoperative pain medications.

In our trial, neither age nor sex distribution substantially differed between patients receiving hyperbaric bupivacaine or levobupivacaine, nor did the vast majority of participants fall into the ASA I–II categories. These demographics enhanced the internal validity of our findings by minimizing confounders such as comorbidities or skewed age brackets. Additionally, the variety of surgical diagnoses and procedures—ranging from orthopedic to urological and general surgical interventions—ensured broad applicability of our results in real-world clinical practice.

Hemodynamic profiles, a central safety concern in spinal anesthesia, revealed that bupivacaine occasionally elicited more pronounced hypotension and bradycardia during the early phase of the subarachnoid block. Levobupivacaine displayed somewhat gentler hemodynamic shifts, which may be advantageous for patients prone

to cardiovascular compromise. Still, these differences were typically transient and well-managed with standard intraoperative measures (e.g., fluid resuscitation and vasoactive support). Therefore, while the distinction in hemodynamic parameters was statistically significant at specific intervals, it did not escalate into severe clinical events.

Of note, the onset of sensory and motor blocks demonstrated noteworthy variation. Patients in the bupivacaine group experienced a more rapid onset of both sensory anesthesia to T8 and complete motor block. By contrast, the levobupivacaine group, although comparable in final block quality, had a slower onset. Clinically, a slightly delayed onset may be tolerable in many scenarios, particularly when balanced against potentially increased cardiovascular stability. Meanwhile, the inclusion of buprenorphine was crucial for enhancing analgesic duration, which is especially important for postoperative comfort.

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INFORMED CONSENT FORM

"COMPARISON OF 0.5% HYPERBARIC BUPIVACAINE AND 0.5% HYPERBARIC LEVOBUPIVACAINE WITH BUPRENORPHINE AS AN ADJUVANT FOR SPINAL ANAESTHESIA IN ADULTS UNDERGOING INFRAUMBILICAL SURGERIES – A ONE YEAR HOSPITAL BASED RANDOMIZED CONTROL TRIAL"

We request you, Mr./Mrs./Miss_____to kindly participate in our study as you are eligible for it. During the study, you will be asked some questions regarding your medical history and we would like to request you to answer to the best of your knowledge.

We would like to state that your participation in this research is completely voluntary. Your reason whether to participate or not will not affect your relationship with J.N.Medical College. If you agree to participate, we would like to also let you know that you are free to withdraw at any point in time.

Purpose of the study:

The purpose of this research is to compare 0.5% Hyperbaric Bupivacaine 15mg with Buprenorphine 60mcg and 0.5% Hyperbaric Levobupivacaine 15mg with Buprenorphine 60mcg for spinal anaesthesia in patients undergoing elective infraumbilical surgeries to evaluate the hemodynamic changes and to study the onset of sensory and motor blockade.

Explanation of the procedure:

If you agree to enroll in my study, I will ask you your present, past and family history. Then you will be clinically examined in detail. Under sterile aseptic precautions, a needle will be introduced in your back (spine) at relevant level. Spinal anesthesia will be performed in the sitting position by using a midline approach and the study drug will be

injected. You will randomly be allotted in one of the two groups: one group will be given hyperbaric bupivacaine + buprenorphine and the other group will be given hyperbaric levobupivacaine + buprenorphine. We will look for the effects on heart rate, blood pressure, oxygen saturation and time of onset of the block in the patient. We will note down the effects which will be seen in the patient.

Withdrawal from participation in the study: Participation in this study is voluntary. You will be free to decide whether to participate in this study or continue participation once enrolled. In case you decide to withdraw your participation, you are free to do so. However, please convey the decision to the principal investigator.

Possible benefits from participating in the study: You will not get any benefits by participating in this study. The data gathered will help population at large.

Possible risks from participating in the study: There are no risks involved in participating in this study.

Privacy and confidentiality: The information collected from you will be coded, to prevent any person to identify you. Your identity will never be revealed. The data collected from you will be kept confidential and only processed or aggregated data will be used for publication.

Financial incentives: You will not receive any payment for participating in this study.

Authorization for publication of aggregated data: Results obtained after processing of the aggregated data will be published for scientific purpose and or presented to scientific groups. However, your identity will never be revealed.

Questions:

If you have any question or complaints with regard to your right as study participant you may contact **Dr Harsha Hegde**, Chairperson, Ethical committee of JNMC, 0831-2473777 Extension 4052.

Legal rights: By signing this consent form, you are not waiving any of your legal rights.

CONSENT STATEMENT

"COMPARISON OF 0.5% HYPERBARIC BUPIVACAINE AND 0.5% HYPERBARIC LEVOBUPIVACAINE WITH BUPRENORPHINE AS AN ADJUVANT FOR SPINAL ANAESTHESIA IN ADULTS UNDERGOING INFRAUMBILICAL SURGERIES – A ONE YEAR HOSPITAL BASED RANDOMIZED CONTROL TRIAL"

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

Subject Name: _____

Signature or the Left Thumb Print of Subject: _____

Date:

Investigator's Name: _____ Signature: _____

Date:

Place:

PROFORMA

"COMPARISON OF 0.5% HYPERBARIC BUPIVACAINE AND 0.5% HYPERBARIC LEVOBUPIVACAINE WITH BUPRENORPHINE AS AN ADJUVANT FOR SPINAL ANAESTHESIA IN ADULTS UNDERGOING INFRAUMBILICAL SURGERIES – A ONE YEAR HOSPITAL BASED RANDOMIZED CONTROL TRIAL"

Patient's Name : I.P No. :

Age : Date of Examination :

Gender : Anesthesiologist :

Address :

Pre-anesthetic evaluation:

Chief complaints:

Past History:

- H/o co-morbidities and drug intake :
- H/o previous surgery/(s) where difficult airway was encountered :
- Previous anesthetic experience:

General physical examination:

Height (cm): Weight (Kg): BMI:

Pallor : Icterus :

Cyanosis : Clubbing : BP :

PR : RR : SpO2:

Systemic examination:

RS: **CVS:**

CNS: **GIT:**

Airway Assessment:

Teeth: Jaw movements:

Investigations:

Hb (gm/dl): TLC: Platelet count:

Serum Creatinine**:** FBS: Chest x-ray: ECG:

Preoperative physical status: ASA Grade I II

Diagnosis:

Proposed surgery:

	HR	**SBP**	**DBP**	**MAP**	**SpO2**
Baseline					
0 minutes					
5 minutes					
10 minutes					
15 minutes					
20 minutes					
25 minutes					
30 minutes					

Onset of sensory blockade:

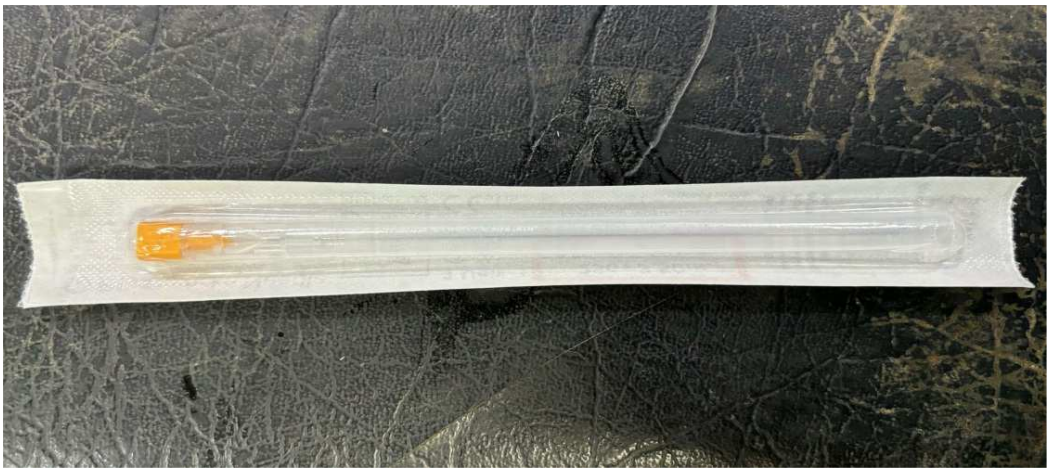
Onset of motor blockade:

PHOTOGRAPHS

Photograph 1: 0.5% Hyperbaric Bupivacaine

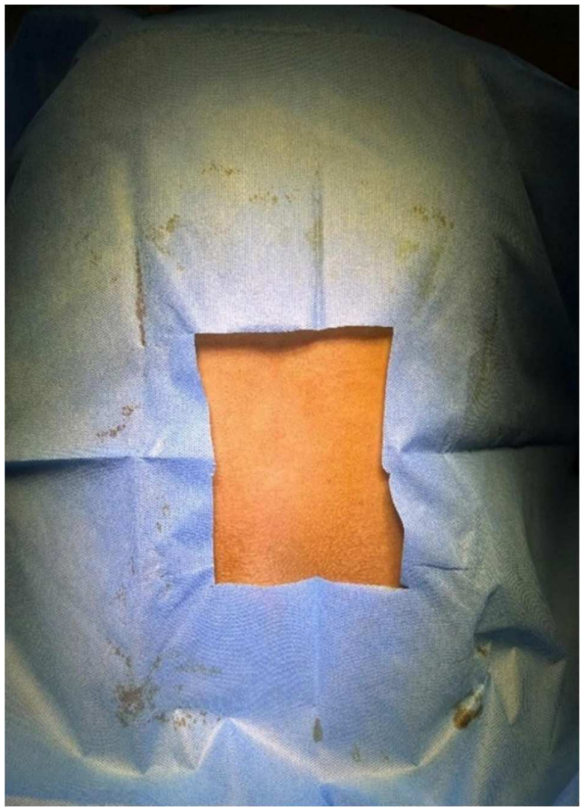
Photograph 2: 0.5% Hyperbaric Levobupivacaine

Photograph 3: Buprenorphine



Photograph 4: 25 gauge Quincke's Spinal Needle

Photograph 5: Spinal Needle



Photograph 6: Painted and Draped Spine

Photograph 7: Monitoring

Sr No.	AGE	SEX	ASA	DIAGNOSIS	SURGERY	GROUP BB/LB	BASELINE VITALS					VITALS AT 0 MINUTES					VITALS AT 5 MINUTES					VITALS	
							HR (bpm)	SBP	DBP	MAP	SpO2	HR (bpm)	SBP	DBP	MAP	Spo2	HR (bpm)	SBP	DBP	MAP	SpO2	HR (bpm)	SBP
1	33	F	I	Right Ureteric Calculi	Right URSL	BB	90	146	106	119	100	92	140	100	113	100	83	120	74	89	100	71	110
2	29	M	I	Urinary Bladder Calculi	Cystolithotripsy	BB	86	148	80	103	100	89	142	84	103	100	70	110	70	84	100	65	104
3	28	M	I	Left Inguinal Hernia	Hernia Repair	BB	83	130	80	97	100	81	134	80	98	100	67	116	72	87	100	63	100
4	30	M	I	Urinary Bladder Calculi	Cystolithotripsy	BB	90	140	100	113	100	93	144	98	113	100	72	120	76	91	100	62	106
5	42	F	I	Left Ankle Bursitis	Excision	BB	94	138	98	111	100	96	130	100	110	100	71	112	82	92	100	65	90
6	45	F	I	Right Knee Baker's Cyst	Excision	BB	70	132	84	100	100	74	136	80	99	100	62	110	68	82	100	57	104
7	55	M	II	Haemorrhoids	Haemorrhoidectomy	BB	70	128	80	96	100	72	136	86	103	100	58	102	58	73	100	54	84
8	38	F	I	ACL Tear	Arthroscopic Reconstruction	BB	90	130	80	97	100	88	134	80	98	100	79	114	68	83	100	62	92
9	34	M	I	Left IT Femur Fracture	ORIF	BB	76	118	80	93	100	80	124	84	97	100	67	106	68	81	100	62	88
10	52	F	II	Left Diabetic Foot Ulcer	Debridement	BB	70	146	106	119	100	75	144	98	113	100	61	124	68	87	100	56	86
11	59	M	II	Right Inguinal Hernia	Hernia Repair	BB	63	152	104	120	100	66	148	100	116	100	60	112	78	89	100	51	92
12	25	M	I	Pilonidal Sinus	Excision	BB	94	118	80	93	100	90	124	78	93	100	78	100	64	76	100	71	96
13	39	M	I	Renal Calculi	RIRS	BB	82	124	76	93	100	85	120	80	90	100	72	110	68	92	100	63	106
14	46	M	II	Epididymal Cyst	Excision	BB	75	132	82	99	100	70	128	76	93	100	66	108	70	83	100	65	114
15	39	M	I	Ureteric Calculi	URSL	BB	89	122	83	96	100	85	119	79	92	100	70	91	45	60	100	66	88
16	60	M	II	BPH	TURP	BB	69	147	93	111	100	67	140	87	105	100	59	102	59	73	100	53	81
17	52	M	I	Ca Colon	Colostomy	BB	71	133	83	100	100	70	116	70	85	100	66	100	53	69	100	54	93
18	59	M	II	BPH	TURP	BB	70	148	87	107	100	68	141	80	100	100	57	102	53	69	100	49	87
19	32	M	I	Ureteric Calculi	URSL	BB	88	133	83	100	100	86	120	80	90	100	72	90	70	77	100	60	84
20	56	M	II	Right Gluteal Abscess	Incision & Drainage	BB	89	140	78	99	100	86	133	81	98	100	70	101	56	71	100	64	79
21	43	M	I	Left Foot Ulcer	Debridement	BB	79	128	71	90	100	73	118	70	86	100	68	100	54	69	100	57	82
22	50	M	II	Left Leg Lipoma	Excision	BB	79	146	86	106	100	76	134	71	92	100	63	100	58	72	100	52	82
23	37	F	I	Left Inguinal Hernia	Repair	BB	86	136	86	103	100	81	130	78	95	100	60	104	60	75	100	56	80
24	50	M	II	Ureteric Calculi	URSL + DJ Stenting	BB	68	148	90	109	100	70	146	96	113	100	60	102	70	81	100	54	80
25	45	F	I	Renal Calculi	Left RGP	BB	78	132	80	97	100	76	136	76	96	100	70	120	68	85	100	72	108
26	32	F	I	Ureteric Calculi	Cystoscopy + DJ Stenting	BB	88	126	80	95	100	89	120	80	90	100	80	102	60	74	100	72	88
27	44	M	II	Left Baker's Cyst	Excision	BB	90	140	80	100	100	84	116	74	88	100	48	92	64	73	100	50	77
28	32	M	I	Left ACL Tear	Arthroscopic Repair	BB	90	140	90	107	100	91	138	72	94	100	88	100	48	65	100	74	98
29	58	F	I	Right Renal Calculi	Right URSL	BB	77	129	94	106	100	64	109	72	84	100	60	92	64	73	100	58	87
30	50	M	II	Right Meniscal Tear	Repair	BB	84	120	70	87	100	80	110	62	78	100	62	96	48	64	100	58	89
31	47	F	I	Right Inguinal Hernia	Repair	BB	90	136	90	105	100	88	130	90	103	100	70	116	70	85	100	64	88
32	35	F	I	Right Calceneal #	Implant Removal	BB	88	120	70	87	100	87	116	60	79	100	71	96	60	72	100	64	78
33	60	M	II	BPH	TURP	BB	84	140	70	93	100	80	110	52	71	100	71	95	62	73	100	64	78
34	50	F	I	UV Prolapse	Vaginal Hysterectomy	BB	74	120	72	88	100	70	116	68	84	100	61	92	54	67	100	55	89
35	30	M	I	VUJ Calculus	Left URSL	BB	74	127	88	101	100	70	110	72	85	100	65	98	44	62	100	60	84
36	43	F	II	UTI	Cystoscopy & Proceed	BB	74	127	74	92	100	64	100	64	76	100	60	99	62	74	100	54	82
37	48	F	II	Right Calceneal #	ORIF	BB	100	100	70	80	100	82	94	62	73	100	80	88	59	69	100	74	84
38	56	M	II	Hydrocele	Excision	BB	90	150	98	115	100	89	148	98	115	100	71	120	70	87	100	64	90
39	31	M	I	Gluteal Abscess	Incision & Drainage	BB	81	130	76	94	100	80	126	80	95	100	70	110	68	82	100	56	80
40	35	M	I	Anal Fissure	Fissurectomy	BB	84	138	76	97	100	81	130	80	97	100	70	110	66	81	100	59	96
41	26	M	I	Left Inguinal Hernia	Repair	BB	86	128	80	96	100	80	120	76	91	100	71	102	60	74	100	67	90
42	35	F	I	Wound Gaping	Secondary Suturing	BB	82	130	80	97	100	78	118	78	91	100	64	94	67	76	100	52	80
43	45	M	I	Hydrocele	Excision	BB	83	136	80	99	100	80	140	80	100	100	78	102	70	81	100	70	82
44	22	M	I	Left Inguinal Hernia	Repair	BB	84	128	80	96	100	80	120	76	91	100	68	104	60	75	100	64	98
45	56	F	I	Infraumbilical Hernia	Repair	BB	79	140	80	100	100	76	138	80	99	100	58	102	60	74	100	49	78
46	52	M	I	Anal Fissure	Fissurectomy	BB	86	146	98	114	100	80	138	90	106	100	63	106	70	82	100	45	70
47	58	M	II	Left Inguinal Hernia	Repair	BB	77	146	96	113	100	69	140	96	111	100	60	108	80	89	100	49	90
48	59	M	II	Right ACL Tear	Arthroscopic Repair	BB	69	146	96	113	100	70	138	100	113	100	64	108	78	88	100	56	110
49	28	F	I	Infraumbilical Hernia	Repair	BB	76	126	70	89	100	71	120	80	90	100	66	100	56	71	100	57	70
50	28	M	I	DJ Stent in situ	Check URS	BB	90	140	90	107	100	92	136	86	103	100	80	110	68	82	100	72	114
51	44	F	II	Infraumbilical Hernia	Repair	BB	84	130	80	97	100	82	130	76	94	100	70	112	70	84	100	56	78
52	52	M	II	Ca Prostate	B/L Orchidectomy	LB	68	150	100	117	100	67	144	98	113	100	64	130	80	97	100	61	114
53	59	M	II	Ca Bladder	Cystoscopy + TURBT	LB	68	156	100	119	100	67	150	100	117	100	60	138	82	101	100	60	128
54	50	M	II	Op/c/o Ulcer over Right Foot	STSG	LB	72	148	102	117	100	70	140	100	113	100	62	116	80	92	100	64	110
55	60	F	II	Right Lower Limb PVD	Right Femoral Artery Embolectomy	LB	68	140	90	107	100	69	140	90	107	100	62	128	78	95	100	57	110
56	37	M	I	Pilonidal Sinus	Excision	LB	87	126	80	95	100	90	126	80	95	100	78	116	70	85	100	75	110
57	60	M	II	BPH	TURP	LB	64	160	98	119	100	69	156	100	119	100	60	138	88	105	100	59	120
58	43	M	I	VUJ Calculus	URS + DJ Stenting	LB	70	130	76	94	100	70	134	70	91	100	64	114	72	86	100	60	102
59	49	M	I	Right IT #	ORIF + Plating	LB	87	126	81	96	100	89	120	79	93	100	78	109	72	72	100	75	102
60	46	F	II	Left Proximal Tibia #	ORIF + Plating	LB	79	130	89	103	100	74	127	87	100	100	71	109	69	82	100	66	100
61	57	M	II	Ulcer over left foot	STSG	LB	67	146	79	101	100	70	143	83	103	100	65	118	67	84	100	61	104
62	39	F	I	Bimalleolar #	ORIF + Plating	LB	89	126	81	96	100	86	121	84	96	100	78	108	70	83	100	71	96
63	56	M	II	Right IT #	ORIF + Plating	LB	60	133	75	94	100	58	119	81	94	100	55	104	70	81	100	51	91
64	37	M	I	Op/C/O Tibia #	Implant Removal	LB	83	120	80	93	100	81	117	77	90	100	75	102	69	80	100	69	108
65	40	F	I	Left ACL Tear	Arthroscopic Repair	LB	69	134	70	91	100	65	120	80	93	100	61	96	61	73	100	58	99
66	58	M	II	Right Lower Limb Cellulitis	Right Below Knee Amputation	LB	77	146	88	107	100	79	139	93	108	100	71	109	70	83	100	59	93
67	49	M	II	Hydrocele	Jabulay's Procedure	LB	71	152	82	105	100	68	143	70	94	100	63	118	75	89	100	57	102
68	57	M	II	Right Lower Limb Cellulitis	Right Below Knee Amputation	LB	60	146	96	113	100	58	131	87	102	100	53	112	78	89	100	49	89
69	48	F	I	UV Prolapse	Vaginal Hysterectomy	LB	89	129	77	94	100	84	115	81	92	100	77	100	58	72	100	68	90
70	41	M	I	Left Inguinal Hernia	Repair	LB	77	130	80	97	100	75	118	76	90	100	69	96	66	76	100	66	91
71	39	F	I	Right Knee Baker's Cyst	Excision	LB	84	118	76	90	100	88	110	81	91	100	71	100	58	72	100	59	106
72	40	F	I	Left Inguinal Hernia	Repair	LB	79	130	82	98	100	76	118	79	92	100	65	92	59	70	100	63	99
73	39	M	I	Ureteric Calculi	URSL	LB	83	129	71	90	100	87	118	70	86	100	76	102	69	80	100	71	104
74	51	M	II	Left Renal Calculi	Left PCNL	LB	85	136	86	103	100	89	128	80	96	100	80	112	73	86	100	73	100
75	57	F	II	Renal Calculi	PCNL	LB	96	140	83	102	100	100	133	80	98	100	88	120	75	90	100	79	109
76	60	M	II	Ca Bladder	TURBT	LB	72	148	88	108	100	76	143	81	102	100	69	118	71	87	100	63	106
77	58	M	II	BPH	TURP	LB	78	138	93	108	100	82	130	85	100	100	76	108	68	81	100	71	92
78	59	M	II	Prostatomegaly	TURP	LB	68	136	100	112	100	70	129	93	105	100	60	116	80	92	100	56	98
79	48	M	I	Renal Calculi	URSL	LB	74	138	91	107	100	71	129	78	95	100	63	112	70	84	100	59	106
80	55	M	I	Vesical Calculus	Cystolithotripsy	LB	64	147	86	106	100	63	140	90	107	100	55	113	61	78	100	48	89
81	60	M	I	Right Inguinal Hernia	Hernia repair	LB	71	150	86	107	100	68	142	78	99	100	60	112	60	77	100	53	100
82	42	M	I	Hemorrhoids	Hemorrhoidectomy	LB	82	140	80	100	100	70	135	89	104	100	67	119	80	93	100	61	108
83	54	F	II	Ischiorectal Abscess	Debridement	LB	90	120	74	89	100	80	175	125	142	100	72	135	95	108	100	66	113
84	25	F	I	Fissure in ano	Fissurectomy	LB	88	122	70	87	100	78	126	89	101	100	70	114	80	91	100	74	103
85	40	M	I	Bladder Stone	Cystolithotripsy	LB	80	120	80	93	100	90	126	77	93	100	86	120	79	93	100	81	109
86	60	M	II	Prostatomegaly	TURP	LB	68	130	82	98	100	84	123	61	82	100	79	109	69	82	100	82	116
87	54	M	II	Op/C/O Right great toe amputation	Debridement and Grafting	LB	84	126	80	95	100	82	140	92	108	100	77	130	80	97	100	71	115
88	38	F	II	Pilonidal Sinus	Excision and repair	LB	80	120	80	93	100	84	128	80	96	100	75	117	65	82	100	76	108
89	40	M	I	Left LL Necrotising fasciitis	Fasciotomy	LB	80	120	80	93	100	82	116	70	85	100	70	102	74	83	100	77	110
90	45	M	I	Perianal abscess	I & D	LB	98	120	70	87	100	88	120	68	85	100	83	126	79	95	100	68	108
91	41	M	II	Raw area over left foot	STSG	LB	88	125	70	88	100	78	129	79	96	100	78	119	60	80	100	71	125
92	54	M	II	Op/C/O Right LL ulcer	STSG	LB	80	140	92	108	100	68	106	70	82	100	65	110	80	90	100	69	121
93	32	F	I	Sebaceous cyst	Excision	LB	78	124	80	95	100	80	130	80	97	100	82	122	86	98	100	77	107
94	28	M	I	Op/C/O Left leg Traumatic amputation	Debridement and grafting	LB	84	118	68	85	100	90	124	77	93	100	85	113	71	85	100	81	128
95	48	M	I	Ulcer Left Lower limb	Debridement and Grafting	LB	100	128	82	97	100	76	140	90	107	100	79	133	86	102	100	68	110
96	50	M	II	Right great toe papilloma	Excision	LB	88	120	80	93	100	84	118	76	90	100	81	120	82	95	100	78	100
97	42	M	I	Right ACL & Medial Meniscus Tear	Arthroscopic Repair	LB	64	124	86	99	100	78	156	86	109	100	86	149	79	102	100	81	109
98	32	M	I	Left ACL + Medial Meniscus Tear	Arthroscopic Repair	LB	70	132	88	103	100	84	160	90	113	100	82	145	83	104	100	77	121
99	24	M	I	Right ACL Tear	Arthroscopic Repair	LB	68	112	72	85	100	78	123	69	87	100	86	120	76	91	100	69	98
100	42	M	I	Left ACL Tear	Arthroscopic Repair	LB	86	124	86	99	100	72	140	90	107	100	69	136	82	100	100	73	104
101	27	M	I	Op/C/O B/L Tibia Fracture	Dynamisation of B/L Nail	LB	84	132	84	100	100	88	99	61	74	100	71	106	77	87	100	75	115
102	38	M	II	Op/C/O Right Tibia Distal End Fracture	Implant Removal	LB	82	150	90	110	100	80	130	70	90	100	76	118	78	91	100	71	109

S AT 10 MINUTES			VITALS AT 15 MINUTES					VITALS AT 20 MINUTES					VITALS AT 25 MINUTES					VITALS AT 30 MINUTES					SENSORY BLOCKADE	MOTOR BLOCKADE
DBP	MAP	SpO2	HR (bpm)	SBP	DBP	MAP	SpO2	HR (bpm)	SBP	DBP	MAP	SpO2	HR (bpm)	SBP	DBP	MAP	SpO2	HR (bpm)	SBP	DBP	MAP	SpO2	Onset at T8 Level (minutes)	Onset of Complete Motor Blockade
70	83	100	67	108	70	83	100	59	102	66	78	100	58	102	60	74	100	60	110	62	78	100	1.5	2
70	81	100	63	100	60	73	100	62	98	60	73	100	64	108	72	84	100	57	106	68	81	100	1	1.5
60	73	100	64	94	74	81	100	60	98	80	86	100	61	102	78	86	100	60	100	60	73	100	1	2
70	82	100	63	96	66	76	100	65	98	70	79	100	62	108	68	81	100	66	110	70	83	100	1	3
60	70	100	62	86	60	69	100	69	100	78	85	100	70	94	78	83	100	71	104	66	79	100	1	1.5
70	81	100	58	108	66	80	100	56	90	58	69	100	59	98	78	85	100	60	100	60	73	100	1	2
50	61	100	56	90	50	63	100	51	96	76	83	100	53	94	78	83	100	56	100	70	80	100	1	1.5
56	68	100	66	102	58	73	100	65	100	60	73	100	69	114	74	87	100	63	118	80	93	100	1	2
56	67	100	60	96	70	79	100	62	110	72	85	100	65	108	68	81	100	67	104	78	87	100	1	1.5
56	66	100	58	98	68	78	100	55	106	80	89	100	59	116	70	85	100	57	120	80	90	100	1	1.5
56	68	100	49	90	50	63	100	58	102	68	79	100	57	110	60	77	100	60	114	74	87	100	1	2
68	75	100	68	94	74	81	100	69	116	72	87	100	70	120	80	90	100	72	128	76	93	100	1.5	2
78	87	100	67	116	76	89	100	74	124	84	93	100	70	118	70	86	100	71	110	82	91	100	1	2
72	86	100	68	110	70	83	100	65	116	76	89	100	68	110	70	83	100	69	124	70	88	100	1	1.5
56	67	100	68	96	70	79	100	61	116	81	93	100	69	108	70	83	100	68	102	69	80	100	0.5	1
49	60	100	58	86	66	73	100	61	98	70	79	100	59	104	80	88	100	66	119	83	95	100	0.5	1.5
49	64	100	50	98	61	73	100	59	108	76	87	100	63	118	80	93	100	60	110	73	85	100	1	2
41	56	100	51	80	56	64	100	55	92	63	73	100	56	101	60	74	100	59	108	69	82	100	1	1.5
61	69	100	49	77	45	56	100	56	88	60	69	100	57	102	64	77	100	66	110	79	89	100	0.5	1.5
51	60	100	53	84	60	68	100	59	98	63	75	100	60	100	70	80	100	60	96	66	76	100	1	1.5
52	62	100	56	90	56	67	100	60	100	60	73	100	61	98	58	71	100	59	106	70	82	100	0.5	2
47	59	100	50	87	57	67	100	56	96	70	79	100	60	104	66	79	100	59	110	70	83	100	1	2
44	56	100	51	88	50	63	100	59	96	68	77	100	62	102	70	81	100	60	108	70	83	100	0.5	1
50	60	100	49	94	66	75	100	58	102	70	81	100	57	110	76	87	100	60	114	80	91	100	0.5	1.5
70	83	100	64	114	66	82	100	65	104	70	81	100	71	110	80	90	100	69	118	74	89	100	1	2
48	60	100	67	96	70	79	100	70	106	76	86	100	68	110	70	83	100	71	110	74	86	100	1	1.5
42	54	100	55	92	56	68	100	69	102	68	79	100	72	118	70	86	100	74	128	82	97	100	0.5	1
52	67	100	56	103	68	80	100	58	114	72	86	100	74	121	74	90	100	60	116	80	92	100	0.5	2
47	60	100	50	79	42	54	100	59	92	74	80	100	62	107	91	96	100	71	113	84	94	100	1	1.5
42	58	100	54	84	49	61	100	64	99	62	74	100	68	108	74	85	100	72	110	80	90	100	0.5	1
56	67	100	55	96	60	72	100	50	104	66	79	100	57	110	70	83	100	59	114	76	89	100	1	1.5
48	58	100	56	86	70	75	100	59	102	66	78	100	61	100	76	84	100	68	110	70	83	100	0.5	1.5
48	58	100	60	86	60	69	100	62	106	66	79	100	70	110	70	83	100	78	100	68	81	100	1	1.5
42	57	100	62	90	61	71	100	68	94	63	73	100	70	100	70	80	100	72	120	80	90	100	1.5	2
52	63	100	56	88	61	70	100	61	92	77	82	100	70	107	74	85	100	72	119	82	94	100	1	1.5
45	57	100	60	94	61	72	100	71	106	70	82	100	74	109	64	79	100	82	118	68	85	100	0.5	1.5
56	65	100	55	78	42	54	100	64	94	62	73	100	68	100	68	79	100	69	110	80	90	100	1	2
58	69	100	52	82	42	55	100	55	90	50	63	100	59	104	66	79	100	62	108	76	87	100	1	1.5
48	59	100	58	88	56	67	100	60	96	60	72	100	62	100	60	73	100	59	108	68	81	100	1	2
56	69	100	46	76	40	52	100	50	98	58	71	100	60	106	60	75	100	59	110	72	85	100	0.5	1.5
58	69	100	54	78	48	58	100	58	88	60	69	100	61	102	66	78	100	66	110	70	83	100	1	1.5
50	60	100	53	88	58	68	100	60	102	70	81	100	61	110	60	77	100	67	118	78	91	100	0.5	1
40	54	100	67	90	70	77	100	60	106	80	89	100	59	118	76	90	100	61	120	80	90	100	0.5	1.5
58	71	100	69	110	70	83	100	71	106	70	82	100	68	126	80	95	100	70	118	70	86	100	0.5	1
50	59	100	52	70	46	54	100	50	94	60	71	100	55	102	66	78	100	61	110	70	83	100	1	2
44	53	100	53	80	60	67	100	57	88	68	75	100	68	98	66	77	100	69	106	70	82	100	1	2
58	69	100	48	76	38	51	100	56	88	60	69	100	59	104	70	81	100	61	102	80	87	100	0.5	1.5
60	77	100	51	116	80	92	100	54	104	80	88	100	56	124	74	91	100	59	114	76	89	100	1	1.5
48	55	100	58	84	60	68	100	60	96	70	79	100	57	102	70	81	100	64	116	76	89	100	1	1.5
60	78	100	60	110	76	87	100	62	118	80	93	100	59	108	76	87	100	63	126	70	89	100	0.5	1.5
58	65	100	58	88	60	69	100	54	100	60	73	100	60	114	70	85	100	61	110	80	90	100	0.5	1
74	87	100	62	110	68	82	100	64	116	76	89	100	68	120	80	90	100	63	114	80	91	100	2	6
70	89	100	62	116	76	89	100	58	110	70	83	100	61	102	76	85	100	59	100	70	80	100	2	5
70	83	100	60	104	74	84	100	59	108	68	81	100	64	100	60	73	100	69	116	80	92	100	2	6
76	87	100	58	90	70	77	100	61	102	68	79	100	65	98	60	73	100	64	96	68	77	100	1.5	5
78	89	100	78	112	84	93	100	76	108	68	81	100	71	114	80	91	100	73	126	76	93	100	2	6
84	96	100	55	108	68	81	100	56	108	78	88	100	59	102	60	74	100	63	124	82	96	100	2	7
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70	81	100	70	99	79	86	100	71	108	81	90	100	68	100	75	83	100	70	106	73	84	100	1.5	5
60	73	100	67	102	68	79	100	62	98	71	80	100	65	103	81	88	100	69	105	75	85	100	2	5.5
60	75	100	59	97	59	72	100	61	101	63	76	100	64	109	72	84	100	60	104	81	89	100	1.5	6
65	75	100	69	102	72	82	100	63	99	69	79	100	60	103	70	81	100	66	108	73	85	100	2	5.5
67	75	100	56	106	69	81	100	54	110	70	83	100	58	118	75	89	100	63	110	66	81	100	1.5	6
75	86	100	67	112	74	87	100	70	119	81	94	100	75	124	79	94	100	71	116	80	92	100	2.5	6.5
70	80	100	59	106	83	91	100	64	110	68	82	100	62	104	73	83	100	66	115	75	88	100	1.5	5
67	76	100	64	90	70	77	100	67	106	69	81	100	68	110	77	88	100	65	106	79	88	100	2	6.5
57	72	100	59	100	63	75	100	55	101	70	80	100	63	109	76	87	100	62	113	73	86	100	2	6
59	69	100	54	98	71	80	100	57	106	70	82	100	61	102	68	79	100	69	118	85	96	100	1.5	6
63	72	100	70	101	70	80	100	66	112	80	91	100	64	103	60	74	100	63	100	79	86	100	3	7
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66	79	100	57	98	60	73	100	62	114	78	90	100	69	123	71	88	100	74	119	80	93	100	2	6
71	80	100	60	106	65	79	100	59	100	70	80	100	64	96	66	76	100	70	112	78	89	100	1.5	6
60	75	100	66	93	61	72	100	60	91	56	68	100	62	103	60	74	100	68	115	75	88	100	3	8
70	80	100	59	102	58	73	100	58	96	70	79	100	60	109	59	76	100	66	114	64	81	100	2	7
68	82	100	74	98	50	66	100	71	101	60	74	100	66	105	65	78	100	62	98	63	75	100	2	6.5
59	75	100	56	90	52	65	100	54	103	66	78	100	59	100	60	73	100	65	109	77	88	100	1.5	6
58	69	100	70	106	71	83	100	66	110	62	78	100	68	118	76	90	100	70	124	83	97	100	2	5.5
52	67	100	59	103	60	74	100	55	100	58	72	100	61	110	71	84	100	65	118	83	95	100	2	8.5
60	75	100	56	93	67	76	100	62	108	71	83	100	65	116	70	85	100	69	122	80	94	100	2	6.5
58	68	100	52	97	60	72	100	57	106	66	79	100	64	110	60	77	100	66	108	73	85	100	2.5	7.5
52	68	100	55	93	58	70	100	60	100	73	82	100	61	100	70	80	100	65	114	72	86	100	2	7
69	82	100	58	105	75	85	100	65	113	81	92	100	63	106	62	77	100	70	104	71	82	100	1.5	8
69	84	100	60	107	65	79	100	71	116	68	84	100	74	118	60	79	100	79	103	70	81	100	3	6.5
71	82	100	70	110	60	77	100	63	98	65	76	100	67	112	71	85	100	79	128	80	96	100	2.5	7.5
64	79	100	77	116	77	90	100	72	100	85	90	100	79	95	63	74	100	76	108	78	88	100	2	6
74	88	100	69	103	59	74	100	70	104	80	88	100	65	110	74	86	100	81	124	83	97	100	3	8.5
70	85	100	73	118	69	85	100	67	102	72	82	100	74	110	72	85	100	80	122	83	96	100	2.5	8
86	93	100	70	116	69	85	100	73	112	80	91	100	76	109	77	88	100	79	127	73	91	100	2	5
69	83	100	68	100	76	84	100	74	109	83	92	100	70	98	68	78	100	68	113	79	90	100	2	6
72	84	100	63	102	63	76	100	69	116	70	85	100	66	102	63	76	100	81	122	80	94	100	1.5	6.5
72	90	100	66	123	73	90	100	64	122	75	91	100	65	124	75	91	100	70	124	75	91	100	3	7.5
71	88	100	73	107	54	72	100	77	102	49	67	100	71	103	49	67	100	66	99	47	64	100	2.5	8.5
47	67	100	70	120	74	89	100	65	118	72	87	100	60	118	72	87	100	62	116	70	85	100	2	8
74	92	100	80	112	78	89	100	78	110	74	86	100	59	114	78	90	100	57	114	76	89	100	3	8.5
74	86	100	65	102	64	77	100	67	106	62	77	100	65	104	58	73	100	58	100	64	76	100	1.5	6
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55	73	100	82	98	75	83	100	76	124	75	91	100	80	124	75	91	100	72	124	75	91	100	2	8.5
71	88	100	69	100	64	76	100	63	100	64	76	100	72	108	66	80	100	76	106	70	82	100	3	7
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