“POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER ABDOMINAL SURGERIES”.

By

Dr. BHAVANA B G

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IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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IN
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Under the guidance of

Dr. RAVI MADHUSUDHANA

PROFESSOR, DEPARTMENT OF ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY AND CRITICAL CARE

SRI DEVARAJ URS MEDICAL COLLEGE

TAMAKA, KOLAR-563101

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Date:

Place: Kolar

Signature of the Guide

Dr. RAVI MADHUSUDHANA

Professor

Department Of Anaesthesiology

Sri Devaraj Urs Medical College,
Tamaka, Kolar.

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Dr. Dinesh K. M.D
Professor and HOD .
Department of Anaesthesiology
Sri Devaraj Urs Medical College,
Tamaka, Kolar.

Dr. Harendra Kumar.M.L .
Principal,
Sri Devaraj Urs Medical College.
Tamaka, Kolar.

Date:

Place: Kolar

Date:

Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA,

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved Dr. BHAVANA B G, Post-Graduate student in the subject of ANAESTHESIOLOGY at Sri Devaraj Urs Medical College, Kolar to take up the Dissertation work entitled **"POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER ABDOMINAL SURGERIES". To be submitted to Sri Devaraj Urs Academy Of Higher Education And Research Centre, Tamaka, Kolar, Karnataka,**

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Dr. BHAVANA B G

LIST OF ABBREVIATIONS USED

Abbreviation	Full Form
ASA	American society of Anaesthesiologists
cc	Cubic centimeter
CNS	Central nervous system
C7	Cervical vertebra
CSF	Cerebrospinal fluid
CVS	Cardiovascular system
^{0}C	Degree Celsius
Cm	Centimeter
DBP	Diastolic blood pressure
ECG	Electrocardiogram
HR	Heart Rate
Hr	Hours
ICP	Intracranial Pressure
IV	Intravenous
IM	Intramuscular
Kg	Kilogram
L_{3-4}	Lumbar Vertebra
MAP	Mean arterial pressure
Min	Minutes
mg/kg	Milligram per kilogram

mcg	Micrograms
ml	Milliliter
mg	Milligram
mm of Hg	Millimeter of mercury
mm of H_2O	Millimeter of water
mg/l	Milligram per liter
mmol /l	Millimoles per liter
ml/sec	Millileter per second
NIBP	Non Invasive Blood Pressure
PDPH	Post dural puncture headache
PR	Pulse rate
$Paco_2$	Partial pressure of carbon dioxide in arterial blood
SAB	Subarachnoid block
SBP	Systolic blood pressure
SD	Standard deviation
S2	Sacral vertebra
T1, T12	Thoracic vertebra
µg/ml	Microgram per millitre

ABSTRACT

POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER ABDOMINAL SURGERIES

Background and objectives:

To compare the effects of intrathecal nalbuphine and fentanyl as adjuvants to hyperbaric bupivacaine in regards to time of onset of sensory blockade, Duration of sensory blockade, Two segment sensory regression time, Duration of effective post- operative analgesia and incidence of side effects

MATERIALS AND METHODS:

After ethical committee permission and patient consent, 124 patients aged 18-55yrs with ASA- I and II were randomly divided into 2 groups.

Group N: Hyperbaric bupivacaine with nalbuphine (300mcg).

Group C: Hyperbaric bupivacaine with fentanyl(25mcg).

Exclusion criteria: Allergic to study medications, other contraindications to SAB

Categorical data:frequencies and proportions

Continuous data: mean+SD

Tests of significance: chi-square and student t test

P value< 0.05 statistically significant

RESULTS:

Duration of onset of sensory blockade was (3.9±0.35)min in group C, (3.1±0.18 min) in group F and. Two segment sensory regression time was prolonged in group C (193.16±39.55) compared to group F (167.41±30.17 min).

CONCLUSION:

From the present study it was concluded that intrathecal nalbuphine in the dose of 300mcg in 3 ml 0.5% heavy bupivacaine in patients undergoing elective lower abdominal surgeries showed, Delay in onset time for sensory blockade, Produced prolonged postoperative analgesia ,prolonged sensory blockade and minimal bradycardia which could be easily managed.

Key words:

bupivacaine, fentanyl, nalbupine,spinal anaesthesia.

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INTRODUCTION

INTRODUCTION

Sub arachnoid blockade is commonly used technique for lower abdominal and lower limb surgeries. It is easier to perform by injecting anaesthetic drug into the subarachnoid space and with rapid onset of anaesthesia, provides analgesia both intra and post operatively. Polypharmacy and problems with airway management of general anaesthesia are avoided.

Spinal anaesthesia with cocaine was given inadvertently in 1885 by Leonard J corning .[1] In 1891 Quincke demonstrated a safe, predictable technique of performing lumbar puncture. August Bier in 1899, used Quincke's technique to inject cocaine to produce operative anaesthesia, this was the first actual spinal anaesthesia.

Spinal anaesthesia are provided with wide range of local anesthetics and additives increases the duration of spinal anaesthesia. Lignocaine was used as local anaesthetic of choice in spinal anaesthesia because of its faster onset and shorter duration of action. Its implication in causing cauda equina syndrome and transient neurological symptoms following spinal anaesthesia made its usage limited.[2]

Hyperbaric Bupivacaine 0.5% is more potent than lignocaine, and has longer duration of action. Its disadvantage is slow onset of action.

The problem is with the duration of action of regular spinal anaesthesia and its conversion to general anaesthesia in cases of prolonged surgeries. Since bupivacaine has to be given in larger doses to achieve the analgesic and anaesthetic effects, the use of adjuvants with bupivacaine have shown to reduce

its dose requirements in spinal anaesthesia with reduced incidence of side effects

Additives like intravenous Benzodiazepines, semi synthetic and synthetic opioids are effective and are commonly used for post-operative pain relief. Neural blockade can be prolonged for postoperative pain relief.

Nalbuphine hydrochloride is primarily a kappa agonist/partial mu antagonist . The concentrations of kappa-receptors is greatest in nociceptive regions are in lamina I and II of Rexed in the spinal cord dorsal horn as well as in the spinal nucleus of the trigeminal nerve (substantia gelatinosa). Taken together, these data suggest that nalbuphine acts primarily at the level of the first synapse in the nociceptive system in producing analgesia.

The μ agonist, fentanyl exerts its action by opening K+ channels and reducing Ca++ influx, resulting in inhibition of transmitter release. The μ agonist also have a direct postsynaptic effect, causing hyper-polarization and a reduction in neuronal activity. Bupivacaine, acts mainly by blockade of voltage gated Na+ channels in the axonal membrane and possibly inhibits calcium channels.

OBJECTIVES

OBJECTIVES OF THE STUDY

Primary objective

- To asses

    1. Time of onset and duration of sensory blockade (pin prick) and motor blockade by Bromage scale
    2. Time for two segment sensory level regression
    3. Total duration of sensory and motor blockade (VAS score)

Secondary objectives

- Number of rescue analgesia given in 24 hours postoperatively,
- Haemodynamics,
- Side effects will be noted.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

APPLIED ANATOMY

ANATOMY OF VERTEBRAL COLUMN:

The vertebral canal extends from foramen magnum till sacral hiatus. It is composed of 33 vertebrae (7 cervical vertebrae, 12 thoracic vertebrae, 5 lumbar vertebrae, 5 fused sacral vertebrae and 4 coccygeal vertebrae). The cervical vertebrae has a body anteriorly, two pedicles posteriorly projecting from the body and two laminae connects the pedicles except in first cervical vertebra. Thoracic and lumbar vertebrae have similar structures. The laminae has transverse processes laterally and there is a spinous process projecting posteriorly. The pedicles contain notch superiorly and inferiorly called as vertebral notch through this notch the spinal nerves comes out of the vertebral canal. The articular processes arises superiorly and inferiorly at the junction of pedicle and lamina and joints are formed with the adjacent vertebrae. The C1 vertebrae ("atlas") is different from the typical structure in which body and spinous process are absent.[3]

There are four curves in vertebral column, the cervical and lumbar curves have convexity anteriorly while the sacral and thoracic curves have convexity posteriorly. These curves influence the spread of local anaesthetics in spinal anesthesia.

The first spinous process which is prominent while running the hand down the nape of the neck is the spinous process of 7^{th} cervical vertebra. Following C7 the most prominent spinous process is T1. To identify 12th thoracic vertebra 12th rib is palpated and traced back as it is attached to T12. When a line is drawn between the iliac crests it crosses the body of L5 vertebra or the L4 L5 inter space.

There are 31 pairs of spinal nerves arising from spinal cord, each spinal nerve is composed of ventral motor root and a dorsal sensory root. The nerve

roots are composed of multiple rootlets. The part of the spinal cord that gives rootlets of a spinal nerve is a cord segment. The skin area supplied by a spinal nerve and its corresponding cord segment is called a dermatome.

The spinal cord ends between L1 and 2, the nerve roots of thoracic , lumbar and sacral run longer distances from the segment of origin till the intervertebral foramen in subarachnoid space and they exit through intervertebral foramen. The nerves extend beyond the end point of spinal cord which are known as the cauda equina.

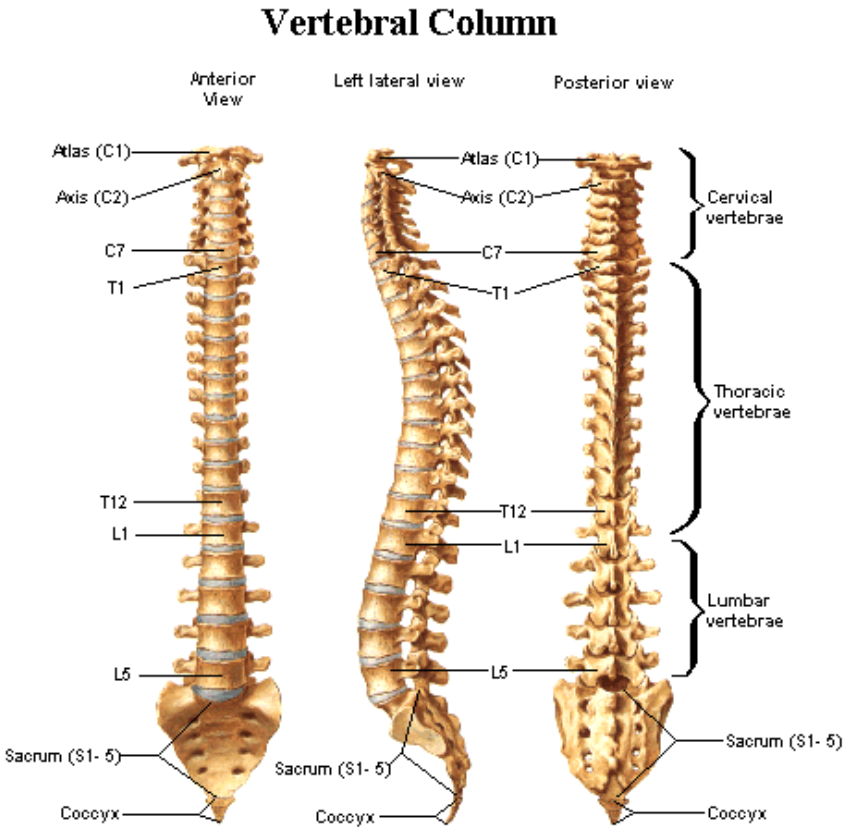

FIGURE 1: CURVES OF THE SPINE

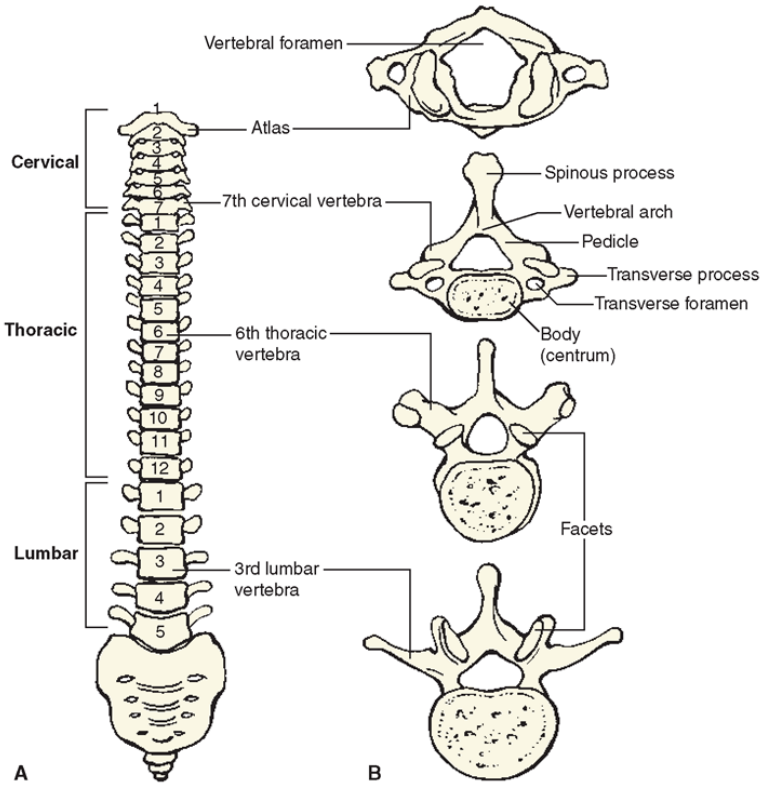

FIGURE 2: VERTEBRAL COLUMN, SUPERIOR VIEW

The vertebral canal is bounded anteriorly by vertebral body ,intervertebral discs and the posterior longitudinal ligament. The vertebral canal has laminae and ligamentum flavum postreriorly, laterally it is bounded by pedicles and laminae. The vertebral canal is narrower at thoracic level and wider at cervical and lumbar levels. [4,5]

The vertebral canal is also bounded by ligaments, these ligaments gives stability and elasticity to the vertebral canal. The ligaments are:

a) Supraspinous ligament
b) Interspinous ligament
c) Ligamentum flavum
d) Longitudinal ligaments.

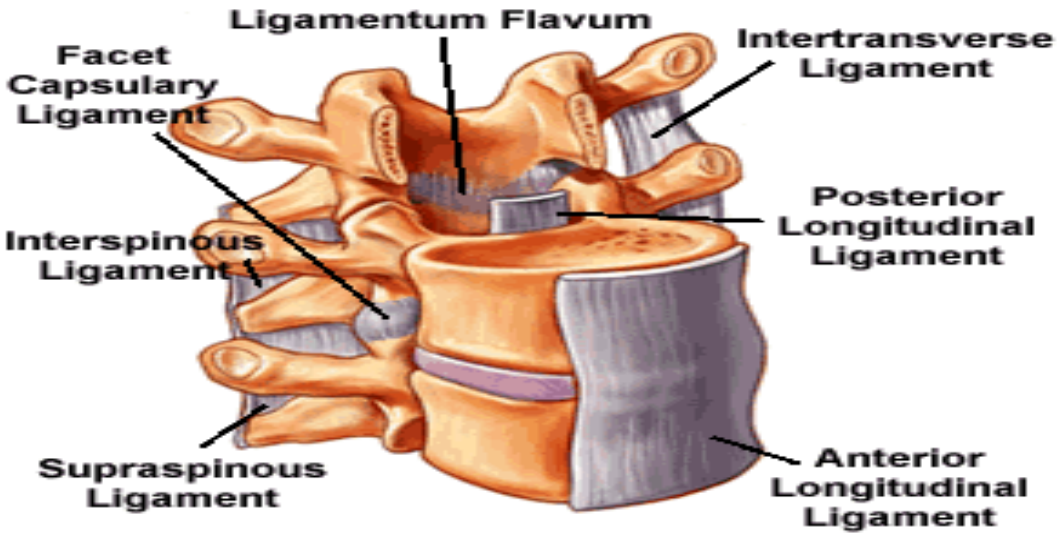

FIGURE 3: LIGAMENTS OF VERTEBRAE

Ligaments of vertebral column.[6]

1) **Supraspinous ligament**: It is a thick, strong, fibrous band. It is thicker and broader at lumbar region. In cervical region this ligament blends with ligaments of the neck and forms ligamentum nuchae.

2) **Interspinous ligament**: It is a fibrous structure, connecting the adjacent spines. The fibers of the ligament are membranous and they extend from the apex of a lower spine to inferior surface of next higher vertebra. This ligament is rectangular in shape.

3) **Ligamentum flavum**: This ligament consists of elastic tissue. They extend from anterior inferior surface of upper lamina to anterior superior surface of lower lamina. Laterally ligament starts at the roots of articular process and extends dorsally and medially to the point where laminae joins to form spinous process. The ligament is thickest and strongest in the lumbar region.

4) **Longitudinal ligaments**: The vertebral bodies are bound together by anterior and posterior longitudinal ligaments.

Posterior longitudinal ligament:

The ligament lies on the posterior surface of vertebral bodies . In cervical and lumbar region the ligament is thinnest.

Anterior longitudinal ligament:

Extends along the ventral aspect of vertebral bodies.

The cervical, thoracic and lumbar vertebrae have certain unique features which differentiate them from each other. The transverse process of cervical vertebrae has foramen transversarium for the vertebral artery, spinous process of cervical vertebra is short and bifid. The bodies of thoracic vertebrae have articular facets for the attachment of ribs . The lumbar vertebrae are distinguished from vertebrae in other regions by their large size. Also they lack facets for articulation with ribs[7].

LUMBAR VERTEBRA:

A lumbar vertebrae has following parts.

1) The body
2) Vertebral arch
3) Transverse and spinous process
4) Superior and inferior articular process

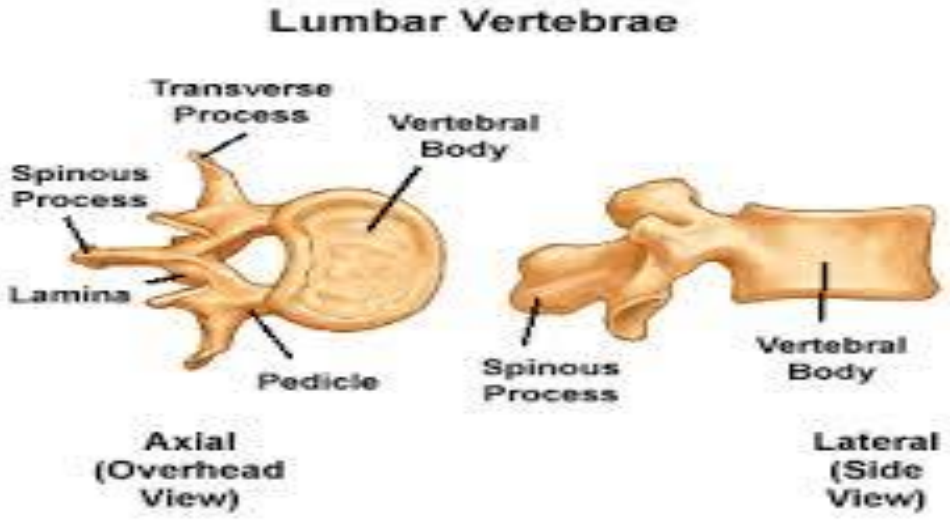

FIGURE 4: LUMBAR VERTEBRAE

BODY: It is kidney shaped. The articular surfaces is covered with hyaline cartilage.

VERTEBRAL ARCH:

It is formed by pedicles and laminae and surrounds and protects the spinal cord. Ventrally the arch is formed by the pedicles. Dorsally it is formed by the lamina. Four articular facets are present on the arches, two are facing superiorly and two are facing inferiorly. These articulate with articular facets of adjacent vertebrae.

At the junction of pedicles and laminae arises a superior articular process. There is an inferior articular processes which extends from inferolateral aspects of the laminae and it lies below the transverse processes and articular facets.

The pedicles has two notches which is between the body and the pedicles (superior and inferior). There is intervertebral foramen formed when adjacent vertebrae articulate on either side. The mixed spinal nerve of that segment issues through the intervertebral foramen . The intervertebral foramen are bounded superiorly and inferiorly by pedicles of adjacent vertebrae, dorsally capsules surrounding the articular processes of adjoining vertebrae and anteriorly by the intervertebral disc and the lower part of the body above it.

Anatomy of the spinal cord.[6]

Below the level of foramen magnum medulla oblongata continues as spinal cord. Spinal cord ends as conus medullaris. In first trimester it extends up to the end of sacrum. At birth, spinal cord ends at the level of 3rd lumbar vertebra and the dural sac ends at S3.

After birth, growth of vertebral column is faster than growth of spinal cord and meninges. At one year, the conus medullaris at the lower border of L2 and the dural sac ends at S2. At 12-16 years, the adult relations are attained, and the

spinal cord ends at lower border of L1 in 50% of individuals and in about 40% it ends opposite to the body of L2.

The average length of the spinal cord in males is around 45 cm, and in females it is around 42 cm.

Spinal segments:

The spinal cord gives 31 pairs of spinal nerves each containing ventral and dorsal roots. The spinal cord giving rise to one nerve is called a cord segment. The skin innervated by a spinal nerve and its corresponding cord segment which is called a dermatome.

31 pair of spinal nerves are:

1. Cervical 8
2. Thoracic 12
3. Lumbar 5
4. Sacral 5
5. Coccygeal 1

Two roots, dorsal and ventral join to form a spinal nerve. Sympathetic preganglionic axons arises from cells which are present in the intermediolateral horn of spinal cord from 1st thoracic to 2nd lumbar vertebra. Dorsal roots are longer than ventral roots and these roots carry efferent impulses from whole body .

Each dorsal root has a ganglion and carry fibers of touch, temperature, pain, deep sensation from bones, joints, muscles and tendons, efferent from the viscera (accompanying sympathetic) and vasodilator fibers.

Segmental levels:

Clavicle	C3-4
Second intercostal space	T2
Nipple	T4-5

Subcostal	T6-9
Umbilicus	T10
Inguinal region	L4
Perineum	S1-4

Meningeal coverings of the spinal cord.[1,6]

The three membranes surrounds the spinal cord in the bony vertebral column. The three membranes are (from inside to outside): the pia mater, arachnoid, and dura mater.

Dura mater - The cranial dura mater continues as spinal dura mater from foramen magnum to 2nd sacral vertebra, at this level the filum terminale merges with the periosteum of the coccyx.

Arachnoid mater - This is the middle layer of the three coverings. It is non-vascular membrane this membrane closely attaches to the dura and ends at the lower border of 2nd sacral vertebra.

Pia mater - this is highly vascular membrane. The pia matter extends laterally to form denticulate ligaments. The denticulate ligament act as struts to hold the spinal cord suspended within the subdural space.

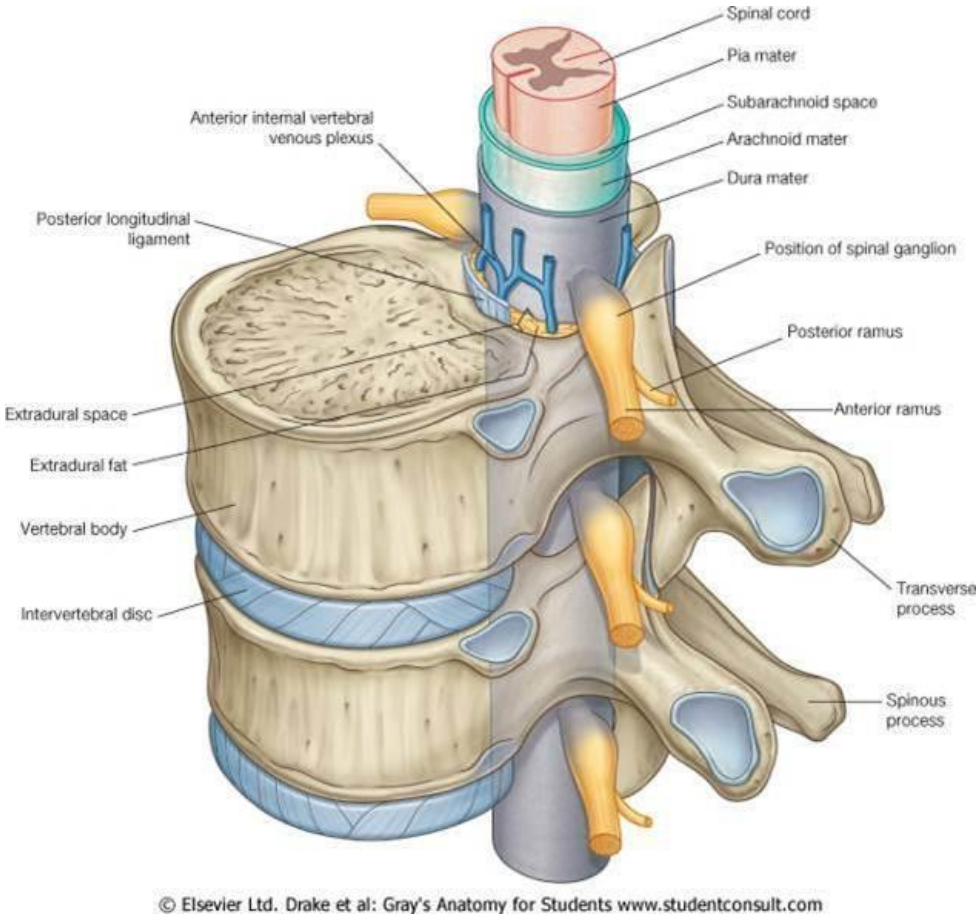

FIGURE 5: MENINGES OF SPINAL CORD

CIRCULATION OF THE SPINAL CORD.[6]

ARTERIAL SUPPLY TO THE SPINAL CORD.

Spinal cord is supplied by one anterior and two pairs of posterior spinal arteries.

The anterior spinal artery is a branch of terminal portion of vertebral artery. It is formed at the level of foramen magnum. It is a large artery and it lies on the anterior median fissure in midline. It supplies anterior two-third of spinal cord along the entire length along with contributing arteries.

The posterior spinal arteries are two pairs of longitudinally descending vessels—two on each side. These arteries are either direct branch of vertebral artery or a primary branch of the posterior inferior cerebellar artery. The posterior one-third of the spinal cord is supplied by the posterior spinal arteries.

FIGURE 6: BLOOD SUPPLY OF SPINAL CORD

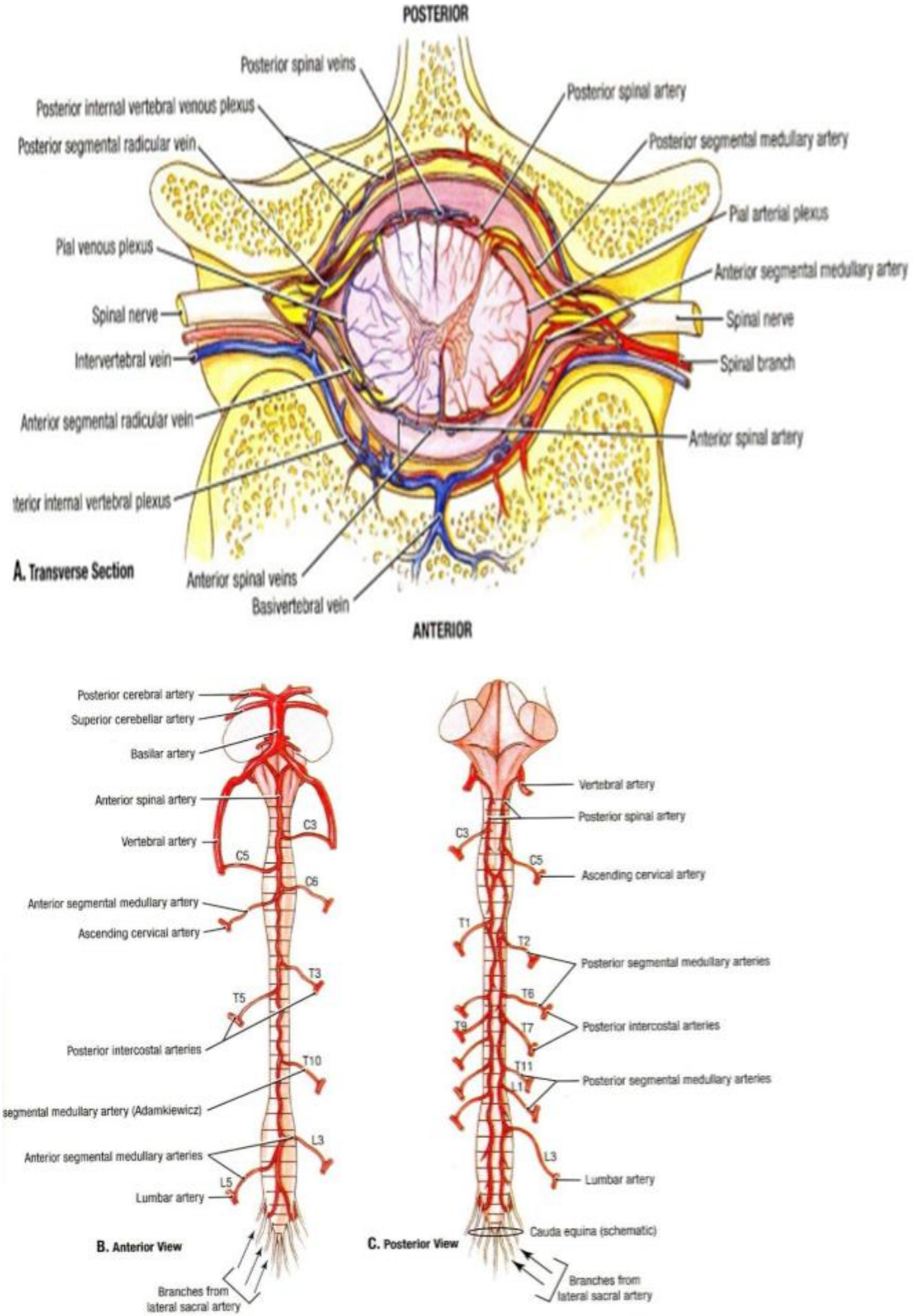

FIGURE 7: BLOOD SUPPLY OF SPINAL CORD

Veins of the spinal cord

The veins of the spinal cord are present in pia mater. There are six veins which together form longitudinal plexiform channels. This plexiform channel drains the parenchyma of the spinal cord. The plexus consist of (1) two median longitudinal veins, and (2) four lateral longitudinal veins. These veins drains into intervertebral veins. The intervertebral veins drains to external vertebral plexus through segmental veins.

Cerebrospinal Fluid.[3,8]

CSF is a solution consisting of electrolytes, proteins, glucose, neurotransmitters, neurotransmitter metabolites, cyclic nucleotides, amino acids, etc. CSF is formed by ultra-filtration of plasma in choroid plexus and cerebral/spinal capillaries. The CSF volume is 100 to 160 ml in adult and the rate of production is 20 to 25 ml/hr. Hence , every 6 hours the entire CSF volume is replaced. CSF is absorbed by arachnoid villi which is in the superior sagittal sinus.

Characteristics and composition of CSF:

Specific gravity	1.003-1.009
Volume in subarachnoid space	20ml
Pressure	110mm of H_2O
Protein	200-400mg/l
Glucose	2.5-4.5mmol/l
Chloride	123-128mmol/l
Sodium	140-150mmol/l
Bicarbonate	250-30mmol/l
pH	7.4-7.6

Spinal Anesthesia[9]

Technique

To perform spinal anesthesia, the pertinent anatomy must be constantly kept in mind while inserting the spinal needle. It is often helpful for the technique to be broken down into a series of steps (i.e., the four P's): preparation, position, projection, and puncture.

Preparation

Preparation of the equipment and drugs is essential for subarachnoid injection. When choosing a drug for subarachnoid injection, the duration of block should be matched to the surgical procedure and to patient variables.

Spinal needles fall into two main categories: those that cut the dura and those with a conical tip. The former include the Quincke-Babcock needle, the traditional disposable spinal needle, and the latter contain the Whitacre and Sprotte needles

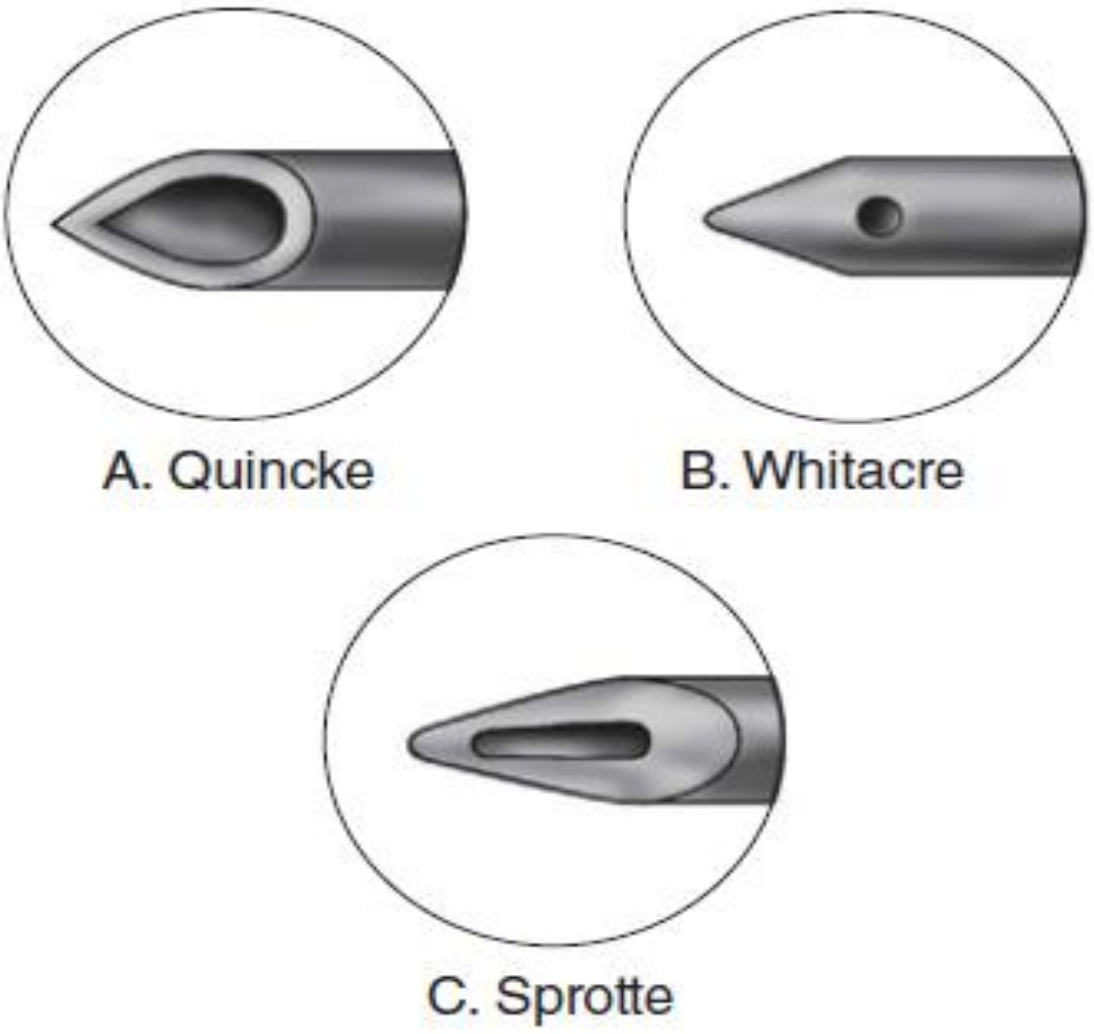

Figure 8: Types of spinal needle

Position[9]

The three primary patient positions include the lateral decubitus, sitting, and prone positions, each with advantages in specific situations.

The lateral decubitus position is the most commonly used because it allows easier administration of more sedation and is less dependent on a well-trained assistant than the sitting position is. Patients are placed with their back parallel to the edge of the operating table nearest the anesthesiologist, their thighs flexed on their abdomen, and their neck flexed to allow the forehead to be as close as possible to the knees.

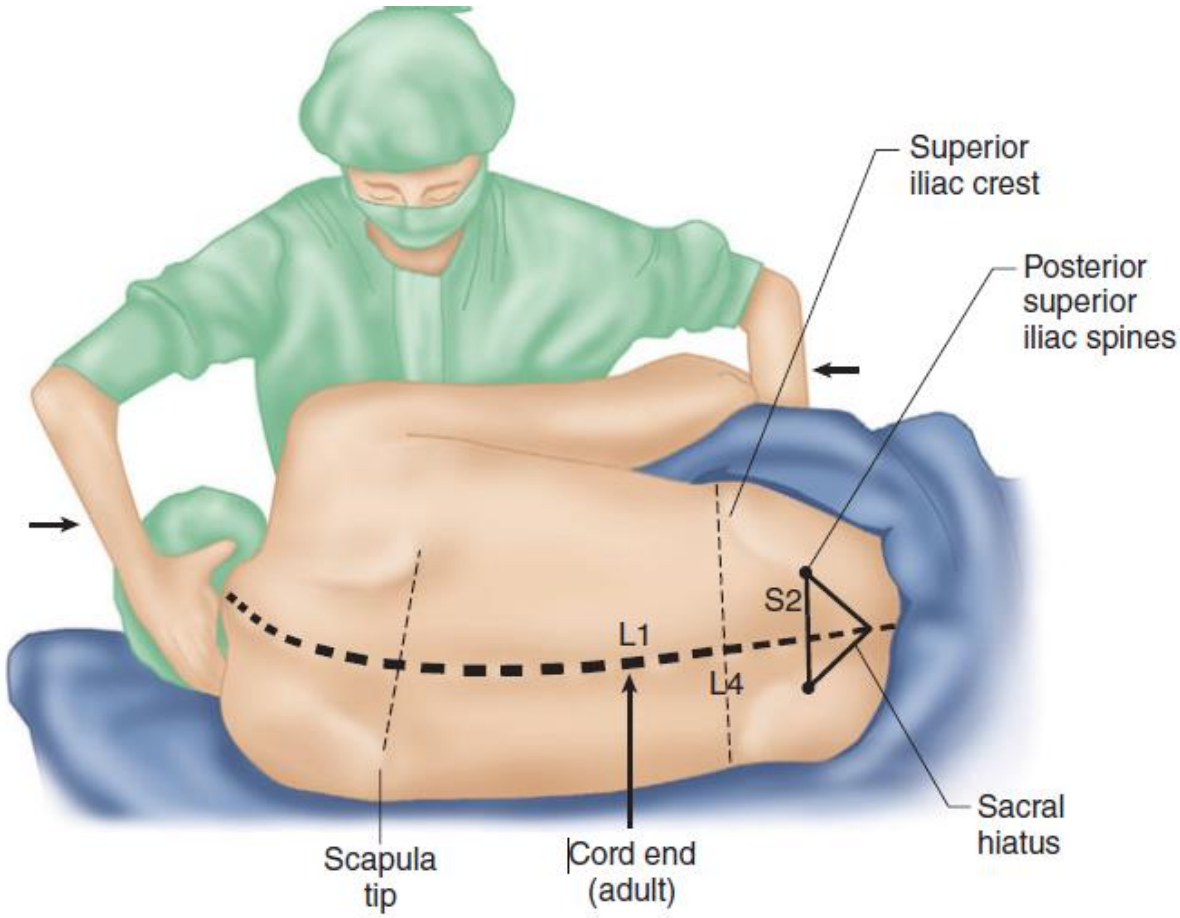

Figure 9: left lateral position for spinal anaesthesia

The sitting position should be chosen when low lumbar and sacral levels of sensory anesthesia are adequate for the surgical procedure, such as perineal and urologic operations, or when obesity or scoliosis makes identification of midline anatomy difficult in the lateral position. When placing patients in this position, a stool can be provided as a footrest and a pillow placed in the lap.

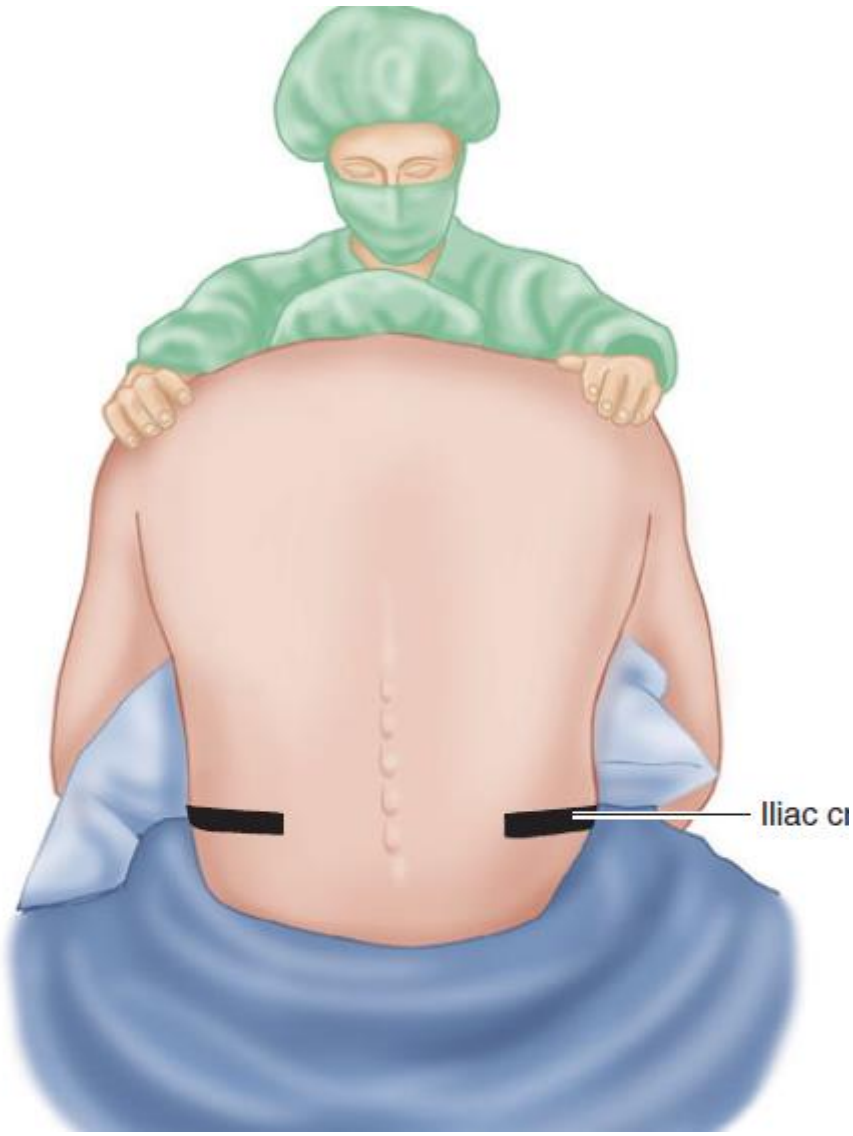

Figure 10: sitting position for spinal anaesthesia

The prone position should be chosen when the patient is to be maintained in that position (often with the jackknife modification) during the surgical procedure. This position is often appropriate for rectal, perineal, or lumbar procedures

Projection and Puncture

After the equipment, local anesthetics and additives, and the patient have been properly prepared, the midline or paramedian spinal puncture can be performed. The midline approach relies on the ability of patients and assistants to minimize

lumbar lordosis and allow access to the subarachnoid space between adjacent spinous processes, usually at the L2-3, L3-4, or sometimes the L4-5 space. The palpating fingers (usually the index and third fingers) should identify the interspinous area by locating the caudad extent of the more cephalad spine and the midline by rolling the fingers in a medial-to-lateral direction . A subcutaneous skin wheal is developed over this space, and the introducer is inserted into the substance of the interspinous ligament. The introducer is grasped with the palpating fingers and steadied while the other hand is used to hold the spinal needle like a dart, and the fifth finger is used as a tripod against the patient's back to prevent patient movement and unintentional insertion to a level deeper than intended. The needle, with its bevel parallel to the midline, is advanced slowly to heighten the sense of tissue planes traversed and to prevent skewing of nerve roots until the characteristic change in resistance is noted as the needle passes through ligamentum flavum and dura. After CSF is freely obtained, the dorsum of the anesthesiologist's nondominant hand steadies the spinal needle against the patient's back while the syringe containing the therapeutic dose is attached to the needle. CSF is again freely aspirated into the syringe, and the anesthetic dose is injected at a rate of approximately 0.2 mL/sec. The patient and operating table should then be placed in the position appropriate for the surgical procedure and drugs chosen.

Structures pierced during subarachnoid block:

1. Skin
2. Subcutaneous tissue
3. Supraspinous ligament
4. Interspinous ligament
5. Ligamentum flavum
6. Areolar tissue or epidural space
7. Spinal dura mater

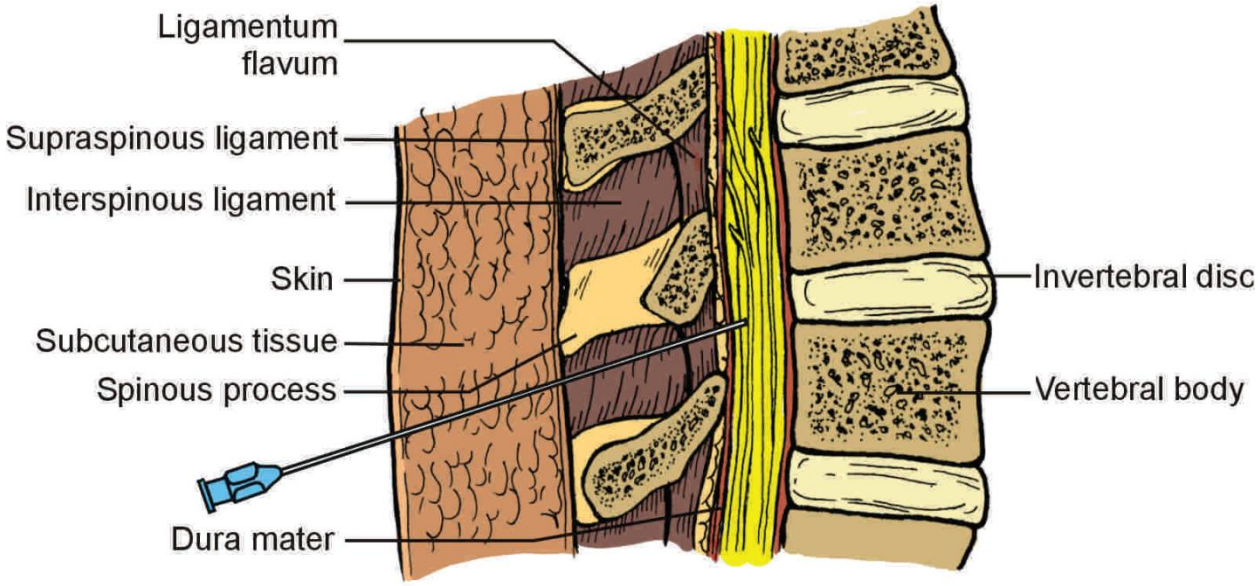

FIGURE 11: STRUCTURES PIERCED DURING SUBARACHNOID BLOCK

Physiology of spinal anaesthesia[1,10]

After deposition of local anaesthetic deposition in subarachnoid space there will be loss of sensation and muscle paralysis which is immediately as a result of direct blocking effects on the transmission of impulses in nerve fibers.

There are three sites of action.

1. Primary- nerve roots of the spinal cord
2. Secondary- dorsal root ganglia
3. Limited and incomplete- in the parenchyma of spinal cord on ascending and descending tracts

DIRECT EFFECTS:

Primary site of action is on the nerve roots of spinal cord both dorsal and ventral. The effect of blocking depends on the size of nerve fiber. Sensory fibers which are small and non medullated are more sensitive to the local anaesthetics and motor fibers are more resistant

If local anaesthetic are used in weaker concentration it will likely result to sensory blockade without motor paralysis. When concentration is

increased it produces more intense block along with motor paralysis. The susceptibility to local anaesthetic is different to different nerve fibres which depends on:

1. Fiber size: small thin myelinated B fibers propagating sympathetic impulses and non-myelinated C fibers propagating pin prick sensation are blocked easily. Large A fibers which carries motor fibers and proprioceptive fibers has slower onset and shorter duration of block.
2. The degree of myelination and the distance between the nodes of Ranvier: As the distance between the nodes and myelination increases, the resistance to penetration of nerve fibres increases. Functional characteristic: nerve fibres which have single axon are more sensitive to local anaesthetic blockade.

Difference in level of block according to fiber type:

Sympathetic paralysis will extend 2-4 segments above the sensory blockade, and it is the first blockade to occur and last blockade to disappear . Motor blockade is 1-4 segments below the sensory levels.

Sequence of nerve modality block.[11]

Vasomotor block results in dilation of cutaneous blood vessels.

↓

Block of cold temperature fibers.

↓

warmth sensation.

↓

discrimination of temperature .

↓

Slow pain.

↓

Fast pain.

↓

Tactile sensation.

↓

Motor blockade.

↓

Pressure sensation.

↓

Proprioception .

During recovery anaesthesia recedes from head and feet areas toward the point of anaesthetic deposition. i.e., point of anaesthetic deposition is the last part to recover.

Factors determining spread of local anaesthetic solutions within the subarachnoid space.[3]

More than 20 factors have been postulated to alter spinal anesthetic block height

Factors Postulated to Be Related to Spinal Anaesthetic Block Height

Patient characteristics

Age

Height

Weight

Gender

Intra-abdominal pressure

Anatomic configuration of the spinal column

Position

Technique of injection

Site of injection

Direction of injection (needle)

Direction of bevel

Use of barbotage

Rate of injection

Characteristics of spinal fluid

Volume

Pressure (cough, strain, Valsalva maneuver)

Density

Characteristics of the anesthetic solution[12]

Density

Amount (mass)

Concentration

Temperature

Volume

Vasoconstrictors

Factors Influencing Block Height

Controllable Factors

Dose (volume × concentration)

Site of injection along the neuraxis

Baricity of the local anesthetic solution

Posture of the patient

Factors Not Controllable

Volume of cerebrospinal fluid

Density of cerebrospinal fluid

Factors Probably Unrelated to Height of the Spinal Anesthetic Block

Added vasoconstrictor

Coughing, straining, or bearing down (labor)

Barbotage

Rate of injection (except hypobaric)

Needle bevel (except Whitacre needles)

Gender

Weight

ACTION ON SPINAL CORD TRACTS:

The local anaesthetic in subarachnoid space mainly act on the nerve roots and nerve root ganglia with minimal effects on the spinal cord tracts.

INDIRECT EFFECTS:

Indirect effects of spinal anaesthesia are due to paralysis of nerve fibers.

Effect on autonomic system:

Sympathetic system is blocked two segments higher than sensory blockade.

In low spinal (level below T4) the levels blocked are lower thoracic and the entire lumbar sympathetics there will be inactivation of their outflow into superior, middle and inferior splanchnics, hence on splachnique bed and viscera there will be vagal predominance. In high spinal (level above T4) almost all the sympathetic fibers are blocked. Because of these effects many physiological disturbances happen on cardiac, respiratory and gastrointestinal system .

Cardiovascular system

The cardiovascular effects of neuraxial blocks are similar in some ways to the combined use of intravenous α1- and β-adrenergic blockers: decreased heart rate and arterial blood pressure . The sympathectomy that accompanies the techniques depends on the height of the block, with the sympathectomy typically described as extending for two to six dermatomes above the sensory level with spinal anesthesia and at the same level with epidural anesthesia. This sympathectomy causes venous and arterial vasodilation, but because of the large amount of blood in the venous system (approximately 75% of the total volume of blood), the venodilation effect predominates as a result of the limited amount of smooth muscle in venules; in contrast, the vascular smooth muscle on the arterial side of the circulation retains a considerable degree of autonomous tone. After neuraxial block–induced sympathectomy, if normal cardiac output is

maintained, total peripheral resistance should decrease only 15% to 18% in normovolemic healthy patients, even with nearly total sympathectomy. In elderly patients with cardiac disease, systemic vascular resistance may decrease almost 25% after spinal anesthesia, whereas cardiac output decreases only 10%. The heart rate during a high neuraxial block typically decreases as a result of blockade of the cardioaccelerator fibers arising from T1 to T4. The heart rate may decrease because of a fall in right atrial filling, which decreases outflow from intrinsic chronotropic stretch receptors located in the right atrium and great veins.

Blood pressure:

Fall in blood pressure invariably accompanies spinal anaesthesia. The mean brachial artery pressure in low spinal falls by about 21% while in high spinal, it averages 44% fall. The diastolic pressure fall is not remarkable compared to systolic pressure.

Hypotension following spinal anaesthesia is primarily due to paralysis of preganglionic sympathetic fibers that transmits motor impulse to smooth muscles of peripheral vasculature. There are two school of taught to show how sympathetic blockade lowers blood pressure.

- Generalized arterial and arteriolar dilatation causes decrease in peripheral vascular resistance
- Decrease in cardiac output as a result of pooling of blood in the peripheries and decreased venous return to heart.

Hypotension following spinal anaesthesia develops in the first 15-20 min, if left untreated the blood pressure reaches its lowest level in 20-25min. For this reason the first half hour is considered dangerous.

Respiratory system

Tidal volume remains unchanged during high spinal anaesthesia. Vital capacity decreases from 4.05 to 3.73 litres and is due to decrease in expiratory

reserve volume related to paralysis of abdominal muscles necessary for forced exhalation.

The rare respiratory arrest associated with spinal anaesthesia is unrelated to phrenic or inspiratory dysfunction, but rather to hypoperfusion of the respiratory centres in the brainstem. This rare respiratory arrest almost always disappears as soon as pharmacologic and fluid therapies have restored cardiac output and blood pressure. This would not be the case if phrenic paralysis due to high levels of local anaesthetic was the cause of apnea. The physiological consideration related to muscle paralysis with spinal anaesthesia should focus on the expiratory muscles which are important for effective coughing and clearing of intrapulmonary secretions. Loss of the joint sense or position sense in the thoracic cage structures may provoke a sensation of not breathing and has been termed affective dyspnea.

Gastrointestinal function

Nausea and vomiting may be associated with spinal anaesthesia and are primarily related to gastrointestinal hyperperistalsis due to unopposed parasympathetic activity. This gastrointestinal hyperperistalsis has the advantage of providing excellent surgical condition because of contracted gut. Blockade of the thoracolumbar sympathetic outflow at levels up to T5 will promote gastric emptying. Motor activity of the gut is enhanced with an increase in peristaltic and segmental motility and with sphincter relaxation.

Genito urinary function

One aspect of genitourinary function that is of clinical importance is the belief that neuraxial blocks are a frequent cause of urinary retention, which delays discharge of outpatients and necessitates bladder catheterization in inpatients. Lower concentrations of local anesthetic are necessary for paralysis of bladder function than for paralysis of motor nerves to the lower extremities

Fate of injected agents:

The local anaesthetic concentration decreases after it is injected to subarachnoid space. Due to

- Dilution and mixing with CSF
- Diffusion into neural tissue
- Uptake by neural tissues
- Systemic absorption and absorption and elimination by arachnoid villi.

Complications of neuraxial anesthesia.[13]

Adverse or exaggerated physiological responses

Urinary retention

High block

Total spinal anesthesia

Cardiac arrest

Anterior spinal artery syndrome

Horner's syndrome

Complications related to needle placement

Backache

Postdural puncture headache

Diplopia

Tinnitus

Neural injury

Nerve root damage

Spinal cord damage

Cauda equina syndrome

Bleeding

Intraspinal hematoma

Inflammation

Arachnoiditis

Infection

Meningitis

Drug toxicity

Systemic local anesthetic toxicity

Transient neurological symptoms

Cauda equina syndrome

Complications of spinal anaesthesia can also classified as immediate or delayed.

Immediate complications

• Hypotension, bradycardia, cardiac arrest.

•Respiratory impairment

•Difficult spinal puncture

•Traumatic spinal puncture

•Broken needle

Hypotension

Hypotension during spinal anaesthesia is result of central neuraxial blockade, this is due to two major changes in cardiovascular systems. First is sympathetic blockade hence blocks vasoconstrictor fibers of arterioles causing arteriolar dilatation resulting in decrease in peripheral vascular resistance. The second because of dilatation of peripheral veins and venules resulting in pooling of blood. This along with paralysis of skeletal muscle and the loss of milking action of muscles reduces venous return.

Sufficient hydration with fluids prior to spinal anaesthesia will improve venous return inturn increasing cardiac output and blood pressure. To treat hypotension resulting due to spinal anaesthesia.

1. Intravenous fluid: Rapid administration of fluid improves the blood volume and circulation.

2.Administration of oxygen by facemask or nasal catheter will improve oxygen content of blood. This will decrease hypoxia and relieve dyspnea. If with these blood pressure will not improve then need to be supported with vasopressors.

3.Vasopressors that constrict veins more than arterioles are more beneficial for treating the hypotension. Commonly used drugs are ephedrine, mephentermine, and phenylephrine. Ephedrine and mephentermine, have both α and β receptor agonist activity and are potent vasoconstrictor whereas the phenylephrine is an α receptor agonist and more potent arteriolar vasoconstrictor.

4.Head down position: Around $5\text{-}8^0$ of head low will increase venous return to the heart . Resulting in increase in stroke volume and cardiac output with a rise in blood pressure. This has done only after fixation of local anaesthestic.

Respiratory impairment-

This is because of high spinal anaesthetic levels because of blockade of the thoracic and cervical segments, ascending paralysis of the intercostal muscles and diaphragm occurs which is progressive. This leads to respiratory insufficiency and apnea.

Nausea and vomiting are the results of sudden alteration of position along with hypotension. They are attributed to hypoxia or excessive rise in blood pressure following administration of a vasopressor.

Traumatic spinal puncture:

Multiple attempts of spinal tap may lead to trauma to nerves, periosteum of vertebra, discs and shearing of spinal nerves. Bloody tap neutralizes the effect

of local anaesthetics and blood in the sub arachnoid space may cause arachnoiditis.

Late complications.[11]

Post spinal anaesthesia headache was first documented by August Bier in 1899. Typically, PDPH is bilateral, frontal or retroorbital, or occipital and extends into the neck. It may be throbbing or constant and associated with photophobia and nausea. The hallmark of PDPH is its association with body position. The pain is aggravated by sitting or standing and relieved or decreased by lying down flat. The onset of headache is usually 12–72 hours following the procedure; however, it may be seen almost immediately. Untreated, the pain may last weeks, and in rare instances, has required surgical repair. PDPH is believed to result from leakage of CSF from a dural defect and intracranial hypotension. Loss of CSF at a rate faster than it can be produced causes traction on structures supporting the brain, particularly the meninges, dura, and tentorium. Increased traction on blood vessels and cranial nerves may also contribute to the pain. Traction on the cranial nerves may occasionally cause diplopia (usually the sixth cranial nerve) and tinnitus. The incidence of PDPH is strongly related to needle size, needle type, and patient population.

Relation to size of needle: A 25 gauge Quincke needle causes less leakage of CSF than with a 22 gauge Quincke needle.

Type of needle design: Whitacre Pencil point or Greene Conical designed needles – less leakage than needles that have a bevel with a cutting edge

Orientation of bevel: A 22 gauge needle parallel to longitudinal dural fibers produces less leakage than when it is perpendicular to the dural axis.

Angle of approach to dural puncture: less leakage at an angle at 30˚ than at an angle of 60˚ or 90˚.

Contraindications to spinal anaesthesia.[1]

Absolute contraindication is patient refusal. Others include patient's inability to maintain stillness during the needle puncture, exposing the neural structures to unacceptable risk of injury and raised intracranial pressure which predisposes to brainstem herniation.

Relative contraindications include intrinsic and idiopathic coagulapathy, skin or soft tissue infection at the proposed site of needle insertion. Severe hypovolemia, preexisting neurological disease.

PHYSIOLOGY OF PAIN[14]

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage.

The term "nociception" which is derived from noci (Latin for harm or injury) All nociception produces pain, but not all pain results from nociception.

Clinically pain is categorized into (1) Acute pain, which is due to nociception, and (2) Chronic pain which may be due to nociception along with it psychological and behavioural factors also plays a major role.

Pain pathway[14,15].

Pain is carried by a three neuron pathways that transmit noxious stimuli from the peripheral receptors to the cerebral cortex.

Primary afferent neurons are present in the dorsal root ganglia. Each neuron has a single axon that bifurcates, one end goes to the peripheral tissues and the other end to the dorsal horn of the spinal cord. In the dorsal horn, there is a synapse between the primary afferent neuron and a second order neuron. The axons of second order neuron crosses the midline and ascend in the contralateral spinothalamic tract and reaches the thalamus. In thalamus there is synapse between second order neuron and third order neuron. Third order

neuron sends projections through the internal capsule and corona radiata to the postcentral gyrus of the cerebral cortex.

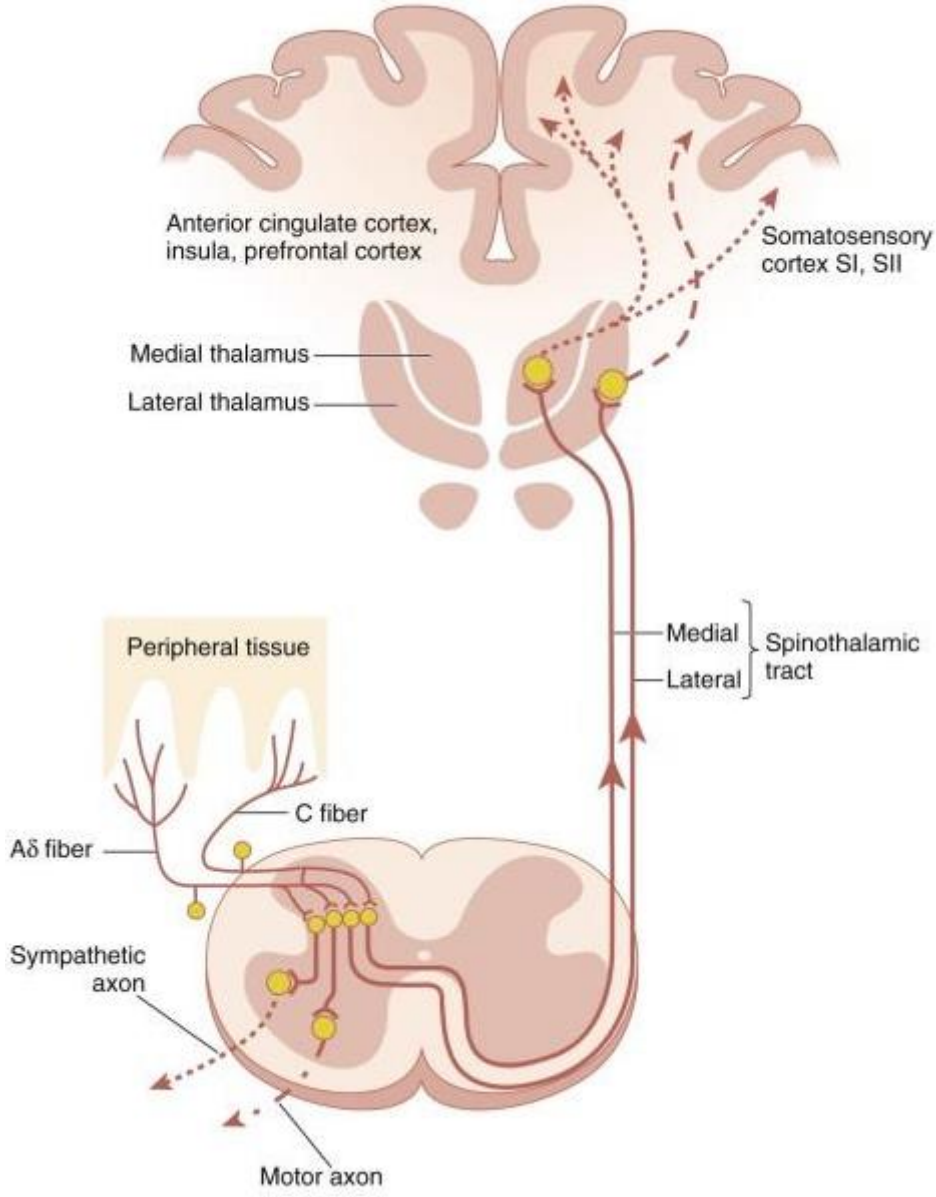

FIGURE 12: PAIN PATHWAY

PHYSIOLOGY OF NOCICEPTION

1. Nociceptors

Nociceptors are characterized by a high threshold for activation and encode the intensity of stimulation by increasing their discharge rates in a graded fashion. Following repeated stimulation, they characteristically display delayed

adaptation, sensitization, and after discharges.

Noxious sensations can often be broken down into two components: a fast, sharp, and well-localized sensation ("first pain"), which is conducted with a short latency (0.1 s) by Aδ fibers (tested by pinprick); and a duller, slower onset, and often poorly localized sensation ("second pain"), which is conducted by C fibers.

Most nociceptors are free nerve endings and different nociceptor include(1) mechanonociceptors, which respond to pinch and pinprick, (2) silent nociceptors, which respond only in the presence of inflammation, and (3) polymodal mechanoheat nociceptors.

Cutaneous Nociceptors

Nociceptors are present in both somatic and visceral tissues. Primary afferent neurons reach tissues by traveling along spinal somatic, sympathetic, or parasympathetic nerves. Somatic nociceptors include those in skin (cutaneous) and deep tissues (muscle, tendons fascia, and bone), whereas visceral nociceptors include those in internal organs.

Visceral Nociceptors

Visceral organs are generally insensitive tissues that mostly contain silent nociceptors. Some organs appear to have specific nociceptors, such as the heart, lung, testis, and bile ducts. Most other organs, such as the intestines, are innervated by polymodal nociceptors that respond to smooth muscle spasm, ischemia, and inflammation (alogens). A few organs, such as the brain, lack nociceptors altogether; however, the brain's meningeal coverings do contain nociceptors.

Like somatic nociceptors, those in the viscera are the free nerve endings of primary afferent neurons whose cell bodies lie in the dorsal horn. Afferent activity from these neurons enters the spinal cord between TI and L2. Nociceptive C fibers from the esophagus, larynx, and trachea travel with the vagus nerve to enter the nucleus solitarius in the brain stem. Afferent pain fibers

from the bladder, prostate, rectum, cervix and urethra, and genitalia are transmitted into the spinal cord via parasympathetic nerves at the level of the S2-S4 nerve roots.

II. Chemical mediators of pain

Several neuropeptides and excitatory amino acids function as neurotransmitters for afferent neurons sub serving pain. Many of the afferent neurons contain more than one neurotransmitters, which are simultaneously co-released. The most important of these peptides are substance P and calcitonin gene-related peptide. Glutamate is the most important excitatory amino acid.

Substance P is an 11 amino acid peptide that is synthesized and released by the first order neurons both peripherally and in the dorsal horn. It facilitates transmission in pain pathways via NK-1 receptor activation.

In the periphery, substance P neurons send collaterals that are closely associated with blood vessels, sweat glands, hair follicles and mast cells in the dermis. Substance P sensitizes nociceptors, degranulates histamine from mast cells and serotonin (5-HT) from platelets, and is a potent vasodilator and a chemoattractant for leukocytes.

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PHARMACOLOGY

Local anaesthetic drugs:

Local anaesthetics have one aromatic lipophilic part (benzene ring) and one hydrophilic part (quarternary ring) connected by an intermediate ring which can be either an ester (-COO-) or an amide (-NHCO-). The lipophilic portion is essential for anaesthetic activity. If butyl group is added to the piperidine nitrogen of mepivacaine it results in bupivacaine. Hence bupivacaine is 35 times more lipid soluble and has a higher potency and three to four times longer duration of action than that of mepivacaine.

BUPIVACAINE[16,17,18,19]

Structural Formula

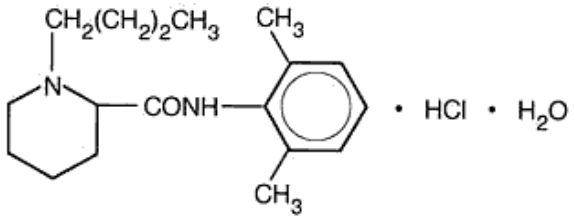


Figure 13: Chemical structure of bupivacaine

Chemical name: l-n-butyl-DL-piperidine-2-carboxylic acid-2, 6 dimethylanilide hydrochloride.

Bupivacaine hydrochloride is an amide type of local anaesthetic drug, which was synthesized by Ekenstam AF in 1957 and used clinically in 1963.

Physicochemical properties

Molecular weight	- 288 (base)
	325 (chloride salt)
pKa	- 8.1
Plasma protein binding	- 95%
Elimination half life	- 2.7 hr
Maximum dose	- 2mg/kg

Solubility: The base is sparingly soluble, but the hydrochloride is readily soluble in water.

Stability and sterilization: Bupivacaine is highly stable and can withstand repeated autoclaving.

Melting point: 258˚C.

Potency: Bupivacaine is around three to four times more potent than lidocaine. Bupivacaine is available as racemic mixture of the enantiomer for clinical use.

Mechanism of action

Local anaesthetics blocks transmission of nerve impulses (conduction blockade) by inhibiting entry of sodium ions through sodium channels in nerve membranes. Failure of sodium ion channel permeability slows the rate of depolarization hence threshold potential is not reached and an action potential is not propagated.

Pharmacokinetics

Local anaesthetics are weak bases they have pKa values above physiologic pH. As a result <50% of the local anaesthetic exists in a non-ionized lipid soluble form at physiologic pH.

Pharmacodynamics:

The drug has slower onset but longest duration of action compared to other local anaesthetics. The degree of motor block increases as the concentration of local anaesthetic increases.

Dosage for spinal anaesthesia:

Weight in kgs	0-5 kg	5-15 kg	>15kg
Bupivacaine 0.5% hyperbaric dose	0.5mg/kg	0.4mg/kg	0.3mg/kg

Table 1: Dosage of bupivacaine for spinal anaesthesia

The dosage should not exceed more than 150mg (30ml of 0.5% solution) at one time or in 4 hour period.

Bupivacaine is available in injectable form in concentrations of 0.25%, 0.5%, and 0.75%.

Peripheral nerve block: 0.25-0.5% concentration, 5-20ml for a dose of 12.5-50mg acts for around 180-360 min.

Caudal block:0.25-0.5% concentration 30-50 ml for a maximum of 225mg resulting in duration of 360-720minutes.

Epidural block: 0.25-0.75% concentration. 15-30ml for a dose of 37.5-225mg resulting in block duration of 180-300 minutes.

Spinal block: 0.5% concentration. 3-4ml for a dose of 15-20mg resulting in block duration of 75-150 minutes. 0.75% concentration, 2-3 ml for a dose of 15-22.5 mg resulting in block duration of 75-150min.

These doses can be repeated in 3-4 hours, the maximum dose being 400mg in 24 hours. The addition of vasoconstrictor has a minimal increase in duration of action. However, the chances of systemic toxicity is reduced as peak blood level is markedly reduced.

Absorption and distribution

Absorption of local anaesthetic into the systemic circulation is affected by the site and dosage of injection , use of epinephrine, and pharmacology of the drug. The final plasma concentration of a local anaesthetic is determined by the rate of tissue distribution and the rate of clearance of the drug.

Lipid solubility affects the redistribution as well as local anaesthetic potency. The local anaesthetic is eliminated from the body by metabolism and excretion. Protein binding of local anaesthetic will effect their distribution and excretion.

For bupivacaine, the first pass pulmonary extraction is dose dependent, suggesting that the uptake process becomes saturated rapidly.

Metabolism

They undergo metabolism by microsomal enzymes primarily in liver. Bupivacaine undergo the slowest metabolism among the amide local anaesthetics. Bupivacaine metabolism include aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation.

Systemic toxicity

Systemic toxicity of a local anaesthetic is due to an increased plasma levels of the drug. Plasma levels depends on the rate of drug entering the systemic circulation and clearance by metabolism.

Central Nervous System toxicity

Early signs- tinnitus, light headedness, confusion and numbness. Intermediate signs- shivering, muscle twitching, tremors, and tonic clonic convulsions.

Late signs- unconsciousness, generalized CNS depression and respiratory arrest.Skeletal muscle twitching is usually first seen in the face and extremities and signals the imminence of tonic-clonic seizures. Drowsiness before the onset of seizures. Seizure is followed by CNS depression which may be accompanied by hypotension and apnea.

The plasma levels associated with seizures is 4.5 to 5.5 µg/ml.

Selective cardiac toxicity

If bupivacaine is accidentally injected intravenously, the protein binding sites (alpha 1 acid glycoprotein and albumin) are quickly saturated, leaving a significant amount of unbound drug for diffusion into the conducting tissue of the heart. This may cause precipitous hypotension, cardiac arrhythmias and heart block.

Cardiotoxic plasma levels of bupivacaine is 8 to 10 µg/ml. if the patient is on drugs which inhibit cardiac impulse propagation such as betablockers, calcium channel blockers, digitalis then threshold for cardiac toxicity is decreased.

Bupivacaine slows conduction of the myocardial action potential showed on the electrocardiogram as prolongation of the P-R interval and QRS intervals and reentry ventricular cardiac arrhythmias. The R enantiomer is more toxic than the S enantiomer.

Hepatotoxicity

There is association between increased liver transaminase enzymes when bupivacaine is injected to epidural space intermittently or continuously.

FENTANYL

Structural formula

Figure 14: chemical structure of fentanyl.

Chemical name

N-(1-(2-phenylethyl)-4-piperidinyl)-N-phenylpropanamide

Physicochemical properties

Molecular weight	- 341.51g/mol
Plasma protein binding	- 80-85%
Elimination half life	- iv: 10-20 min(T1/2β)
	2-4 hours (T1/2γ)

History

In the mid-1990s, fentanyl was introduced for palliative use with the fentanyl patch, followed in the next decade by the introduction of the

fentanyl lollipop, dissolving tablets, and sublingual spray which are absorbed through the tissues inside the mouth. As of 2012, fentanyl was the most widely used synthetic opioid in medicine.

Mechanism of Action

A. Opioids act as agonists at specific opioid receptors at presynaptic and postsynaptic sites in the central nervous system (mainly the brainstem and spinal cord) as well as in the periphery.

B. These opioid receptors normally are activated by three endogenous peptide opioid receptor ligands known as enkephalins, endorphins, and dynorphins. (Opioids mimic the actions of these endogenous ligands by binding to opioid receptors, resulting in activation of pain-modulating [antinociceptive] systems.)

1. The principal effect of opioid receptor activation is a decrease in neurotransmission that occurs largely by presynaptic inhibition of neurotransmitter release (acetylcholine, dopamine, norepinephrine, substance P).

2. The intracellular biochemical events initiated by occupation of opioid receptors with an opioid agonist are characterized by increased potassium conductance (leading to hyperpolarization), calcium channel inactivation, or both, which produce an immediate decrease in neurotransmitter release.

Opioid Receptors

A. Receptors are principally responsible for supraspinal and spinal analgesia.

B. Respiratory depression characteristic of receptor activation is less prominent with receptor activation, although dysphoria and diuresis may accompany activation of these receptors.

1.Receptor–mediated analgesia may be less effective for high-intensity painful stimulation than opioid–mediated.

2. Opioid agonist–antagonists often act principally on receptors.

Pharmacokinetics

a. A single dose of fentanyl administered IV has a more rapid onset and shorter duration of action than morphine. Despite the clinical impression that fentanyl produces a rapid onset, there is a distinct time lag between the peak plasma fentanyl concentration and peak slowing on the electroencephalogram (EEG) (reflects the effect-site equilibration time between blood and the brain for fentanyl, which is 6.4 minutes). The greater potency and more rapid onset of action reflect the across the blood–brain barrier.

b. The lungs also serve as a large inactive storage site, with an estimated 75% of the initial fentanyl dose undergoing first-pass pulmonary uptake. (This nonrespiratory function of the lungs limits the initial amount of drug that reaches the systemic circulation and may play an important role in determining the pharmacokinetic profile of fentanyl.)

Metabolism.

Fentanyl is extensively metabolized by N-demethylation and the pharmacologic activity of fentanyl metabolites is believed to be minimal.

Elimination Half-Time

a. Despite the clinical impression that fentanyl has a short duration of action, its elimination half-time is longer than that for morphine . This longer elimination half-time reflects a larger volume of distribution (Vd) of fentanyl due to its greater lipid solubility and thus more rapid passage into highly vascular tissues compared with the less lipid-soluble morphine (more than 80% of the injected dose leaves the plasma in 5 minutes).

b. The plasma concentrations of fentanyl are maintained by slow reuptake from inactive tissue sites, which accounts for persistent drug effects that parallel the prolonged elimination half-time.

c. A prolonged elimination half-time for fentanyl in elderly patients is due to decreased clearance of the opioid because Vd is not changed in comparison with
younger adults.

Context-Sensitive Half-Time[20].

As the duration of continuous infusion of fentanyl increases beyond about 2 hours, the context-sensitive half-time of this opioid becomes greater than sufentanil . This reflects saturation of inactive tissue sites with fentanyl during prolonged infusions and return of the opioid from peripheral compartments to the plasma. This tissue reservoir of fentanyl replaces fentanyl eliminated by hepatic metabolism so as to slow the rate of decrease in the plasma concentration
of fentanyl when the infusion is discontinued.

Clinical Uses and dosage

- Analgesia (1–2 g/kg IV)
- Adjuvant to inhaled anesthetics to blunt the response to direct laryngoscopy or sudden changes in the level of surgical stimulation (2–20 g/kg IV) (consider effect-site equilibration time)
- Decrease doses of inhaled anesthetics needed to blunt sympathetic nervous system responses to surgical stimulation (1.5–3 g/kg IV 5 min before induction of anesthesia)
- Produce surgical anesthesia (50–150g/kg IV)
- Analgesia for early labor (25g intrathecal)
- Preoperative medication (transmucosal)
- Postoperative analgesia (transdermal patch)

  Side effects

  Side effects of fentanyl resemble those of morphine (persistent or recurrent depression of ventilation).

Pruritus

Pruritus induced by neuraxial opioids is likely due to cephalad migration of the opioid in CSF and subsequent interaction with opioid receptors in the trigeminal nucleus.

Cardiovascular Effects.

Unlike morphine, fentanyl, even in large doses (50g/kg IV), does not evoke the release of histamine. Bradycardia is more prominent with fentanyl than morphine and may lead to occasional decreases in blood pressure and cardiac output.

Seizure Activity. In the absence of EEG evidence of seizure activity, it is difficult to distinguish opioid-induced skeletal muscle rigidity or myoclonus from seizure activity.

Intracranial Pressure. Administration of fentanyl and sufentanil to head injury patients has been associated with modest increases (6 to 9 mm Hg) in ICP despite maintenance of an unchanged $Paco_2$.

Depression of ventilation

This is the most serious side effect of neuraxial (may occur within minutes of administration or may be delayed for hours). The incidence of ventilatory depression requiring intervention after conventional doses of neuraxial opioids is about 1%, which is the same as that after conventional doses of IV or IM opioids.

a. Early depression of ventilation occurs within 2 hours of neuraxial injection of the opioid, whereas delayed depression of ventilation occurs more than 2 hours after neuraxial opioid administration and reflects cephalad migration of the opioid in the CSF and subsequent interaction with opioid receptors located in the ventral medulla.

b. Factors that increase the risk of delayed depression of ventilation, especially concomitant use of any IV opioid or sedative, must be considered in determining the dose of neuraxial opioid .

c. Pulse oximetry reliably detects opioid-induced arterial hypoxemia, and supplemental oxygen (2 L/min) is an effective treatment. The most reliable clinical sign of depression of ventilation is a depressed level of consciousness, possibly caused by hypercarbia.

Sedation

After administration of neuraxial opioids appears to be dose related and occurs with all opioids but is most commonly associated with the use of sufentanil. When sedation occurs with neuraxial opioids, depression of ventilation must be considered.

Central Nervous System Excitation

a. Tonic skeletal muscle rigidity resembling seizure activity is a well-known side effect of large IV doses of opioids, but this response is rarely observed after neuraxial administration.

b. Cephalad migration of the opioid in CSF and subsequent interaction with nonopioid receptors in the brainstem or basal ganglia is the most likely explanation for opioid-induced CNS excitation.

NALBUPHINE

Structural formula

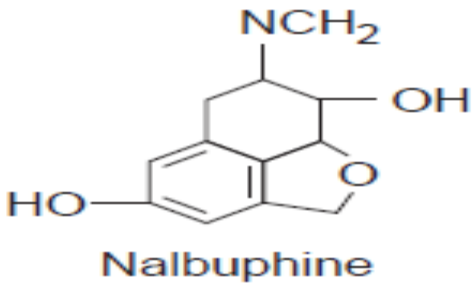


Figure 15: chemical structure of nalbuphine

Chemical name

(-)-17(cyclobutylmethyl)-4,5α-epoxymorphinan-3,6α,14-triol

Properties

Nalbuphine is available in ampules in a sterile, paraben-free formulation in two concentrations, 10 mg and 20 mg of nalbuphine hydrochloride per mL. One mL of each strength contains 0.94% sodium citrate hydrous, and 1.26% citric acid anhydrous. The 10 mg/mL strength contains 0.2% sodium chloride. An intramuscular dose of 10 mg nalbuphine is equianalgesic to 10 mg morphine, with similar onset and duration of analgesic and subjective effects.[21]

CLINICAL PHARMACOLOGY

Mechanism of Action

Nalbuphine is an agonist at kappa opioid receptors and an antagonist at mu opioid receptors.

Pharmacodynamics

Nalbuphine is a potent analgesic. Its analgesic potency is essentially equivalent to that of morphine on a milligram basis up to a dosage of approximately 30 mg.

The opioid antagonist activity of Nalbuphine is one-fourth as potent as nalorphine and 10 times that of pentazocine. Nalbuphine may produce the same degree of respiratory depression as equianalgesic doses of morphine.

However, Nalbuphine exhibits a ceiling effect such that increase in dose greater than 30 mg do not produce further respiratory depression in the absence of other CNS active medications affecting respiration.

Nalbuphine by itself has potent opioid antagonist activity at doses equal to or lower than its analgesic dose. When administered following or concurrent with mu agonist opioid analgesics (e.g., morphine, oxymorphone, fentanyl), Nalbuphine may partially reverse or block opioid-induced respiratory depression from the mu agonist analgesic.

Nalbuphine may precipitate withdrawal in patients dependent on opioid drugs. Nalbuphine should be used with caution in patients who have been receiving mu opioid analgesics on a regular basis.

Effects on the Central Nervous System

- Nalbuphine produces respiratory depression by direct action on brain stem respiratory centers.
- The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.
- There may be a ceiling effect for the respiratory depression caused by nalbuphine.
- Although a mixed agonist/antagonist, the respiratory depressant effects of nalbuphine can be reversed by naloxone.
- Nalbuphine causes miosis, even in total darkness.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

- Nalbuphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum

Effects on the Cardiovascular System

- During use of nalbuphine during anesthesia, a higher incidence of bradycardia has been reported in patients who did not receive atropine pre-operatively.

Pharmacokinetics

- The onset of action of Nalbuphine occurs within 2 to 3 minutes after intravenous administration, and in less than 15 minutes following subcutaneous or intramuscular injection.

- The plasma half-life of Nalbuphine is 5 hours, and in clinical studies the duration of analgesic activity has been reported to range from 3 to 6 hours.
- The metabolic pathway for nalbuphine has not been defined, but is likely hepatic.

Dosage

- Injectable solution available: 10mg/ml, 20mg/ml
- Anaesthesia supplement: 0.3-3mg/kg IV over 10-15 min then 0.25-0.5mg/kg as needed
- Intrathecal as adjuvant: 0.4mg without increasing the side effects[30].

Side effects

The most frequent side effect in patients treated with nalbuphine was sedation.

- CNS effects: Nervousness, depression, restlessness, crying, euphoria, flushing, hostility, unusual dreams, confusion, faintness, hallucinations, dysphoria, feeling of heaviness, numbness, tingling, unreality.
- Cardiovascular: Hypertension, hypotension, bradycardia, tachycardia, pulmonary edema.
- Gastrointestinal: Cramps, dyspepsia, bitter taste.
- Respiration: Depression, dyspnea, asthma.
- Dermatological: Itching, burning, urticaria.

REVIEW OF LITERATURE

History of review of literature[1,22]

Cerebrospinal fluid was discovered by Domenico Cotugno in 1764 and description of its flow was given by F. Magendie in 1825.

Alexander wood introduced hollow needle and glass syringe in 1853. Cocaine was first isolated from erythroxylon coca in 1860, its analgesic properties were first described in 1862 by Schroff and introduced in medicine as local analgesic for ophthalmological procedures by Carl Koller in 1884.

J. Leonard Corning in 1885, a neurologist in New York injected cocaine into the subarachnoid space by accidently piercing duramater and obtained loss of sensation in legs and perineum

Heinrich Iraneus Quincke of Germany standardized lumbar puncture as a simple procedure in 1891. In the same year Essex Wynter described lumbar puncture in England.

On 16th of August 1898 August Bier performed the first planned spinal anaesthesia in man. 3 ml of 0.5% cocaine was injected into the subarachnoid space of a 34yr old laborer for the operation on the lower limb. He and his assistant injected cocaine into each other's theca after using it in 6 other people.

Heinrich Braun, a German surgeon used procaine for operation under spinal anaesthesia in 1905. He also reported the use of intrathecal epinephrine to prolong the duration of spinal anaesthesia. In 1945 Prickett and his associates published a report on neurological safety of intrathecal epinephrine to prolong the duration of spinal anaesthesia.

Post spinal headache was a common problem in first practitioners and their patients. Study by Leroy Vandam and Robert Dripps confirmed Bier's suggestion that CSF leakage through dural rent was the causative

factor. Use of small bore needle has reduced the incidence of post spinal headache. Epidural blood patch an innovative treatment for dural puncture headache was suggested by James B Gormely in 1960 and further described by Anthony J Digiovanni and Burdett S Dunbar in 1970.

HISTORY OF SPINAL ANAESTHESIS:

1885- J. Leonard Corning used cocaine in spinal anaesthesia for pain relief

1891- Heinrich Iraneus Quincke standardized lumbar puncture

1899- August Bier first cocaine spinal anaesthesia in 6 patients

1905-Einhorn- introduced procaine for spinal anaesthesia

H. Braun-firstused Procaine spinal anaesthesia

1907- Barker- hyperbaric procaine using glucose, hypobaric procaine using alcohol, factors involved in spread of local anaesthetics.

1930-jones – Dibucaine spinal anaesthesia

1935-Sise- Tetracaine spinal anaesthesia

1940- Lemmon- continuous spinal anaesthesia

1943- Lofgren introduced lignocaine

1945-Prickett- report on neurological safety of intrathecal epinephrine

1954- Dripps and Vandam- study demonstrating absence of neurological effects of spinal

1957- Ekenstam introduced bupivacaine

1965- Reemergence of use of spinal anaesthesia

1971-Demonstartion of existence of opioid receptors by A. Goldstein

1973-Demonstration of opioid receptors in brain

Pert and Synder isolated opioid receptors

1976-Demonstartion of opioid receptors in spinal cord

1979-First intrathecal use of opioids in man.

1980- Effect of cholinesterase inhibitors in subarachnoid space in animals.

1994- First human study published on the effects of cholinesterse inhibitors in SA.

REVIEW OF CLINICAL STUDIES:

Bogra J, Arora N, Srivastava P[23] in 2005 did a study on Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anaesthesia for cesarean section and concluded that Spinal anaesthesia in obstetric patients needs proper dosage calculations. Because of the synergistic, effect of fentanyl and bupivacaine in spinal anaesthesia, bupivacaine dose can be reduced and also its harmful effects.

Ben-David B, Solomon E, Levin H, Admoni H, Goldik Z [24]**,** in 1997 did a study on lntrathecal Fentanyl With Small-Dose Dilute Bupivacaine:Better Anesthesia Without Prolonging Recovery and concluded that because of the neurotoxicity of lidocaine there was a search for an alternative for spinal anaestheasia . They studied 50 patients posted for ambulatory surgical arthroscopy and studied that small-dose of bupivacaine was inadequate for the procedure, the addition of fentanyl makes it reliable.

Nelson KE, Rauch T, Terebuh V, D'Angelo R.[25]did a study in 2002 A Comparison of Intrathecal Fentanyl and Sufentanil for Labor Analgesia and concluded that : The potency of sufentanil to fentanyl injected intrathecally is 4.4:1 for labor analgesia. 8g sufentanil when used alone intrathecally for labour analgesia produces analgesia which lasts around 25 min longer than 36g of sole intrathecal fentanyl, without any statistically significant increase in side effects.

Kumar B, Williams A, Liddle D, Verghese M[26] Compared intrathecal bupivacaine-fentanyl and bupivacaine-butorphanol mixtures for lower limb orthopedic procedures and found that intrathecal bupivacaine-butorphanol mixture had longer duration of sensory blockade and better analgesia than intrathecal fentanyl-bupivacaine .

Weigl W, Bierylo A, Wielgus M, Krzemień-Wiczyńska S, Szymusik I, Kolacz M, Dabrowski MJ [27] studied the analgesic efficacy of intrathecal fentanyl as analgesic demand was highest immediately after cesarean section which was first 12 hours after spinal anaesthesia. As they used intrathecal fentanyl had effective intraoperative analgesia and reduced postoperative opioid consumption without any untoward consequences for mother and neonate.

Jagtap S, Chhabra A, Dawoodi S, Jain A [28] compared intrathecal ropivacaine-fentanyl with bupivacaine-fentanyl for lower limb orthopaedic surgery and conclude that intrathecal ropivacaine fentanyl sensory blockade similar to bupivacaine-fentanyl but shorter duration of motor block which helped in early ambulation and voiding.

Kilickaya R, Orak Y, Balci MA, Balci F, Unal I[29] compared intrathecal fentanyl and morphine in Elective Total Knee Replacement Surgery and concluded that fentanyl group had lesser first analgesic requirement time compared to morphine.

Mukherjee A, Pal A, Agrawal J, Mehrotra A, Dawar N [30] in 2014 did a study on different doses (0.2, 0.4 and 0.8 mg) of intrathecal nalbuphine as an

adjuvant for spinal anaesthesia in orthopedic lower limb surgeries to find the effective dose. Analgesia was prolonged in groups receiving 0.4 mg nalbuphine and 0.8 mg nalbuphine ($P<0.05$), and the incidence of side-effects was significantly higher in group receiving 0.8 mg nalbuphine ($P<0.05$) compared with the other groups. Hence concluded that Nalbuphine used intrathecally , in a dose of 0.4 mg, increases postoperative analgesia without increased side-effects.

Gomaa HM, Mohamed NN, Zoheira HA, Mohamad SA [31] compared two groups in one group received intrathecal nalbuphine 0.8mg with bupivacaine and the other group received 25mcg of fentanyl with bupivacaine intrathecally in cesarean section and studied postoperative analgesic efficacy and concluded that intrathecal nalbuphine 0.8 mg and intrathecal fentanyl 25 μg combined with 10 mg bupivacaine both results good intra-operative and early post-operative analgesia in cesarean section

Chatrath V, Attri JP, Bala A, Khetarpal R, Ahuja D, Kaur S [32] compared nalbuphine and tramadol for epidural in orthopedic surgeries and concluded that the group receiving nalbuphine with bupivacaine had better postoperative analgesia and better patient satisfaction score than tramadol.

Manjula R, Chaithra G, Amit G, Upakara SR, Aditi V P [33]Compared Bupivacaine with Nalbuphine and Bupivacaine alone for Post-Operative Analgesia in SubArachniod Block for Lower Limb Surgeries in 2017, they concluded that addition of nalbuphine hydrochloride in dosage of 1mg to intrathecal bupivacaine 0.5% prolongs the duration of sensory blockade and also gives excellent and prolonged duration of post operative analgesia,

increases the duration of the 2 segment regression with stable haemodynamics without any significant side effects in patients undergoing lower limb orthopaedic surgeries.

Shakooh S, Bhosle P [34] studied nalbuphine intrathecally as adjuvant for postoperative analgesia and conclude that nalbuphine as an adjuvant to spinal anaesthesia decreases time for onset of sensory and motor block, increases the duration of sensory and motor blockade, gives effective postoperative analgesia and increases the time for first rescue analgesia, provides desirable sedation intraoperatively and does not result in any major adverse effects.

Sapate M, Sahu P, Thatte WS, Dubey R [35]**,** did A randomized, double blind, control study of the effects of adding nalbuphine to spinal bupivacaine for lower abdominal surgeries in elderly patients they had 2 groups in the study Group I (Study group): Inj. bupivacaine hyperbaric 0.5% 3 ml + inj. nalbupine 0.5 mg intrathecally

Group II (Control group): Inj. bupivacaine hyperbaric 0.5% 3 ml + inj. normal saline 0.5 ml intrathecally and found that intrathecal nalbuphine added to hyperbaric bupivacaine gives better quality of block as than bupivacaine alone. It also increases duration of postoperative analgesia for almost 8-9 hours when used as adjuvant to bupivacaine without any significant adverse effects .

Saleh RH, Yousef MF, Nassar HM, Younes TF [36] studied in 2015 effect of nalbuphine as an adjuvant on levobupivacaine for caudal analgesia in children. They included children of 1-9 years and had two groups

Group L: caudal block was given with levobupivacaine 0.25% at 1ml/kg after induction of GA

Group L+N: caudal block was given with levobupivacaine 0.25% at 1ml/kg and nalbuphine at 0.1ml/kg after induction of general anaesthesia

they found that mean time for first rescue analgesia was 5.9±1 hour in group L And in group L+N it was11.2±1.6 hour and they concluded that nalbuphine is safe in pediatric surgeries nalbuphine may cause early postoperative sedation, yet without respiratory depression.

Khan FA, Hameedullah[37]. Compared fentanyl and nalbuphine in total intravenous anaesthesia (TIVA). They found that fentanyl had better haemodynamic stability and better analgesia than nalbuphine when used in TIVA with propofol in laparoscopic cholecystectomy cases. In their study the recovery profile with both drugs was similar. Lesser number of patients required analgesia in the recovery in the nalbuphine group

Gupta K, Rastogi B, Gupta PK, Singh I, Bansal M, Tyagi V [38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016 and concluded that nalbuphine 2mg with 17.5 mg of 0.5% hyperbaric bupivacaine for subarachnoid blockade was more efficient than fentanyl for extending the duration of sensory motor block and enhancing the postoperative analgesia and adverse effects were negligible.

Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A[39] did a comparative study on analgesic efficacy of intrathecal nalbuphine and fentanyl as an adjuvant in Lower Limb Orthopaedic Surgery in 2017 and showed that there was no significant advantage of intrathecal fentanyl or 1.6 mg nalbuphine over low dose 0.8 mg nalbuphine.

Singh N, Kumar S, Tyagi RK [40]did a comparative study on Intrathecal Nalbuphine Versus Intrathecal Fentanyl Added to 0.5% Hyperbaric Bupivacaine For Perioperative Anaesthesia And Analgesia in Lower Abdominal Surgeries concluded that the addition of Nalbuphine to intrathecal bupivacaine has prolonged the duration of sensory block and post-operative analgesia and requirement of analgesics in post-operative period is also decreased without increasing the side effects or complication. Addition of Fentanyl has the same effect but lesser than nalbuphine.

Bisht S, Rashmi D [41]**,** compared intrathecal fentanyl and nalbuphine in total abdominal hysterectomies and found that the time to onset and peak sensory level is longer with nalbuphine as intrathecal adjuvant than fentanyl, two segments regression of sensory blockade and the postoperative analgesia time is longer with nalbuphine. So, nalbuphine is a good adjuvant in spinal anesthesia and has an advantage in centers without narcotics license.

Ben-David B, Miller G, Gavriel R, Gurevitch A [42] did a study in 2000 Minidose Bupivacaine–Fentanyl Spinal Anesthesia for Surgical Repair of Hip Fracture in the Aged concluded that A small dose of 4 mg bupivacaine along with 20 mg fentanyl gives spinal anesthesia for repair of hip fracture in elderly. The minidose combination resulted dramatically low hypotension compared to 10 mg bupivacaine.

Liu S, Chiu AA, Carpenter RL, Mulroy MF, Allen HW, Neal JM et al[43] studied that after adding 20 mcg of fentanyl to lidocaine in spinal anesthesia improved the duration of sensory blockade without prolonging the time of recovery of motor functioning or time of micturition.

MATERIALS & METHODS

MATERIAL AND METHODS:

SOURCE OF DATA:

- This is a randomized double blind prospective study.
- 124 patients admitted for lower abdominal and lower limb surgeries admitted under surgery, orthopedics, Obstetrics and gynecology , plastic surgery and urology done under spinal anaesthesia at R. L. Jalappa Hospital and Research Centre, Tamaka , Kolar, during the period of January 2016 to January 2017.

METHOD OF COLLECTION OF DATA:

Inclusion criteria:

- Patients belonging to ASA grade I and II
- Age 18-55yrs
- Weight- more than 45 kg less than100 kg
- Height- more than 150cm

Exclusion criteria:

- Patients suffering from cardiac arrhythmias, heart blocks and bradycardia.
- Patients with known allergy to test drug.
- Patients with gross spinal abnormality, localised skin sepsis, haemorrhagic diathesis, neurological involvement/diseases.
- Patients with head injury, raised intra cranial pressure.
- Patients who are haemodynamically unstable.

Sampling Procedure:

After obtaining informed consent, 124 patients were randomly divided into two groups of 62 each. Randomization was done by computer generated table.

Group N: Hyperbaric bupivacaine with nalbuphine (300mcg).

Group C: Hyperbaric bupivacaine with fentanyl (25mcg).

Patients were examined a day before surgery. They were kept fasting overnight after 10:00pm and will receive tab. Rantidine 150mg orally and tab. Alprazolam 0.5mg orally as premedication at night before surgery and at 6:00am with sip of water in the morning on the day of surgery.

Patients were preloaded with 5ml/kg ringer lactate solution after securing IV access with 18G cannula.

After the patient was shifted to operation theatre, pulse rate, blood pressure, ECG and SPO2 were monitored.

Under all aseptic precautions after putting patient in left lateral position, using 25G quincke spinal needle spinal block was performed at L3-L4 interspace through a midline approach and patient put to supine position. Patients in group C received 3ml of 0.5% hyperbaric bupivacaine with 25mcg of fentanyl . Patients in group N received 3ml of hyperbaric 0.5% bupivacaine with 300mcg of nalbuphine. Total volume made up to 3.5 ml with distilled water.

The time of intrathecal injection is considered as 0 and the following parameters were observed.

Parameters observed:

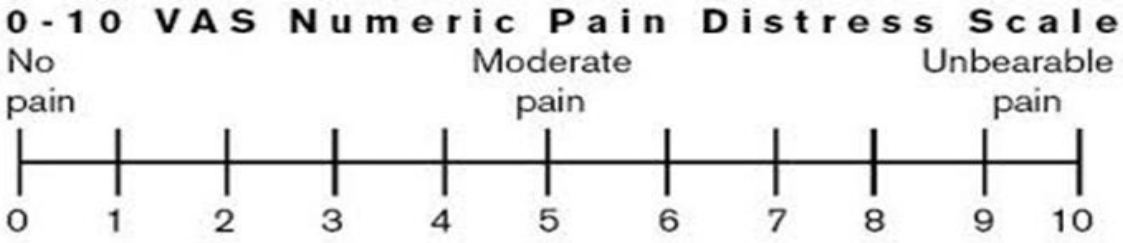
Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, Spo2 and respiratory rate were recorded every

2min for 10 min and then every 10 mins throughout the intra operative period and at the end of surgery.

1) Time of onset of sensory blockade.
2) The height of sensory blockade.
3) Motor blockade as per Bromage scale.
4) Total duration of sensory blockade & motor blockade
5) Quality of analgesia.(VAS score)
6) Two segment sensory regression time.
7) Time to first rescue analgesic & number of rescue analgesics in 24 hours
8) Adverse effects if any.

- The vital signs were recorded at time 0, 2min, 5min and then every 10 min for first hour and half hourly till the end of surgery.
- **Onset of sensory blockade**: Defined as time taken from the completion of injection of the study drug till the patient does not feel the pin prick at T10 level.
- **Onset of motor blockade**: Defined as time taken for complete inability to flex both lower limbs at hip joint.
- **Duration of sensory blockade**: Defined as time taken from the onset of sensory blockade till the two segment regression time.
- **Duration of motor blockade**: Defined as time taken from onset of motor blockade to the time when the patient is able to lift the extended leg.
- **Duration of effective analgesia:** Defined as time taken from the completion of injection of the study drug till the patient complains of pain.
- **Rescue analgesia**: Defined as time taken from the completion of injection of the study drug till the patient complains of pain.

- **Hypotension:**
    - Defined as reduction of systolic blood pressure more than 30% below baseline value and it will be treated with increased rate of intravenous fluids and if needed injection mephenteramine 6mg increments given IV.
- **Bradycardia:**
    - Defined as heart rate less than 60/minute and will be treated with injection atropine 0.6mg IV.
- Quality of analgesia was assessed by visual analogue scale.
- Visual analogue scale for pain:
    - 0 No pain
    - 1-3 Mild pain
    - 4-6 Moderate pain
    - 7-10 Severe pain



Motor blockade was assessed using modified Bromage scale.

Modified Bromage scale: Grade Definition

0- Full flexion of knee and feet.

1- Inability to raise extended leg; able to move knee and feet

2- Inability to raise extended leg and move knee; able to move feet

3- Complete block of lower limb

Adverse effects: patients were monitored for any cardiovascular side effects like changes in blood pressure, heartrate and rhythm, central nervous system depression, respiratory depression and any hypersensitivity reactions for drugs.

STATISTICAL ANALYSIS

Sample size estimated based on the outcome variable duration of grade 4 motor block in a study by Ravikiran J Thote , Prashant Lomate , Shilpa Gaikwad , Jyotsna S Paranjpe , Manohar Mane.

It was found that the average variance for duration of grade 4 motor block in minutes is found to be 8.3 minutes with a mean difference of 4.2 minutes to detect a difference of 4.2 minutes in grade 4 motor block with 80% power with 95% confidence interval the required sample size is 62 per treatment group.

The collected data were coded and entered into an excel format. The quantitative data were presented using mean and standard deviation and confidence intervals and the qualitative data by proportions. Independent T test was used to compare the significance of difference in means and chi square test for proportions. P value < / = 0.05 was considered as statistically significant.

Statistical evaluation of data or parameters was done as follows

Sample Size

$$n=\frac{2\sigma^2(Z_{\alpha}+Z_{1-\beta})^2}{d^2}$$

Z_{α} = 95% confidence level = 1.96

$Z_{1-\beta}$ = power at 80%= 0.84

σ^2 = average variance =8.3

RESULTS

RESULTS:

	Group New				P value
	Group N		Group C		
	Mean	SD	Mean	SD	
Age	41.62	15.32	43.85	14.88	0.430

Table 2: age distribution

Mean age of subjects in group N (nalbuphine) was 41.62±15.32 years and in groupC(fentanyl)was43.85±14.88years.

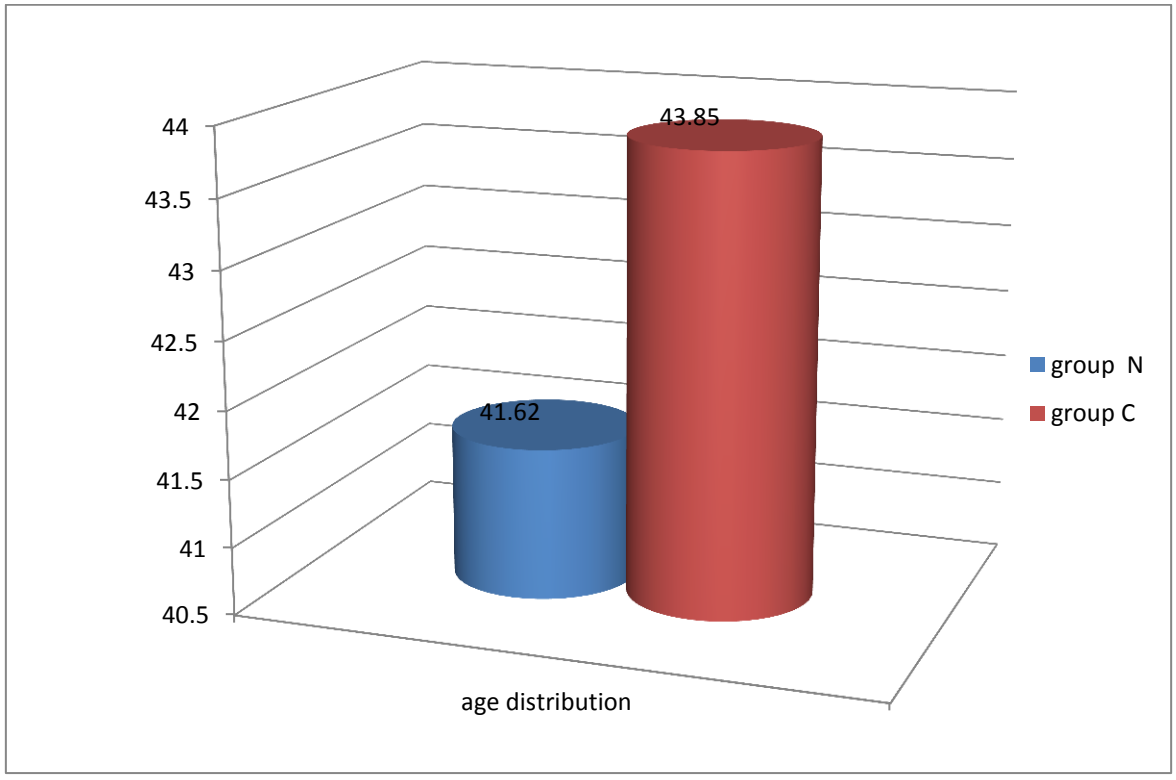


Figure 16:Bar diagram showing age distribution of subjects in both the groups

Gender	Group N	Group C
Female	14(21.7%)	31(50%)
Male	48(78.3%)	31(50%)

P=0.001**, Significant, Chi-Square test

Table 3: gender distribution

In group N (nalbuphine) 14 (21.7%) were female and 48(78.3%) were male and in group C (fentanyl) 31(50%) were female and 31(50%) were male. There was a significant difference in gender distribution between the two groups.

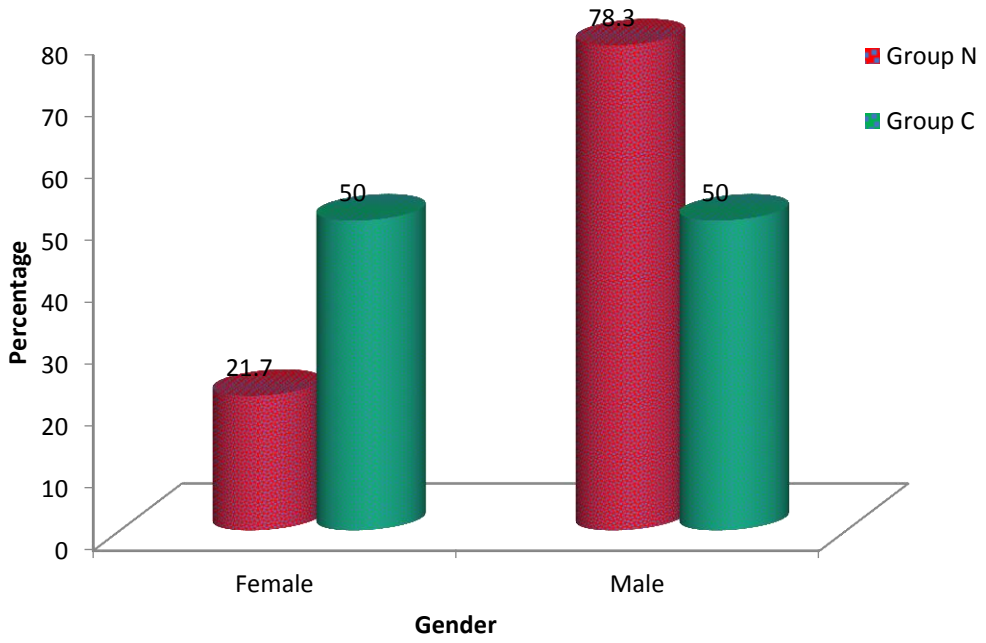


Figure 17: Bar diagram showing Gender distribution of subjects

Heart rate (bpm)	Group N	Group C	P value
Basal	78.18±14.66	74.63±7.54	0.098+
3 min	74.50±15.17	71.67±7.47	0.197
6min	67.43±11.32	72.63±7.52	0.004**
9min	64.05±8.72	73.22±7.29	<0.001**
12min	68.37±9.55	73.35±6.88	0.001**
15min	71.35±10.33	73.67±7.37	0.160
18min	73.27±10.86	73.27±6.72	1.000
20min	74.25±11.34	74.3±6.79	0.977
25min	75.33±11.99	75.23±6.97	0.956
30min	75.53±11.39	74.62±7.07	0.597
35min	76.15±10.41	73.83±6.74	0.150
40min	76.40±11.25	74.20±6.83	0.198
45 min	76.10±11.03	74.53±6.93	0.354
50 min	75.55±12.19	74.50±6.27	0.554
55 min	76.37±11.57	75.02±6.82	0.438
60 min	76.37±11.85	74.82±7.24	0.389
75 min	76.62±11.88	74.20±7.47	0.185
90 min	76.83±11.30	74.25±8.11	0.153
105 min	76.60±10.85	74.27±7.40	0.171
120 min	76.40±12.01	74.57±7.55	0.319
150 min	75.62±11.61	74.30±7.18	0.456
180 min	74.88±11.32	73.87±6.72	0.551
210 min	75.18±11.33	74.68±6.21	0.765
240 min	74.93±11.28	75.07±5.89	0.935

Table4: Heart rate at various intervals

Significant difference was observed in HR between two groups was observed at 6, 9 and 12 min.

Lower HR was observed in Nalbuphine group than fentanyl group during the above said durations.

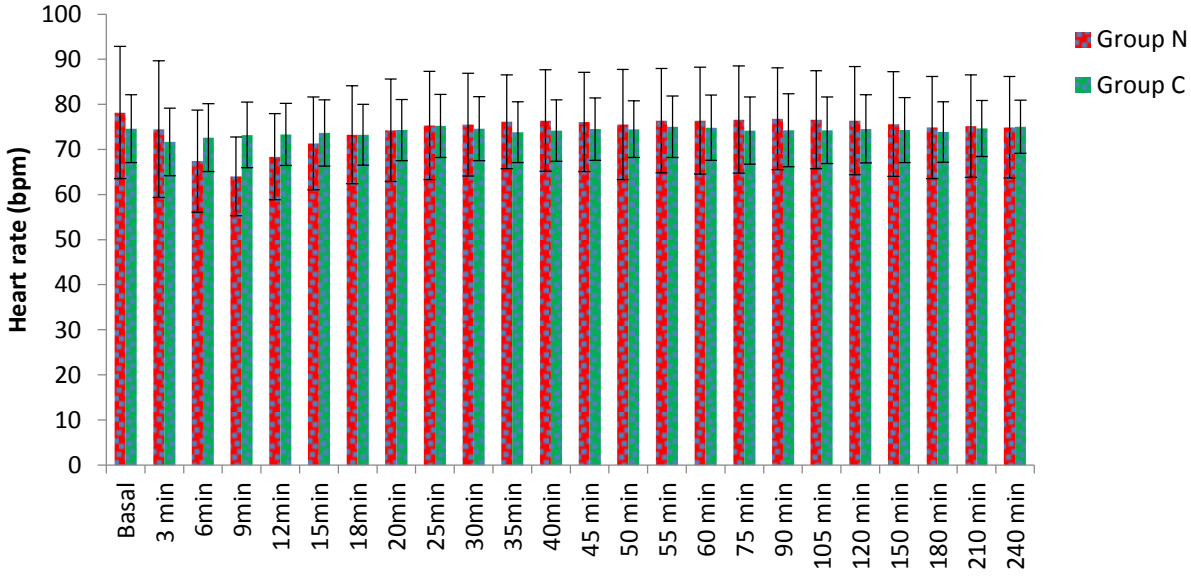


Figure 18: Bar diagram showing Heart rate variation between two groups

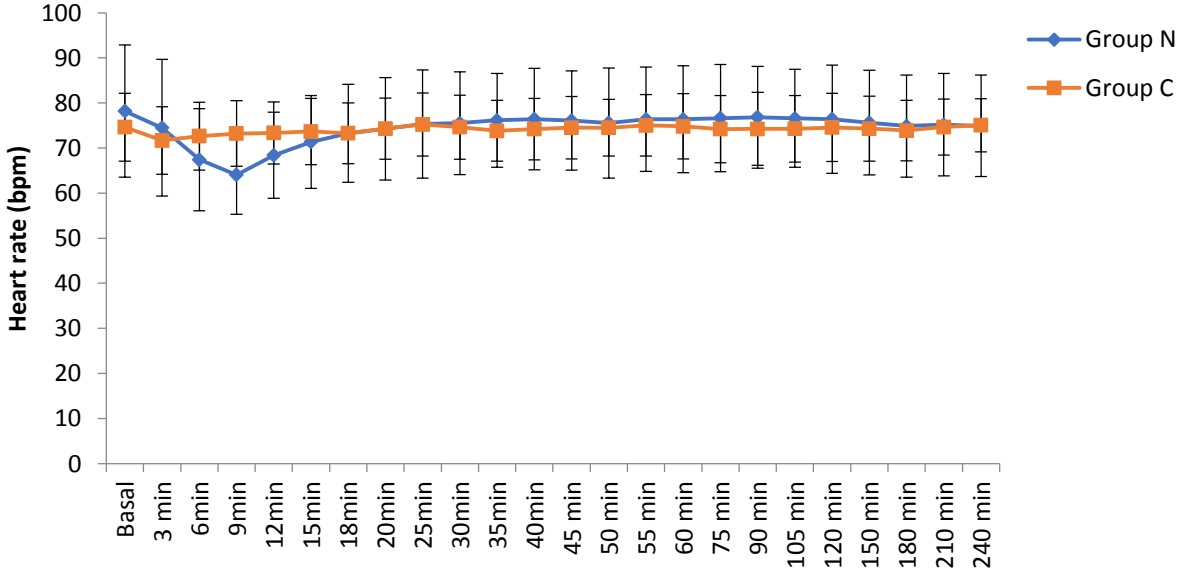


Figure 19 :Line diagram showing Heart rate variation between two groups

SBP (mm Hg)	Group N	Group C	P value
Basal	120.80±11.48	117.27±12.21	0.105
3 min	117.43±11.53	114.47±12.39	0.177
6min	111.13±10.27	99.43±8.90	<0.001**
9min	110.50±9.46	102.60±7.44	<0.001**
12min	110.23±9.91	106.20±6.52	0.010**
15min	112.52±10.3	108.47±7.32	0.014*
18min	112.87±8.26	109.03±7.69	0.010**
20min	116.20±7.88	111.93±7.78	0.003**
25min	116.90±8.14	114.43±6.80	0.074+
30min	117.70±9.76	115.93±7.22	0.262
35min	119.47±8.63	117.97±7.26	0.305
40min	120.67±9.32	118.63±6.55	0.169
45 min	119.67±8.87	120.37±5.76	0.609
50 min	117.87±7.67	117.07±5.35	0.509
55 min	121.07±8.90	120.77±6.61	0.834
60 min	118.63±10.11	117.97±7.74	0.686
75 min	119.23±9.58	119.77±7.54	0.735
90 min	118.87±9.50	118.70±7.29	0.914
105 min	120.47±9.94	120.93±7.08	0.768
120 min	120.97±10.08	122.27±7.51	0.425
150 min	120.63±10.06	120.70±6.82	0.966
180 min	119.03±10.15	120.13±6.81	0.487
210 min	119.77±10.24	121.6±7.51	0.266
240 min	119.87±10.87	119.43±7.45	0.799

Table 5:Comparison of SBP (mm Hg) distribution in two groups of patients studied

Significant difference was observed in systolic blood pressure between two groups was observed at 6, 9, 12, 15,18 and 20 min.

Lower systolic blood pressure was observed in fentanyl group than nalbuphine group during the above said durations.

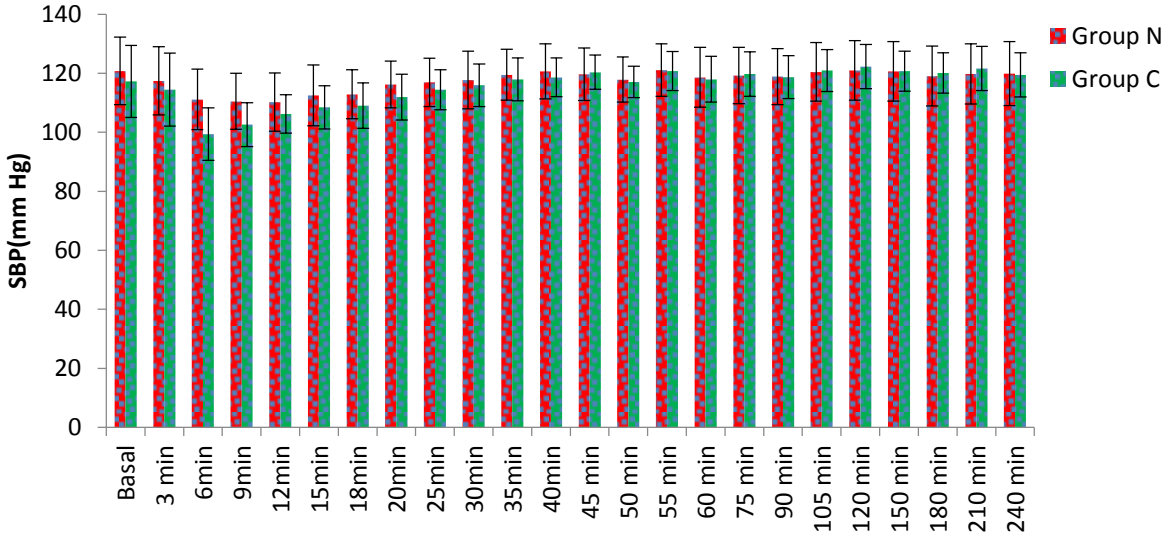


Figure 20: Bar diagram showing systolic blood pressure variation between two groups

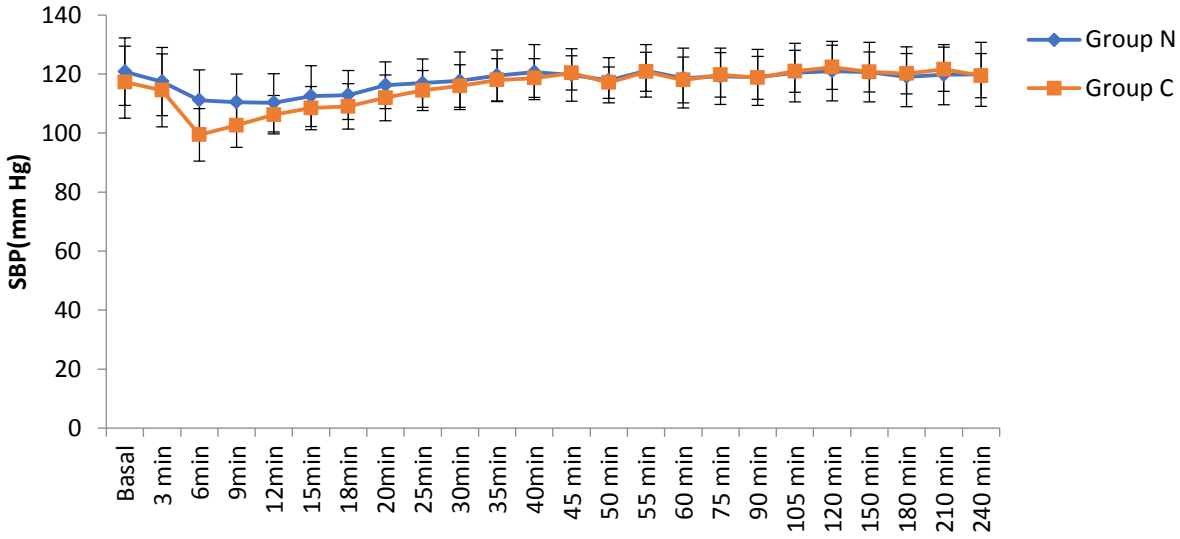


Figure 21:Line diagram showing systolic blood pressure variation between two groups

DBP (mm Hg)	Group N	Group C	P value
Basal	74.90±10.52	70.53±9.58	0.019*
3 min	71.63±10.53	67.95±9.97	0.052+
6min	70.60±7.83	62.63±4.93	<0.001**
9min	69.87±7.87	63.87±5.42	<0.001**
12min	69.63±8.04	65.07±5.82	0.001**
15min	71.20±8.78	68.30±7.26	0.051+
18min	72.13±8.50	68.80±6.55	0.018*
20min	72.87±10.48	69.13±6.55	0.021*
25min	70.03±8.54	68.83±6.81	0.397
30min	72.13±8.96	70.70±7.51	0.344
35min	72.70±8.46	73.73±6.47	0.454
40min	77.50±8.16	76.33±6.11	0.377
45 min	75.23±7.63	76.53±6.59	0.320
50 min	75.20±5.34	75.90±4.59	0.443
55 min	76.80±7.49	77.80±6.50	0.437
60 min	76.03±8.95	75.10±6.69	0.519
75 min	78.13±8.11	78.50±6.57	0.786
90 min	76.40±7.64	76.00±6.68	0.761
105 min	76.93±8.28	78.53±5.98	0.227
120 min	78.50±8.59	80.00±6.02	0.270
150 min	76.53±9.38	79.17±5.90	0.068+
180 min	77.50±7.76	78.33±4.89	0.483
210 min	78.33±8.90	81.00±5.50	0.051+
240 min	78.13±7.76	79.73±5.91	0.206

Table 6: Comparison of DBP (mm Hg) distribution in two groups of patients studied

Significant difference was observed in diastolic blood pressure between two groups was observed at 6, 9, 12,18 and 20 min.

Lower diastolic blood pressure was observed in fentanyl group than nalbuphine group during the above said durations.

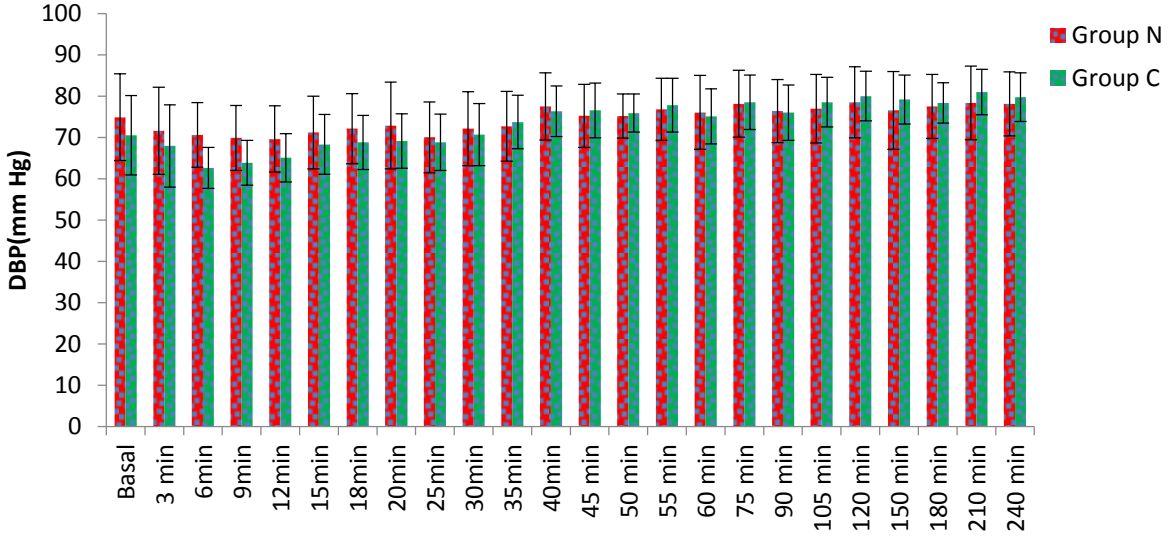


Figure 22: Bar diagram showing diastolic blood pressure variation between two groups

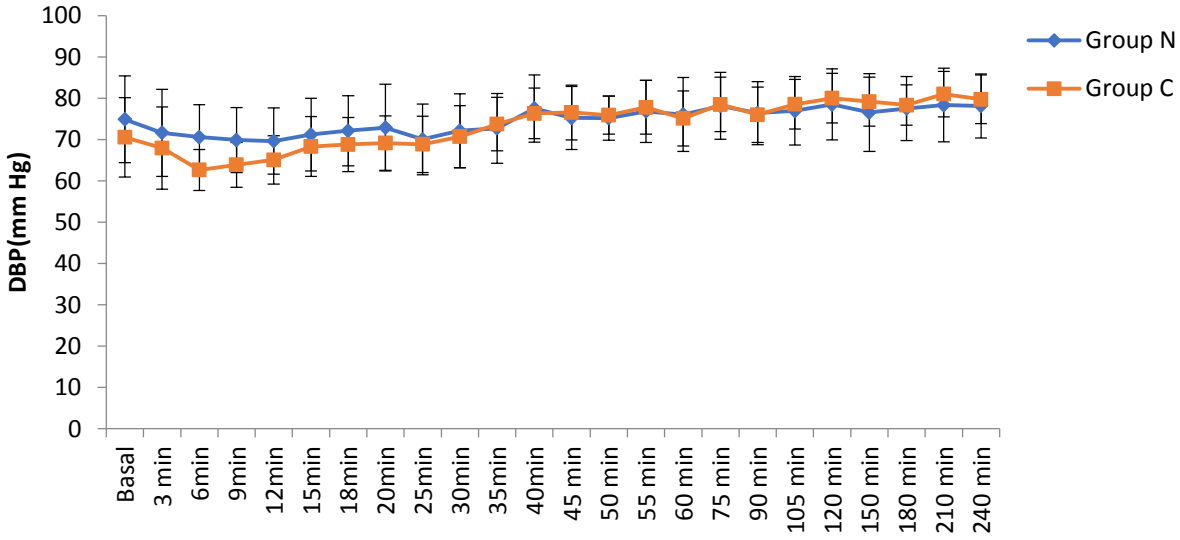


Figure 23: Line diagram showing diastolic blood pressure variation between two groups

MAP (mm Hg)	Group N	Group C	P value
Basal	90.20±10.37	88.11±9.75	0.028*
3 min	86.9±10.42	83.46±10.07	0.068+
6min	84.11±8.16	74.90±6.08	<0.001**
9min	83.41±8.11	76.78±5.78	<0.001**
12min	83.17±8.51	78.78±5.78	0.001**
15min	84.97±9.17	81.69±7.03	0.030*
18min	85.71±7.73	82.21±6.55	0.009**
20min	87.31±9.11	83.40±6.38	0.007**
25min	85.66±8.15	84.03±6.48	0.230
30min	87.32±8.92	85.78±7.07	0.295
35min	88.29±8.20	88.48±6.31	0.888
40min	91.89±8.25	90.43±5.85	0.267
45 min	90.04±7.87	91.14±5.95	0.390
50 min	89.42±5.75	89.62±4.46	0.832
55 min	91.56±7.82	92.12±6.37	0.664
60 min	90.23±9.16	89.39±6.83	0.568
75 min	91.83±8.48	92.26±6.57	0.761
90 min	90.56±8.07	90.23±6.18	0.807
105 min	91.44±8.34	92.67±5.90	0.356
120 min	92.66±8.93	94.09±6.05	0.305
150 min	91.23±9.32	93.01±5.74	0.211
180 min	91.34±8.41	92.27±5.10	0.469
210 min	92.14±8.97	94.53±5.81	0.086+
240 min	92.04±8.59	92.97±5.91	0.495

Table 7:Comparison of MAP (mm Hg) distribution in two groups of patients studied

Significant difference was observed in mean arterial blood pressure between two groups at 6, 9, 12,18 and 20 min.

Lower mean arterial blood pressure was observed in fentanyl group than nalbuphine group during the above said durations.

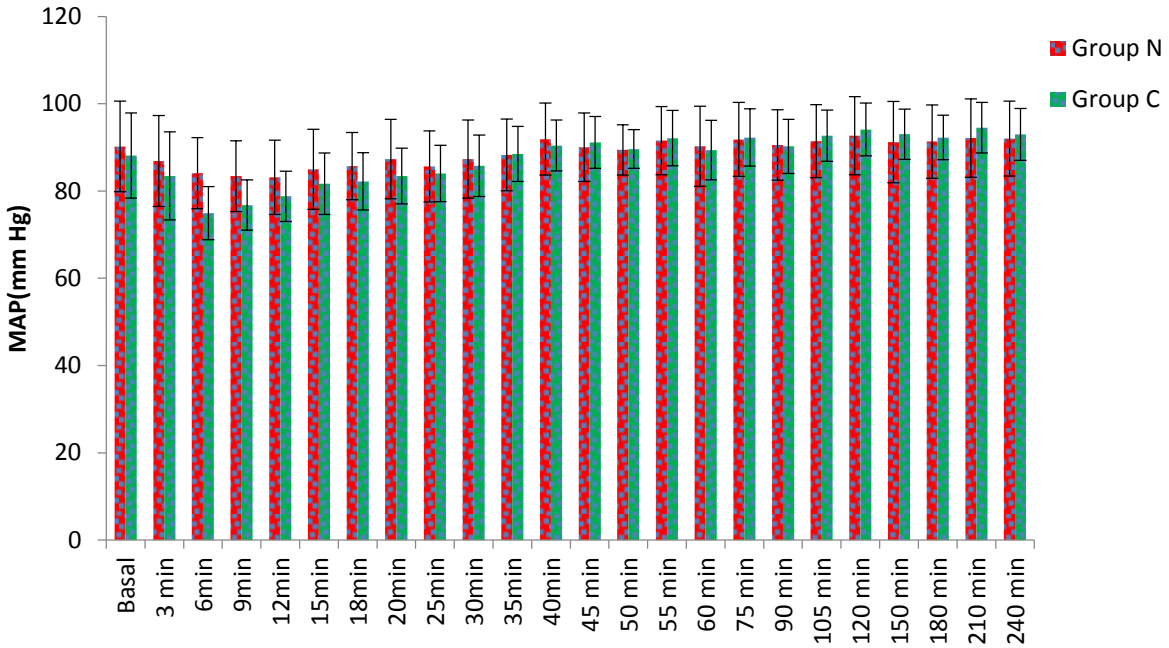


Figure 24: Bar diagram showing mean arterial blood pressure variation between two groups

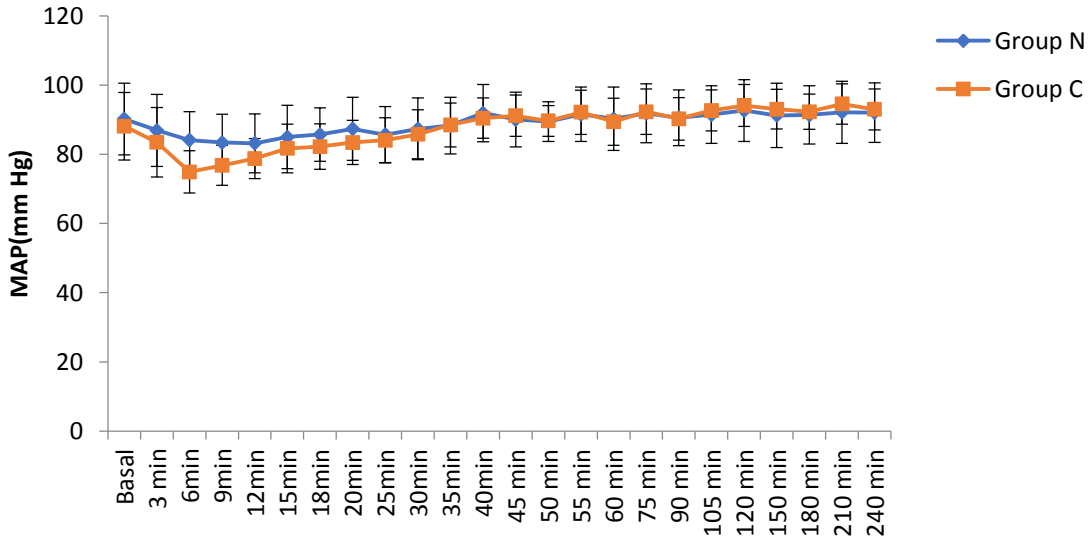


Figure 25: Line diagram showing mean arterial blood pressure variation between two groups

	Group N	Group C
Onset of sensory blockade	3.9±0.35	3.1±0.18

P<0.001**, Significant, Student t test

Table 8: Onset of Sensory Block (min) distribution in two groups of patients studied

There is significant difference in onset of sensory blockade in both groups nalbuphine group (group N) showed delayed onset of sensory blockade 3.9±0.35 min compared to fentanyl group(group C) 3.1±0.18min

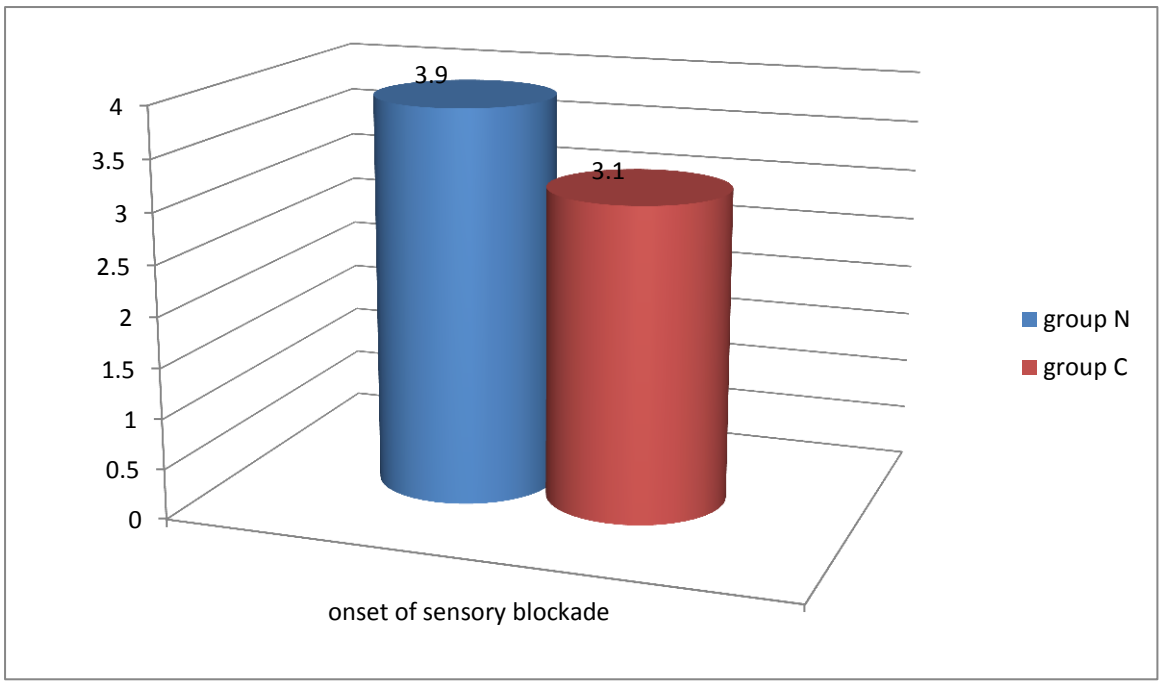


Figure 26: Bar diagram showing onset of Sensory Block (min) distribution in two groups

	Group N	Group C
2 segment regression	193.16±39.55	167.41±30.17

P<0.001**, Significant, Chi-Square test

Table 9: 2 Segment regressions distribution in two groups of patients studied

The duration for two segment regression in nalbuphine group was 193.16±39.55 min which was significantly prolonged as compared to fentanyl group which was 167.41±30.17 min

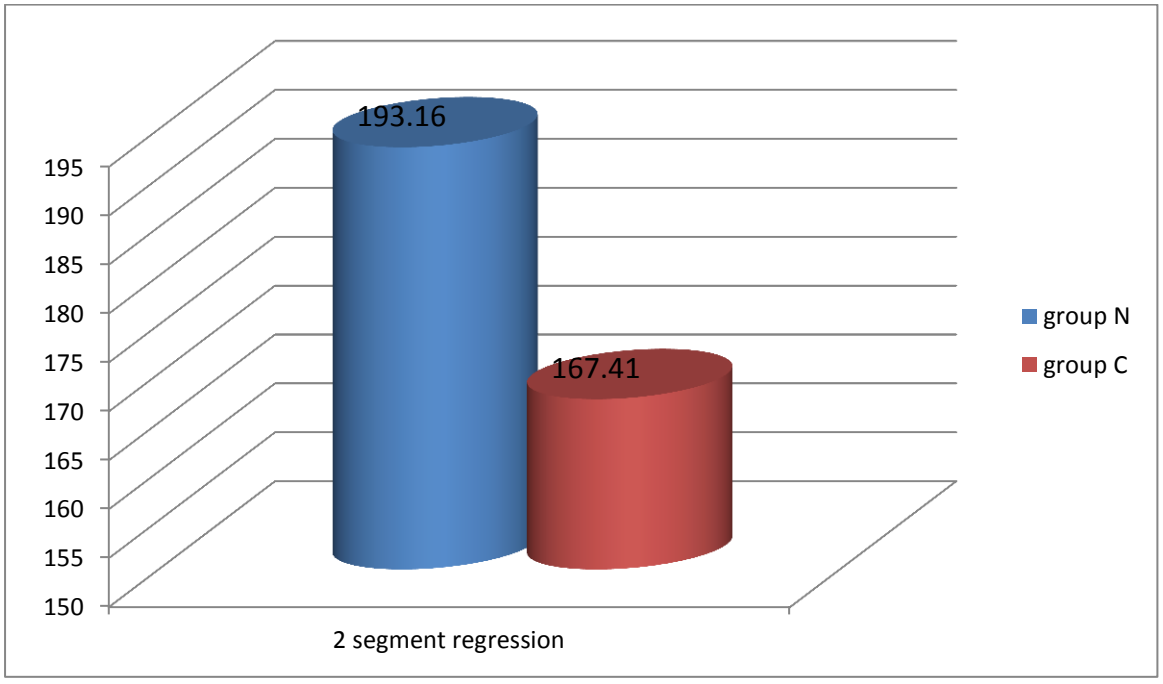


Figure 27: Bar diagram showing time for 2 segment regression (min) in two groups

	Group N	Group C
Rescue analgesia	268.33±44.44	220.91±24.36

P<0.001**, Significant, Fisher Exact test

Table 10: Rescue analgesia time (min) distribution in two groups of patients studied

Rescue analgesia was given at 268.33±44.44 min in nalbuphine group which was significantly prolonged as compared to fentanyl group in which rescue analgesia was given at 220.91±24.36 min.

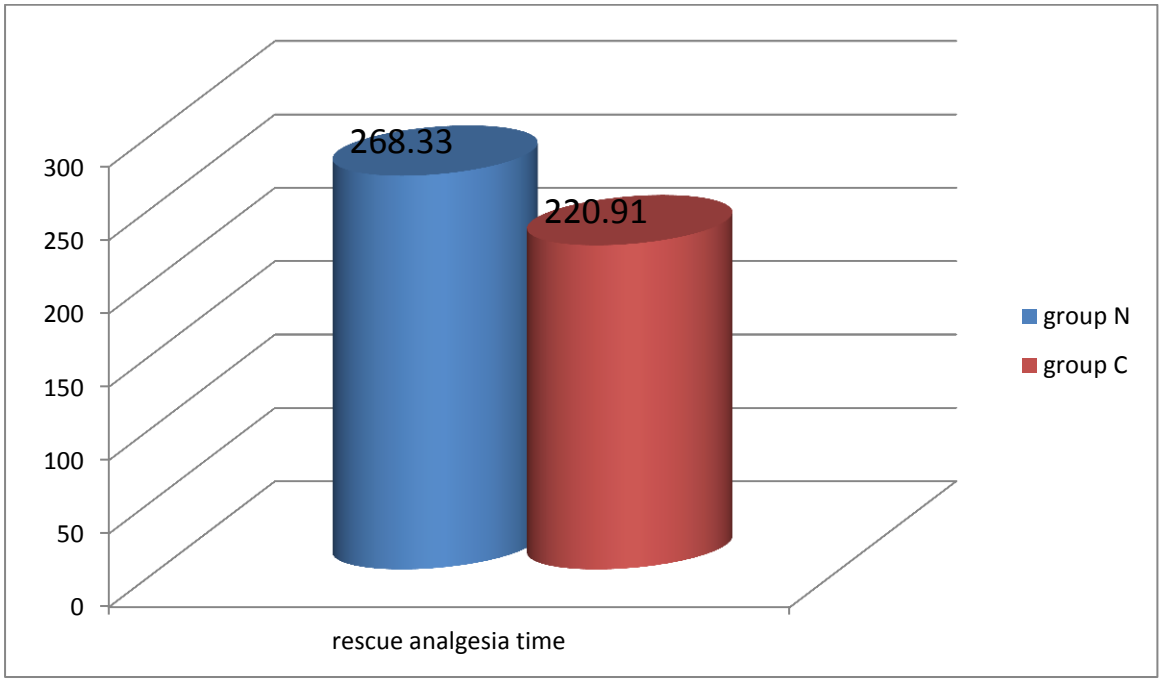


Figure 28: Bar diagram showing time for rescue analgesia (min) in two groups

Rescue analgesia doses in 24 hrs	Group N (n=62)	Group C (n=62)
one	54(87.09%)	50(80.6%)
More than one	8(12.9%)	12(19.35%)

Table 11:Rescue analgesia doses in 24 hrs distribution in two groups of patients studied

Rescue analgesia was given when VAS score of the patient was 4 and in group N 54(87.09%) required only 1 rescue analgesia and 8(12.9%) required >1 rescue analgesia. In group C 50(80.6%) required 1 rescue analgesia in 24 hours and 12(19.35%) required >1 rescue analgesia in 24 hours.

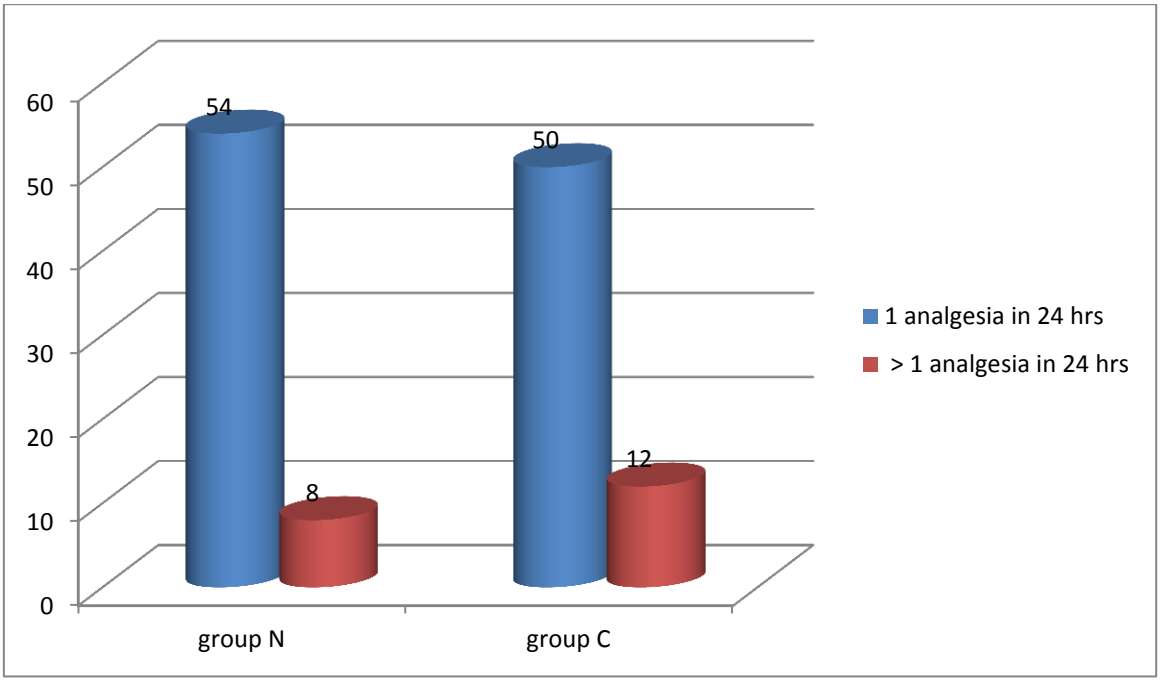


Figure 29: Bar diagram showing Rescue analgesia doses in 24 hrs distribution in two groups of patients studied

	Group N	Group C
hypotension	0(0%)	10 (16.12%)
bradycardia	8(12.90%)	0(0%)

Table 12: Side effects between two groups

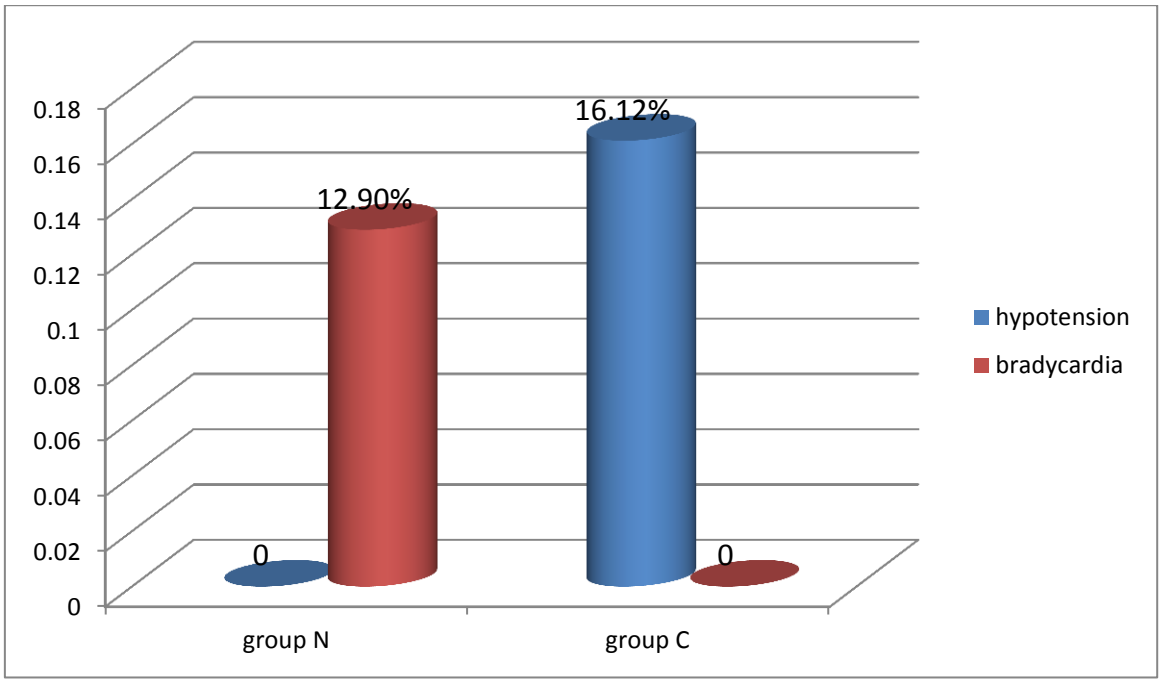


Figure 30:Bar diagram showing side effects between the two groups.

DISCUSSION

DISCUSSION

Spinal anaesthesia has been most commonly used for lower abdominal and lower limb surgeries because it is simple, fast , reliable and advantage of avoiding polypharmacy. Spinal anaesthesia gives good analgesia and reduces the blood loss and the incidence of deep venous thrombosis (DVT), pulmonary embolism, and to avoid the adverse effects of general anesthesia. The local anaesthetics commonly used for intrathecal anaesthesia are Lignocaine and Bupivacaine in India. Bupivacaine 0.5% heavy intrathecal injection once provides analgesia for about 2-2.5hrs. Other ways of increasing the duration of analgesia are continuous epidural analgesia, which is difficult technically and not cost effective.

Hence, adding intrathecal additives to the local anaesthetics prolongs post-operative analgesia and to increase the duration of anaesthesia. As this is simple and less cumbersome, it has gained a wide acceptance.

Many additives have been used to enhance analgesic effect of neuraxial blocks such as clonidine, magnesium, ketamine, opioids, vasoconstrictor agents and steroids.

In our study we hypothesized that nalbuphine may provide a better pain relief after lower abdominal and lower limb surgeries under spinal anesthesia compared to fentanyl. To test our hypothesis, we designed this randomized double-blind, comparative study to compare the postoperative analgesic effect of intratechal nalbuphine and fentanyl added to bupivacaine in patients undergoing lower abdominal and lower limb surgeries.

Analysis of data between the groups:

Sensory block characteristics

Onset of sensory blockade

In our study Mean time taken for the onset of sensory blockade among Nalbuphine(group N) was 3.9±0.35 min and in fentanyl (group C) 3.1±0.18

min. There was significant difference(0.8±0.17 min) in onset of sensory between two groups.

This is correlated with the study conducted by Bisht S, Rashmi D[41]. Comparison of intrathecal fentanyl and nalbuphine: A prospective randomized controlled study in patients undergoing total abdominal hysterectomy

group FB: 15 mg of 0.5% bupivacaine (3ml) plus 25 mcg of fentanyl

Group NB : 15 mg of 0.5% bupivacaine (3ml) plus 1 mg nalbuphine (0.5ml).

Onset of sensory blockade in group NB was 4.20±0.52 and in group FB was 3.09±0.47. The onset of sensory block was faster in group FB than in group NB which was statistically significant

Gupta K, Rastogi B, Prashant K Gupta, Singh I, Bansal M, Tyagi V[38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016and concluded that 2mg of nalbuphine + 17.5 mg of hyperbaric bupivacaine intrathecally required 3.91±2.25 min for onset of sensory blockade as compared to 4.30±0.79 min for 25 mcg of fentanyl+ 17.5 mg of hyperbaric bupivacaine intrathecally. There was no statistically significant difference in onset of sensory blockade between the two groups.

Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A[39] did a comparative study on analgesic efficacy of intrathecal nalbuphine(0.8 mg and 1.6mg) and fentanyl (25mcg) as an adjuvant with 12.5mg of 0.5% bupivacaine in Lower Limb Orthopaedic Surgery in 2017 and concluded that there was no significant difference in onset of sensory level in nalbuphine group (0.8 mg : 9.8± 4.15 min 1.6mg: 12.3±6.73min) and fentanyl group (8.1±3.84 min)

Duration of effective post-operative analgesia

In our study the duration of analgesia was analysed as period between complete onset of sensory blockade to the time at which patient started complaining of pain or first rescue analgesia which was given using VAS score. On statistical analysis, patients of group C complained of pain earlier than that of group N. There was statistically significant delay in the onset of pain between group C and group N.

Rescue analgesia was given at 268.33±44.44 min in nalbuphine group which was significantly prolonged (47.42±20.08min) as compared to fentanyl group in which rescue analgesia was given at 220.91±24.36 min.

This correlated with the study done by Bisht S, Rashmi D[41]. Comparison of intrathecal fentanyl and nalbuphine: A prospective randomized controlled study in patients undergoing total abdominal hysterectomy

group FB: 15 mg of 0.5% bupivacaine (3ml) plus 25 mcg of fentanyl

Group NB : 15 mg of 0.5% bupivacaine (3ml) plus 1 mg nalbuphine (0.5ml). In this study first rescue analgesia in group FB was at 283.44±78.97 min and for group NB it was at 460.78±77.98 min which was statistically significant difference between the two groups.

This is also correlated with the study done by Neelam S , Sumit K , Rakesh KT [40] (2017)comparative study on Intrathecal Nalbuphine Versus Intrathecal Fentanyl Added to 0.5% Hyperbaric Bupivacaine For Perioperative Anaesthesia And Analgesia in Lower Abdominal Surgeries in which they compared three groups

Group F: Received 25mcg of fentanyl + 12.5 mg of 0.5% bupivacaine heavy intrathecally

Group NL : Received 0.8 mcg of nalbuphine + 12.5 mg of 0.5% bupivacaine heavy intrathecally

Group NH : Recieved 1.6 mcg of nalbuphine + 12.5 mg of 0.5% bupivacaine heavy intrathecally

Showed that duration of analgesia was 441±119.69 min and 450 ±109.38 min for Group NL Group NH respectively which was significantly greater than the duration of analgesia in Group F 300±88.53 min.

Gupta K, Rastogi B, Prashant K Gupta, Singh I, Bansal M, Tyagi V[38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016 concluded that duration for rescue analgesia was prolonged by 39.9±7.75 min when 2mg of nalbuphine + 17.5 mg of hyperbaric bupivacaine was given intrathecally as compared to 25 mcg of fentanyl+ 17.5 mg of hyperbaric bupivacaine intrathecally. This prolonged duration for rescue analgesia was statistically significant.

Two segment regression of sensory block

In our study the duration for two segment regression of sensory block in nalbuphine group was 193.16±39.55 min which was significantly prolonged as compared to fentanyl group which was 167.41±30.17 min

This is correlated with the study done by Gupta K, Rastogi B, Prashant K Gupta, Singh I, Bansal M, Tyagi V[38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016 concluded that two segment regression of sensory block was prolonged by 11.11±5.41 min when 2mg of nalbuphine + 17.5 mg of hyperbaric bupivacaine was given intrathecally as compared to 25 mcg of

fentanyl+ 17.5 mg of hyperbaric bupivacaine intrathecally. This prolonged duration for rescue analgesia was statistically significant.

Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A[39]. Did a comparative study on analgesic efficacy of intrathecal nalbuphine(group NL :0.8 mg and group NH: 1.6mg) and fentanyl (group F: 25mcg) as an adjuvant with 12.5mg of 0.5% bupivacaine in Lower Limb Orthopaedic Surgery in 2017 and concluded that time of two segment sensory regression were comparable between groups NL(91.6±31.12min) and NH (73.5±17.95 min) and were significantly less (p=0.03) when compared with F group (108±32.03 min)

Bisht S, Rashmi D[41]. Did a Comparison of intrathecal fentanyl and nalbuphine: A prospective randomized controlled study in patients undergoing total abdominal hysterectomy

group FB: 15 mg of 0.5% bupivacaine (3ml) plus 25 mcg of fentanyl

Group NB : 15 mg of 0.5% bupivacaine (3ml) plus 1 mg nalbuphine (0.5ml).

They found that time for two segment regression for group FB was 88.88±9.48 min and for group NB was 97.72± 9.50 min which was statistically significant (8.84±0.02min) difference.

HEMODYNAMIC EFFECTS

MEAN ARTERIAL BLOOD PRESSURE

In our study significant difference was observed in mean arterial blood pressure between two groups at 6, 9, 12,18 and 20 min.

Lower mean arterial blood pressure was observed in fentanyl group than nalbuphine group during the above said durations. There was hypotension in

10 (16.12%) patients in group C and was treated with intravascular fluids and vasopressors.

According to the study done by Gupta K, Rastogi B, Prashant K Gupta, Singh I, Bansal M, Tyagi V[38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016 there was no statistically significant difference in HR, SBP, and SpO 2 during intra- and post-operative periods between the two groups (2mg of nalbuphine + 17.5 mg of hyperbaric bupivacaine intrathecally as compared to 25 mcg of fentanyl+ 17.5 mg of hyperbaric bupivacaine intrathecally.). Incidence of hypotension and bradycardia during intraoperative period was minimal and did not require any medical intervention.

Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A[39] did a comparative study on analgesic efficacy of intrathecal nalbuphine(group NL :0.8 mg and group NH: 1.6mg) and fentanyl (group F: 25mcg) as an adjuvant with 12.5mg of 0.5% bupivacaine in Lower Limb Orthopaedic Surgery in 2017 and concluded that All the three groups were haemodynamically stable . Six patients in Group F, three patients in NL Group and none of the patients in NH Group reported hypotension which was mild and easily corrected by giving one or two boluses of injection mephentermine.

HEART RATE:

In our study significant difference was observed in HR between two groups was observed at 6, 9 and 12 min.

Lower HR was observed in Nalbuphine group than fentanyl group during the above said durations. There was bradycardia in 8(12.90%) patients in group N and was treated with inj. Atropine 0.02mg/kg.

ADVERSE EFFECTS:

In our study there was bradycardia in 12.9% of cases in nalbuphine group and 16.12% of patients had hypotension in fentanyl group.

According to the study done by Gupta K, Rastogi B, Prashant K Gupta, Singh I, Bansal M, Tyagi V [38] studied Intrathecal nalbuphine versus intrathecal fentanyl as an additive with bupivacaine for orthopedic surgery of lower limbs in 2016 2mg of nalbuphine + 17.5 mg of hyperbaric bupivacaine intrathecally as compared to 25 mcg of fentanyl+ 17.5 mg of hyperbaric bupivacaine intrathecally. Mild pruritus was observed in 5 (14.7%) patients of fentanyl group they treated it with IV injection pheniramine. The incidence of respiratory depression in the study was minimal and comparable. There were no incidence of postspinal shivering, nausea, vomiting, or respiratory depression.

Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A [39]did a comparative study on analgesic efficacy of intrathecal nalbuphine(group NL :0.8 mg and group NH: 1.6mg) and fentanyl (group F: 25mcg) as an adjuvant with 12.5mg of 0.5% bupivacaine in Lower Limb Orthopaedic Surgery in 2017 and concluded that The adverse effects were more in fentanyl group than nalbuphine groups. These were comparable between NH and NL groups. The incidence of nausea and vomiting was maximum in NH followed by F than NL.

Bisht S, Rashmi D[41]. Did a Comparison of intrathecal fentanyl and nalbuphine: A prospective randomized controlled study in patients undergoing total abdominal hysterectomy

group FB: 15 mg of 0.5% bupivacaine (3ml) plus 25 mcg of fentanyl

Group NB : 15 mg of 0.5% bupivacaine (3ml) plus 1 mg nalbuphine (0.5ml).

This study showed that there were 2(4%) patients had hypotension in group FB and 2 (4%) patients in group FB and 2 (4%) patients in group NB had nausea.

CONCLUSION

CONCLUSION

From the present study it can be concluded that intrathecal nalbuphine in the dose of 300mcg in 3 ml 0.5% heavy bupivacaine in patients undergoing elective lower abdominal surgeries showed,

- Delay in onset time for sensory blockade.
- Produces prolonged postoperative analgesia.
- Produces prolonged sensory blockade.
- Produces minimal bradycardia which could be easily managed.

SUMMARY

SUMMARY

The present study entitled **"POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER ABDOMINAL SURGERIES- A RANDOMISED DOUBLE BLIND STUDY"**

This study was conducted in 124 patients of either sex, in age group of 18-55yrs weighing more than 45 kgs and height more than 150 cms, belonging to ASA class I and II admitted to Sri R.L.Jalappa medical college hospital and research centre , Kolar.

Group N : 62 patients received intrathecal hyperbaric bupivacaine 0.5% (3 cc) with 300mcg of Nalbuphine .

Group C : 62 patients received intrathecal hyperbaric bupivacaine 0.5% (3 cc) with 25mcg of fentanyl.

The dose of nalbuphine was selected as 300mcg as previous studies have shown that 800mcg is the minimal dose nalbuphine provides good postoperative analgesia with reduced incidence of adverse effects.

Time of onset and duration of sensory blockade , time to two segment regression, hemodynamic status and adverse effects were studied.

Results obtained in our present study

	Group				P value
	Nalbuphine		Fentanyl		
	Mean	SD	Mean	SD	
Onset of sensory blockade (min)	3.9	0.35	3.1	0.18	<0.001
Two segment regression (min)	193.16	39.55	167.41	30.17	<0.001
Duration of analgesia (min)	268.33	44.44	220.91	24.36	<0.001

Table 13:Results obtained in our present study

In our present study , there was delay in onset of sensory blockade by addition of intrathecal nalbuphine when compared to fentanyl. The mean duration of analgesia from the onset of complete sensory blockade with Nalbuphine was 268.33 ±44.44 min and with fentanyl 220.91± 24.36 min. thus suggesting that there was statistically significant delay in the onset of pain between group N and group C. The post operative pain after regression of analgesia was easily managed by injection tramadol 100mg intravenously. Intrathecal nalbuphine thereby provides good quality of analgesia ,thus reducing requirement of postoperative analgesic consumption.

There was significant changes in the hemodynamic parameters such as heart rate, blood pressure between the two groups which were statistically significant. Bradycardia which was seen in nalbuphine group was controlled by injection atropine intravenously. While hypotension which were seen in group C were managed with IV fluids and vasopressors.

Thus nalbuphine when added to bupivacaine showed better results in prolonging duration of sensory and post-operative analgesia compared to fentanyl as additive to bupivacaine

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ANNEXURES

ANNEXURE-1

PROFORMA

"POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER LIMB AND LOWER ABDOMINAL SURGERIES".

Investigators: DR .BHAVANA B.G

Guide: DR RAVI.M

NAME: **DATE:**

AGE: **I.P.NO:**

SEX:

PRE-OPERATIVE EVALUATION:

GENERAL PHYSICAL EXAMINATION:

PR	BP	RR	Temp	Wt	Ht	Spine

AIRWAY:

SYSTEMIC EXAMINATION:

RS:

CVS:

OTHERS:

INVESTIGATIONS:

Hb%:	BLOOD SUGAR:	URINE ANALYSIS:
ECG:	CHEST X-RAY:	BT:
CT:		
B.UREA:	S.CREATININE:	OTHERS:

DIAGNOSIS:

PROPOSED SURGERY:

PREMEDICATION: Tab.Alprazolam 0.5 mg, Tab.Ranitidine 150 mg.

ASA CLASS:

DRUGS : Intrathecal Hyperbaric Bupivacaine 3ml+ Nalbuphine 300 mcg

Intrathecal Hyperbaric Bupivacaine 3ml+Fentanyl 25 mcg

PARAMETERS NOTED DURING SPINAL ANAESTHESIA:

a) Time of administration:

b) Onset of block:

Sensory level attained(segment):

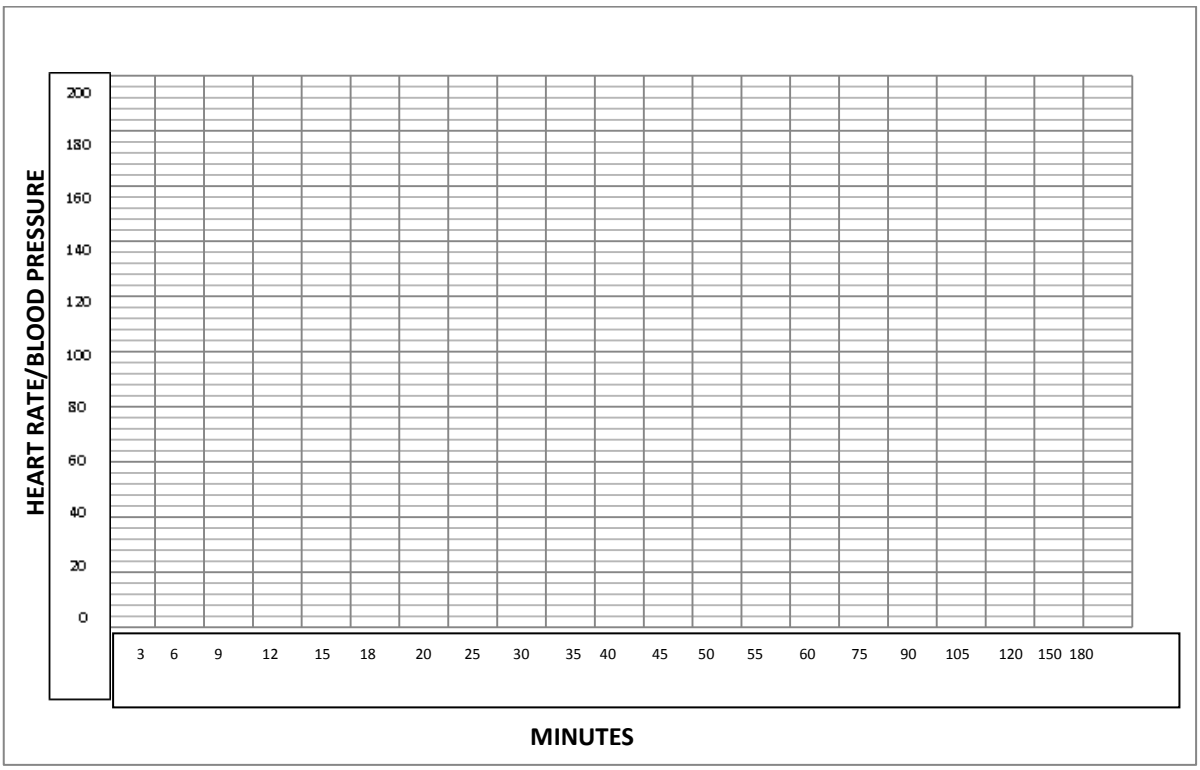
Motor: Modified Bromage scale 0:

Modified Bromage scale 1:

Modified Bromage scale 2:

Modified Bromage scale 3:

c) INTRAOPERATIVE OBSERVATION:



• ***pulse∧ systolic BP*** ***∨ Diastolic BP***

c)TIME TO TWO SEGMENT REGRESSION OF SENSORY LEVEL:

d) EFFECTIVE DURATION OF ANALGESIA (VAS score):

e)TIME FOR COMPLETE MOTOR RECOVERY:

ASSESSEMENT OF SEDATION:

Ramsay Sedation Scale

1 Anxious and agitated, restless

2 Co-operative, oriented, tranquil

3 Responsive to verbal commands, drowsy

4 Asleep, responsive to light stimulation(loud noise, tapping)

5 Asleep, slow response to stimulation

6 No response to stimulation

POST OPERATIVE VITALS:

HR: (bpm) BP: mm of Hg SpO_2:

SIDEEFFECTS:DRY MOUTH, NAUSEA, VOMITING, BRADYCARDIA, HYPOTENSION, BRADYCARDIA, RESPIRATORY DEPRESSION,SHIVERING,HEADACHE.

- Bradycardia-less than 60beats per minute : Treat with Inj Atropine 0.6mg IV
- Hypotension- SBP less than 30% of baseline: Treat with Inj Mephentermine 6mg IV.
- If VAS score >4 : Treat with rescue analgesia Inj Tramadol 50mg and Inj Emeset 4mg IV.

Annexure-II

INFORMATION SHEET

Title: "POSTOPERATIVE ANALGESIC EFFICACY OF INTRATHECAL FENTANYL VERSUS NALBUPHINE ADDED TO BUPIVACAINE IN SPINAL ANAESTHESIA FOR LOWER LIMB AND LOWER ABDOMINAL SURGERIES".

My name is Dr. Bhavana B.G, Post Graduate in the department of Anaesthesiology, Sri Devaraj Urs Medical College, Kolar. We are carrying out a study on subarachnoid block. The study has been reviewed by the local ethical review board and has been started only after their formal approval.

We would be using adjuncts Fentanyl / nalbuphine along with the routinely used local anaesthetic bupivacaine intrathecally for your surgery to provide the needed anaesthesia. These drugs have been proved to be safe when used in the prescribed dose.Test dose of local anesthethetic Bupivacaine will be given before the day of surgery to check for allergy and if any will be treated with Inj Avil25 mg and Inj Hydrocortisone 100mg.

Participation in this study doesn't involve any cost for you. The results gathered from this study will be beneficial in estimating efficacy of these drugs and will be used for presentation or publication. (Name is kept confidential)

I request you to kindly give consent for the clinical examination,
There is no compulsion to participate in this study. You will be no way affected if you don't wish to participate in this study. You are required to sign only if you voluntarily agree to participate in this study. Further, you are at a liberty to withdraw from the study at any time, if you wish to do so. Be assured that your

withdrawal will not affect your treatment by the concerned physician in any way. It is up to you to decide whether to participate.

For any further clarification you are free to contact the principal investigator,

Dr. Ravi.M: Mobile No: 9845287591;Dr. Bhavana B.G Mobile No: 9481907984

CONSENT FORM

I have been explained in a language understandable to me regarding the procedure i.e; spinal anaesthesia and about the drugs to be used.

I have also been explained the need for comparing intrathecal hyperbaric bupivacaine with nalbuphine and hyperbaric bupivacaine with fentanyl. The associated side effects such as hypotension , bradycardia have been enlisted to me and the way they are treated(bradycardia , HR <60 treated with Inj Atropine 0.6 mg IV; Hypotension SBP<90 treated with IV fluids and Inj Mephentermine6 mg).

I have read the information and I have had the opportunity to ask questions regarding various aspects of the study and my questions have been answered to my satisfaction.

I am aware that I am entitled to refrain/withdraw from the study at any point .

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information as outlined in this consent form.

Subject's/guardian's name and signature/thumb impression:

Date:

Name and signature of witness:

Date:

Name and signature of principle investigator:

Date:

A copy of this informed consent form has been provided to the participant.

| d_row | fips | sex | name_of_place | pct_of_region_in_urban_areas | pop | pop_f | pop_m | male_female_ratio | pop_density | pop_density_f | pop_density_m | male_female_density_ratio | median_age | median_age_f | median_age_m | male_female_median_age_ratio | sex_ratio | sex_ratio_f | sex_ratio_m | male_female_sex_ratio_ratio | age_under_5 | age_under_5_f | age_under_5_m | male_female_age_under_5_ratio | age_5_to_17 | age_5_to_17_f | age_5_to_17_m | male_female_age_5_to_17_ratio | age_18_to_64 | age_18_to_64_f | age_18_to_64_m | male_female_age_18_to_64_ratio | age_65_and_over | age_65_and_over_f | age_65_and_over_m | male_female_age_65_and_over_ratio | pct_under_5 | pct_under_5_f | pct_under_5_m | male_female_pct_under_5_ratio | pct_5_to_17 | pct_5_to_17_f | pct_5_to_17_m | male_female_pct_5_to_17_ratio | pct_18_to_64 | pct_18_to_64_f | pct_18_to_64_m | male_female_pct_18_to_64_ratio | pct_65_and_over | pct_65_and_over_f | pct_65_and_over_m | male_female_pct_65_and_over_ratio | pop_white | pop_white_f | pop_white_m | male_female_pop_white_ratio | pct_white | pct_white_f | pct_white_m | male_female_pct_white_ratio | pop_black | pop_black_f | pop_black_m | male_female_pop_black_ratio | pct_black | pct_black_f | pct_black_m | male_female_pct_black_ratio | pop_amerindian | pop_amerindian_f | pop_amerindian_m | male_female_pop_amerindian_ratio | pct_amerindian | pct_amerindian_f | pct_amerindian_m | male_female_pct_amerindian_ratio | pop_asian_pacific | pop_asian_pacific_f | pop_asian_pacific_m | male_female_pop_asian_pacific_ratio | pct_asian_pacific | pct_asian_pacific_f | pct_asian_pacific_m | male_female_pct_asian_pacific_ratio | pop_other | pop_other_f | pop_other_m | male_female_pop_other_ratio | pct_other | pct_other_f | pct_other_m | male_female_pct_other_ratio | pop_hispanic | pop_hispanic_f | pop_hispanic_m | male_female_pop_hispanic_ratio | pct_hispanic | pct_hispanic_f | pct_hispanic_m | male_female_pct_hispanic_ratio | pop_not_hispanic | pop_not_hispanic_f | pop_not_hispanic_m | male_female_pop_not_hispanic_ratio | pct_not_hispanic | pct_not_hispanic_f | pct_not_hispanic_m | male_female_pct_not_hispanic_ratio | pop_same_house_1995 | pop_same_house_1995_f | pop_same_house_1995_m | male_female_pop_same_house_1995_ratio | pct_same_house_1995 | pct_same_house_1995_f | pct_same_house_1995_m | male_female_pct_same_house_1995_ratio | pop_same_county_1995 | pop_same_county_1995_f | pop_same_county_1995_m | male_female_pop_same_county_1995_ratio | pct_same_county_1995 | pct_same_county_1995_f | pct_same_county_1995_m | male_female_pct_same_county_1995_ratio | pop_same_state_1995 | pop_same_state_1995_f | pop_same_state_1995_m | male_female_pop_same_state_1995_ratio | pct_same_state_1995 | pct_same_state_1995_f | pct_same_state_1995_m | male_female_pct_same_state_1995_ratio | pop_abroad_1995 | pop_abroad_1995_f | pop_abroad_1995_m | male_female_pop_abroad_1995_ratio | pct_abroad_1995 | pct_abroad_1995_f | pct_abroad_1995_m | male_female_pct_abroad_1995_ratio | pop_different_house_1995 | pop_different_house_1995_f | pop_different_house_1995_m | male_female_pop_different_house_1995_ratio | pct_different_house_1995 | pct_different_house_1995_f | pct_different_house_1995_m | male_female_pct_different_house_1995_ratio | pop_different_county_1995 | pop_different_county_1995_f | pop_different_county_1995_m | male_female_pop_different_county_1995_ratio | pct_different_county_1995 | pct_different_county_1995_f | pct_different_county_1995_m | male_female_pct_different_county_1995_ratio | pop_different_state_1995 | pop_different_state_1995_f | pop_different_state_1995_m | male_female_pop_different_state_1995_ratio | pct_different_state_1995 | pct_different_state_1995_f | pct_different_state_1995_m | male_female_pct_different_state_1995_ratio | pop_elementary | pop_elementary_f | pop_elementary_m | male_female_pop_elementary_ratio | pct_elementary | pct_elementary_f | pct_elementary_m | male_female_pct_elementary_ratio | pop_high_school | pop_high_school_f | pop_high_school_m | male_female_pop_high_school_ratio | pct_high_school | pct_high_school_f | pct_high_school_m | male_female_pct_high_school_ratio | pop_some_college | pop_some_college_f | pop_some_college_m | male_female_pop_some_college_ratio | pct_some_college | pct_some_college_f | pct_some_college_m | male_female_pct_some_college_ratio | pop_bachelor | pop_bachelor_f | pop_bachelor_m | male_female_pop_bachelor_ratio | pct_bachelor | pct_bachelor_f | pct_bachelor_m | male_female_pct_bachelor_ratio | pop_master | pop_master_f | pop_master_m | male_female_pop_master_ratio | pct_master | pct_master_f | pct_master_m | male_female_pct_master_ratio | pop_professional | pop_professional_f | pop_professional_m | male_female_pop_professional_ratio | pct_professional | pct_professional_f | pct_professional_m | male_female_pct_professional_ratio | pop_doctorate | pop_doctorate_f | pop_doctorate_m | male_female_pop_doctorate_ratio | pct_doctorate | pct_doctorate_f | pct_doctorate_m | male_female_pct_doctorate_ratio | pop_labor_force | pop_labor_force_f | pop_labor_force_m | male_female_pop_labor_force_ratio | pct_labor_force | pct_labor_force_f | pct_labor_force_m | male_female_pct_labor_force_ratio | pop_employed | pop_employed_f | pop_employed_m | male_female_pop_employed_ratio | pct_employed | pct_employed_f | pct_employed_m | male_female_pct_employed_ratio | pop_unemployed | pop_unemployed_f | pop_unemployed_m | male_female_pop_unemployed_ratio | pct_unemployed | pct_unemployed_f | pct_unemployed_m | male_female_pct_unemployed_ratio | pop_not_in_labor_force | pop_not_in_labor_force_f | pop_not_in_labor_force_m | male_female_pop_not_in_labor_force_ratio | pct_not_in_labor_force | pct_not_in_labor_force_f | pct_not_in_labor_force_m | male_female_pct_not_in_labor_force_ratio | pop_service_occupations | pop_service_occupations_f | pop_service_occupations_m | male_female_pop_service_occupations_ratio | pct_service_occupations | pct_service_occupations_f | pct_service_occupations_m | male_female_pct_service_occupations_ratio | pop_sales_occupations | pop_sales_occupations_f | pop_sales_occupations_m | male_female_pop_sales_occupations_ratio | pct_sales_occupations | pct_sales_occupations_f | pct_sales_occupations_m | male_female_pct_sales_occupations_ratio | pop_farming_occupations | pop_farming_occupations_f | pop_farming_occupations_m | male_female_pop_farming_occupations_ratio | pct_farming_occupations | pct_farming_occupations_f | pct_farming_occupations_m | male_female_pct_farming_occupations_ratio | pop_construction_occupations | pop_construction_occupations_f | pop_construction_occupations_m | male_female_pop_construction_occupations_ratio | pct_construction_occupations | pct_construction_occupations_f | pct_construction_occupations_m | male_female_pct_construction_occupations_ratio | pop_maintenance_occupations | pop_maintenance_occupations_f | pop_maintenance_occupations_m | male_female_pop_maintenance_occupations_ratio | pct_maintenance_occupations | pct_maintenance_occupations_f | pct_maintenance_occupations_m | male_female_pct_maintenance_occupations_ratio | pop_production_occupations | pop_production_occupations_f | pop_production_occupations_m | male_female_pop_production_occupations_ratio | pct_production_occupations | pct_production_occupations_f | pct_production_occupations_m | male_female_pct_production_occupations_ratio | pop_transportation_occupations | pop_transportation_occupations_f | pop_transportation_occupations_m | male_female_pop_transportation_occupations_ratio | pct_transportation_occupations | pct_transportation_occupations_f | pct_transportation_occupations_m | male_female_pct_transportation_occupations_ratio | pop_military_occupations | pop_military_occupations_f | pop_military_occupations_m | male_female_pop_military_occupations_ratio | pct_military_occupations | pct_military_occupations_f | pct_military_occupations_m | male_female_pct_military_occupations_ratio | pop_in_armed_forces | pop_in_armed_forces_f | pop_in_armed_forces_m | male_female_pop_in_armed_forces_ratio | pct_in_armed_forces | pct_in_armed_forces_f | pct_in_armed_forces_m | male_female_pct_in_armed_forces_ratio | pop_civilian_labor_force | pop_civilian_labor_force_f | pop_civilian_labor_force_m | male_female_pop_civilian_labor_force_ratio | pct_civilian_labor_force | pct_civilian_labor_force_f | pct_civilian_labor_force_m | male_female_pct_civilian_labor_force_ratio | pop_in_private_industry | pop_in_private_industry_f | pop_in_private_industry_m | male_female_pop_in_private_industry_ratio | pct_in_private_industry | pct_in_private_industry_f | pct_in_private_industry_m | male_female_pct_in_private_industry_ratio | pop_self_employed | pop_self_employed_f | pop_self_employed_m | male_female_pop_self_employed_ratio | pct_self_employed | pct_self_employed_f | pct_self_employed_m | male_female_pct_self_employed_ratio | pop_in_government | pop_in_government_f | pop_in_government_m | male_female_pop_in_government_ratio | pct_in_government | pct_in_government_f | pct_in_government_m | male_female_pct_in_government_ratio | pop_unpaid | pop_unpaid_f | pop_unpaid_m | male_female_pop_unpaid_ratio | pct_unpaid | pct_unpaid_f | pct_unpaid_m | male_female_pct_unpaid_ratio | pop_poverty | pop_poverty_f | pop_poverty_m | male_female_pop_poverty_ratio | pct_poverty | pct_poverty_f | pct_poverty_m | male_female_pct_poverty_ratio | pop_poverty_known | pop_poverty_known_f | pop_poverty_known_m | male_female_pop_poverty_known_ratio | pct_poverty_known | pct_poverty_known_f | pct_poverty_known_m | male_female_pct_poverty_known_ratio | pop_public_assistance | pop_public_assistance_f | pop_public_assistance_m | male_female_pop_public_assistance_ratio | pct_public_assistance | pct_public_assistance_f | pct_public_assistance_m | male_female_pct_public_assistance_ratio | pop_retirement | pop_retirement_f | pop_retirement_m | male_female_pop_retirement_ratio | pct_retirement | pct_retirement_f | pct_retirement_m | male_female_pct_retirement_ratio | pop_group_quarters | pop_group_quarters_f | pop_group_quarters_m | male_female_pop_group_quarters_ratio | pct_group_quarters | pct_group_quarters_f | pct_group_quarters_m | male_female_pct_group_quarters_ratio | pop_military_quarters | pop_military_quarters_f | pop_military_quarters_m | male_female_pop_military_quarters_ratio | pct_military_quarters | pct_military_quarters_f | pct_military_quarters_m | male_female_pct_military_quarters_ratio | pop_college_quarters | pop_college_quarters_f | pop_college_quarters_m | male_female_pop_college_quarters_ratio | pct_college_quarters | pct_college_quarters_f | pct_college_quarters_m | male_female_pct_college_quarters_ratio | pop_other_quarters | pop_other_quarters_f | pop_other_quarters_m | male_female_pop_other_quarters_ratio | pct_other_quarters | pct_other_quarters_f | pct_other_quarters_m | male_female_pct_other_quarters_ratio | pop_in_households | pop_in_households_f | pop_in_households_m | male_female_pop_in_households_ratio | pct_in_households | pct_in_households_f | pct_in_households_m | male_female_pct_in_households_ratio | pop_householder | pop_householder_f | pop_householder_m | male_female_pop_householder_ratio | pct_householder | pct_householder_f | pct_householder_m | male_female_pct_householder_ratio | pop_husband | pop_husband_f | pop_husband_m | male_female_pop_husband_ratio | pct_husband | pct_husband_f | pct_husband_m | male_female_pct_husband_ratio | pop_spouse_present | pop_spouse_present_f | pop_spouse_present_m | male_female_pop_spouse_present_ratio | pct_spouse_present | pct_spouse_present_f | pct_spouse_present_m | male_female_pct_spouse_present_ratio | pop_wife | pop_wife_f | pop_wife_m | male_female_pop_wife_ratio | pct_wife | pct_wife_f | pct_wife_m | male_female_pct_wife_ratio | pop_child | pop_child_f | pop_child_m | male_female_pop_child_ratio | pct_child | pct_child_f | pct_child_m | male_female_pct_child_ratio | pop_child_under_6 | pop_child_under_6_f | pop_child_under_6_m | male_female_pop_child_under_6_ratio | pct_child_under_6 | pct_child_under_6_f | pct_child_under_6_m | male_female_pct_child_under_6_ratio | pop_child_6_to_17 | pop_child_6_to_17_f | pop_child_6_to_17_m | male_female_pop_child_6_to_17_ratio | pct_child_6_to_17 | pct_child_6_to_17_f | pct_child_6_to_17_m | male_female_pct_child_6_to_17_ratio | pop_child_18_to_24 | pop_child_18_to_24_f | pop_child_18_to_24_m | male_female_pop_child_18_to_24_ratio | pct_child_18_to_24 | pct_child_18_to_24_f | pct_child_18_to_24_m | male_female_pct_child_18_to_24_ratio | pop_child_25_and_over | pop_child_25_and_over_f | pop_child_25_and_over_m | male_female_pop_child_25_and_over_ratio | pct_child_25_and_over | pct_child_25_and_over_f | pct_child_25_and_over_m | male_female_pct_child_25_and_over_ratio | pop_other_relatives | pop_other_relatives_f | pop_other_relatives_m | male_female_pop_other_relatives_ratio | pct_other_relatives | pct_other_relatives_f | pct_other_relatives_m | male_female_pct_other_relatives_ratio | pop_under_6 | pop_under_6_f | pop_under_6_m | male_female_pop_under_6_ratio | pct_under_6 | pct_under_6_f | pct_under_6_m | male_female_pct_under_6_ratio | pop_6_to_17 | pop_6_to_17_f | pop_6_to_17_m | male_female_pop_6_to_17_ratio | pct_6_to_17 | pct_6_to_17_f | pct_6_to_17_m | male_female_pct_6_to_17_ratio | pop_18_to_24 | pop_18_to_24_f | pop_18_to_24_m | male_female_pop_18_to_24_ratio | pct_18_to_24 | pct_18_to_24_f | pct_18_to_24_m | male_female_pct_18_to_24_ratio | pop_25_and_over | pop_25_and_over_f | pop_25_and_over_m | male_female_pop_25_and_over_ratio | pct_25_and_over | pct_25_and_over_f | pct_25_and_over_m | male_female_pct_25_and_over_ratio | pop_nonrelatives | pop_nonrelatives_f | pop_nonrelatives_m | male_female_pop_nonrelatives_ratio | pct_nonrelatives | pct_nonrelatives_f | pct_nonrelatives_m | male_female_pct_nonrelatives_ratio | pop_unmarried_partner | pop_unmarried_partner_f | pop_unmarried_partner_m | male_female_pop_unmarried_partner_ratio | pct_unmarried_partner | pct_unmarried_partner_f | pct_unmarried_partner_m | male_female_pct_unmarried_partner_ratio | pop_family_households | pop_family_households_f | pop_family_households_m | male_female_pop_family_households_ratio | pct_family_households | pct_family_households_f | pct_family_households_m | male_female_pct_family_households_ratio | pop_husband_present | pop_husband_present_f | pop_husband_present_m | male_female_pop_husband_present_ratio | pct_husband_present | pct_husband_present_f | pct_husband_present_m | male_female_pct_husband_present_ratio | pop_female_householder | pop_female_householder_f | pop_female_householder_m | male_female_pop_female_householder_ratio | pct_female_householder | pct_female_householder_f | pct_female_householder_m | male_female_pct_female_householder_ratio | pop_nonfamily_households | pop_nonfamily_households_f | pop_nonfamily_households_m | male_female_pop_nonfamily_households_ratio | pct_nonfamily_households | pct_nonfamily_households_f | pct_nonfamily_households_m | male_female_pct_nonfamily_households_ratio | pop_female_householder | pop_female_householder_f | pop_female_householder_m | male_female_pop_female_householder_ratio | pct_female_householder | pct_female_householder_f | pct_female_householder_m | male_female_pct_female_householder_ratio | pop_living_alone | pop_living_alone_f | pop_living_alone_m | male_female_pop_living_alone_ratio | pct_living_alone | pct_living_alone_f | pct_living_alone_m | male_female_pct_living_alone_ratio | pop_not_living_alone | pop_not_living_alone_f | pop_not_living_alone_m | male_female_pop_not_living_alone_ratio | pct_not_living_alone | pct_not_living_alone_f | pct_not_living_alone_m | male_female_pct_not_living_alone_ratio | pop_households | pop_households_f | pop_households_m | male_female_pop_households_ratio | pct_households | pct_households_f | pct_households_m | male_female_pct_households_ratio | pop_group_quarters | pop_group_quarters_f | pop_group_quarters_m | male_female_pop_group_quarters_ratio | pct_group_quarters | pct_group_quarters_f | pct_group_quarters_m | male_female_pct_group_quarters_ratio | pop_urban | pop_urban_f | pop_urban_m | male_female_pop_urban_ratio | pct_urban | pct_urban_f | pct_urban_m | male_female_pct_urban_ratio | pop_urban_area | pop_urban_area_f | pop_urban_area_m | male_female_pop_urban_area_ratio | pct_urban_area | pct_urban_area_f | pct_urban_area_m | male_female_pct_urban_area_ratio | pop_urban_place | pop_urban_place_f | pop_urban_place_m | male_female_pop_urban_place_ratio | pct_urban_place | pct_urban_place_f | pct_urban_place_m | male_female_pct_urban_place_ratio | pop_not_urban | pop_not_urban_f | pop_not_urban_m | male_female_pop_not_urban_ratio | pct_not_urban | pct_not_urban_f | pct_not_urban_m | male_female_pct_not_urban_ratio |
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